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An *in situ* masking strategy enables radical monodecarboxylative C–C bond coupling of malonic acid derivatives†

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The utilization of malonic acids in radical decarboxylative functionalization is still underexploited, and the few existing examples are primarily limited to bisdecarboxylative functionalization. While radical monodecarboxylative functionalization is highly desirable, it is challenging because of the difficulty in suppressing the second radical decarboxylation step. Herein, we report the successful radical monodecarboxylative C–C bond coupling of malonic acids with ethynylbenziodoxolone (EBX) reagents enabled by an *in situ* masking strategy, affording synthetically useful 2(3*H*)-furanones in satisfactory yields. The keys to the success of this transformation include (1) the dual role of a silver catalyst as a single-electron transfer catalyst to drive the radical decarboxylative alkynylation and as a Lewis acid catalyst to promote the 5-*endo*-*dig* cyclization and (2) the dual function of the alkynyl reagent as a radical trapper and as an *in situ* masking group. Notably, the latent carboxylate group in the furanones could be readily released, which could serve as a versatile synthetic handle for further elaborations. Thus, both carboxylic acid groups in malonic acid derivatives have been well utilized for the rapid construction of molecular complexity.

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Introduction

Recently, the radical decarboxylative functionalization (RDF) has appeared as a robust tool to rapidly increase molecular complexity, in which a variety of monocarboxylic acids, such as fatty acids, amino acids and α-oxocarboxylic acids, have been extensively exploited as promising alkyl radical precursors for a diverse array of radical C–C and C–heteroatom coupling reactions (Fig. 1a).[1–4] Malonic acid derivatives, which bear two carboxylic acid groups on the same carbon atom, are fundamental building blocks in organic chemistry. However, the development of corresponding RDFs of readily accessible malonic acid derivatives is still in its infancy. The underdevelopment of malonic acids in RDFs probably stems from their increased oxidation potential and the chemoselectivity issue with respect to mono- and bisdecarboxylation.[5,6] Prior work demonstrated the latent capacity of utilizing malonic acid derivatives in RDFs, with sporadic examples focusing exclusively on bisdecarboxylative functionalizations, such as the double Hunsdiecker reaction,[7] oxidative decarboxylation[8] and hydrodecarboxylation reaction,[5] by which two identical functional groups could be introduced on the same carbon atom (Fig. 1b). Although radical monodecarboxylative

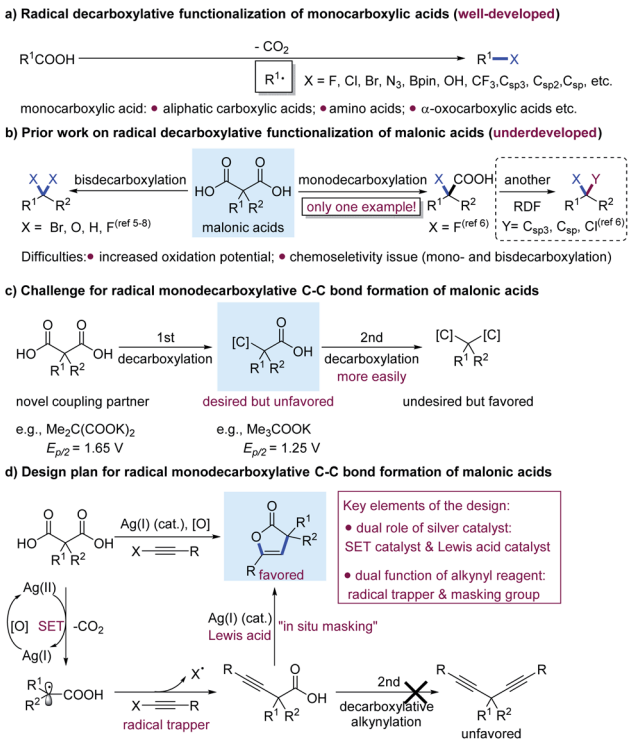

Fig. 1 Radical decarboxylative functionalization of carboxylic acids.

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functionalization of malonic acids is highly desirable, it is still largely elusive. Our group recently discovered a chemoselective mono- and bisdecarboxylative fluorination of malonic acids, providing unprecedented entry to either *gem*-difluoroalkanes or α-fluorocarboxylic acids (Fig. 1b).[6] The effectiveness of α-fluorocarboxylic acid products to generate more diverse compounds *via* another RDF highlighted the benefits of implementing monodecarboxylative functionalization. As such, the development of a novel and chemoselectivity-controlled radical monodecarboxylative functionalization of malonic acid derivatives would find broad appeal, as the remaining carboxylic acid group in the product would serve as a versatile platform for the rapid buildup of molecular complexity.

