PAPER

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Synthesis of α-chloro-β-ketoesters *via* ytterbium (III) triflate-mediated decarboxylative Claisen-type condensation

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A Yb(OTf)$_3$-mediated decarboxylative Claisen-type condensation is established to access α-chloro-β-ketoesters. Operating under mild conditions, this method delivers products in 78–95% yields while circumventing the functional-group incompatibility and side reactions associated with conventional electrophilic chlorination of β-ketoesters. The synthetic utility of this method is further demonstrated by the synthesis of chlorinated 2-pyrones and asperphenylpyrone analogues, highlighting its potential for constructing structurally diverse and bioactive molecules.

Introduction

α-Chloro-β-ketoesters are widely used intermediates and building blocks in organic synthesis owing to their high reactivity. They serve as key precursors to bioactive chlorine-containing compounds, such as 3-chlorocoumarins,[1] 4-chloro-1,2-dithiole-3-thiones,[2] and 5-chloropyrimidines.[3] Thanks to the high reactivity of chlorine towards substitution, they have also been used for constructing aromatic heterocycles, including thiazoles,[4] imidazoles,[5] 1,2,4-triazoles,[6] furans,[7] and imidazopyridines.[8]

The synthesis of α-chloro-β-ketoesters is typically achieved through direct chlorination of β-ketoesters using electrophilic chlorinating reagents (Scheme 1a), such as SO$_2$Cl$_2$,[9] *N*-chlorosuccinimide (NCS),[10] 1,3-dichloro-5,5-dimethylhydantoin,[11] trichloroisocyanuric acid,[12] NH$_4$Cl/O$_3$,[13] HCl/PhIO,[14] and HCl/Cu(OTf)$_2$.[15] However, these methods often suffer from poor selectivity for α-monochlorination, affording mixtures of α-mono- and α,α-dichlorinated products, and exhibit limited functional-group compatibility under the required harsh acidic or oxidizing conditions. Consequently, there remains a clear need for the development of an efficient and versatile synthetic route to α-chloro-β-ketoesters.

One feasible alternative strategy involves the Claisen condensation, employing chloroacetates or their equivalents. However, this approach has rarely been explored, not only due to the challenges posed by undesired self-condensation, but also due to complications induced by the α-chlorine under typical Claisen condensation conditions, such as dechlorina-

tion.[16] In the 1980s, the Claisen condensation approach was first applied by Tanabe and Mukaiyama, to obtain a specific α-chloro-β-ketoester.[17,18] Despite the low yield of 45%, they successfully prevented the loss of the base-sensitive α-chlorine by using Lewis acid TiCl$_2$(OTf)$_2$. In 2023, Presset and coworkers reported a Grignard reagent-mediated decarboxylative Claisen-type condensation method to access α-substituted β-ketoesters (Scheme 1b).[19] By employing magnesium enolates of substituted malonic acid half oxyesters,[20] they demonstrated the synthesis of a variety of α-substituted β-ketoesters, including one α-chloro-β-ketoester obtained in 91% yield. Nevertheless, the method also exhibits inherent limitations, particularly its poor functional-group compatibility and the tendency to induce halogen loss, arising from the harsh conditions provided by Grignard reagents.
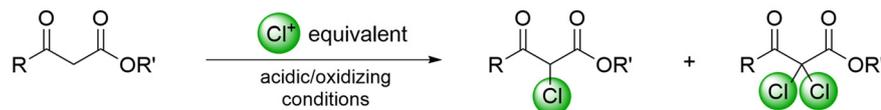
Given these precedents, we envisioned establishing an efficient synthetic method for α-chloro-β-ketoesters through decarboxylative Claisen-type condensation under mild Lewis acidic conditions. In our previous work, the superior compatibility and reactivity of Lewis acid Mg(OTf)$_2$ compared to Grignard reagents have been demonstrated for the construction of β-keto thioesters *via* decarboxylative Claisen-type condensation of malonic acid half thioesters (MAHTs).[21] Iterative application of this method further enabled the construction of various naturally occurring polyketides, including 2-pyrone derivatives (Scheme 1c). On the other hand, a preliminary result reported by Presset and co-workers on the synthesis of α-substituted β-ketoesters showed that Mg(OTf)$_2$ is ineffective in mediating the decarboxylative Claisen-type condensation of substituted malonic acid half oxyesters.[19]

