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Iron Catalyzed Dual-Oxidative Dehydrogenative (DOD) Tandem Annulation of Glycine Derivatives with Tetrahydrofurans

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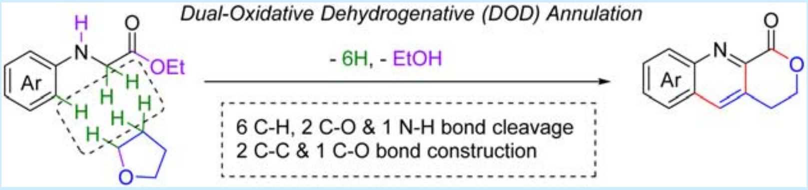
Ⓢ *Supporting Information*



ABSTRACT: A novel iron-catalyzed dual-oxidative dehydrogenative (DOD) tandem annulation of glycine derivatives with tetrahydrofurans (THFs) for the synthesis of high value quinoline fused lactones has been developed. The reactions were performed under mild reaction conditions. And the use of cheap substrates (glycine derivatives and THF) and an even cheaper simple inorganic iron salt as the catalyst makes this protocol very attractive for potential synthetic applications.

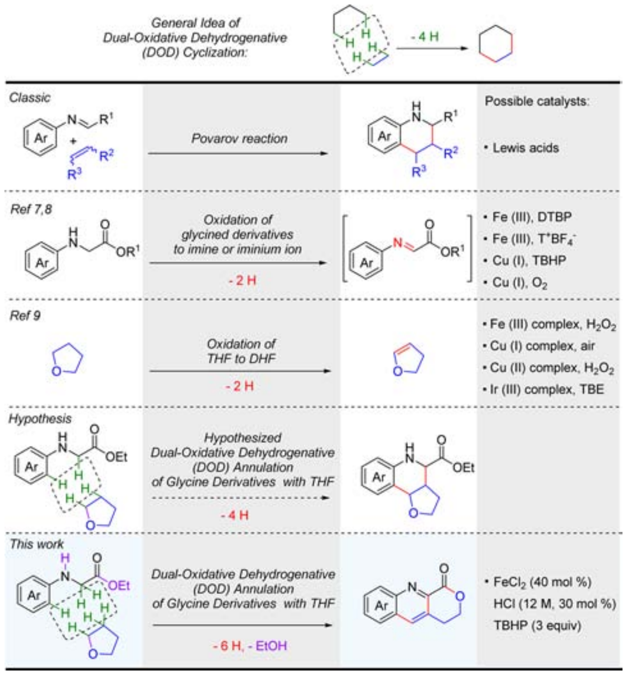
Iron is the fourth most abundant element and the second most abundant metal in the Earth's crust. It accounts for over 5% of the Earth's crust and is one of the cheapest of all metals. Moreover, various iron compounds are incorporated in biological systems, resulting in low toxicity and importance in the pharmaceutical and food industry. Thus, due to the aforementioned advantages, iron has recently become a catalytically active metal in organic synthesis and tremendous progress with iron salt catalyzed transformations has been achieved.[1]

Cross-dehydrogenative coupling (CDC), the direct coupling between two C−H bonds, has become a growing and attractive field with the requirements of green chemistry.[2] The iron-catalyzed CDC reaction was first reported by Li et al. in 2007 using $FeCl_2$ (20 mol %) as the catalyst in the presence of di-*tert*-butylperoxide (DTBP, 200 mol %) as the oxidant.[3] Since then, quite a few prominent examples have been reported in this project.[4]

In the 1960s, Povarov described the formal [4 + 2] cyclization of aromatic imines and electron-rich olefins to form tetrahydroquinolines.[5] Today, the reaction is known as the Povarov reaction or imino Diels−Alder reaction and has been widely used in heterocyclic synthetic chemistry (Scheme 1, "Classic" reaction).[6]

In 2011, an oxidative Povarov/aromatization tandem reaction of glycine derivatives with alkenes using $FeCl_3$ as the catalyst and 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) oxoammonium salt as the oxidant was first reported by Mancheño et al.[7] In 2014, we developed a similar tandem process under auto-oxidation conditions.[8] The reaction was performed in the absence of any redox-active catalyst and chemical oxidant under mild aerobic conditions. The oxidation mechanism involving the oxidation of the secondary amine substrates to generate reactive imine intermediates was generally proposed for the aforementioned reactions of glycine derivatives (Scheme 1, "Ref 7,8" reaction).

