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Double Reformatsky Reaction: Divergent Synthesis of δ-Hydroxy-β-ketoesters

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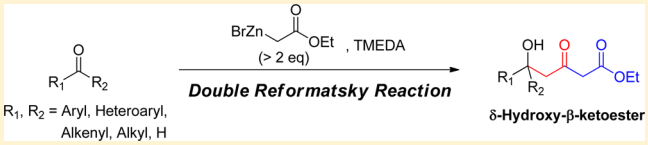
Supporting Information

ABSTRACT: The double Reformatsky reaction, tandem addition of two molecules of zinc alkanoate to a carbonyl compound, and its synthetic application to a series of δ-hydroxy-β-ketoesters has been developed. The key to accelerate the double Reformatsky reaction is considered to be a complex-induced proximity effect of the in situ generated zinc alkoxide coordinated with the pyridyl group of the substrate or bidentate amines. A noteworthy feature of the reaction system is its high tolerance of functional groups due to the moderate nucleophilicity of organozinc reagents and the mild reaction conditions. Moreover, spectroscopic and crystallographic analyses of the zinc complex of the double Reformatsky product support the proposed mechanism of reaction site discrimination for ketones, aldehydes, nitriles, carboxylic acid anhydrides, and esters.



1. INTRODUCTION

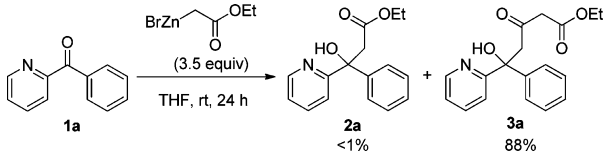
Metal-mediated C−C bond formation is an essential tool for the development of synthetic routes to complex organic molecules. In the history of organic chemistry, a large number of metal-mediated nucleophilic additions to electrophiles have been developed and applied to the synthesis of complex molecules. As most of the targeted organic molecules contain electrophilic groups, the use of highly reactive organometallic reagents has often been limited due to poor functional group tolerance. However, among the known organometallic nucleophiles, organozinc reagents have recently attracted renewed attention due to their high tolerance toward functional groups.[1] In particular, the classical Reformatsky reaction has been considered as a practical tool to produce various β-hydroxyalkanoates from α-haloalkanoates and aldehydes or ketones.[2,3] In recent years, the scope of the Reformatsky reaction has been extended beyond aldehydes and ketones, and continuous efforts have been directed to the development of reactions with a great variety of electrophiles, such as nitriles[4] and carboxylic acid anhydrides.[5] In contrast, ester groups are known to be essentially unreactive to Reformatsky reaction. Though some reports of Reformatsky reaction proceeding with esters have emerged, most of them are limited to cyclic and/or activated esters.[6,7]

In the course of our recent drug research and development program, we found an unexpected Reformatsky reaction when 2-benzoylpyridine (**1a**) reacting with ethyl bromozincacetate at room temperature did not give the desired β-hydroxyalkanoates (**2a**) but δ-hydroxy-β-ketoester (**3a**) instead, as the sole product (Scheme 1).

The result intrigued us because this kind of reaction to afford δ-hydroxy-β-ketoesters directly from carbonyl compounds and zinc alkanoates under such a mild condition has not been described to date. In addition, the product δ-hydroxy-β-ketoester can be an important building block for various biologically active compounds.[8] Extensive efforts have been devoted to the development of δ-hydroxy-β-ketoester synthetic methodology, such as the addition of Chan's diene,[9] Wieler's dianion,[10] or diketene[11] to carbonyl compounds. While these chemistries have contributed to the efficient syntheses of the compounds, especially in the field of asymmetric synthesis, we expected our finding would lead to another convenient and efficient synthetic method for δ-hydroxy-β-ketoesters using Reformatsky reagents, which have already been well-developed as a reliable synthetic tool and recognized as highly functional group tolerant reagents. Consequently, the detailed investigation of this reaction was considered to be a topic of great importance for organic synthesis.

Herein, we disclose the unusual addition of zinc alkanoates to the ester group of in situ generated β-hydroxyalkanoates and the establishment of a general synthesis of δ-hydroxy-β-ketoesters directly from carbonyl compounds and zinc alkanoates under a mild condition.

Scheme 1. Unexpected Reformatsky Reaction of 1a



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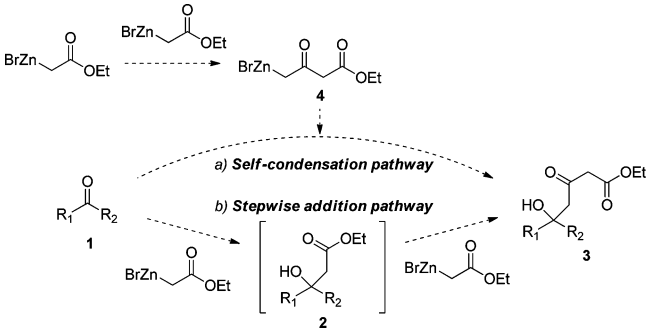
2. RESULTS AND DISCUSSION

2.1. Reaction Pathway. At the outset of this study, our efforts were focused on identifying the reaction pathway. The following two plausible reaction pathways were considered: (i) self-condensation pathway, the attack of self-condensed Reformatsky reagent (**4**) on carbonyl substrate (**1**) (Scheme 2, path *a*); (ii) stepwise addition pathway, after usual Reformatsky reaction, the tandem attack of zinc alkanoate on *β*-hydroxyalkanoates (**2**) (Scheme 2, path *b*).