In this study, we present a comprehensive investigation on Lewis acid-mediated decarboxylative Claisen-type condensation of chlorinated malonic acid half oxyester (Cl-MAHO)

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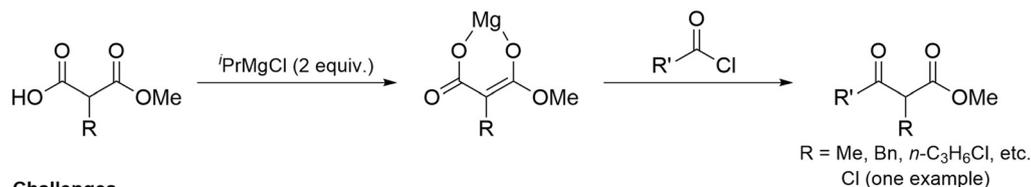
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a) Current electrophilic chlorinating strategies

Challenges
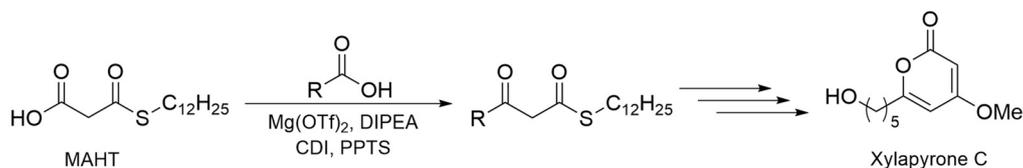- Poor selectivity for α-monochlorination
- Incompatible with functional groups

b) Grignard reagent-mediated decarboxylative condensation (*ref. 19*)

R = Me, Bn, *n*-C₃H₆Cl, etc.
Cl (one example)

Challenges
- Poor functional group compatibility
- Competitive magnesium–halide exchange reaction

c) Lewis acid-mediated decarboxylative condensation of MAHT (*ref. 21*)

MAHT

Xylapyrone C

d) Lewis acid-mediated decarboxylative condensation of Cl-MAHO (**This work**)

Cl-MAHO

14 examples, up to 95% yields

Chlorinated 2-pyrone
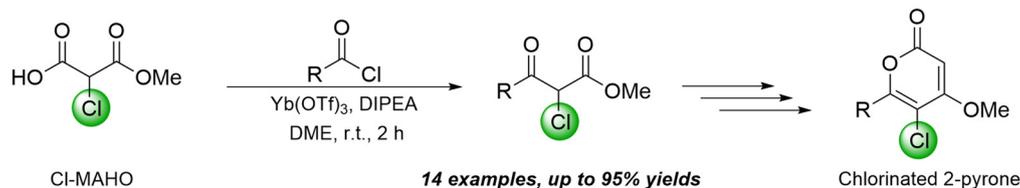
- ✔ Chlorinating reagent-free
- ✔ Mild conditions
- ✔ Broad functional group compatibility
- ✔ Easily applied to synthesis of bioactive compounds

Scheme 1 Strategies for the synthesis of α-chloro-β-ketoesters and decarboxylative Claisen-type condensation reaction.

