



## Iron-catalyzed Michael reactions revisited: a synthetically useful process for the preparation of tri-carbonyl compounds and chiral warfarin

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### ABSTRACT

The LBAs (Lewis acid-assisted Brønsted acid catalysis) is proposed as possible mechanistic process in the simple FeCl<sub>3</sub>-catalyzed Michael reactions of chalcones with active methylene compounds in organic solvents. And iron salts were found to be effective promoters in the asymmetric Michael addition of 4-hydroxycoumarin to  $\alpha,\beta$ -unsaturated ketone, which resulted in excellent yield and high level of enantioselectivity (up to 91% ee) in the presence of low catalytic amount of iron and simple chiral primary amine.

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The Michael reaction of appropriate carboanionic reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds is the most direct approach for the preparation of polysubstituted tri-carbonyl compounds, which also is an efficient method for carbon–carbon bond formation and has extensive applications to remote functionalization in organic synthesis.<sup>1</sup> In the past decades, the reaction has been traditionally performed using various basic catalysts or reagents, such as NaOH,<sup>2</sup> Ba(OH)<sub>2</sub>,<sup>3</sup> and Mg–Al–O–*t*-Bu hydrotalcite.<sup>4</sup> However, there are some disadvantages under the strong basic conditions. For example, in the presence of strong bases, side reactions, such as aldol or self-aldol addition, polymerizations, retrogressions, and rearrangements, are frequently encountered. Recently, various Michael reactions promoted by organic base/acid catalysts or under microwave irradiation have been developed to avoid the usual drawbacks of the basic process.<sup>5</sup> Among the various metal salts used to catalyze this Michael reaction, iron salts, such as iron(III) chloride hexahydrate (FeCl<sub>3</sub>·6H<sub>2</sub>O), were clearly the catalysts of choice for the Michael reaction of alkyl enones with  $\beta$ -keto esters.<sup>6</sup> Interestingly, in their report,<sup>6a</sup> the FeCl<sub>3</sub>·6H<sub>2</sub>O showed poor catalytic activity at room temperature in organic media.

In most cases, iron and its compounds are low-toxic and environmentally friendly, therefore, it has been attracted much attention in a great deal of useful organic transformations in recent years.<sup>7</sup> Since 1982,<sup>8</sup> the iron-catalyzed Michael reaction has been

well documented and successfully used in the synthesis of multi-carbonyl compounds from aliphatic enones or nitroolefins and dicarbonyl compounds under solvent-free conditions.<sup>6</sup> While the mechanistic proposal of one-center template reaction is in accordance with experimental observations, ESI, and DFT calculations,<sup>9</sup> more information and evidence are desired to supplement or understand the mechanism of Michael reaction. In addition, despite the potential of iron salts as privileged catalysts in organic synthesis being realized, the development of highly enantioselective iron-catalyzed organic transformation is highly desired.<sup>10</sup>

Herein, we focused on the iron-catalyzed Michael reactions by using chalcones and active methylene as model substrates to evaluate the possible mechanistic process of LBAs (Lewis acid-assisted Brønsted acid catalysis). Another aim of the present work is to establish a novel and efficient LBAs-based chiral catalyst system for asymmetric Michael reaction of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one to make chiral warfarin.

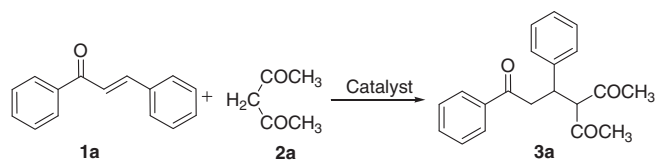
To investigate the solvent effect and catalytic efficiency of different iron salts in organic media, the Michael addition of active methylenes to aromatic chalcones was considered as the ideal model reaction. Initially, we carried out the optimization of a variety of reaction conditions, employing different iron salts for the model Michael reaction of chalcone and acetylacetone. As shown in Table 1, acceptable yield (39–79%) of the desired product was obtained with FeCl<sub>3</sub>·6H<sub>2</sub>O or Fe(ClO<sub>4</sub>)<sub>3</sub>·xH<sub>2</sub>O as catalyst in toluene at room temperature after 12 h (entries 1 and 2), however, the Michael reaction did not proceed at all with several iron salts, such as FeSO<sub>4</sub>·7H<sub>2</sub>O, FeCl<sub>2</sub>·4H<sub>2</sub>O, Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, and Fe(OAc)<sub>2</sub> (entries

