Bismuth- and Iron-Catalyzed Three-Component Synthesis of α-Amino Acid Derivatives: A Simple and Convenient Route to α-Arylglycines

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Abstract Efficient bismuth- and iron-catalyzed three-component syntheses of α-arylglycines have been developed. These methods provide a general, atom-economic route to various N-protected α-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.

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

α-Amino acids are of fundamental importance for biology, biochemistry, and chemistry.1,2 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.1,2 Many proteinogenic and nonproteinogenic α-amino acids have important biological, nonprotein-related functions, such as glutamate,1 an important neurotransmitter or glycine,1 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) α-amino acids have gained increasing attention.1,2 Among these nonproteinogenic α-amino acids, α-arylglycines are of particular importance, as they are building blocks for various drugs, such as cardiovascular agents4 and β-lactam antibiotics5 like amoxicillin and norcardicin A (Figure 1). The α-arylglycine moiety is also part of numerous natural products, such as vancomycin6 or chloropeptin I7 (Figure 1). Expanding the organic chemist’s tool box with novel efficient, modular and practical methods for the synthesis of the α-arylglycine structure is therefore of great interest.8,9 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,10 the Strecker reaction,11 the Petasis–(Borono–Mannich) reaction,12 or aza-Friedel–Crafts-type reactions13 (Scheme 1).
However, these methods have some decisive drawbacks. Cyanides used in the Strecker reaction are highly toxic and the subsequent hydrolysis of the nitrile function under acidic conditions curtails the functional group tolerance (Scheme 1, path A). The Petasis–(Borono–Mannich) reaction and related processes require prefunctionalized and often expensive boronic acid derivatives (Scheme 1, path B). Another important approach is the direct amino- and amidoalkylation of unfunctionalized (hetero)arenes or require stoichiometric amounts of strong Brønsted or Lewis acids.14 These aza-Friedel–Crafts-type reactions are based on nucleophilic addition of arenes to highly electrophilic imines and especially based on nucleophilic addition of arenes to highly electro-expensive and nontoxic bismuth and iron catalysts.16a,b

These reactions provide straightforward access to a broad scope of α-arylglycines with 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.17

To identify a suitable catalyst system, the reaction of benzamide (1a) with commercially available ethyl glyoxalate (2a)18 and the moderately reactive m-xylene (3a)19 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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe(CIO4)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.

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.20,21 Therefore, iron-based catalysts were investigated in more detail. During our previous research on amidoalkylation reactions, Bi(OTf)3 was identified as a very active, nontoxic, and relatively cheap catalyst.22,23 Thus, we decided to take

![Scheme 1](image-url)
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.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(ClO4)3 and FeCl3·6H2O gave similar yields during the initial optimization reactions (Table 2, entries 1 and 7), Fe(ClO4)3 led to higher yields in general. Additionally, for Fe(ClO4)3 the catalyst loading can be decreased without significant loss of efficiency (entry 9). Whereas 1 mol% FeCl3 dropped to 18% (entry 5). The corresponding Fe2+ salts could catalyze the model reaction with similar efficiency (entries 6 and 11). However, as judged by the observed rapid color change, we assume a fast oxidation of Fe2+ to Fe3+ under our aerobic reaction conditions. To rule out a possible ‘hidden’ catalysis by Bronsted acids, the reaction was performed in the presence of the proton scavenger 2,6-di-tert-butylpyridine (dbpy, entry 12). No significant decrease in yield was observed. Therefore, we concluded that a Fe3+ species is the active catalyst.

Next, different solvents were examined for our three-component reaction (Table 2, entries 13–16). Best results were obtained in nitromethane. All other tested solvents led to lower yields (1,2-dichloroethane, dichloromethane, or 1,4-dioxane) or complete shutdown of the reaction (THF, H2O, EtOAc). A similar screening of reaction parameters was performed with the Bi-catalyzed three-component synthesis. As shown in Table 3, Bi(OTf)3 proved to be the optimal catalyst. Other bismuth salts like BiCl3 or BiBr3 afforded the product in lower yields (Table 3, entries 5 and 6). Notably, the catalyst loading of Bi(OTf)3 could be reduced to only 0.5 mol% without a significant change in yield and even with 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. To further exclude a possible Brønsted acid catalysis a control reaction with the proton scavenger dbpy was performed also in the case of Bi(OTf)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

### Table 2 Optimization of the Reaction Parameters for Fe-Catalyzed Three-Component Reaction for the Synthesis of α-Arylglycine 4a

<table>
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<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeCl3·6H2O (5 mol%)</td>
<td>MeNO2</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>FeCl3·6H2O (2 mol%)</td>
<td>MeNO2</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>anhyd FeCl3 (5 mol%)</td>
<td>MeNO2</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>anhyd FeCl3 (2 mol%)</td>
<td>MeNO2</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>anhyd FeCl3 (1 mol%)</td>
<td>MeNO2</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>FeCl3·4H2O (2 mol%)</td>
<td>MeNO2</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>Fe(ClO4)3·xH2O (5 mol%)</td>
<td>MeNO2</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>Fe(ClO4)3·xH2O (1 mol%)</td>
<td>MeNO2</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>Fe(ClO4)3·xH2O (0.5 mol%)</td>
<td>MeNO2</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>Fe(ClO4)3·xH2O (0.1 mol%)</td>
<td>MeNO2</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>Fe(ClO4)3·xH2O (2 mol%)</td>
<td>MeNO2</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>Fe(ClO4)3·xH2O (5 mol%) + dbpy (10 mol%)</td>
<td>MeNO2</td>
<td>86</td>
</tr>
<tr>
<td>13</td>
<td>FeCl3·6H2O (2 mol%)</td>
<td>DCE</td>
<td>39</td>
</tr>
<tr>
<td>14</td>
<td>FeCl3·6H2O (2 mol%)</td>
<td>CH2Cl2</td>
<td>23</td>
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<tr>
<td>15</td>
<td>FeCl3·6H2O (2 mol%)</td>
<td>1,4-dioxane</td>
<td>&lt;10</td>
</tr>
<tr>
<td>16</td>
<td>FeCl3·6H2O (2 mol%)</td>
<td>MeCN</td>
<td>10</td>
</tr>
</tbody>
</table>