(Scheme 1d). This approach represents, to our knowledge, the first versatile alternative to electrophilic α-chlorination for the synthesis of α-chloro-β-ketoesters. Furthermore, we showcase the utility of this method and α-chloro-β-ketoesters by synthesizing chlorinated 2-pyrones and asperphenylpyrone analogues.
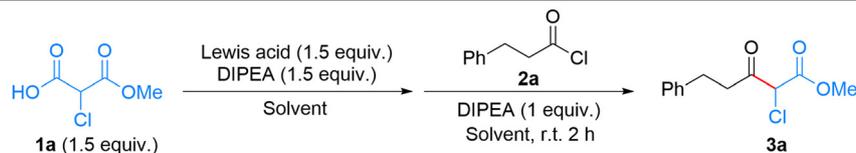
Results and discussion

Our study initially focused on the reaction between Cl-MAHO **1a** and 3-phenylpropionic acid.[22] As Claisen acceptors, combinations of carboxylic acids and coupling reagents have proven effective in our previous work and related decarboxylative Claisen-type condensation reactions.[21,23–26] However, in the present case, none of the coupling reagents examined afforded

the α-chloro-β-ketoester **3a** in yields exceeding 35%, even when mediated by a Grignard reagent (Table S1). This poor reactivity is presumably attributable to the steric and inductive effects of the α-chlorine substituent, which reduce the nucleophilicity of **1a** toward the Claisen acceptor.[27,28]

We then altered the Claisen acceptor with 3-phenylpropionyl chloride (**2a**). The decarboxylative Claisen-type condensation between **1a** and **2a**, mediated by the Grignard reagent *i*PrMgBr, afforded **3a** in 73% yield (Table 1, entry 1). Subsequently, studies regarding Lewis acids were performed. Instead of the Grignard reagent, a Lewis acid and an external base were employed in order to generate a metal–ester enolate complex from **1a**, which was expected to further react with **2a** to afford **3a**. We screened several magnesium salts as Lewis acids for their effectiveness in the reaction. Compared to *i*PrMgBr, the combinations of Mg(OTf)₂, MgCl₂, and MgBr₂

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Table 1 Optimization of reaction conditions

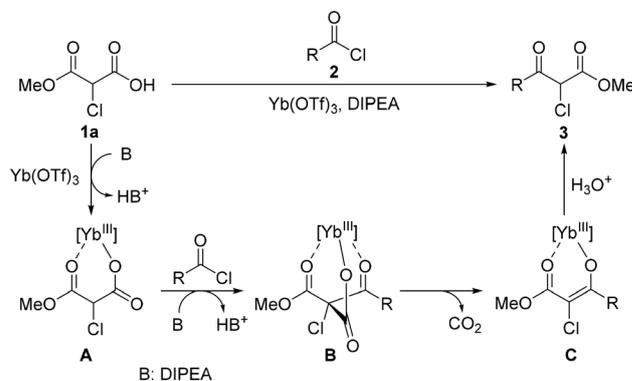| Entry	Lewis acid	Solvent	Yield[a] [%]
1	^{i}PrMgBr	DME	73
2	Mg(OTf)$_2$	DME	48
3	MgCl$_2$	DME	55
4	MgBr$_2$	DME	62
5	LiCl	DME	3
6	ZnCl$_2$	DME	n.r.[b]
7	Cu(OTf)$_2$	DME	n.r.
8	Sc(OTf)$_3$	DME	Trace
9	CeCl$_3$	DME	Trace
10	La(OTf)$_3$	DME	79
11	Eu(OTf)$_3$	DME	77
12	**Yb(OTf)$_3$**	**DME**	**81**
13	Lu(OTf)$_3$	DME	62
14	Yb(OTf)$_3$	DCM	3
15	Yb(OTf)$_3$	MeCN	32
16	Yb(OTf)$_3$	THF	43
17	Yb(OTf)$_3$	Dioxane	42
18[c]	Yb(OTf)$_3$	DME	72
19[d]	Yb(OTf)$_3$	DME	79
20[e]	**Yb(OTf)$_3$**	**DME**	**89 (86)[f]**

[a] Yields were determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [b] n.r.: no reaction. [c] DMAP was used instead of DIPEA. [d] DBU was used instead of DIPEA. [e] Yb(OTf)$_3$ (2 equiv.), **1a** (2 equiv.), and DIPEA (2 equiv. + 1 equiv.) were used. [f] Isolated yield.