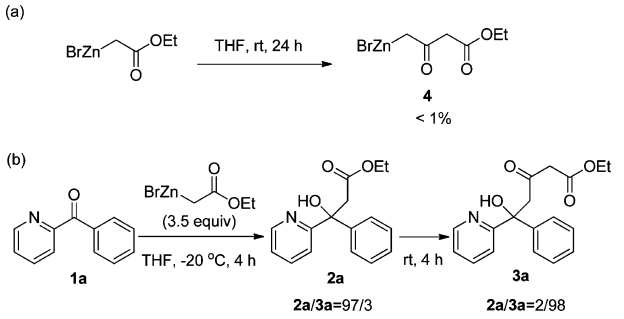
Scheme 2. Plausible Reaction Pathways



An intensive survey of the prior literature revealed some reports suggesting the self-condensation pathway.[12] Newman and co-workers investigated the self-condensation of Reformatsky reagents and indicated that self-condensation was promoted at higher temperatures and with decreasing bulkiness of ester alkyl groups.[13] Following their study, Vaughan and co-workers reported further studies on the behavior of self-condensed Reformatsky reagents with carbonyl compounds.[14] In both of their studies, self-condensed Reformatsky reagents were considered to be unreactive toward carbonyl compounds. In addition, Utimoto and co-workers reported a synthetic method to give *δ*-hydroxy-*β*-ketoesters directly from carbonyl compounds and *α*-haloalkanoates, through the intermediacy of SmI_2, in which they disclosed that *α*-haloalkanoates can be self-condensed and the self-condensed samarium species coupled with carbonyl compounds to afford *δ*-hydroxy-*β*-ketoesters.[15] As for the stepwise addition pathway, there has been one example that demonstrated a secondary attack of a Reformatsky reagent on the ester group of an *α*,*β*-unsaturated ester, with a dithioacetal moiety that was derived from a first Reformatsky reaction followed by subsequent dehydration.[16]

To identify if *δ*-hydroxy-*β*-ketoesters were formed via a self-condensation pathway or a stepwise addition pathway, two model experiments were conducted. First, the amount of self-condensed Reformatsky reagent (**4**) generated during the reaction was evaluated (Scheme 3 (a)). Ethyl bromozincacetate was stirred under the same conditions as for Scheme 1 (at room temperature for 24 h), but **4** was obtained in less than 1% yield (evaluated by GC),[17] which indicated that self-condensation of Reformatsky reagents at room temperature only occurred at a very low level. Next, the product ratio under a reactivity-modulated condition (controlling the reaction temperature) was investigated (Scheme 3 (b)). When a reaction mixture containing **1a** and 3.5 equiv of ethyl bromozincacetate was stirred at −20 °C for 4 h, the ratio of **2a**/**3a** was 97/3. Subsequently, the mixture was stirred for 4 h at room temperature and the ratio of **2a**/**3a** switched to 2/98, which indicated that **3a** was formed via a stepwise addition pathway.

Scheme 3

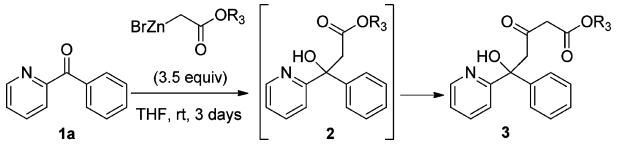


Based on the identified reaction pathway, we termed this a "double Reformatsky reaction".

2.2. Evaluation of Reaction Promotion Factors. We continued our studies by examining the factors that promoted the reaction. Initially, the effect of a Lewis acid was studied. Reformatsky reaction is known to be accelerated by Lewis acids such as TMSCl[18] and $TiCl_4$.[19] Since a catalytic amount of TMSCl was used for the activation of zinc in the preparation of the Reformatsky reagent, it was necessary to check if TMSCl was promoting the double Reformatsky reaction. The reaction of **1a** with a TMSCl-free Reformatsky reagent was attempted, and the reaction was found to proceed to full conversion in the same manner as for the reaction with the TMSCl-contained Reformatsky reagent, which demonstrated that the additional Lewis acid was not the driving force for the double Reformatsky reaction.[20]

Our attention was subsequently directed to the bulkiness of the zinc alkanoate. Table 1 shows the relationship between the

Table 1. Effect of Bulkiness of the Zinc Alkanoates[a]



run	R_3	ratio (**1a**/**2**/**3**)[b]
1	Me	0/<1/>99
2	Et	0/<1/>99
3	*i*-Pr	0/75/25
4	*t*-Bu	0/98/2

[a]Reaction conditions: **1a** (2.5 mmol), alkyl bromozincacetate (3.5 equiv), THF (16 mL), room temperature, 3 days, under N_2. [b]Determined by HPLC analysis

bulkiness of the zinc alkanoate alkyl groups and the degree of double Reformatsky reaction. Reactions with the less hindered methyl bromozincacetate and ethyl bromozincacetate were fully completed (runs 1 and 2), whereas reaction with the more hindered isopropyl bromozincacetate stopped at incomplete conversion, and the much hindered *tert*-butyl bromozincacetate only afforded a trace amount of double adduct **3** (runs 3 and 4). The result indicated that the reaction can only readily proceed when the zinc alkanoate has small unhindered alkyl groups.

Next, in order to clarify the substituent effect of the 2-pyridyl group,[7a,21] the reactivity of structurally and electrically analogous ketones (**1**) and aldehydes (**5**), with and without neighboring coordination groups, was investigated. As shown in Table 2, **1a** and 2-picolinaldehyde (**5a**), containing neighboring coordination groups, were fully converted to the double

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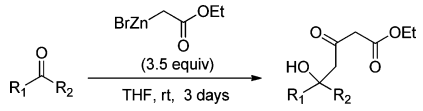
Table 2. Examination of the Substituent Effect of a 2-Pyridyl Group[a]



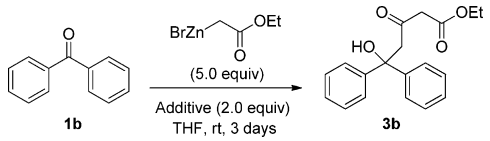
run	substrate	R_1	R_2	conversion[b] (%)
1	**1a**	2-pyridyl	phenyl	98
2	**1b**	phenyl	phenyl	16
3	**1c**	3-pyridyl	phenyl	41
4	**1d**	4-pyridyl	phenyl	67
5	**5a**	2-pyridyl	H	97
6	**5b**	phenyl	H	39
7	**5c**	3-pyridyl	H	7
8	**5d**	4-pyridyl	H	38

[a]Reaction conditions: substrate (2.5 mmol), ethyl bromozincacetate (3.5 equiv), THF (16 mL), room temperature, 3 days, under N_2. [b]Determined by HPLC analysis.