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

### Table 3 Optimization of the Reaction Parameters for Bi-Catalyzed Three-Component Reaction for the Synthesis of α-Arylglycine 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bi(OTf)3 (5 mol%)</td>
<td>MeNO2</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Bi(OTf)3 (2 mol%)</td>
<td>MeNO2</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>Bi(OTf)3 (1 mol%)</td>
<td>MeNO2</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Bi(OTf)3 (0.5 mol%)</td>
<td>MeNO2</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>BiCl3 (5 mol%)</td>
<td>MeNO2</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>BiBr3 (5 mol%)</td>
<td>MeNO2</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>Bi(OTf)3 (5 mol%) + dbpy (10 mol%)</td>
<td>MeNO2</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>Bi(OTf)3 (5 mol%)</td>
<td>DCE</td>
<td>52</td>
</tr>
</tbody>
</table>

*Yields are given for the isolated product. The product was obtained as a 98:2 mixture of regioisomers. Only the major regioisomer is shown.*
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-url)
75:25), 4m (95:5 vs. 71:29), or 4p (67:33 vs 50:50). So far we do not have a conclusive explanation for this phenomenon.

Next, the reactions of different amides and carbamates with ethyl glyoxalate (2a) and mesitylene (3b) were examined (Scheme 3). To our delight different benzamide derivatives were compatible with both catalysts systems and the desired products 5a–c were obtained in excellent yields (68–94%). Alkyl-substituted primary amides are also suitable substrates and arylglycine derivatives 5d–f were obtained in 70–88% yield with iron catalysis and in 79–81% yield with bismuth catalysis. Even acid-sensitive amides such as acrylamide were transformed into the desired product 5g in 82% (Bi) or 85% (Fe) yield. Carbamates are suitable substrates for the bismuth- and the iron-catalyzed three-component reactions. Different N-protected α-arylglycines 5h–k, such as 5i bearing a Cbz-protecting group or the Fmoc-derivative 5k, were obtained in high yields. Unfortunately reaction with tert-butyl carbamate did not furnish the desired Boc-protected arylglycine 5l. Sterically more demanding secondary amides or electron-deficient trifluoracetyl amide proved to be unsuitable for our method and the desired products 5m and 5n could not be obtained.

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). 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 amidoalkylated 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 \( \text{N}^{\text{f}} \)-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 amidokylated 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 Fe^{3+}). 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 Fe^{3+} 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.

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...
Investigations into Stereoselective Reactions

Since most of the natural α-arylglucelines 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 Bi^{3+} or Fe^{3+} salts (Scheme 10).29 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 In^{3+} and Yb^{3+}, promising Lewis acids in our initial screening, were studied. Again no asymmetric induction was observed.

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-arylglycine 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. 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.
or NMR). Neither were we able to detect any reactive methods available at our department (GC, HPLC, React-IR, diates during the course of the reaction with the analytical we were not able to quantify the amount of both interme-
acylimine species. As expected, the reaction of benzamide homogenous again. Due to the insolubility of bisamide completely and at the end the reaction mixture becomes 25a yields. Indeed, the formation and precipitation of bisamide 25a at 80 °C led to the formation of bisamide (Scheme 15). Longer reaction times (96 h) or heating to nomic and ecologic aspects of iron(III) salts.
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Synthesis
Figure 3 Rates of product formation with different catalyst loadings
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We assumed that two factors contribute to the observed low stereo-
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-compo-
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Figure 3 NMR spectra of 2a, 4a, and 25a (100 MHz, CDCl3, 25 °C).
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(Figure 3). Therefore, Fe(ClO4)3 is the catalyst of choice for more reactive arenes, considering the activity and the eco-
We assumed that two factors contribute to the observed low stereo-
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-compo-
and hemiaminal 25a, led to the expected reaction conditions, bisamide 25a, favored under kinetic control, can decompose to yield the reactive N-acylimine 28. In the presence of a suitable, nucleophilic arene, the N-
We assumed that two factors contribute to the observed low stereo-
ntivity of the used catalyst greatly depends on two factors. The high intrin-
Mechanistic studies and postulated reaction pathway

**Scheme 15**: Mechanistic studies and postulated reaction pathway.
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. This places the catalyst far away from the reactive center, thereby severely hampering any stereochemical 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)₃- and Fe(ClO₄)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(ClO₄)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)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 azas-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 availalbe 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, I₂, 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 ¹H 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-pyrrrole, 1-tosyl-1H-indole, N-[(o-tolyl)pivalamide, N-(2-methoxy-phenyl)pivalamide, N-(4-methoxyphenyl)pivalamide, methanesulfonamide, 4-methylbenzenesulfonamide, 4-methoxybenzenesulfonamide, and 2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanamide were synthesized according to literature. Ethyl glyoxalate was obtained as 50 wt% solution in toluene. Glyoxyl acid was obtained as 50 wt% solution in H₂O and used as received. All other starting materials were purchased from commercial sources and used without further purification. Fe(ClO₄)₃ was obtained as undefined hydrate (Fe(ClO₄)₃·xH₂O, yellow form, reagent grade) from different providers. The exact H₂O content was determined by elemental analysis. Depending on the provider and storage time (or even the time for weighing out a defined amount for elemental analysis) Fe(ClO₄)₃ contained from one up to ten molecules of H₂O. Therefore, the amount of Fe(ClO₄)₃ used is always calculated on anhydrous Fe(ClO₄)₃. No changes in catalytic activity were observed for different batches of Fe(ClO₄)₃ or upon prolonged storage times. No special precautions were taken to avoid exposure of Fe(ClO₄)₃ or upon prolonged storage times. No special precautions were taken to avoid exposure of Fe(ClO₄)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 anhydrous perchlorate salts, we strongly advise to use the hydrated form of Fe(ClO₄)₃. Under no circumstances should Fe(ClO₄)₃ be dried or handled in its anhydrous form. Since similar yields are obtained even with the decahydrate Fe(ClO₄)₃·10H₂O, 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(ClO₄)₃. Even prolonged heating of Fe(ClO₄)₃ in MeNO₂ up to 120 °C did not lead to any decomposition. (In fact it is known the anhydrous LiClO₄ is stable in Et₂O at temperatures up to ≥150 °C. For further information on perchlorate safety and stability, we recommend the article of Long.