with N,N-diisopropylethylamine (DIPEA) showed reduced reactivity, giving **3a** in 48%, 55%, and 62% yields, respectively (entries 2–4). Moreover, reactions employing other Lewis acids did not proceed (entries 5–9), and the acyl chloride **2a** was recovered as the corresponding carboxylic acid after aqueous workup. The ineffectiveness of common metal salts prompted us to explore lanthanoid Lewis acids.[29] Indeed, several lanthanoid triflates effectively mediated the reaction (entries 10–13), among which Yb(OTf)$_3$ afforded the highest yield of **3a** (81%, entry 12). This enhanced performance likely reflects the optimal balance of ionic radius, Lewis acidity, and oxophilicity of the ytterbium(III) ion in promoting this reaction.[30,31]

Subsequently, we evaluated the effects of other reaction parameters. The investigation on a series of solvents revealed the essentialness of 1,2-dimethoxyethane (DME), as other common solvents diminished the yield significantly (entries 14–17). We speculate that DME functions not only as a solvent but also as a bidentate ligand that forms five-membered chelate rings with Yb(OTf)$_3$.[32,33] Such chelation may restrict excessive substrate coordination and suppress unproductive *trans*-coordination between reaction partners on the ytterbium center, thereby driving the reaction toward product formation. The use of other bases such as 4-(dimethylamino)pyridine (DMAP) (entry 18) and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (entry 19) instead of DIPEA showed no significant effect on yield. Further investigation of reaction stoichiometry (Table S2) showed that using two equivalents of the metal–

ester enolate complex (the combination of Cl-MAHO, Yb (OTf)$_3$, and DIPEA) increased the yield to 89% (entry 20).

Based on literature precedents,[27,34–36] a plausible mechanism for this reaction (Scheme 2) is proposed; it involves the initial formation of the Yb(III)–Cl-MAHO carboxylate **A**, followed by deprotonation to generate a nucleophilic species that reacts with acyl chloride **2** to afford intermediate **B**. Subsequent decarboxylation is envisaged to occur after the formation of the C(Cl)–C bond, and aqueous workup finally furnishes the α-chloro-β-ketoester **3**. Notably, a total of 3 equivalents of DIPEA was employed (Table S2, entry 7), which may

Scheme 2 Mechanistic hypothesis for the formation of the products.

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serve to deprotonate the carboxylic acid moiety of Cl-MAHO (**1a** → **A**) and to scavenge the HCl generated during the C(Cl)–C bond formation step (**A** → **B**).

With the optimal conditions in hand, we then investigated the scope and generality of acyl chloride **2** in this reaction. As shown in Table 2, a scale-up experiment was performed with 5 mmol of **2a**, which provided product **3a** (0.98 g) in 82% yield. A series of benzoyl chlorides bearing various functional groups, such as nitro,[19] chloro, bromo, trifluoromethyl, and methoxy groups,[37] at the *m*-/*p*-positions smoothly afforded the corresponding α-chloro-β-ketoesters **3b–h** in good yields, ranging from 80 to 95%. In contrast, sterically demanding acyl chlorides, such as *o*-methylbenzoyl chloride and 1-naphthoyl chloride, provided the desired products **3i** and **3j** only in 1% and 10% yields, respectively. We speculate that the key ytterbium complex intermediate is highly sterically demanding, such that

acyl chlorides with substituents near the reaction center are likely to hinder the C–C bond formation with **1a**. By comparison, this steric effect was much less pronounced in the magnesium-based Lewis acid-mediated reaction. Replacing Yb (OTf)$_3$ with MgCl$_2$ furnished **3i** and **3j** in 51% and 58% yields, respectively. This result is consistent with the lower coordination number and less sterically congested coordination environment typically associated with the magnesium ion.[38,39]