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**Table 1**

Michael addition reaction of acetylacetone with chalcone promoted by different metal salt



Entry <sup>a</sup>	Metal salt	Solvent	Yield <sup>b</sup> (%)
1	FeCl <sub>3</sub> ·6H <sub>2</sub> O	Toluene	39
2	Fe(ClO <sub>4</sub> ) <sub>3</sub> ·xH <sub>2</sub> O	Toluene	79
3	FeCl <sub>2</sub> ·4H <sub>2</sub> O	Toluene	NR <sup>c</sup>
4	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	Toluene	NR <sup>c</sup>
5	Fe(OAc) <sub>2</sub>	Toluene	NR <sup>c</sup>
6	FeSO <sub>4</sub> ·7H <sub>2</sub> O	Toluene	NR <sup>c</sup>
7	FeBr <sub>3</sub>	Toluene	91
8	FeCl <sub>3</sub>	Toluene	97
9	FeCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	88
10 <sup>d</sup>	FeCl <sub>3</sub>	THF	10
11 <sup>e</sup>	FeCl <sub>3</sub>	CH <sub>3</sub> OH	7
12 <sup>f</sup>	FeCl <sub>3</sub>	Ethanol	Trace
13	Fe(acac) <sub>3</sub>	Toluene	NR <sup>c</sup>
14	HCl	Toluene	20 <sup>g</sup>
15	Fe(acac) <sub>3</sub> + HCl	Toluene	>95
16	Fe(acac) <sub>3</sub> + TsOH	Toluene	>95

<sup>a</sup> Reaction conditions: 15 mol % of metal salt, 1.5 mmol/1.0 mmol, of acetylacetone/chalcone; and 1.5 mL of solvent at room temperature for 12 h unless otherwise noted.

<sup>b</sup> Isolated yields.

<sup>c</sup> No reaction.

<sup>d</sup> 24 h.

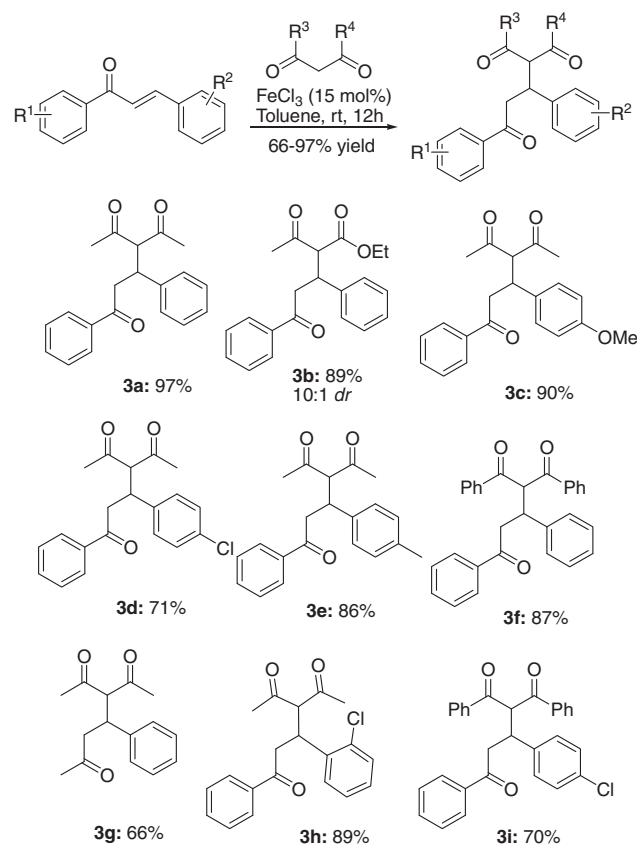
<sup>e</sup> 48 h.

<sup>f</sup> 70 h.

<sup>g</sup> There are many by-products in this reaction.