Anhyd Bi(OTf)₃ was obtained from different providers and used directly. No special precautions were taken to avoid exposure of Bi(OTf)₃ to moisture. Therefore, we cannot rule out the formation of Bi(OTf)₃·xH₂O during storage. Indeed, depending on the provider and storage time (or even the time for weighing out a defined amount for elemental analysis) Bi(OTf)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)₃ used is always calculated on anhydrous Bi(OTf)₃. The actual catalyst loading for particular reactions might be slightly lower, depending on the batch quality and storage time.

¹H and ¹³C 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 CDCl₃ or DMSO-d₆ peak (δ = 7.26 for ¹H and δ = 77.16 for ¹³C; δ = 2.50 for ¹H and δ = 39.52 for ¹³C). 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⁻¹. The absorption bands were reported in wave numbers (cm⁻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)₃ (1–5 mol%), the appropriate amide (1.0 equiv), and MeNO₂ (4.0 mL/mmol amide) or DCE wherever applicable. Ethyl glyoxalate (1.2 equiv) and the appropriate aromatic compound.
(3.0 equiv) were added under vigorous stirring. Ethyl glyoxalate was used as a 50 wt% solution in toluene (technical form) and used as received for the reactions with iron(III) salts. For the reaction with Bi(OTf)₃, toluene was removed in vacuo (1 mbar, 3 h) in order to avoid side reactions. The resulting oil was redissolved in MeNO₂. The reaction mixture was heated to 40–100 °C and stirred at this temperature. After cooling to r.t., the reaction mixture was diluted with EtOAc and filtered through a short plug of Celite and silica gel. The plug was rinsed with additional EtOAc. The combined filtrates were concentrated under reduced pressure. Purification of the crude residue by column chromatography (cyclohexane/EtOAc, then n-hexane/EtOAc) afforded the analytically pure product.

Ethyl 2-Benzamido-2-(2,4-dimethylphenyl)acetate (4a)

**Bi Catalysis**

Compound 4a was synthesized according to the GP from benzamidine (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 (13 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 (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (376 mg, 91%; r.r. = >98:2). Further purification of the major regioisomer afforded the analytically pure product.

**Fe Catalysis**

Ethyl 2-Benzamido-2-(4-methoxyphenyl)acetate (4c)

**Bi Catalysis**

Compound 4c 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), m-xylene (0.18 mL, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.050 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 (153 mg, 94%; r.r. = 78:22, as judged by 1H NMR analysis). Analytical data were obtained for this purified mixture.

**Fe Catalysis**

Ethyl 2-Benzamido-2-(4-methoxy-3-methylphenyl)acetate (4d)

**Bi Catalysis**

Compound 4d was synthesized according to the GP from benzamidine (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), anisole (0.32 mm, 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 (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (236 mg, 97%, r.r. = 75:25). Further purification of the major regioisomer was achieved by precipitation from hexane/CH₂Cl₂ (r.r. = 78:22, as judged by 1H NMR analysis). Analytical data were obtained for this purified mixture.

**Fe Catalysis**

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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 (115 mg, 70%; r.r. = >98:2).

**Fe Catalysis:** Compound 4d 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-2-methylbenzene (0.37 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 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (223 mg, 68%; r.r. = 94:6). Further purification of the major regioisomer could be achieved by precipitation from hexane/CH₂Cl₂ (only major regioisomer, as judged by 1H NMR analysis). Analytical data were obtained for this purified regioisomer.

IR (ATR): 3343 (w), 2937 (w), 1732 (s), 1638 (s), 1611 (m), 1579 (m), 1508 (m), 1486 (m), 1451 (w), 1347 (m), 1315 (m), 1278 (m), 1249 (s), 878 (m), 751 (m), 691 cm⁻¹ (s).

**HRMS (MALDI):** [M + Na]+ calcd for C₁₉H₂₁NO₄Na: 350.1; found: 350.2.

**EtU 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 (61 mg, 0.6 mmol, 1.2 equiv), 1-methoxy-3-methylbenzene (0.19 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 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 (97 mg, 59%; 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 (0.24 mL, 1.2 mmol, 1.2 equiv), 1-methoxy-4-methylbenzene (0.38 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 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (205 mg, 63%; r.r. = >98:2).

**EtU 2-Benzamido-2-(4-methoxy-2-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 (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 (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 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 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (205 mg, 63%; r.r. = >98:2).

The product 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 (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 (205 mg, 63%; r.r. = >98:2).

**Bi Catalysis**

**Fe Catalysis**
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 Fe(ClO₄)₃ (18 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, 88%; r.r. = 99:2).

**Fe Catalysis:** Compound 4h was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.30 mL, 1.5 mmol, 1.5 equiv), 2-bromoanisole (0.37 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 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless solid (355 mg, 81%; r.r. = 99:2).

**Ethyl 2-Benzamido-2-(3-bromo-4-methoxyphenyl)acetate (4i)**

**Bi Catalysis:** Compound 4i was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.30 mL, 1.5 mmol, 1.5 equiv), 2-bromoanisole (0.37 mL, 3.0 mmol, 3.0 equiv), and Bi(OTf)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%; r.r. = 99:2).

**Fe Catalysis:** Compound 4i 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(OTf)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%; r.r. = 99:2).

**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 (122 mg, 1.2 mmol), 4-bromoanisole (0.38 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 16 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless solid (125 mg, 34%; r.r. = 99:2).

**Fe 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 Fe(ClO₄)₃ (18 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 (125 mg, 34%; r.r. = 99:2).