We next applied this method to the synthesis of α-chloro-β-ketoesters that are considered to be challenging to access under previously reported acidic/oxidizing conditions. Heteroaryl-substituted products, such as **3k** and **3l**, were obtained in 94% and 80% yields, respectively. Cinnamoyl chloride, which bears a conjugated double bond, was also compatible, affording the unsaturated α-chloro-β-ketoester **3m** in 81% yield. The oxidation-sensitive *S*-dodecyl-Cl-MAHT (**1b**) gave the α-chloro-β-ketothioester **3n** in 87% yield.[40] Moreover, this method is amenable to iterative application, allowing sequential extension of the α-chlorocarbonyl chain. For example, a second decarboxylative Claisen-type condensation using α-chloroacyl chloride **2o**, prepared from **3a**, afforded the α,γ-dichloro-β-ketoester **3o** in 78% yield. The successful synthesis of these compounds demonstrates the broad compatibility and distinct advantage of our approach. Notably, no halogen loss was observed for the α-halogenated aliphatic substrate **2o**, nor for aromatic substrates bearing halogen substituents (Br: **2g**; Cl: **2d** and **2h**), in sharp contrast to Grignard reagent-mediated reactions.[19]

Encouraged by the success of this method in the synthesis of α-chloro-β-ketoesters, we also explored its feasibility with monomethyl bromomalonate (Br-MAHO, **1c**) (Tables S3 and S4). By extending the reaction time to 24 h, α-bromo-β-ketoester **3p** was synthesized in 56% yield from benzoyl bromide **2p**.

Next, the synthetic versatility of our method was showcased by transforming the α-chloro-β-ketoester **3l** into synthetically challenging biheteroaryl compounds.[41,42] As shown in Scheme 3, the Pechmann condensation of **3l** with *m*-cresol afforded the coumarin derivative **4** in 79% yield.[43] In addition, the reaction of **3l** with thiobenzamide furnished the thiazole derivative **5** in 76% yield.[44] These transformations highlight a straightforward route to valuable, functionalized pharmacophore scaffolds.[45–48]

Furthermore, we applied the present method to the construction of chlorinated 2-pyrones and their derivatives. Chlorinated 2-pyrones have recently attracted great interest for their potential bioactivities[49,50] and synthetic utilities.[51–53] Despite extensive research on 3-chloro-2-pyrones,[54,55] both the synthesis and application of 5-chloro-2-pyrones remain unexplored, likely owing to the inherently higher reactivity of the C-3 position of 2-pyrones toward electrophilic chlorination. On the basis of our previously reported strategy for polyketide synthesis, we envisioned that 5-chloro-2-pyrones can be accessed by integrating the present method into the iterative chain-elongation sequence.[25,26]

The synthesis commenced from α-chloro-β-ketoester **3a** (Scheme 4). To construct the triketide-derived 2-pyrone core, an additional iteration of the decarboxylative condensation