3–6), which showed the anion of iron salt has a pronounced effect in activation of carbonyl substrates. We then carried out the reaction in the presence of anhydrous FeCl<sub>3</sub> and FeBr<sub>3</sub> in toluene at room temperature, the reaction is clean and the yield was increased to higher level (entries 7 and 8: 97% and 91%, respectively). The screening of the solvent revealed that poor results were displayed in other solvents, such as THF and CH<sub>3</sub>OH (entries 10 and 11), and the reaction did not proceed at all when using ethanol as the solvent (entry 12). Very interestingly, the reaction performed with Fe(acac)<sub>3</sub> failed in providing the desired Michael adduct. The observed acceleration of the iron-mediated Michael addition showed that the anion of iron salt played a crucial role when counterion was changed from acetate to chloride.

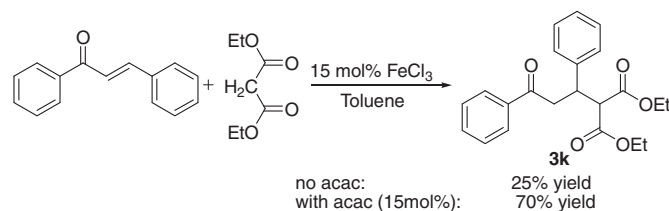
We then investigated the reaction scope of this catalytic system and its tolerance of functional groups in the case of other chalcones **1** and active methylene compounds **2**. As shown in Scheme 1, the optimized reaction conditions were applicable to various substrates. Whether using aromatic or aliphatic diketones, iron efficiently promoted the reaction with good to excellent yields. Ethyl acetoacetate was also found to be a suitable substrate. Unfortunately, the reaction of diethyl malonate with chalcone afforded the desired product in only 25% yield with trace byproduct. On the basis of previous results, we felt that the use of an appropriate additive to form iron enolate of dimethyl malonate would allow us to realize a mild and general procedure for the synthesis of **3k**. As we expected, using acetylacetone as an additive in the Michael reaction of dimethyl malonate with chalcone, the reaction was proceeded successfully with good yield (70% isolated yield). To the best of our knowledge, this is the first example of the iron-catalyzed Michael reactions of chalcones and inactive malonate compounds promoted by acetylacetone, which maybe due to the activation of iron enolate (Scheme 2). In this case, the replacement



**Scheme 1.** FeCl<sub>3</sub>-catalyzed Michael reactions of active methylene compounds with chalcones: 15 mol % of FeCl<sub>3</sub>, 1.5 mmol/1.0 mmol, of active methylene compounds/chalcones; and 1.5 mL of toluene at room temperature for 12 h.

of FeCl<sub>3</sub>/acac system with Fe(acac)<sub>3</sub>/HCl resulted in low yield (10%), which is due to low nucleophilic activity of ethyl malonate.

The mechanism of iron-catalyzed Michael reaction of 1,3-dicarbonyl compounds has been reported by Christoffers and co-workers, in which a one-center template mode was established.<sup>9</sup> It is reasonable that Fe(acac)<sub>3</sub> is significantly less active than the FeCl<sub>3</sub>·6H<sub>2</sub>O or FeCl<sub>3</sub> because it does not readily offer a vacant coordination site for the enone. However, it is difficult to explain why anhydrous FeCl<sub>3</sub> is significantly more active than FeCl<sub>3</sub>·6H<sub>2</sub>O in toluene. In addition, Fe(acac)<sub>3</sub> is also an excellent catalyst in the presence of catalytic amount of Brønsted acid, such as TsOH and HCl. Based on our experimental results and macroscopic opinion, a suggested and more practical mechanism with Lewis acid-assisted Brønsted acid catalysis (LBA)<sup>11</sup> is proposed in Scheme 3. The reasons for this proposal of LBA are as follows: (a) The Fe(acac)<sub>3</sub>-catalyzed Michael addition reactions of acetylacetone with chalcone gave no desired product, indicating that the Michael addition proceeded with Brønsted acidic HCl as catalyst. (b) Without the iron catalyst, the reaction proceeded with low yield and poor chemoselectivity. Many products of side reactions with mixtures formed in the presence of only HCl. Therefore, the major role of the iron



**Scheme 2.** FeCl<sub>3</sub>-catalyzed Michael reaction of diethyl malonate with chalcone.

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