Reformatsky products. In contrast, the reactions with other analogues containing no neighboring coordination groups (**1b–d** and **5b–d**) resulted in remarkably decreased reactivity and incomplete conversions. The result indicated that a pyridine–nitrogen adjacent to the carbonyl group is beneficial to obtain high conversion.

Subsequently, we attempted to extend the scope of available substrates without neighboring coordination groups. To enhance the reactivity of simple substrates, we introduced bases as additives to the reaction, as Ojida and co-workers indicated that pyridine might promote Reformatsky reaction (Table 3).[21] Benzophenone (**1b**) was used as a model substrate, with 5 equiv of ethyl bromozincacetate,[22] and it was found that pyridine gave considerable increase in reactivity (runs 1 and 2). Encouraged by this result, we further examined various quantities and basicities of monodentate amines.

Table 3. Effect of Base on Double Reformatsky Reaction of 1b[a]



run	additive	conversion[b] (%)
1		48
2	pyridine	78
3	pyridine (4.0 equiv)	75
4	*N*-methylimidazole	67
5	*i*-Pr_2NEt	52
6	DBU	67
7	2,2-bipyridine	91
8	1,10-phenanthroline	80
9	DABCO	91
10	TMEDA	95
11	K_2CO_3	64
12	$NaHCO_3$	46
13	thiophene	63
14	L-proline	3

[a]Reaction conditions: **1b** (2.5 mmol), ethyl bromozincacetate (5.0 equiv), THF (23 mL), additive (2.0 eq), 25 °C, 3 days under N_2. [b]Determined by HPLC analysis.

However, it was found that the reactivity was independent of the quantity and basicity of monodentate amines (runs 3–6). On the other hand, we were encouraged to find that bidentate amines significantly accelerated the reaction (runs 7–10). In particular, TMEDA gave almost full conversion and was selected as the base of choice for further studies (run 10). Although more detailed data should be accumulated to elucidate the beneficial effect of bidentate amines, we assume that they may coordinate to zinc and dissociate the Reformatsky reagent dimeric complexes,[23] enhancing the coordination ability of the β-zinc alkoxide to the ester carbonyl as well as the reactivity of the Reformatsky reagent. Inorganic bases did not promote the reaction (runs 11 and 12). Also, thiophene[24] and L-proline,[25] which have been reported as coordinating additives to zinc, did not remarkably promote the reaction (runs 13 and 14).

2.3. Scope and Limitations. With an efficient procedure for the double Reformatsky reaction in hand,[26] the reactions with ketones, aldehydes, nitriles, and carboxylic acid anhydrides were performed under the optimal conditions (ethyl bromozincacetate (5.0 equiv), TMEDA (2.0 equiv) in THF) (Table 4).[27] It was found that various electronically and structurally diverse ketones and aldehydes could be used in the reaction to give the corresponding δ-hydroxy-β-ketoesters in good to excellent yields (runs 1–11). Interestingly, in the case of *p*-formylbenzoic acid methyl ester (**5h**), the formyl moiety was readily converted to the δ-hydroxy-β-ketoester whereas an ester on an aromatic ring remained unchanged (run 6). Moreover, *p*-nitrobenzaldehyde (**5i**) and *p*-bromobenzaldehyde (**5j**) underwent reaction leaving the nitro and halide groups unreacted, making the method attractive for further functionalizations (runs 7 and 8). The reaction also proceeded well in the presence of a hetero aryl group (run 9). Other than aryl aldehydes, the reaction with alkenyl aldehyde (**5l**) and alkyl aldehyde (**5m**) gave the corresponding products in satisfactory yields, without any side reactions (runs 10 and 11).[28]

To further expand the scope of this reaction, the application to nitriles and carboxylic acid anhydrides was examined (runs 12 and 13). The reaction of zinc alkanoate with a nitrile, namely the Blaise reaction,[4] is known to provide β-ketoesters after acidic workup. Similarly, Reformatsky-type reaction with carboxylic acid anhydride can also provide β-ketoesters.[5] If the double addition of zinc alkanoate proceeds for nitriles and carboxylic acid anhydrides, β,δ-diketoesters were expected to be obtained, which would expand the synthetic utility of the reaction. However, when the double Reformatsky reactions of benzonitrile (**7**) and benzoic (ethyl carbonic) anhydride (**8**) were attempted, both of them afforded β-ketoester (**9**) as the sole product, and no β,δ-diketoesters (**10**) were observed.

All products from ketones and aldehydes in Table 4 were isolated in the form of ketoesters, and enol structures were not observed. Furthermore, it should be stressed that all ketones and aldehydes were exclusively converted to δ-hydroxy-β-ketoesters, and neither β,δ-dihydroxydiesters[29] (**11**) nor ζ-hyroxy-β,δ-diketoesters[30] (**12**) were detected (Figure 1).