**Synthesis**

Mp 102.4 °C; Rf = 0.46 (cyclohexane/EtOAc = 7:3).

IR (ATR): 3277 (w), 3054 (w), 2933 (w), 2835 (w), 1739 (s), 1637 (s), 1602 (w), 1578 (w), 1523 (m), 1486 (s), 1456 (m), 1391 (w), 1366 (w), 1336 (m), 1317 (m), 1294 (m), 1247 (s), 1188 (s), 1134 (m), 1093 (m), 1025 (s), 800 (m), 689 cm⁻¹ (s).

1H NMR (400 MHz, CDCl₃): δ = 7.83–7.75 (m, J = 13.0, 7.6 Hz, 2 H), 7.75–7.68 (m, 1 H), 7.63–7.37 (m, 4 H), 7.31–7.20 (m, 1 H), 6.71–6.64 (m, 1 H), 5.86 (d, J = 8.0 Hz, 1 H), 4.26–4.15 (m, 2 H), 3.82 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 170.7, 166.7, 157.2, 139.2, 138.6, 134.1, 131.9, 128.7, 128.4, 127.3, 113.5, 83.2, 62.0, 55.9, 53.3, 14.3.

MS (ESI): [M + Na]⁺ calcd for C₁₈H₁₉INO₄: 397.2; found: 397.2.


**Ethyl 2-Benzamido-2-(3,5-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 (61 mg, 0.6 mmol, 1.2 equiv), p-xylene (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 oil (62 mg, 40%).

**Fe Catalysis:** Compound 4l 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 (270 mg, 1.5 mmol, 3.0 equiv), and FeCl₃ (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%; Rf = 0.38 (cyclohexane/EtOAc = 7:3).

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The product 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), 1,2,3-trimethoxynaphthalene (505 mg, 3.0 mmol, 3.0 equiv), Fe(ClO$_4$)$_3$ (18 mg, 0.05 mmol, 5 mol%), and 2,2'-bipyridine (0.06 mmol, 6 mol%, 9 mg) in MeNO$_2$ (4.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1 → 7:3) yielded the product as a colorless oil (136 mg, 58%; $R_f = 0.36$ (cyclohexane/EtOAc = 7:3)).

**Fe 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 MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as an orange oil (89 mg, 49%).

**Fe Catalysis**: Compound 4q 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), 2-methoxynaphthalene (237 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (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 = 9:1 → 4:1) yielded the product as an orange oil (123 mg, 64%; $R_f = 0.31$ (cyclohexane/EtOAc = 7:3)).

**MS (ESI)**: $m/z$ [M + Na$^+$$]$ calcd for C$_{22}$H$_{22}$NO$_4$Na: 364.1544; found: 364.1540.

**HRMS (MALDI)**: $m/z$ [M + H$^+$] calcd for C$_{22}$H$_{22}$NO$_4$: 364.1543; found: 364.1543.

**Ethyl 2-Benzamido-2-(4-methoxy-2,6-dimethylphenyl)acetate (4p)**

**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), 1-methoxy-3,5-dimethylbenzene (204 mg, 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 16 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 9:1 → 4:1) yielded the product as a yellowish oil (115 mg, 57%; $R_f = 0.57$ (cyclohexane/EtOAc = 7:3)).

**Fe Catalysis**: Compound 4p 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), 1-methoxy-3,5-dimethylbenzene (204 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (9 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1 → 4:1) yielded the product as a yellowish oil (106 mg, 62%; $R_f = 0.50$; $R_f = 0.57$ (cyclohexane/EtOAc = 7:3)).

**Ethyl 2-Benzamido-2-(4-methoxy-2,6-dimethylphenyl)acetate (4q)**

**Bi Catalysis**: Compound 4q 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 MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as an orange oil (123 mg, 64%; $R_f = 0.31$ (cyclohexane/EtOAc = 7:3)).

**Fe Catalysis**: Compound 4q 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), 2-methoxynaphthalene (237 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (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 = 9:1 → 4:1) yielded the product as an orange oil (123 mg, 64%; $R_f = 0.31$ (cyclohexane/EtOAc = 7:3)).

**Ethyl 2-Benzamido-2-(4-methoxy-2,6-dimethylphenyl)acetate (4q)**

**Bi Catalysis**: Compound 4r 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), pyrene (303 mg, 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 18 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (111 mg, 54%; $R_f = 0.98$ for 4q).

**Fe Catalysis**: Compound 4r 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), pyrene (303 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (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 = 20:1 → 9:1 → 4:1) yielded the product as a colorless solid (115 mg, 57%; $R_f = 0.98$ for 4r).

**MS (ESI)**: $m/z$ [M + H$^+$] calcd for C$_{22}$H$_{22}$NO$_4$: 364.1543; found: 364.1543.
1H NMR (400 MHz, CDCl3): δ = 8.61–8.54 (m, 1 H), 8.25–8.01 (m, 8 H), 7.86–7.79 (m, 2 H), 7.49 (d, J = 14.0, 6.6 Hz, 1 H), 7.40–7.35 (m, 3 H), 7.26 (s, 1 H), 6.83 (d, J = 7.3 Hz, 1 H), 4.36–4.15 (m, 2 H), 1.18 (t, J = 7.1 Hz, 3 H). 13C NMR (101 MHz, CDCl3): δ = 171.8, 166.9, 133.8, 132.0, 131.8, 131.4, 130.9, 129.3, 128.9, 128.7, 128.2, 127.4, 127.3, 126.4, 125.8, 125.7, 125.4, 125.2, 124.8, 122.8, 62.3, 54.3, 14.2.

IR (ATR): 3119 (s), 2978 (w), 1732 (s), 1635 (m), 1599 (m), 1593 (m), 1349 (s), 1232 (s), 1193 (s), 1175 (s), 1088 (m), 1021 (s), 845 (s), 767 cm−1 (m).


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 = 4:1) yielded the product as a colorless solid (172 mg, 85%).

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 (145 mg, 81%).