Table 2 Substrate scope of the reaction[a]
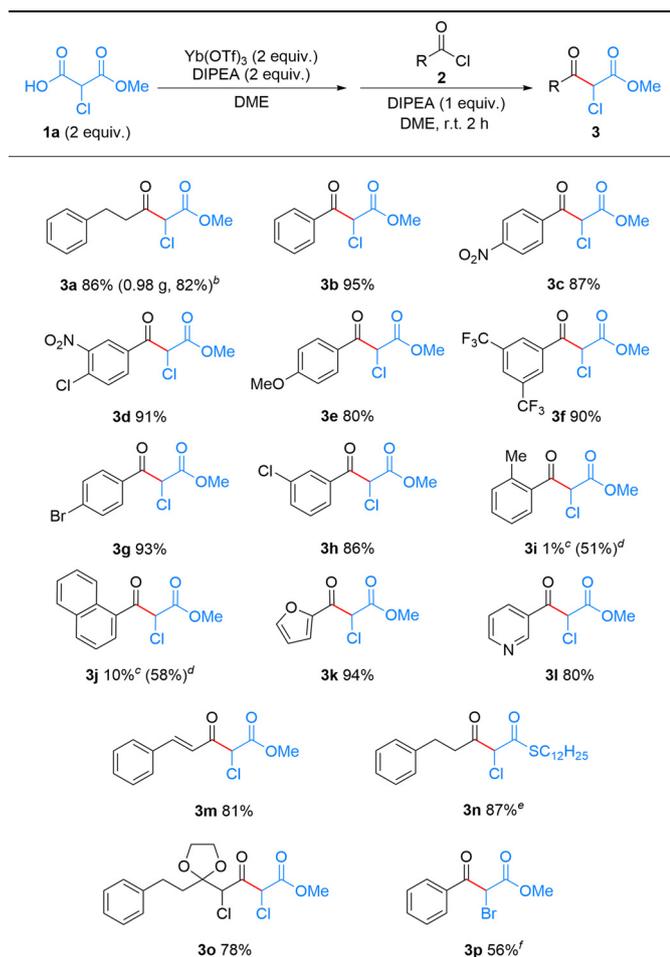
[a] Unless otherwise specified, all reactions were carried out on a 0.1 mmol scale, and isolated yields are provided. [b] The reaction was performed on a 5 mmol scale of **2a**. [c] ^{1}H NMR yield (determined using 1,4-dimethoxybenzene as an internal standard). [d] MgCl$_2$ was used instead of Yb(OTf)$_3$. [e] *S*-Dodecyl-Cl-MAHT **1b** was used instead of Cl-MAHO **1a**. [f] Br-MAHO **1c** and benzoyl bromide were used instead of Cl-MAHO **1a** and benzoyl chloride. The reaction time was 24 h.
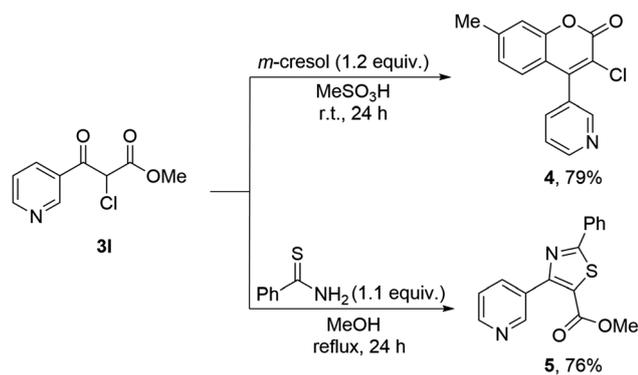
**Scheme 3** Synthesis of coumarin and thiazole derivatives.

was required. Treatment of **3a** with (trimethylsilyl)diazomethane (TMSCHN$_2$) smoothly afforded a mixture of *E*- and *Z*-isomers of methyl enol ether **6**, which was then subjected to the ester hydrolysis.[56–59] Recrystallization of the crude hydrolysis product provided the corresponding *Z*-configured carboxylic acid **7** in 55% yield. Subsequent decarboxylative condensation of **7** with *S*-dodecyl-MAHT furnished the triketide

linear precursor **8**. Acidic hydrolysis of the methyl enol ether followed by DBU-promoted Claisen-type lactonization generated the unstable intermediate 5-chloro-4-hydroxy-2-pyrone **9**. Final methylation of the 4-hydroxy group of **9** yielded 5-chlorinated dihydro-5,6-dehydrokavain (DDK) **10**. In total, starting from α-chloro-β-ketoester **3a**, this five-step procedure succeeded in the synthesis of 5-chlorinated DDK **10** with an overall yield of 34%.