2.4. Mechanistic Consideration. On the basis of the above results, the mechanism for the double Reformatsky reaction, taking the example of reactions with **5h**, **7**, and **8**, can be considered as follows (Scheme 4). In the case of **5h**, after the usual Reformatsky reaction at the formyl moiety, the newly formed terminal ester of intermediate **A** is activated by the β-zinc alkoxide–TMEDA complex as an internal Lewis acid (complex-induced proximity effect), and it is subjected to

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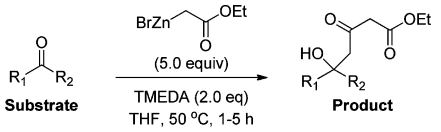
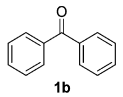
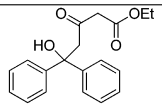
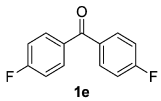
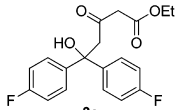
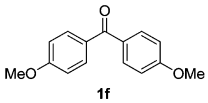
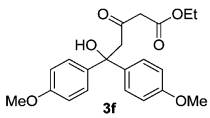
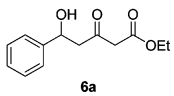
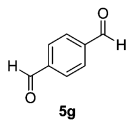
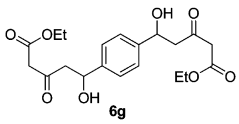
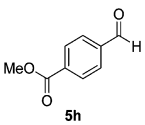
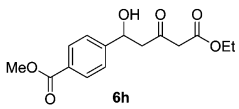
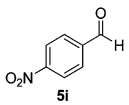
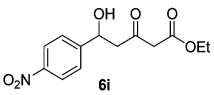
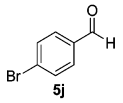
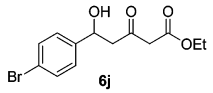
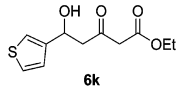
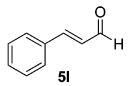
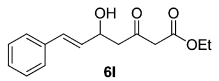
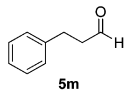
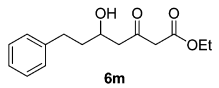
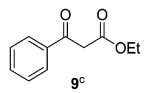
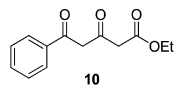
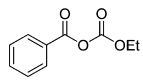
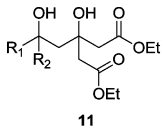
Table 4. Synthesis of Various δ-Hydroxy-β-ketoesters[a]



Run	Substrate	Product	Isolated yield (%)
1	 1b	 3b	76
2	 1e	 3e	87
3	 1f	 3f	85
4	 5a	 6a	90
5[b]	 5g	 6g	87
6	 5h	 6h	90
7	 5i	 6i	73
8	 5j	 6j	84
9	 5k	 6k	82
10	 5l	 6l	94
11	 5m	 6m	74
12	 7	 9[c]	85
		 10	0
13	 8	9[c]	55
		10	0

[a]Reaction conditions: substrate (2.5 mmol), ethyl bromozincacetate (5.0 equiv), TMEDA (2.0 equiv), THF (23 mL), 50 °C, 1−5 h, under N_2. [b]Ethyl bromozincacetate (10.0 equiv), TMEDA (4.0 equiv). [c]Isolated as keto−enol tautomer (mainly β-ketoester conformation).


11

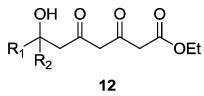

12

Figure 1. Structure of **11** and **12** (undetected potential byproducts).

secondary addition of zinc alkanoate, whereas the aromatic ester remains unreactive due to the absence of any chelation-assisted activation (Scheme 4 (a)). After secondary addition of zinc alkanoate to the β-hydroxyester of **A**, zinc complex **B** is formed with an ester-conjugated enolate, as described below. The conformation of **B** gives an appropriate explanation to the fact that **11** and **12** were never detected because the terminal ester of **B** will be stabilized by conjugation even under the activation by the internal Lewis acid. In sharp contrast, after addition of zinc alkanoate to nitrile **7**, complex **C** is formed and stabilized in imine−enamine tautomeric equibrium with complex **D**, and consequently, secondary addition of zinc alkanoate is unlikely to occur (Scheme 4 (b)). Similarly, after addition of zinc alkanoate to carboxylic acid anhydride **8**, rapid β-elimination provides ester-conjugated enolate **F** that is stabilized by conjugation, which probably prohibits any further addition of zinc alkanoate (Scheme 4 (c)).

The assumption that doubly coupled intermediates such as complex **B** are in the form of ester-conjugated enolates was reinforced by analytical results. In the course of this study, we obtained a white crystalline precipitate after double Reformatsky reaction of **1a**. As the precipitate was converted to **3a** after simple acidic workup, it was considered to be the zinc complex of **3a.** Judging from the results of ^{1}H NMR and ICP-MS, the structure seemed to consist of three atoms of zinc, two molecules of **3a**, and one molecule of THF.[31]

The 1D and 2D NMR analyses of the zinc complex of **3a** were conducted, and full assignment of the ^{1}H and ^{13}C chemical shifts was achieved by evaluating the HMQC and HMBC spectra.[32] During the evaluations, we paid attention to a characteristic singlet proton that is considered to be an olefinic