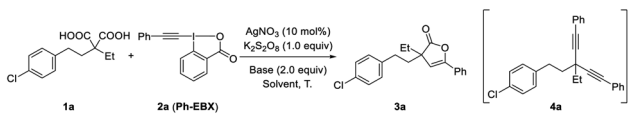
Encouraged by the significant advancements of radical decarboxylative C–C coupling of monocarboxylic acids,[1,2,4] we are interested in exploiting malonic acid derivatives as novel C_{sp^3} coupling partners for C–C bond formation by taking advantage of a radical strategy. However, in the oxidative decarboxylation scenario, synthetically desired monodecarboxylative functionalization products with relatively low oxidation potential compared with that of malonic acid derivatives[9] are highly prone to undergo second radical decarboxylation, affording synthetically less useful bisdecarboxylation products (Fig. 1c). As a result, the realization of controllable radical monodecarboxylative C–C bond coupling of malonic acids represents a challenging goal. To achieve this aim, we hypothesized that the second decarboxylation reaction might be suppressed by masking the remaining carboxylate with an appropriate functionality that was introduced by the first RDF of malonic acids. Inspired by the unique properties of silver catalysts, such as their strong oxidant[1f] and Lewis acidity, as well as, in particular, their alkynophilicity,[10] an *in situ* masking plan was proposed, as shown in Fig. 1d. Malonic acids could be oxidized by Ag(II) (E° = 1.98 V, Ag^{2+}/Ag^{+})[11] *via* single-electron transfer[6] after CO_2 extrusion to deliver α-carboxylic acid radicals. Despite the lack of precedent, we proposed that the newly generated nucleophilic radical could be trapped by an alkynyl reagent to afford an α-alkynyl carboxylate.[12] The remaining carboxylate would be rapidly intercepted by the alkynyl group in the presence of a silver catalyst *via* 5-*endo-dig* cyclization.[13] Thus, the undesired second decarboxylation could be well obviated, with 2(3*H*)-furanones obtained as the final products. Of note, 2(3*H*)-furanone is not only a structural motif widely found in natural products[14] but also an important building block in organic synthesis.[15] Precedent reports for their syntheses rely heavily on the transformations of specific precursors, which often require multistep preparation.[13a,16] Therefore, the development of practical methods for the assembly of 2(3*H*)-furanones from readily accessible precursors is also desirable.

Herein, we present the successful controllable radical monodecarboxylative C–C bond coupling of malonic acid derivatives for the first time, providing an unprecedented route to a variety of 2(3*H*)-furanones bearing all-carbon quaternary centers. Notably, the latent carboxylic acid group in the product could be readily released, which may act as a versatile synthetic handle for further manipulations.

Results and discussion

To validate our hypothesis, we initiated our investigations with the reactions of 2-(4-chlorophenethyl)-2-ethylmalonic acid (**1a**) and phenylethynylbenziodoxolone (**2a**) in the presence of $AgNO_3$

Table 1 Optimization of reaction conditions[a]