Fe Catalysis: Compound 5a was synthesized according to the GP from 4-methoxybenzamide (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 = 4:1) yielded the product as a colorless solid (125 mg, 68%).

Etethyl 2-(4-Bromobenzamido)-2-mesitylacate (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 = 4:1) yielded the product as a colorless solid (121 mg, 81%).

Fe Catalysis: Compound 5b was synthesized according to the GP from 4-bromobenzamide (166 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 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 (cyclohexane/EtOAc = 9:1 → 4:1) yielded the product as a colorless solid (329 mg, 89%).

Etethyl 2-(2-Chloroacetamido)-2-mesitylacate (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%); Rp = 0.30 (cyclohexane/EtOAc = 7:3).
Ethyl 2-Acetamido-2-mesitylacetate (5e)

**Bi Catalysis**

Compound 5e was synthesized according to the GP from acetylamide (59 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 (7 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 = 4:1) yielded the product as a colorless solid (209 mg, 79%).

**Fe Catalysis**

Compound 5e was synthesized according to the GP from acetylamide (30 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.02 mL, 0.2 mmol, 1 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 oil (93 mg, 70%).

Ethyl 2-Acrylamido-2-mesitylacetate (5g)

**Bi Catalysis**

Compound 5g was synthesized according to the GP from acetylamide (71 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 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 (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 (226 mg, 82%).

**Fe Catalysis**

Compound 5g was synthesized according to the GP from acetylamide (71 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 FeCl3·6H2O (7 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 = 7:3) yielded the product as a colorless solid (233 mg, 85%).

"m"P 117.2 °C; Rf = 0.43 (cyclohexane/EtOAc = 7:3).

IR (ATR): 3304.43 (s), 2983 (s), 1748 (s), 1652 (m), 1614 (m), 1519 (s), 1463 (w), 1366 (m), 1310 (w), 1281 (w), 1211 (s), 1192 (s), 1149 (m), 1124 (m), 1113 (m), 1072 (s), 1023 (m), 990 (m), 958 (m), 856 (s), 858 (m), 810 (m), 604 cm−1 (m).

"m"H NMR (300 MHz, CDCl3): δ = 6.83 (s, 2 H), 6.58 (d, J = 6.0 Hz, 1 H), 5.96 (d, J = 5.0 Hz, 1 H); 4.00–3.84 (m, 3 H), 2.40 (s, 6 H), 2.24 (s, 3 H), 1.24–1.16 (m, 12 H).

**HRMS (MALDI):** m/z [M + H]⁺ calcd for C18H28NO3: 306.2; found: 306.2.

Ethyl 2-[Ethoxycarbonyl]amino]-2-mesitylacetate (5h)

**Bi Catalysis**

Compound 5h was synthesized according to the GP from ethyl carbamate (59 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), and BiCl3·3H2O (5 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 (248 mg, 81%).
**Ethyl 2-[[Benzoxyl]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[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 = 9:1) yielded the product as a colorless solid (116 mg, 65%).

**Fe 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 FeCl$_3$·6H$_2$O (5 mg, 0.020 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 = 9:1) yielded the product as a colorless solid (185 mg, 83%).

**Ethyl 2-[[[(9-Fluoren-9-yl)methoxy]carbonyl]amino]-2-mesitylacetate (5k)**

**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 (0.21 mL, 1.5 mmol, 3.0 equiv), and Bi[OTf]$_3$ (7 mg, 0.01 mmol, 2 mol%) in MeNO$_2$ (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%); $R_f$ = 0.69 (cyclohexane/EtOAc = 7:3).

**Fe 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 (0.21 mL, 1.5 mmol, 3.0 equiv), and FeCl$_3$·6H$_2$O (5 mg, 0.020 mmol, 2 mol%) in MeNO$_2$ (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%); $R_f$ = 0.69 (cyclohexane/EtOAc = 7:3).
1H NMR (400 MHz, CDCl3): δ = 7.83 (d, J = 7.7 Hz, 2 H), 7.57–7.51 (m, 1 H), 7.49–7.43 (m, 2 H), 7.16–7.08 (m, 1 H), 6.94–6.77 (m, 2 H), 5.99–5.92 (m, 1 H), 4.37–4.23 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H) (peaks not assigned to regioisomers).

13C NMR (75 MHz, CDCl3): δ = 169.6, 166.7, 140.7, 137.8, 133.4, 132.3, 130.0, 128.8, 127.3, 126.6, 126.2, 125.7, 112.7, 62.8, 52.6, 14.2 (peaks not assigned to regioisomers).


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 (4.0 mL). The reaction mixture was stirred for 48 h at 40 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1 → 4:1) yielded the product as a yellow solid (161 mg, 50%; r.r. = 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 = 4.37–4.23 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H) (peaks not assigned to regioisomers).


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, 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/EtOAc = 9:1 → 4:1) yielded the product as a yellow solid (219 mg, 75%; r.r. = >98:2).

IR (ATR): 3305 (m), 2978 (w), 2929 (w), 2918 (w), 1743 (s), 1372 (m), 1295 (m), 1257 (m), 780 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).

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 = 4.37–4.23 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H) (peaks not assigned to regioisomers).


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 (w).

11C NMR (75 MHz, CDCl 3): 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).


Ethyl 2-(Benzofuran-2-yl)-2-[(ethoxycarbonyl)amino]acetate (7h)

Bi 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 (0.16 mL, 1.5 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 16 h at 60 °C. Purification by chromatography (cyclohexane/ETOAc = 9:1 → 4:1) 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 (128 mg, 88%; r.r. = >98:2). Further purification of the major regioisomer could be achieved by precipitation from hexane/CH2Cl2 (91:9 mixture of regioisomers, as judged by 1H NMR analysis). Analytical data were obtained for this purified mixture.

Mp 60.3 °C; Rf = 0.56 (cyclohexane/ETOAc = 7:3).

IR (ATR): 3263 (w), 2983 (w), 1742 (m), 1688 (s), 1605 (w), 1533 (m), 1453 (m), 1369 (m), 1245 (s), 1200 (s), 1093 (m), 1049 (s), 953 (m), 937 (m), 753 cm–1 (s).