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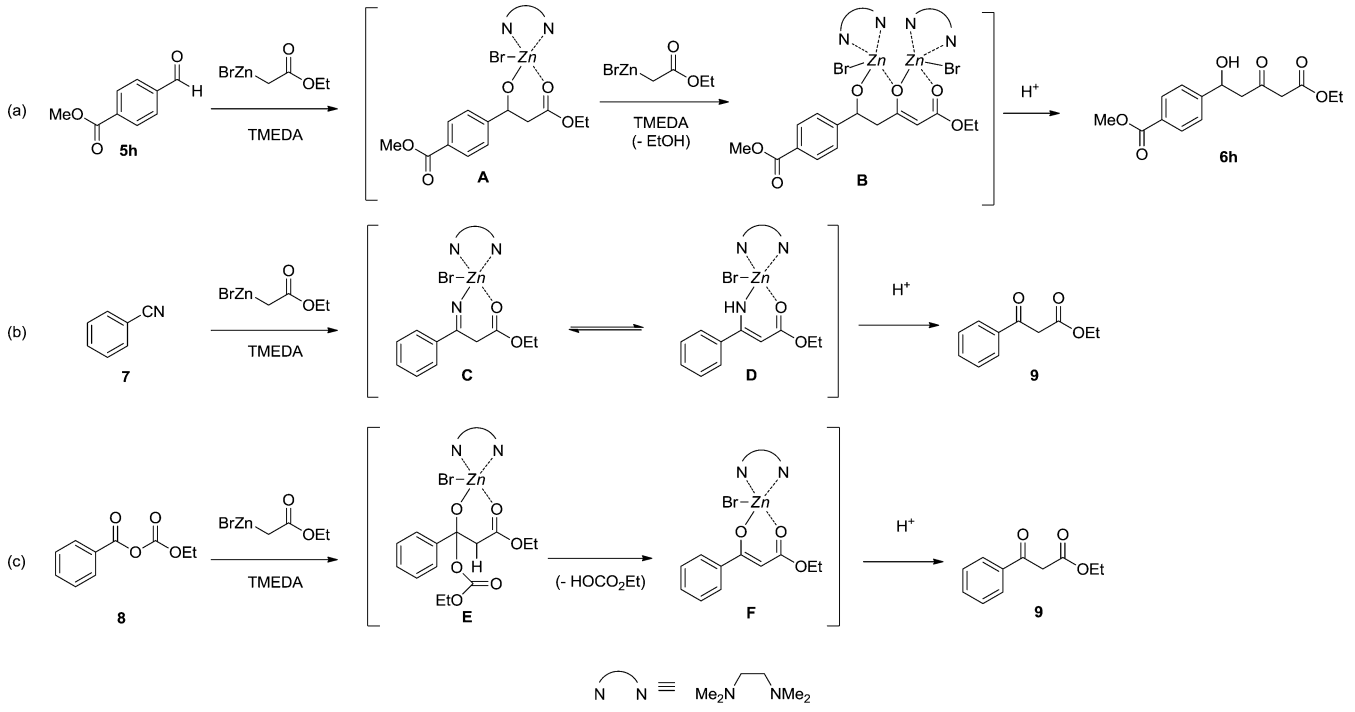
Scheme 4. Plausible Reaction Mechanism



proton. According to the HMBC spectra, the olefinic proton was found to be coupled with C16 and C19, which indicated that the proton was H18, and the structure of the zinc complex of **3a** involved the ester-conjugated enolate form (Figure 2).

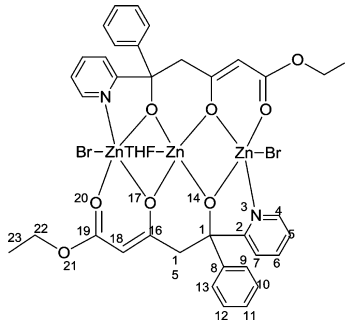


Figure 2. Plausible structure of the zinc complex of **3a** THF solvate.

Furthermore, a single crystal was obtained from ethanol and acetone (zinc complex of **3a** ethanol solvate) and submitted for X-ray single-crystal structure analysis, which revealed the intermolecular coordination of the pyridyl group to zinc alkoxide as proposed in Figure 2.[33] Additionally, the bond length of C16−C18 (1.358 Å) is found to be a typical olefinic double bond length,[34] which also endorses our assumption that the doubly coupled intermediates are in the form of ester-conjugated enolates.

The coordination of the pyridyl group to the zinc alkoxide indicates the pyridyl group works in the same manner as TMEDA. Therefore, it is considered that the double Reformatsky reaction of **1a** to **3a** proceeds through the activation of the ester carbonyl group of intermediate **2a** by the zinc alkoxide coordinated with the pyridyl group (Figure 3). Furthermore, the consideration that the zinc alkoxide−pyridine complex works as an internal Lewis acid is consistent with the

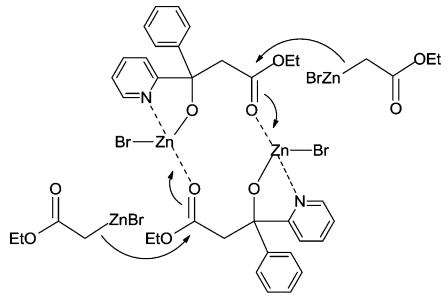


Figure 3. Potential transition state of the reaction of **2a** to **3a**.

observation that external Lewis acids, such as TMSCl, are not required to promote the reaction.

3. CONCLUSION

Double Reformatsky reaction and the synthesis of various *δ*-hydroxy-*β*-ketoesters have been developed. The key to accelerate the double Reformatsky reaction is considered to be a complex-induced proximity effect of the in situ generated zinc alkoxide coordinated with the pyridyl group of the substrate or bidentate amines. A noteworthy feature of the reaction system is its high tolerance of functional groups due to the moderate nucleophilicity of organozinc reagents and the mild reaction conditions. Moreover, NMR and X-ray single-crystal structure analyses of the zinc complex of the double Reformatsky product have supported the proposed mechanism of reaction site discrimination for ketones, aldehydes, nitriles, carboxylic acid anhydrides and esters. The present versatile synthesis can complement the known synthetic methods for *δ*-hydroxy-*β*-ketoesters in terms of functional group flexibility. Furthermore, since several asymmetric Reformatsky reactions have been reported,[21,35] this method can potentially be applied to asymmetric reactions, which is the focus of ongoing research.

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EXPERIMETAL SECTION

General Methods. All chemicals were obtained from commercial suppliers and used without further purification. NMR was recorded on 500 MHz spectrometer with tetramethylsilane as an internal standard. Chemical shifts are shown in ppm. High-resolution mass spectra (HRMS) were measured by ESI-Orbitrap mass spectrometer.

$BrZnCH_2CO_2Me$, $BrZnCH_2CO_2Et$, and $BrZnCH_2CO_2$-i-Pr. Under N_2 atmosphere, to a 200 mL round-bottom flask were added zinc powder (11.5 g, 175.8 mmol, 2.0 equiv), dry THF (44 mL), and TMSCl (0.96 g, 8.8 mmol, 0.1 equiv). The suspension was warmed to 40−50 °C, and α-bromoester (88.2 mmol, 1.0 equiv) in THF (110 mL) was added dropwise to the suspension. After insoluble matter precipitated, the light yellow supernatant solution was decanted and used for subsequent experiments.