Then, a series of derivatization reactions of **10** were investigated (Scheme 5). First, we took a closer look at the reaction conditions for the Suzuki–Miyaura coupling between **10** and (4-methoxyphenyl)boronic acid. It was found that the Buchwald phosphine ligand XPhos shows its efficiency in this reaction, which proceeded to provide 5-aryl DDK **11** in 89%.[60] Next, we attempted a modification of the C-3 position of **10**. In the presence of a catalytic amount of trifluoroacetic acid (TFA), treating **10** with *N*-bromosuccinimide (NBS) smoothly yielded 3-bromo-5-chlorinated DDK **12b** in 91%. Likewise, 3,5-dichlorinated DDK **12a** was obtained in 96% yield using NCS. Finally, sequential Suzuki–Miyaura couplings were performed on the different halogen-substituted DDK **12b**, giving asperphenylpyrone analogue **14** in 64% yield.[61]
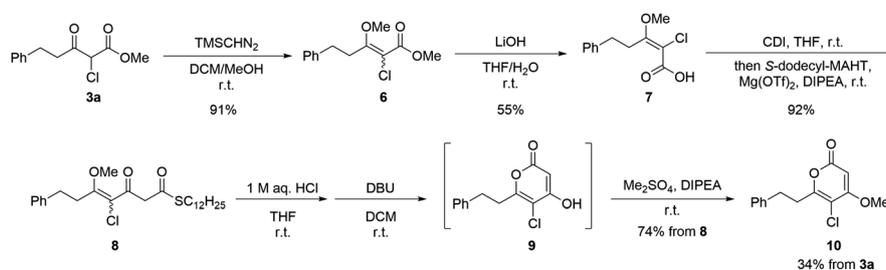
Scheme 4 Synthesis of 5-chloro-2-pyrone **10**.
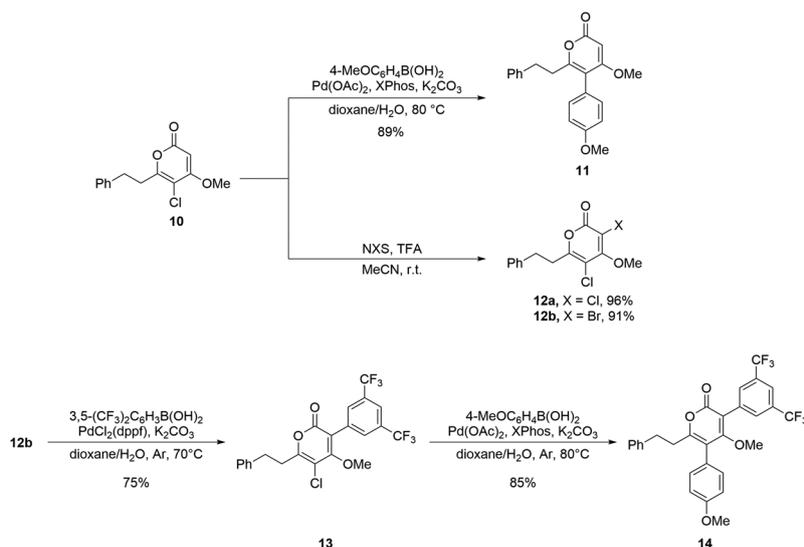
Scheme 5 Derivatization of 5-chloro-2-pyrone **10** and synthesis of its asperphenylpyrone analogue.

Conclusions

In summary, we have developed an efficient method for synthesizing α-chloro-β-ketoesters through Yb(OTf)$_3$-mediated decarboxylative Claisen-type condensation of Cl-MAHO. This strategy exhibits broad compatibility with a variety of functional groups and delivers yields of up to 95%. A comprehensive investigation of the reaction conditions revealed that both Yb(OTf)$_3$ and DME are crucial for this transformation. The synthetic utilities of this strategy and the resulting α-chloro-β-ketoesters were demonstrated by the synthesis of coumarin and thiazole derivatives, 5-chloro-2-pyrone DDK and its derivatives. Overall, the present strategy circumvents the challenges of electrophilic chlorination, providing a complementary approach to existing methods and expanding the synthetic toolbox for the construction of chlorine-containing molecules.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5ob01966d.

CCDC 2502623 contains the supplementary crystallographic data for this paper.[62]

Acknowledgements

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