1H NMR (400 MHz, CDCl 3): δ = 7.89–7.82 (m, 2 H), 7.60–7.42 (m, 5 H), 7.35–7.19 (m, 3 H), 6.85 (s, 1 H), 6.09 (d, J = 7.7 Hz, 1 H), 4.37–4.21 (m, 2 H), 1.28 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl 3): δ = 168.7, 166.8, 155.1, 151.5, 133.6, 132.2, 128.8, 128.1, 127.4, 124.9, 124.3, 121.5, 111.5, 106.1, 62.8, 51.3, 14.2.


HRMS (MALDI): m/z [M + H]+ calcd for C15H17NO4: 324.1230; found: 324.1229.

Ethyl 2-(Benzofuran-2-yl)-2-[(ethoxycarbonyl)amino]acetate (7i)

Fe Catalysis: Compound 7i was synthesized according to the GP from benzofuran (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), benzofuran (0.32 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 → 4:1) yielded the product as a yellow oil (205 mg, 62%; r.r. = >98:2; Rf = 0.57 (cyclohexane/ETOAc = 7:3).
Ethyl 2-[(Ethoxycarbonyl)amino]-2-(1-tosyl-1-pyrrol-2-yl)acetate (7j)

**Bi Catalysis**: Compound 7j was synthesized according to the GP from urethane (46 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.6 mg, 1.0 mmol, 1.2 equiv), N-tosylpyrrole (332 mg, 1.5 mmol, 3.0 equiv), and FeClO₄ (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 (123 mg, 62%; r.r. = >98:2).

**Fe Catalysis**: Compound 7j 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), N-tosylpyrrole (664 mg, 3.0 mmol, 3.0 equiv), and FeClO₄ (18 mg, 0.05 mmol, 5 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 40 °C. Purification by chromatography (cyclohexane/ETOAc = 9:1 → 4:1) yielded the product as a yellow solid (302 mg, 75%; r.r. = >98:2).

Methyl 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, 0.55 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), N-tosylindole (203 mg, 0.75 mmol, 1.5 equiv), and FeClO₄ (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 → 4:1) yielded the product as a colorless solid (94 mg, 50%; r.r. = 82:18).

**Bi Catalysis**: Compound 7l was synthesized according to the GP from benzamide (66 mg, 0.55 mmol, 1.0 equiv), isopropyl 2-oxoacetate (0.12 mL, 1.2 mmol, 1.2 equiv), N-tosylindole (814 mg, 3.0 mmol, 3.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 60 °C. Purification by chromatography (cyclohexane/ETOAc = 9:1 → 4:1) yielded the product as a colorless oil (369 mg, 83%; r.r. = >98:2).

**Isopropyl 2-Benzamido-2-mesitylacetate (11a)**

**Bi Catalysis**: Compound 11a was synthesized according to the GP from benzamide (66 mg, 0.55 mmol, 1.0 equiv), isopropyl 2-oxoacetate (75 mg, 0.65 mmol, 1.18 equiv), mesitylene (0.21 mL, 3.0 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 → 1:1) yielded the product as colorless solid (94 mg, 50%).
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 Fe(ClO₄)₃ (18 mg, 0.050 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 → 1:1) yielded the product as a colorless solid (281 mg, 83%).

Bi Catalysis: 2-(Ethoxycarbonyl)amino]-2-mesitylacetic Acid (11c)

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 FeCl₃·6H₂O (7 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 (CH₂Cl₂/MeOH = 50:1 → 20:1) yielded the product as a colorless solid (66 mg, 50%).

Bi Catalysis: Compound 11d was synthesized according to the GP from 9-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 FeCl₃·6H₂O (7 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 = 7:3 → 1:1) yielded the product as a colorless oil (94 mg, 45%).
(311 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (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 = 9:1 → 7:3 → 1:1) yielded the product as a colorless solid (184 mg, 89%; r.r. = 98:2).

**Bi Catalysis:** Compound 12a was synthesized according to the GP from benzamidine (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), N-(4-methoxyphenyl)pivalamide (311 mg, 1.5 mmol, 3.0 equiv), and Bi(OTf)$_3$ (7 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1 → 7:3 → 1:1) yielded the product as a colorless solid (128 mg, 62%; r.r. = 98:2).

**Fe Catalysis:** Compound 12b was synthesized according to the GP from benzamidine (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), N-(2-methoxyphenyl)pivalamide (311 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (9 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1 → 7:3 → 1:1) yielded the product as a colorless solid (164 mg, 80%, obtained as a 1:6 mixture of regioisomers). Further purification of the major regioisomer could be achieved by precipitation from hexane/CH$_2$Cl$_2$ (92:8 mixture of regioisomers, as judged by $^1$H NMR analysis). Analytical data were obtained for this purified mixture.

Mp 127.6 °C; $R_f$ = 0.34 (cyclohexane/EtOAc = 7:3).

**Bi Catalysis:** Compound 12c was synthesized according to the GP from benzamidine (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 2-methylpivalamide (287 mg, 1.5 mmol, 3.0 equiv), and Bi(OTf)$_3$ (16 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (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 benzamidine (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), 2-methylpivalamide (287 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (9 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (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).

ethyl 2-Benzamido-2-(4-methyl-3-pivalamidophenyl)acetate (12b)

**Fe Catalysis:** Compound 12b was synthesized according to the GP from benzamidine (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), N-(2-methoxyphenyl)pivalamide (311 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (9 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (128 mg, 74%).

**Fe Catalysis:** Compound 12d was synthesized according to the GP from benzamidine (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), 1,4-dimethoxybenzene (207 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO$_4$)$_3$ (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 = 4:1) yielded the product as a colorless solid (128 mg, 74%).
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)3 (12 mg, 0.025 mmol, 5 mol%) in MeNO2 (2.0 ml). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/MeOH = 9:1 → 4:1) yielded the product as a low-melting solid (123 mg, 65%; r.r. = 98:2).