TMSCl-Free $BrZnCH_2CO_2Et$. To a 500 mL round-bottom flask were added zinc powder (20 g) and aqueous 0.1 N aq HCl (200 mL). The suspension was stirred vigorously for 10 min. The precipitate was collected by filtration and dried in vacuo at 100 °C for at least 4 h. Under N_2 atmosphere, to a 200 mL round-bottom flask were added the above activated zinc (11.5 g, 175.8 mmol, 2.0 equiv) and dry THF (44 mL). The suspension was warmed to 40−50 °C, and ethyl bromoacetate (14.7 g, 88.2 mmol, 1.0 equiv) in THF (110 mL) was added dropwise. After insoluble matter precipitated, the light yellow supernatant solution was decanted and used for subsequent experiments.

$BrZnCH_2CO_2$-t-Bu. To a 500 mL round-bottom flask were added zinc powder (20 g) and 0.1 N aq HCl (200 mL). After being stirred for 10 min at room temperature, the precipitate was collected by filtration and dried at 100 °C for at least 4 h. Under N_2 atmosphere, to a 200 mL round-bottom flask were added the above activated zinc powder (11.5 g, 175.8 mmol, 2.0 equiv), THF (44 mL), and TMSCl (0.96 g, 8.8 mmol, 0.1 equiv). The suspension was warmed to 40−50 °C, and *tert*-butyl bromoacetate (17.2 g, 88.2 mmol, 1.0 equiv) in THF (110 mL) was added dropwise. After zinc powder precipitated, the light yellow supernatant solution was decanted and used for subsequent experiments.

*Ethyl 5-Hydroxy-3-oxo-5-phenyl-5-(pyridin-2-yl)pentanoate (**3a**).* To a 100 mL round-bottom flask were added ca. 0.54 mol/L of ethyl bromozincacetate/THF solution (16.1 mL, ca. 8.7 mmol, 3.5 equiv) and 2-benzoyl pyridine (**1a**) (458.0 mg, 2.5 mmol). The yellow solution was stirred at room temperature for 24 h. The mixture was diluted with EtOAc (50 mL). The solution was successively washed with 20% aq citric acid (25 mL), 10% aq NaCl (25 mL), 5% aq $NaHCO_3$ (25 mL), and water (25 mL). The organic layer was concentrated in vacuo to give the crude oil. The crude oil was purified by flash chromatography (EtOAc/Hexane) to give the title compound as a yellow oil (651.8 mg, 83% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 3.46 (d, J = 15.8 Hz, 1H), 3.49 (s, 2H), 3.77 (d, J = 15.5 Hz, 1H), 4.03 (q, J = 7.3 Hz, 2H), 6.10 (s, 1H), 7.15−7.16 (m, 1H), 7.17−7.23 (m, 1H), 7.27 (t, J = 7.0 Hz, 2H), 7.45−7.47 (m, 2H), 7.59 (d, J = 7.9 Hz, 1H), 7.73−7.76 (m, 1H), 8.47−8.48 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.9, 50.2, 53.0, 60.3, 77.1, 120.3, 121.9, 125.3, 126.6, 127.9, 136.9, 146.2, 147.6, 164.6, 167.0, 201.9; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{18}H_{20}NO_4$ 314.1387, found 314.1376.

General Procedure. *δ-Hydroxy-β-ketoesters.* To a 100 mL round-bottom flask were added ca. 0.54 mol/L of ethyl bromozincacetate/THF solution (23.3 mL, ca. 12.5 mmol, 5 equiv), TMEDA (0.75 mL, 5 mmol, 2.0 equiv), and carbonyl compound (2.5 mmol, 1.0 equiv). The solution was warmed to 50 °C and stirred for 1−5 h. After being cooled to room temperature, the mixture was diluted with EtOAc (50 mL). The solution was successively washed with 20% aq citric acid (25 mL), 10% aq NaCl (25 mL), 5% aq $NaHCO_3$ (25 mL), and water (25 mL). The organic layer was concentrated in vacuo to give the crude oil. The crude oil was purified by flash chromatography (EtOAc/hexane) to give the pure δ-hydroxy-β-ketoesters.

*Ethyl 5-Hydroxy-3-oxo-5,5-diphenylpentanoate (**3b**).* The title compound was prepared according to the general procedure and isolated as a white solid (590.6 mg, 76% yield): mp 66−67 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 3.48 (s, 2H), 3.55 (s, 2H), 4.02 (q, J = 7.3 Hz, 2H), 5.94 (s, 1H), 7.16−7.19 (m, 2H), 7.29 (t, J = 7.7 Hz, 4H), 7.42−7.44 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.9, 50.2, 53.7, 60.3, 75.8, 125.5, 126.4, 127.9, 147.2, 167.0, 202.0; HRMS (ESI-Orbitrap) m/z [M + NH_4]$^+$ calcd for $C_{19}H_{24}NO_4$ 330.1700, found 330.1703.

*Ethyl 5,5-Bis(4-fluorophenyl)-5-hydroxy-3-oxopentanoate (**3e**).* The title compound was prepared according to the general procedure and isolated as a yellow oil (788.6 mg, 85% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.42 (s, 2H), 3.53 (s, 2H), 4.18 (q, J = 7.3 Hz, 2H), 4.70 (s, 1H), 6.96−6.99 (m, 4H), 7.32−7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 50.3, 53.0, 61.8, 76.4, 115.2 (d, J_{C-F} = 22.5 Hz), 127.4 (d, J_{C-F} = 8.8 Hz), 141.7 (d, J_{C-F} = 3.8 Hz), 161.9 (d, J_{C-F} = 245.0 Hz), 166.6, 203.8; HRMS (ESI-Orbitrap) m/z [M + NH_4]$^+$ calcd for $C_{19}H_{22}F_2NO_4$ 366.1511, found 366.1513.

