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# One-pot iron chloride-catalyzed sustainable syntheses of quinolines from amino acids, alkyl lactate and arylamine†

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An iron(III)- and oxygen-promoted one-pot method for the efficient syntheses of quinolines from amino acids, alkyl lactate, and arylamine was carried out. The efficient tandem cyclization of the three components begins with the breaking of the amino acids' C–C and C–N bonds and the lactate's O–H bond, followed by sequential condensation and coupling to form new C–N and C–C bonds. The reaction is based on biomass-based amino acids and alkyl lactate, using earth-abundant metals as catalysts and oxygen as the oxidizer, without adding additional solvents; renewable aldehydes are generated and the reuse of alkyl lactate is realized, which is remarkable for its green and sustainable characteristics. More than 40 quinolines were synthesized in isolated yields of up to 75%. This one-pot, multi-step synthesis method significantly shortens the life cycle of the biomass-based conversion process. This study demonstrates the promise of biomass conversion in sustainable organic synthesis and lays the foundation for the sustainable conversion of small biomolecules *in vitro* and bio-based feedstocks into high-value-added chemicals.

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## Sustainability spotlight

Because of the societal goals of carbon peaking and carbon neutrality, multicomponent reactions are valuable tools in green chemistry, although they usually involve non-renewable fossil-based feedstocks, additives, and complex catalysts. The reduction of fossil-based feedstocks and wastes in multicomponent reactions is an important development in the field of sustainable chemistry and pharmaceuticals, in particular for the high-value conversion of biomass under green and simple conditions. In this paper, we have efficiently synthesized quinolines from small biomolecules such as amino acids, biomass-based alkyl lactates, and aryl amines using iron(III) and oxygen-promoted one-pot methods. Our work emphasizes the importance of the following UN sustainable development goals: affordable and clean energy (SDG 7), industry, innovation and infrastructure (SDG 9), responsible consumption and production (SDG 12), and climate action (SDG 13).

## Introduction

Heterocyclic compounds have a wide range of applications in industry and medicinal chemistry.<sup>1</sup> As one of the most common heterocyclic rings, quinoline and its derivatives have a broad spectrum of pharmacological and biological activities,<sup>2</sup> such as anticancer, anti-malarial,<sup>3</sup> anti-analgesic,<sup>4</sup> anti-tuberculosis, and antimicrobial<sup>5</sup> and so on. Therefore, they have attracted the attention of a wide range of researchers.<sup>6</sup> To date, the most

common method of making them is the Skraup synthesis technique,<sup>7</sup> which involves heating aniline with glycerol in the presence of sulfuric acid, ferrous sulfate, and *N*-nitrobenzene. In addition, there are many routes to synthesize the quinoline skeleton, *e.g.*, the Friedlander,<sup>8c</sup> Povarov,<sup>8f</sup> Gould-Jacob,<sup>8f</sup> Skraup, and Doebner-von Miller<sup>8m</sup> reactions, most of which require fossil-based feedstocks and non-green, harsh conditions.<sup>8</sup> However, while many of these technologies have been highly successful, they are not environmentally conscious because they generate large amounts of debris that must be disposed of, and many of the feedstocks are derived from fossil resources. Therefore, the option of adopting a “green synthesis” approach, which may be considered superior and more environmentally viable, has become critical. Such an approach could address environmental pollution issues such as global warming and reduce chemical consumption and reaction times. Research into reducing the consumption of fossil resources, replacing fossil-based feedstocks with exclusively biomass-based feedstocks,<sup>9</sup> and

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developing methods for the green and sustainable synthesis of quinolines, remains a great challenge.<sup>10</sup>

In nature, amino acids are prebiotic raw materials for the biosynthesis of heterocyclic alkaloids.<sup>11</sup> Amino acids can be obtained by industrial fermentation and are widely used as renewable raw materials in biochemistry,<sup>12</sup> medicinal chemistry,<sup>13</sup> and total synthesis.<sup>14</sup> And more importantly, amino acid degradation catalysts are non-heme metalloproteins, which are oxidizing catalysts. The ability of transition metal-containing enzymes to exist in a variety of stable oxidation states makes them useful catalysts for biological processes that require electron transfer.<sup>15</sup> According to the principle of degradation of amino acids by transition metal-containing enzymes, there have been many studies in recent years on the use of transition metal-catalyzed amino acids. Today, the degradation of amino acids,<sup>16</sup> syntheses of heterocyclic compounds,<sup>17</sup> and construction of peptide scaffolds<sup>18</sup> have been realized. Although there are now many methods for converting  $\alpha$ -amino acids into heterocyclic compounds,<sup>19</sup> these methods require the addition of solvents, noble metal ligands, or specific oxidants to achieve decarboxylation and deamination of amino acids, and then coupling them into heterocyclic compounds (Scheme 1a–c). On the premise of decarboxylation and deamination of amino acids using cheap metal catalysts, green oxidants, and no added solvents in a one-pot method, the conversion of C–C into heterocycles after re-breaking remains a great challenge.