**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 (516 mg, 3.0 mmol, 3.0 equiv), and Bi(OTf)3 (7 mg, 0.005 mmol, 1 mol%) in MeNO2 (4.0 ml). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/MeOH = 9:1 → 4:1) yielded the product as a low-melting solid (39 mg, 11%; r.r. = 98:2).

**HRMS (MALDI):** [M + Na]+ calcd for C17H16BrNO4Na: 400.0; found: 400.1.

**MS (ESI):** m/z [M + Na]+ calcd for C17H16BrNO4Na: 400.0; found: 400.1.

**HRMS (MALDI):** m/z [M + H]+ calcd for C17H16BrNO4: 378.0335; found: 378.0335.

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

**Bi Catalysis:** Compound 12f 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), o-xylene (0.36 ml, 3.0 mmol, 3.0 equiv), and Bi(OTf)3 (13 mg, 0.025 mmol, 2 mol%) in MeNO2 (4.0 ml). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/MeOH = 4:1) yielded the product as a colorless solid (278 mg, 89%; r.r. = 89:11).

**Fe Catalysis:** Compound 12h 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), and Fe(ClO4)3 (15 mg, 0.0375 mmol, 2 mol%) in MeNO2 (2.0 ml). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/MeOH = 4:1) yielded the product as a low-melting solid (225 mg, 76%; r.r. = 99:1).

**HRMS (MALDI):** m/z [M + H]+ calcd for C17H16BrNO4: 378.0335; found: 378.0335.

**Synthesis**

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Ethyl 2-Benzamido-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 (116 mg, 34%; Rᵣ = 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 FeCl₃·6H₂O (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv). 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 (234 mg, 80%; Rᵣ = 75:25).

**MS (ESI):** m/z [M + H]⁺ calcd for C₁₈H₂₀NO₃: 298.1438; found: 298.5.

**HRMS (MALDI):** m/z [M + H]⁺ calcd for C₁₈H₂₀NO₃: 298.1259; found: 298.1259.

**Ethyl 2-Benzamido-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), toluene (0.22 mL, 2.1 mmol, 4.2 equiv), and Bi(OTf)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 (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (12 mg, 8%).

**Fe Catalysis:** Compound 12j was synthesized according to the GP from benzamide (121 mg, 1.0 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 (12 mg, 8%).

**1H NMR (300 MHz, CDCl₃):** δ = 8.67 (s, 2 H), 6.12 (s, 1 H), 4.33–4.11 (m, 2 H), 3.66 (m, 1 H), 2.93 (m, 1 H), 2.56–2.35 (m, 2 H), 2.26 (d, J = 4.5 Hz, 9 H), 2.10–1.99 (m, 1 H), 1.86–1.79 (m, 1 H), 1.24 (t, J = 7.2 Hz, 3 H).

**13C NMR (75 MHz, CDCl₃):** δ = 175.3, 171.7, 138.1, 130.1, 128.2, 61.8, 54.0, 44.2, 30.8, 21.0, 20.6, 18.3, 14.2.

**MS (ESI):** m/z [M + H]⁺ calcd for C₁₈H₂₂NO₄: 292.2; found: 292.2.

Anal. Calcd for C₁₈H₂₂NO₄: C, 65.96; H, 7.27; N, 4.66. Found: C, 65.82; H, 7.97; N, 4.66.

**Ethyl 2-Mesityl-2-(2-oxopyrrolidin-1-yl)acetate (14a)**

**Bi Catalysis:** Compound 14a was synthesized according to the GP from pyrrolidin-2-one (85 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), and Bi(OTf)₃ (13 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 (182 mg, 63%).

**Fe Catalysis:** Compound 14a was synthesized according to the GP from pyrrolidin-2-one (43 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 (12 mg, 8%).

**1H NMR (300 MHz, CDCl₃):** δ = 8.8 Hz, 1 H), 5.88 (d, J = 8.8 Hz, 1 H), 4.24–4.17 (m, 2 H), 3.85 (s, 3 H), 1.21 (t, J = 7.2 Hz, 3 H).

**13C NMR (75 MHz, CDCl₃):** δ = 170.6, 166.5, 157.7, 134.0, 131.7, 130.6, 129.4, 128.6, 127.4, 127.2, 125.9, 112.3, 61.9, 56.0, 53.3, 14.1.

**MS (ESI):** m/z [M + H]⁺ calcd for C₁₇H₂₃NO₃: 290.2; found: 290.2.

Anal. Calcd for C₁₇H₂₃NO₃: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.47; H, 7.97; N, 4.66.

**Ethyl 2-Mesityl-2-(2-oxooxazolidin-3-yl)acetate (14b)**

**Bi Catalysis:** Compound 14b was synthesized according to the GP from oxazolidin-2-one (87 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), and Bi(OTf)₃ (13 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 (234 mg, 80%).

**IR (ATR):** 2988 (w), 2926 (w), 1743 (s), 1681 (s), 1610 (m), 1491 (m), 1460 (m), 1245 (m), 1187 (s), 1023 (m), 903 (w), 860 (m), 673 cm⁻¹ (m).

**MS (ESI):** m/z [M + H]⁺ calcd for C₁₉H₂₄NO₃: 312.2; found: 312.2.

Anal. Calcd for C₁₉H₂₄NO₃: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.47; H, 7.97; N, 4.66.
The reaction mixture was stirred for 20 h at 80 °C. Purification by chromatography (n-hexane/ EtOAc = 4:1) yielded the product as a colorless solid (81 mg, 54%).

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

IR (ATR): 3309 (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 (w), 764 (w), 740 (s), 724 (m), 703 (w), 615 (s), 593 (m), 562 (s), 533 (s), 532 (m), 475 cm–1 (m).