*Ethyl 5-Hydroxy-5,5-bis(4-methoxyphenyl)-3-oxopentanoate (**3f**).* The title compound was prepared according to the general procedure and isolated as a yellow oil (755.9 mg, 87% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.3 Hz, 3H), 3.40 (s, 2H), 3.51 (s, 2H), 3.77 (s, 6H), 4.18 (q, J = 7.3 Hz, 2H), 4.53 (s, 1H), 6.81−6.83 (m, 4H), 7.26−7.28 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 50.5, 53.2, 55.2, 61.6, 76.5, 113.6, 126.9, 138.4, 158.5, 166.7, 204.0; HRMS (ESI-Orbitrap) m/z [M + NH_4]$^+$ calcd for $C_{21}H_{28}NO_6$ 390.1911, found 390.1909.

*Ethyl 5-Hydroxy-3-oxo-5-phenylpentanoate (**6a**).* The title compound was prepared according to the general procedure and isolated as a colorless oil (528.4 mg, 90% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 2.92 (dd, J = 17.3, 3.5 Hz, 1H), 3.00 (dd, J = 17.3, 9.1 Hz, 1H), 3.48 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 5.19 (dd, J = 9.1, 3.5 Hz, 1H), 7.20−7.42 (m, 5H). Analysis of the spectroscopic data matched reported data.[36]

*Diethyl 5,5′-(1,4-Phenylene)bis(5-hydroxy-3-oxopentanoate) (**6g**).* The title compound was prepared according to the general procedure (terephthalaldehyde **14**, 167.7 mg, 1.25 mmol) with Reformatsky reagent (23.3 mL, 10 equiv), and TMEDA (0.75 mL, 4 equiv) and isolated as a light yellow oil (856.9 mg, 87% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 6H), 2.91 (dd, J = 17.5, 3.2 Hz, 2H), 2.99 (dd, J = 17.5, 9.1 Hz, 2H), 3.08 (brs, 2H), 3.49 (s, 4H), 4.20 (q, J = 7.1 Hz, 4H), 5.19 (dd, J = 9.1, 3.2 Hz, 2H), 7.35−7.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 49.9, 51.5, 61.6, 69.6, 125.9, 142.2, 166.9, 202.8; HRMS (ESI-Orbitrap) m/z [M + NH_4]$^+$ calcd for $C_{20}H_{30}NO_8$ 412.1966, found 412.1977.

*Methyl 4-(5-ethoxy-1-hydroxy-3,5-dioxopentyl)benzoate (**6h**).* The title compound was prepared according to the general procedure and isolated as a colorless oil (614.4 mg, 84% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 2.94 (dd, J = 17.6, 3.8 Hz, 1H), 2.99 (dd, J = 17.6, 8.5 Hz, 1H), 3.27 (brs, 1H), 3.49 (s, 2H), 3.91 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 5.26 (dd, J = 8.5, 3.5 Hz,1H), 7.43−7.45 (m, 2H), 8.01−8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 49.8, 51.4, 52.1, 61.6, 69.3, 125.5, 125.6, 129.5, 129.9, 147.6, 166.8, 202.6; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{15}H_{18}O_6$ 295.1176, found 295.1181.

*Ethyl 5-Hydroxy-5-(4-nitrophenyl)-3-oxopentanoate (**6i**).* The title compound was prepared according to the general procedure and isolated as an off-white solid (625.2 mg, 90% yield): mp 75−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 2.97−2.99 (m, 2H), 3.40 (d, J = 3.5 Hz, 1H), 3.51 (s, 2H), 4.21 (q, J = 7.3 Hz, 2H), 5.32 (ddd, J = 6.9, 5.2, 3.5 Hz 1H), 7.55−7.57 (m, 2H), 8.20−8.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 49.7, 51.2, 61.8, 68.9, 123.8, 126.5, 147.4, 149.7, 166.7, 202.5; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{13}H_{15}NO_6$ 282.0972, found 282.0974.

*Ethyl 5-(4-Bromophenyl)-5-hydroxy-3-oxopentanoate (**6j**).* The title compound was prepared according to the general procedure and isolated as a colorless oil (577.3 mg, 73% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 2.90 (d, J = 17.6, 3.4 Hz, 1H), 2.96 (dd, J = 17.6, 8.8 Hz, 1H), 3.12 (d, J = 3.4 Hz, 1H), 3.48 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 5.16 (dt, J = 8.8, 3.4 Hz, 1H), 7.24−7.26 (m, 2H), 7.47−7.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 49.9, 51.4,

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61.7, 69.2, 121.6, 127.4, 131.7, 141.5, 166.8, 202.7; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for 315.0226 (^{79}Br) and 317.0206 (^{81}Br), found 315.0230 (^{79}Br) and 317.0208 (^{81}Br).

*Ethyl 5-Hydroxy-3-oxo-5-(thiophene-3-yl)pentanoate (**6k**).* The title compound was prepared according to the general procedure and isolated as a yellow oil (496.6 mg, 82% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 2.91 (dd, J = 17.0, 3.6 Hz, 1H), 2.99 (dd, J = 17.0, 8.8 Hz, 1H), 3.46 (s, 2H), 3.56 (brs, 1H), 4.16 (q, J = 7.1 Hz, 2H), 5.21 (dd, J = 8.8, 3.6 Hz, 1H), 7.03 (dd, J = 5.0, 1.3 Hz, 1H), 7.18−7.19 (m, 1H), 7.27 (dd, J = 5.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 49.8, 50.8, 61.5, 66.1, 121.0, 125.5, 126.3, 144.2, 167.1, 202.6; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{11}H_{15}O_4S$ 243.0686, found 243.0688.

*Ethyl (6E)-5-Hydroxy-3-oxo-7-phenylhept-6-enoate (**6l**).* The title compound was prepared according to the general procedure and isolated as a pale yellow oil (617.5 mg, 95% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.3 Hz, 3H), 2.86−2.87 (m, 2H), 2.96 (brs, 1H), 3.50 (s, 2H), 4.20 (q, J = 7.3 Hz, 2H), 4.79 (d, J = 6.0 Hz, 1H), 6.20 (dd, J = 15.9, 6.1 Hz, 1H), 6.63−6.66 (m, 1H), 7.24−7.26 (m, 1H), 7.29−7.32 (m, 2H), 7.36−7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 49.6, 50.0, 61.6, 68.4, 126.5, 127.8, 128.6, 129.9, 130.7, 136.4, 166.9, 202.7; HRMS (ESI-Orbitrap) m/z $[M + NH_4]^+$ calcd for $C_{15}H_{22}NO_4$ 280.1543, found 280.1543.