Scheme 1. Design of Dual-Oxidative Dehydrogenative (DOD) annulation



Moreover, after a thorough literature review, we found tetrahydrofuran (THF) could donate two H atoms to a H

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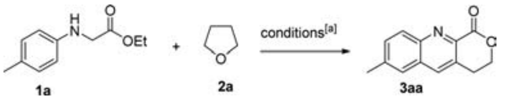
acceptor to give dihydrofuran (DHF) in the presence of transition metal complexes including some iron complexes in rare cases (Scheme 1, "Ref 9" reaction).[9]

From a green and atom-economic point of view, a dual-oxidative-dehydrogenative (DOD) cyclization reaction from four C−H bonds will be highly desired (Scheme 1, General Idea). As a start, we became interested in whether it is possible to oxidize the glycine derivative (to generate an aryl imine) and THF (to generate an electron-rich alkene) in the same reaction mixture under an iron catalysis system and with the following Povarov reaction to possibly offer an interesting opportunity for a new type of annulation reactions (Scheme 1, "Hypothesis" reaction).

Herein we report the initial realization of the above envisioned dual-oxidative dehydrogenative (DOD) annulation reaction of glycine derivatives with THFs under an Fe(II)/HCl/TBHP catalyst system (Scheme 1, "This work" reaction). Although it is just the preliminary result, this DOD annulation strategy offers opportunities for the development of novel transformations with expected future broad applications.

To prove the feasibility of our proposed assumption, we started our investigation by utilizing glycine ester (**1a**) and THF (**2a**) as model substrates. First, various oxidants (Table 1, entries 1−4) were screened for the reaction in acetonitrile at room temperature in the presence of $FeCl_2$ (40 mol %) and HCl (40 mol %). To our delight, the desired product **3aa** was obtained in a 63% yield when TBHP was applied as the terminal oxidant. Other iron and copper salts were then tested (Table 1, entries 5−11), but no better yield was observed. Notably, the use of $FeBr_3$ gave similar results to $FeCl_2$, thus demonstrating that both Fe(II) and Fe(III) catalyst precursors were able to facilitate this transformation. It is possible that the conversion between Fe(II) and Fe(III) species might occur during this reaction process.[10] Among the Brønsted acids we had tested (Table 1, entries 12−15), the use of HCl provided the best yield of **3aa**. A lower or higher loading of $FeCl_2$ or HCl resulted in lower yields (Table 1, entries 16−21). The influence of the solvent was also studied. When other solvents such as DCM, THF, toluene, and water were applied instead of CH_3CN, lower yields of the designed product were observed (Table 1, entries 22−25). After various reaction parameters were optimized, the best results were found to be $FeCl_2$ (40 mol %), HCl (12 M, 40 mol %), and TBHP (3 equiv) in MeCN. Under these reaction conditions, a 63% yield of **3aa** was obtained after 24 h.