1H NMR (300 MHz, CDCl3): δ = 6.86 (s, 2 H), 5.64 (d, J = 4.0 Hz, 1 H), 5.41 (br d, J = 3.5 Hz, 1 H), 4.29–4.13 (m, 2 H), 2.61 (s, 3 H), 2.35 (s, 6 H), 2.26 (s, 3 H), 1.20 (t, J = 7.1 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 171.21, 138.51, 137.35, 130.28, 129.78, 62.68, 55.24, 42.03, 21.04, 20.10, 14.20.


IR (ATR): 3309 (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 (w), 764 (w), 740 (s), 724 (m), 703 (w), 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), 2.20 (s, 6 H), 2.19 (s, 3 H), 1.14 (t, J = 7.1 Hz, 3 H).

1C NMR (75 MHz, CDCl3): δ = 170.65, 139.23, 138.40, 137.17, 131.58, 129.83, 128.78, 128.32, 127.12, 126.68, 55.01, 20.88, 20.01, 14.09.

HRMS (MALDI): m/z [M + K]+ calcd for C19H23BrNO5SNa: 462.0; found: 462.0.

Ethyl 2-Mesityl-2-(4-methylphenylsulfonylamido)acetate (16b, R = Me)

**Bi Catalysis:** Compound 16b was synthesized according to the GP from 4-methylbenzenesulfonamide (87 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 18 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (148 mg, 79%).

Mp 128–130 °C; Rf = 0.6 (hexane/EtOAc = 9:1).

IR (ATR): 3434 (w), 2964 (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 (w), 764 (w), 740 (s), 724 (m), 703 (w), 615 (s), 593 (m), 562 (s), 533 (s), 532 (m), 475 cm–1 (m).

1H NMR (300 MHz, CDCl3): δ = 6.86 (s, 2 H), 5.64 (d, J = 4.0 Hz, 1 H), 5.41 (br d, J = 3.5 Hz, 1 H), 4.29–4.13 (m, 2 H), 2.61 (s, 3 H), 2.35 (s, 6 H), 2.26 (s, 3 H), 1.20 (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, 126.68, 55.01, 20.88, 20.01, 14.09.

HRMS (MALDI): m/z [M + K]+ calcd for C19H23BrNO5SNa: 462.0; found: 462.0.

**Bi Catalysis:** Compound 16b (R = OMe) was synthesized according to the GP from 4-methylbenzenesulfonamide (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 18 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (126 mg, 64%).

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

IR (ATR): 3274 (w), 2923 (w), 1738 (m), 1594 (m), 1496 (m), 1437 (w), 1412 (m), 1329 (m), 1311 (w), 1288 (w), 1263 (s), 1228 (m), 1183 (m), 1157 (m), 1196 (m), 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]+ calcd for C22H24NO3SNa: 414.1; found: 414.08.

Ethyl 3,5,10,10a-Tetrahydro-3-oxo-1H-oxazol-4,4-bisoxoquinoline-5-carboxylate (21)

Bi Catalysis: Compound 21 was synthesized according to the GP from (R)-4-benzoxazolizin-2-one (59 mg, 0.3 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 2.0 equiv), and Bi(OTf)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 = 4:1) yielded the product as a colorless solid (72 mg, 84%).

Mp 58–59 °C; Rₜ = 0.2 (cyclohexane/EtOAc = 7:3).

IR (ATR): 2980 (w), 2936 (w), 2084 (w), 1760 (s), 1726 (m), 1705 (s), 1676 (s), 1525 (s), 1466 (m), 827 (w), 766 (w), 725 (s), 708 (m), 688 (w), 613 (s), 604 cm⁻¹ (s).

1H NMR (300 MHz, CDCl₃): δ = 8.10 (br d, J = 7.2 Hz, 1 H), 7.90–7.88 (m, 2 H), 7.77–7.74 (m, 2 H), 6.83 (s, 2 H), 5.99 (d, J = 7.3 Hz, 1 H), 4.44 (d, J = 11.5 Hz, 1 H), 4.20–4.03 (m, 2 H), 2.86–2.74 (m, 1 H), 2.39 (s, 6 H), 2.25 (s, 3 H), 1.11 (t, J = 7.1 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 171.38, 168.61, 168.33, 137.69, 137.05, 134.54, 131.57, 130.90, 130.01, 123.88, 63.58, 61.85, 52.40, 27.89, 21.01, 20.29, 19.62, 14.11.

Diastereomer a

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

1H NMR (300 MHz, CDCl₃): δ = 7.44 (dd, J = 5.0, 1.2 Hz, 1 H), 7.24 (dd, J = 3.8, 1.3 Hz, 1 H), 6.88–6.85 (m, 1 H), 6.72 (s, 2 H), 5.87 (br d, J = 4.9 Hz, 1 H), 5.59 (d, J = 5.0 Hz, 1 H), 4.22–4.05 (m, 2 H), 2.26 (s, 6 H), 2.21 (s, 3 H), 1.14 (t, J = 7.1 Hz, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 170.98, 141.13, 138.13, 137.21, 132.19, 131.93, 129.96, 129.35, 127.00, 62.67, 55.28, 20.96, 20.16, 14.11.

MS (ESI): m/z [M + H]^+ calc'd for C₁₄H₁₅NO₄S: 268.1; found: 268.1.

HRMS (MALDI): m/z [M + H]^+ calc'd for C₁₄H₁₅NO₄S: 268.1; found: 268.1.
Mp 100–106 °C; \( R_f = 0.72 \) (n-hexane/EtOAc = 9:1).

1H 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-mesitylacetate (27)**

*Fe Catalysis*

Compounds 27 was synthesized according to the GP from ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.0 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), 2,2'-bipyridine (5 mg, 0.03 mmol, 3 mol%), and Fe(ClO\(_4\))\(_3\) (7 mg, 0.02 mmol, 2 mol%) in MeNO\(_2\) (2.0 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 oil (176 mg, 66%).

Analytical data are consistent with those reported in the literature.39

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**Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561499.

**References**

(4) van Bambeke, F.; van Laethem, Y.; Courvalin, P.; Tulkens, P. M. Drugs 2004, 64, 913.
(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 anhydrous 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 nucleophilicity of arenes 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 Soueidman, 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.