*Ethyl 5-Hydroxy-3-oxo-7-phenylheptanoate (**6m**).* The title compound was prepared according to the general procedure and isolated as a yellow oil (486.2 mg, 74% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 1.71−1.72 (m, 1H), 1.81−1.83 (m, 1H), 2.65−2.71 (m, 3H), 2.77−2.83 (m, 1H), 2.99 (brs, 1H), 3.44, 3.45 (ABq, J = 15.8 Hz, 2H), 4.08−4.12 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 7.16−7.20 (m, 3H), 7.26−7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 31.7, 38.1, 49.7, 49.9, 61.5, 66.8, 125.9, 128.43, 128.44, 141.7, 167.0, 203.6; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_4$ 265.1434, found 265.1435.

*Benzoic (Ethyl carbonic) Anhydride (**8**).* To a solution of benzoic acid (353.0 mg, 2.5 mmol) and THF (5 mL) was added triethylamine (253.0 mg, 2.5 mmol, 1 equiv). The mixture was cooled to 0−10 °C. Ethyl chloroformate (271.3 mg, 2.5 mmol, 1 equiv) was added to the mixture, and the solution was stirred for 0.5 h at the same temperature. The precipitate was filtered off and washed with THF (2 mL × 2). The combined filtrate was concentrated in vacuo to give the crude oil. The crude oil was used for further experiments without any purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.0 Hz, 2H), 7.49 (t, J = 7.9 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 8.08 (dd, J = 8.4, 1.7 Hz, 2H).

*Ethyl 3-Oxo-3-phenylpropanoate (**9**).* The title compound was prepared according to the general procedure (the reaction mixture diluted with EtOAc and aqueous citric acid (20%) was stirred overnight) (benzonitrile **27**, 257.6 mg, 2.5 mmol) and isolated as a light brown oil (410.0 mg, 85.3% yield)). Keto tautomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.3 Hz, 3H), 3.99 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 7.47 (t, J = 7.9 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.91−7.97 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 46.0, 61.4, 128.5, 128.8, 133.7, 136.1, 167.1, 192.5. Enol tautomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H), 4.26 (q, J = 7.1 Hz, 2H), 5.67 (s, 1H), 7.38−7.45 (m, 3H), 7.74−7.81 (m, 2H), 12.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 60.3, 87.4, 126.0, 128.5, 131.2, 133.5, 171.4, 173.2; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{11}H_{12}O_3$ 193.0859, found 193.0861. Analysis of the spectroscopic data matched reported data.[37]

*Zinc Complex of **3a** THF Solvate.* To a 100 mL round-bottom flask were added ca. 0.54 mol/L of ethyl bromozincacetate/THF solution (16.1 mL, ca. 8.7 mmol, 3.5 equiv) and 2-benzoylpyridine (**1a**) (458.0 mg, 2.5 mmol). The yellow solution was stirred at room temperature for 24 h. The white precipitate was collected by filtration, washed with THF (4 mL), and dried in vacuo at 50 °C to give a white crystalline solid: mp 209−210 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3H), 1.66−1.85 (m, 2H, 0.5THF), 2.68 (d, J = 12.6 Hz, 1H), 3.50−3.66 (m, 2H, 0.5THF), 3.82 (d, J = 12.6 Hz, 1H), 3.98 (dd, J = 10.9, 7.1 Hz, 1H), 4.14 (dd, J = 10.9, 7.1 Hz, 1H), 4.73 (s, 1H), 7.08−7.18 (m, 1H), 7.18−7.31 (m, 2H), 7.43−7.56 (m, 1H), 7.81 (d, J = 7.9 Hz, 2H), 8.01−8.13 (m, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.47 (dd, J = 5.2, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 25.1, 51.4, 59.7, 67.0, 78.8, 89.1, 123.5, 123.9, 126.1, 126.4, 127.5, 139.5, 146.3, 149.2, 164.8, 172.3, 182.6.

*Zinc Complex of **3a** Ethanol Solvate.* Zinc complex of **3a** THF solvate was dissolved in acetone and ethanol. The solvent was evaporated under atmospheric pressure to give a colorless single crystal: mp 206−207 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, J = 6.9 Hz, 1.5H, 0.5EtOH), 1.17 (t, J = 7.1 Hz, 3H), 2.72 (d, J = 12.6 Hz, 1H), 3.45 (qd, J = 7.0, 5.0 Hz, 1H, 0.5EtOH), 3.80 (d, J = 12.6 Hz, 1H), 3.91−4.08 (m, 1H), 4.08−4.26 (m, 1H), 4.74 (s, 1H), 7.08−7.20 (m, 1H), 7.20−7.34 (m, 2H), 7.42−7.60 (m, 1H), 7.79 (d, J = 7.9 Hz, 2H), 8.01−8.17 (m, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.39−8.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.5, 51.3, 56.0, 59.8, 78.8, 89.1, 123.6, 124.0, 126.1, 126.4, 127.6, 139.6, 146.4, 149.2, 164.8, 172.4, 182.6. Crystal structure: see the Supporting Information (CCDC-923389).

■ ASSOCIATED CONTENT

Supporting Information

Additional studies on the reaction promotion factors; copies of ^{1}H NMR and ^{13}C NMR data for all new compounds and HMBC and HMQC spectra of zinc complex of **3a** THF solvate; X-ray crystallographic data (CIF) and ORTEP plot for the zinc complex of **3a** ethanol solvate. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(33) Details are described in the Supporting Information, including a CIF and an ORTEP plot. Additionally, CCDC-923389 contains all crystallographic data of this publication and is available free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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