Table 1. Screening of Reaction Conditions

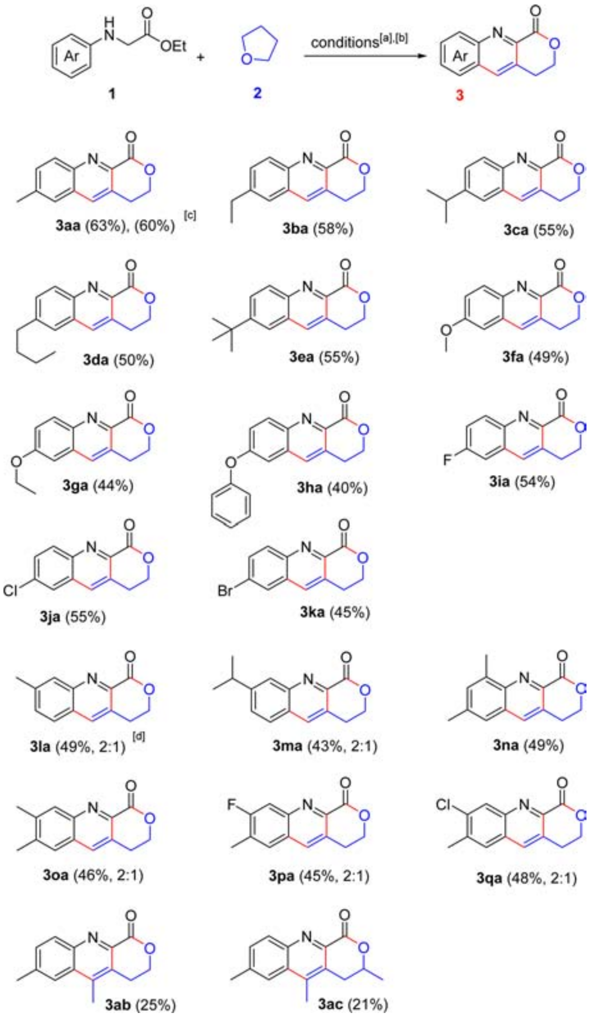


Entry	Catalyst	Additive	Oxidant	Solvent	**3aa** (yield %)[b]
1	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	63%
2	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP [c]	CH_3CN	62%
3	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	DTBP	CH_3CN	5%
4	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	O_2	CH_3CN	9%
5	$FeCl_3$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	39%
6	$FeBr_3$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	50%
7	$FeBr_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	61%
8	$Fe(acac)_3$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	16%
9	$Fe(acac)_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	11%
10	$CuCl_2$ (5 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	25%
11	CuCl (5 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	8%
12	$FeCl_2$ (40 mol %)	H_2SO_4(18 M, 20 mol %)	TBHP	CH_3CN	40%
13	$FeCl_2$ (40 mol %)	TsOH (40 mol %)	TBHP	CH_3CN	32%
14	$FeCl_2$ (40 mol %)	TfOH (40 mol %)	TBHP	CH_3CN	40%
15	$FeCl_2$ (40 mol %)	AcOH (40 mol %)	TBHP	CH_3CN	48%
16	$FeCl_2$ (20 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	45%
17	$FeCl_2$ (30 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	48%
18	$FeCl_2$ (50 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_3CN	58%
19	$FeCl_2$ (40 mol %)	HCl(12 M, 20 mol %)	TBHP	CH_3CN	51%
20	$FeCl_2$ (40 mol %)	HCl(12 M, 30 mol %)	TBHP	CH_3CN	53%
21	$FeCl_2$ (40 mol %)	HCl(12 M, 50 mol %)	TBHP	CH_3CN	55%
22	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	CH_2Cl_2	47%
23	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	THF	16%
24	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	toluene	30%
25	$FeCl_2$ (40 mol %)	HCl(12 M, 40 mol %)	TBHP	H_2O	10%

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (30 equiv), T-Hydro (TBHP, 70 wt % in H_2O, 3 equiv), solvent (20 mL), air, 24 h, rt. [b] Isolated yields. [c] TBHP (5.5 M in decane, 3 equiv).

With the optimized conditions in hand, various substituted aryl glycine esters were subjected to the iron-catalyzed dual-oxidative-dehydrogenative (DOD) cyclization/acidic ring opening/aromatization/intramolecular ester exchange tandem annulation to test the substrate scope and generality. As is shown in Scheme 2, the reaction with aryl glycine esters bearing electron-

Scheme 2. Dual-Oxidative Dehydrogenative (DOD) Annulation Reaction of Glycine Esters with THFs

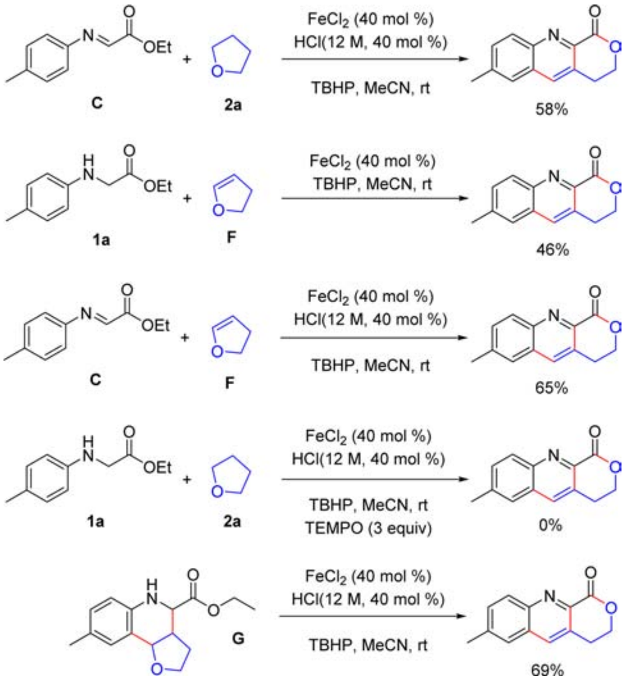


[a] Reaction conditions: **1** (1.0 mmol), **2** (30 equiv), T-Hydro (3 equiv), $FeCl_2$ (40 mol %), HCl (12 M, 40 mol %), MeCN (20 mL), 24 h, rt. [b] Isolated yields. [c] Gram scale (10 mmol of **1a**, 1.93 g). [d] Isomer ratio (*p*:*o*).

donating and electron-withdrawing groups at the *para-*, *meta-*, and *ortho*-position of the phenyl ring of **1** proceeded smoothly to afford the desired quinoline fused lactones in moderate to good yield (Scheme 2, **3aa**−**3qa**). Multiple substituted glycine esters also delivered the fused ring compounds in moderate to good yields (Scheme 2, **3na**−**3qa**). Halogen substituents such as F, Cl, and Br were well tolerated, affording the corresponding products in good yields (Scheme 2, **3ia**−**3ka**, **3pa**, **3qa**) which made this methodology more useful for further transformations. It is worth noting that corresponding quinoline fused lactones **3ab** and **3ac** were achieved in moderate yield using 2-methyltetrahydrofuran or 2,5-dimethyltetrahydrofuran as substrates. To evaluate the practicability of this method, the reaction between glycine ester **1a** and THF had been performed on a gram scale (**1a**, 10 mmol, 1.93 g) in a single batch. No obvious loss of yield was observed (isolated yield: 60%).