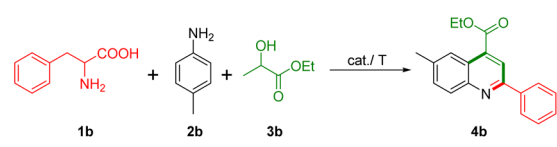
Many studies have shown that iron atoms are important in amino acid modification,<sup>17a,20</sup> catalytic lactic acid esters,<sup>21</sup> and biological nitrogen fixation.<sup>22</sup> Based on the metal activity of iron described above, the classical Povarov reaction,<sup>8i</sup> and our group's research in the synthesis of heterocyclic compounds,<sup>23</sup> we developed a new method for the direct synthesis of quinolines from amino acids, alkyl lactates, and aromatic amines, catalyzed by iron(III) as shown in Scheme 1d and e. The main pathway of this method is the decarboxylation of phenylalanine by Fe(III)-catalysis and O<sub>2</sub>-oxidation, and after deamination the C–C bond is broken again, and then renewable benzaldehyde is produced. This thesis presents a pioneering one-pot method for

the sustainable synthesis of quinoline compounds. The incomparable advantages of green synthesis in this method include (a) efficient one-pot multi-component synthesis; (b) biomass amino acids and alcohols as starting materials; (c) earth-abundant metals as catalysts, FeCl<sub>3</sub>; (d) green oxidizer O<sub>2</sub>. This strategy, using biomass-based alcohols and amino acids as pivotal components, underscores its sustainability and significant advantages in quinoline synthesis.

## Results and discussion

To determine the optimal reaction conditions, phenylalanine (**1b**), *p*-toluidine (**2b**), and ethyl lactate (EL) (**3b**) were used as templates. Firstly, we screened inorganic, organic, and Lewis acids to identify a suitable acid (entries 1–5, Table 1), and FeCl<sub>3</sub> was the most effective acid, producing the target product **4b** in 30% yield. Secondly, the oxidizing agent was screened to determine the most suitable oxidizing agent (entries 5–10), and oxygen proved to be the most effective oxidizing agent, yielding 50% of product **4b**. Thirdly, parallel experiments at different temperatures were performed to screen the temperatures and it was shown that 110 °C was the optimal reaction temperature (entries 6 and 11–13). Finally, we screened the amount of FeCl<sub>3</sub> (entries 12 and 14–16) and showed that an amount of 0.3 equivalent FeCl<sub>3</sub> turned out to be optimal. We screened whether iodine was needed (entries 15 and 17), and the results showed that iodine had a significant promoting effect on the reaction.

Table 1 Optimization of reaction conditions for synthesis of **4b**<sup>a</sup>



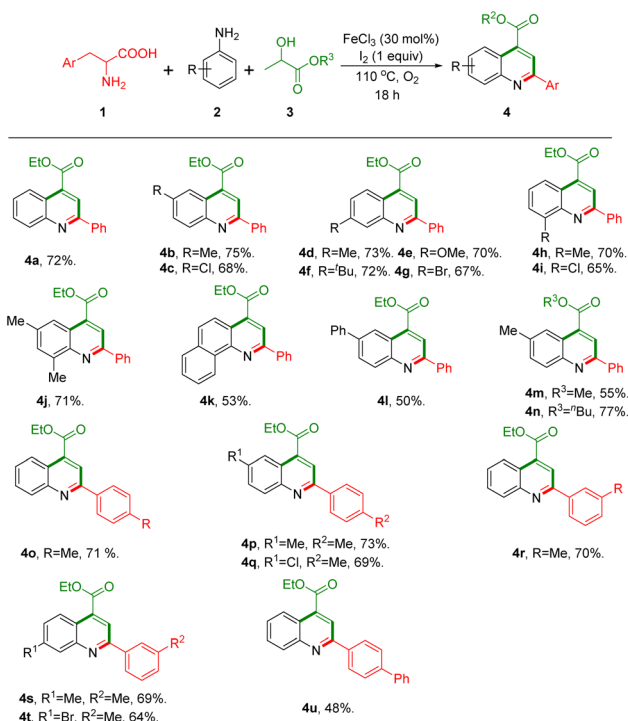
Entry	Acid	Oxidant	Temp (°C)	Yield <sup>b</sup> (%)
1	TfOH	Air	100	No
2	HCl	Air	100	No
3	AlCl <sub>3</sub>	Air	100	Trace
4	MnCl <sub>2</sub>	Air	100	10
5	FeCl <sub>3</sub>	Air	100	30
6	FeCl <sub>3</sub>	O <sub>2</sub>	100	50
7	FeCl <sub>3</sub>	N <sub>2</sub>	100	No
8	FeCl <sub>3</sub>	H <sub>2</sub> O <sub>2</sub>	100	35
9	FeCl <sub>3</sub>	TBHP	100	No
10	FeCl <sub>3</sub>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	100	Trace
11	FeCl <sub>3</sub>	O <sub>2</sub>	90	No
12 <sup>c</sup>	FeCl <sub>3</sub>	O <sub>2</sub>	110	60
13	FeCl <sub>3</sub>	O <sub>2</sub>	120	30
14 <sup>d</sup>	FeCl <sub>3</sub>	O <sub>2</sub>	110	Trace
15 <sup>e</sup>	FeCl <sub>3</sub>	O <sub>2</sub>	110	75
16 <sup>f</sup>	FeCl <sub>3</sub>	O <sub>2</sub>	110	68
17 <sup>g</sup>	FeCl <sub>3</sub>	O <sub>2</sub>	110	5