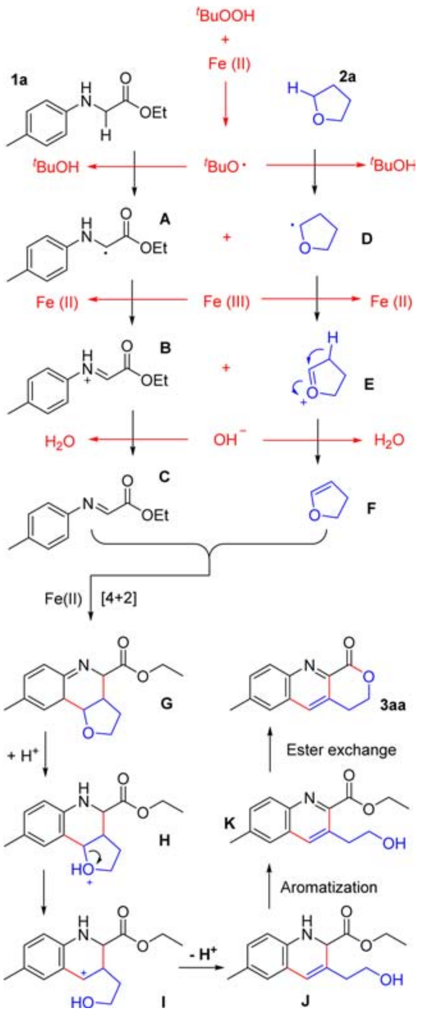
To clarify the reaction mechanism, we carried out the following control experiments. First, the reaction between **1a** and **2a** in the presence of $FeCl_2$ (40 mol %) but without HCl was carried out and gave the desired product **3aa** in 45% yield. At the same time, reactions between **1a** and **2a** in the presence of HCl (40 mol %) but without $FeCl_2$ and in the absence of $FeCl_2$ and HCl were conducted too. No desired product **3aa** was obtained. These control reactions suggest the iron salt is very important to this transformation. Subsequently, the reaction of imine **C** and THF **2a**, the reaction of glycine ester **1a** and DHF **F**, and the reaction of imine **C** and DHF **F** were investigated (Scheme 3). The results indicate that imine and DHF can be involved as intermediates in this iron-catalyzed tandem process. A radical trapping experiment was also conducted by employing TEMPO as a radical scavenger (Scheme 3). No desired product was observed in the reaction of **1a** with **2a**. This result suggests that the reaction includes a radical process. To further probe the reaction mechanism, compound **G** was synthesized and subjected to standard conditions, and product **3aa** was obtained in 69% yield (Scheme 3). It indicates that the adduct **G** may be involved as the key intermediate in this transformation.

Scheme 3. Control Experiments



On the basis of the above results and previous work, a proposed mechanism for the iron-catalyzed dual-oxidative dehydrogenative (DOD) cyclization tandem annulation reaction of glycine esters with THFs is shown in Scheme 4. First, glycine ester (**1a**) and THF (**2a**) were converted to aryl imine (**C**) and DHF (**F**) under mild conditions by using TBHP as the oxidant and iron salt as the catalyst. Then, an imino Diels−Alder reaction of **C** with **F** occurred to generate corresponding tetrahydroquinazoline intermediate **G**. Subsequently, **G** is transformed to 2,3-disubstituted quinoline intermediate **J** under acidic conditions. Finally, aromatization of intermediate **J** and the following intramolecular ester exchange ring closure occurred to afford the desired product **3aa**.

Scheme 4. Proposed Mechanism of the Reaction between 1a and 2a



In conclusion, we have demonstrated a novel iron-catalyzed dual-oxidative dehydrogenative (DOD) cyclization/acidic ring opening/aromatization/intramolecular ester exchange tandem annulation reaction of glycine derivatives with THFs which leads to complex quinoline fused lactone derivatives. And the use of cheap substrates (glycine derivatives and THF) and an even cheaper simple inorganic iron salt as the catalyst makes this protocol very attractive for potential synthetic applications.

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Despite the fact that the substrates were confined to glycine derivatives and THF in this letter, we have demonstrated the proof-of-concept for the green and atom-economic dual-oxidative dehydrogenative (DOD) annulation. Further investigations into the DOD annulation reactions are now ongoing in this laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02504.

Experimental details, compound characterization, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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