<sup>a</sup> Reaction conditions: **1b** (0.50 mmol), **2b** (0.50 mmol), **3b** (2 mL), I<sub>2</sub> (1 equiv.) and FeCl<sub>3</sub> (0.15 mmol), in an O<sub>2</sub> environment, stirred for 18 h. <sup>b</sup> Isolated yield relative to **1b**. <sup>c</sup> With 0.10 mmol FeCl<sub>3</sub>. <sup>d</sup> With 0.005 mmol FeCl<sub>3</sub>. <sup>e</sup> With 0.15 mmol FeCl<sub>3</sub>. <sup>f</sup> With 0.20 mmol FeCl<sub>3</sub>. <sup>g</sup> Without I<sub>2</sub>.



Scheme 1 Amino acid development and utilization.

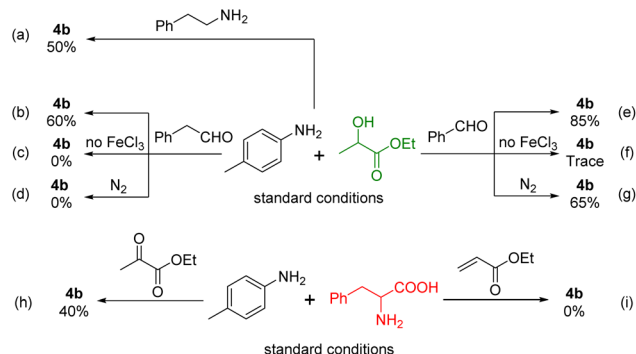


**Table 2** Scope for the synthesis of quinolines from phenylalanine and alkyl lactate<sup>ab</sup>

<sup>a</sup> General conditions: **1** (0.50 mmol), **2** (0.50 mmol),  $\text{I}_2$  (1 equiv.) and  $\text{FeCl}_3$  (0.15 mmol) were stirred in 2 mL of **3** for 18 hours in an  $\text{O}_2$  atmosphere. <sup>b</sup> Isolated yield relative to **1**.

Based on the optimization results, we investigated the range of quinoline structures synthesized from amino acids, amines, and alkyl lactate esters. The results are shown in Table 2 and the method showed good tolerance for all the three raw materials involved. Aniline derivatives with electron-donating and electron-absorbing substituents at *para*- (**4a–4c**, Table 2), *meta*- (**4d–4g**), and *ortho*-positions (**4h–4i**) showed good tolerance. Anilines with methyl substitution in the *para*- and *ortho*-positions (**4j**) also showed good tolerance. The method was further extended to synthesize quinoline compounds (**4k** and **4l**) using naphthalen-1-amine and [1,1'-biphenyl]-4-amine as substrates. Substrate scope studies using methyl lactate and butyl lactate instead of ethyl lactate resulted in the generation of quinoline compounds in comparable yields (**4m** and **4n**). Phenylpropionic acid derivatives with electron-donating substituents in the *para*- (**4o–4q**) and *meta*-positions (**4r–4t**) can yield the corresponding quinoline compounds. A substrate range study of 3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid led to the quinoline compound (**4u**) in appreciable yield.

We conducted a series of controlled experiments to verify the possible mechanisms. Initially, *p*-toluidine was reacted with 2-phenylethan-1-amine, phenylacetaldehyde, and benzaldehyde, respectively, under standard conditions, all of which afforded the target product **4b** (Scheme 2a, b and e), suggesting that 2-phenylethan-1-amine, phenylacetaldehyde, and benzaldehyde may be the intermediates in this reaction. Next, *p*-toluidine and

**Scheme 2** Control experiments.

phenylacetaldehyde did not give the product **4b** in the absence of  $\text{FeCl}_3$  (Scheme 2c), suggesting that  $\text{FeCl}_3$  is required to catalyze the formation of the product **4b** from phenylacetaldehyde, *p*-toluidine, and ethyl lactate. At the same time, only trace amounts of product **4b** were generated from *p*-toluidine and benzaldehyde in the absence of  $\text{FeCl}_3$  (Scheme 2f), suggesting that  $\text{FeCl}_3$  promotes the generation of the target product **4b** from benzaldehyde, *p*-toluidine, and ethyl lactate. The reaction of *p*-toluidine, phenylacetaldehyde and ethyl lactate under a  $\text{N}_2$  atmosphere does not yield product **4b** (Scheme 2d), whereas the reaction of *p*-toluidine, benzaldehyde, and ethyl lactate yields product **4b** (Scheme 2g), a comparison that indicates that oxidation of  $\text{O}_2$  is required for the conversion of phenylacetaldehyde to benzaldehyde. Finally, the reaction with phenylalanine, *p*-toluidine, and ethyl pyruvate under standard conditions afforded **4b** (Scheme 2h) in 40% yield, whereas the reaction of phenylalanine, *p*-toluidine, and ethyl acrylate under standard conditions did not yield **4b** (Scheme 2g), suggesting that ethyl pyruvate is an intermediate in this reaction and ethyl acrylate is not an intermediate in this reaction.

Based on a combination of controlled experiments and previous work,<sup>23a,24</sup> we propose a possible mechanism in Scheme 3. Firstly, amino acid **1b** was decarboxylated to 2-phenylethan-1-amine **5b** under the action of iodine. The amine **5b** is then rapidly hydrolyzed in a medium to form phenylacetaldehyde **6b** and  $\text{NH}_3$ . The aldehyde **6b** then generates enol iron **7b** in the presence of  $\text{Fe(III)}$ , which in the presence of  $\text{O}_2$  generates the iron-coordinated peroxide **7b'**. Hydrogen ions attack the peroxide **7b'** to form the intermediate **7b''**, which undergoes C–C rupture to form benzaldehyde **8b** and formate. Benzaldehyde **8b** and *p*-toluidine **2b** form the imine intermediate **9b** in the presence of  $\text{Fe(III)}$ . The intermediate **10b'** resulting from the dehydrogenation of EL **3b** can be captured by the imine **9b** and coupled *via* a C–C bond to form the intermediate **11b**. Compound **11b** is subsequently dehydrated by intramolecular addition of a nucleophilic aryl C–H bond to a keto-carbonyl group to form intermediate **12b**, which undergoes oxidative arylation to yield the target product **4b**.

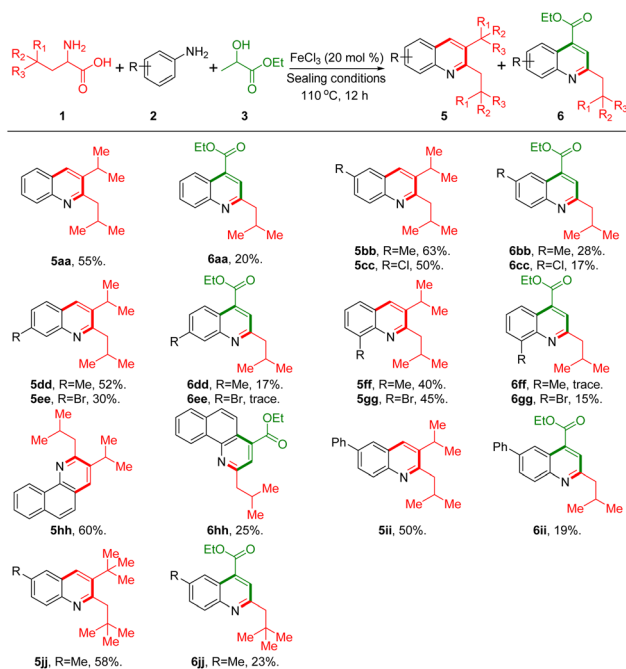
We tried to develop the utilization of more kinds of amino acids with alkyl-substituted amino acids instead of aryl-substituted amino acids, and surprisingly two new quinoline



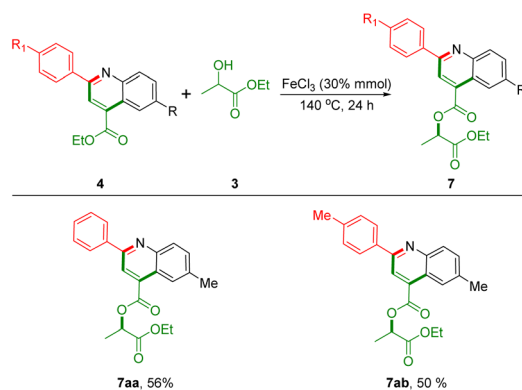


Scheme 3 Plausible reaction mechanism.

compounds were obtained. Based on the results of the optimization of the conditions (conditional filtering in the ESI<sup>+</sup>), we investigated the synthesis of the main product quinoline 5 and the by-product quinoline 6 substrate range from amino acids, amines, and ethyl lactate. The results are shown in Table

Table 3 Scope for the synthesis of two types of quinolines from phenylalanine<sup>ab</sup>

<sup>a</sup> General conditions: 1 (0.50 mmol), 2 (0.50 mmol), 3 (2 mL), and FeCl<sub>3</sub> (0.1 mmol) were stirred at 110 °C for 12 h in a closed atmosphere.  
<sup>b</sup> Isolated yield relative to 2.

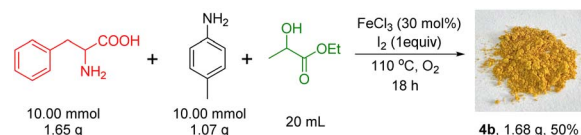
Table 4 Reutilization of alkyl lactate<sup>ab</sup>

<sup>a</sup> General conditions: 4 (0.50 mmol), 3 (2 mL), FeCl<sub>3</sub> (0.15 mmol), stirred at 140 °C for 24 h. <sup>b</sup> Isolated yield relative to 4.

3 and the method showed good tolerance to both amino acids and amines. Aniline derivatives with electron-donating and electron-withdrawing substituents in the *para*- (5aa–5cc, Table 4), *meta*- (5dd and 5ee), and *ortho*-positions (5ff and 5gg) all yield the major product quinoline compound 5. The generalizability of the method was further explored by using naphthalen-1-amine and [1,1'-biphenyl]-4-amine as substrates, and the corresponding main products (5hh and 5ii) were obtained in certain yields. Finally, 2-amino-4,4-dimethylpentanoic acid was attempted and fortunately, the corresponding main product (5jj) was also obtained. Because of the low yield of the by-products, and the limit is very close to that of the main product, it brings some difficulties to the separation and purification. However, to confirm the structure of the by-products, we used IR, HRMS, and NMR assays (detailed test results, controlled experiments, and possible mechanisms in the ESI<sup>+</sup>). This work further validates the reaction mechanism of the amino acid, lactic acid alkyl ester system, gives us a clearer understanding of the pathways of amino acid and lactic acid alkyl ester utilization, and broadens the range of amino acid applications.

Reflecting on the importance of biomass synthesis, scale-up experiments were conducted. Under the optimal conditions, the separation yield of the target product 4b was 50% with 10.00 mmol phenylalanine as the template, which verified the practical application potential of this method in the conversion of biomass into quinoline compounds (Scheme 4).

From a sustainability point of view, enhancing biomass utilization, the reuse of reactants, and dual utilization of feed-stock are all essential. We tried to further react the reactant EL



Scheme 4 Gram scale reaction.



**3b** again with the synthesis product **4**. Fortunately, we realized the reuse of EL **3b** and successfully synthesized new quinoline compounds (**7aa-7ab**, Table 4).

## Conclusions

In conclusion, we have developed a three-component, one-pot method for the sustainable synthesis of quinolines using biomass-based feedstock amino acids, alkyl lactate, and arylamines in the presence of iron(III) and oxygen. This efficient biomass-based conversion method not only realizes the previous processes of decarboxylation and deamination of amino acids but also allows the decarboxylation and deamination to be followed by a decarbonylation reaction again to produce renewable aldehydes. It offers a variety of advantages including a shortened life cycle for high-value conversion of biomass-based amino acids and alkyl lactates, *in vitro* conversion of small biomolecules, green oxidant O<sub>2</sub>, earth-abundant metal catalysts, no additional solvent required, reuse of EL, simple and efficient one-pot methods, and synthesis of a variety of quinoline compounds. This work will be helpful for the *in vitro* development and utilization of small biomolecule amino acid and lactic acid derivatives and lays the foundation for the sustainable production of high-value-added *N*-heterocyclic compounds.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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