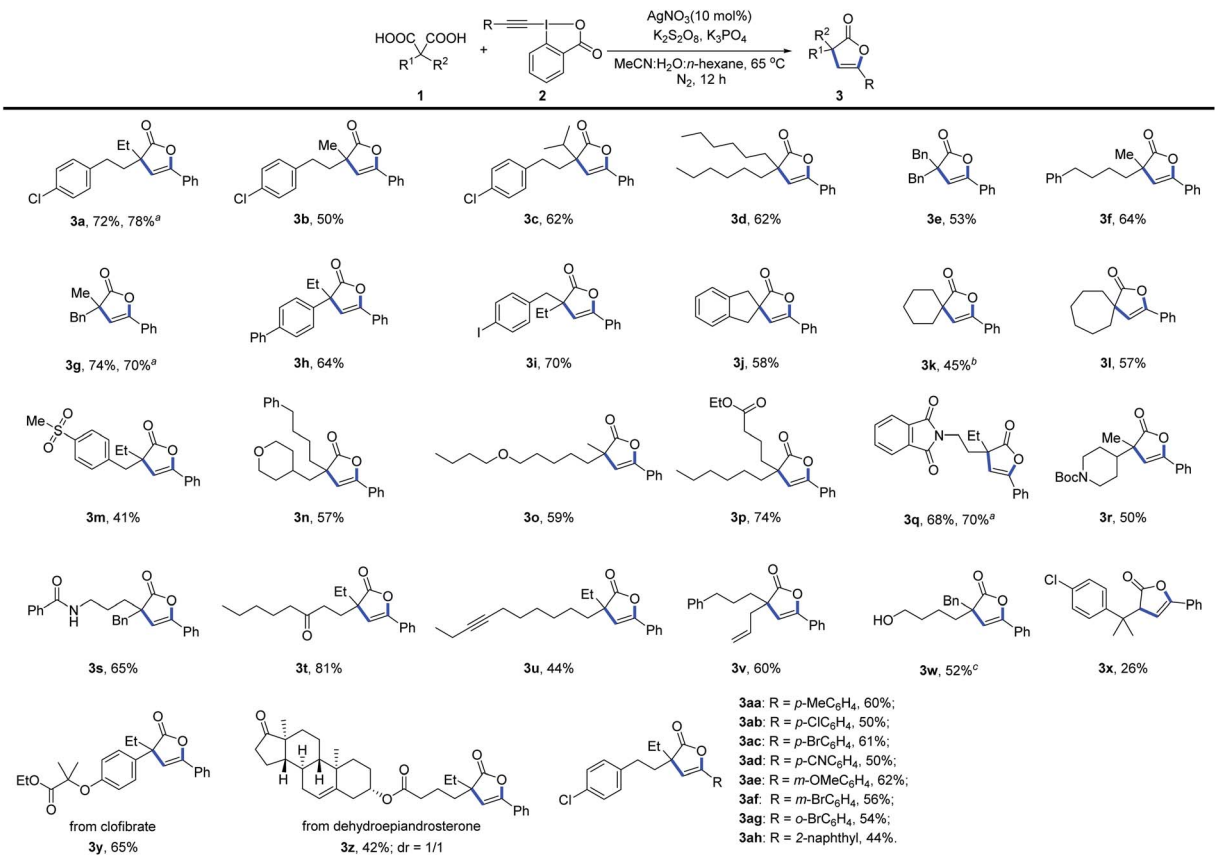
Entry	Base	Ph-EBX (equiv.)	Solvent (v/v)	T (°C)	Yield of **3a**[b] (%)
1	—	1.0	MeCN : H_2O = 1 : 1 (4 mL)	50	0
2	—	1.0	Acetone : H_2O = 1 : 1 (4 mL)	50	0
3	—	1.0	DMF : H_2O = 1 : 1 (4 mL)	50	0
4	PhCOOK	1.0	MeCN : H_2O = 1 : 1 (4 mL)	50	5
5	KF	1.0	MeCN : H_2O = 1 : 1 (4 mL)	50	8
6	K_2HPO_4	1.0	MeCN : H_2O = 1 : 1 (4 mL)	50	30
7	K_2CO_3	1.0	MeCN : H_2O = 1 : 1 (4 mL)	50	10
8	KOH	1.0	MeCN : H_2O = 1 : 1 (4 mL)	50	42
9	K_3PO_4	1.0	MeCN : H_2O = 1 : 1 (4 mL)	50	42
10	K_3PO_4	1.0	Acetone : H_2O = 1 : 1 (4 mL)	50	27
11	K_3PO_4	1.0	DMF : H_2O = 1 : 1 (4 mL)	50	35
12	K_3PO_4	1.0	*n*-Hex : H_2O = 1 : 1 (4 mL)	50	16
13	K_3PO_4	1.5	MeCN : H_2O : *n*-Hex = 1 : 3 : 4 (8 mL)	65	72
14[c]	K_3PO_4	1.5	MeCN : H_2O : *n*-Hex = 1 : 3 : 4 (8 mL)	65	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2–0.3 mmol), $AgNO_3$ (0.02 mmol), $K_2S_2O_8$ (0.2 mmol), base (0.4 mmol), solvent under N_2 at 50 °C or 65 °C for 12 h. [b] Isolated yield. [c] Without $AgNO_3$. *n*-Hex = *n*-hexane.

(10 mol%) and $K_2S_2O_8$ (1.0 equiv.) in aqueous acetonitrile, acetone or dimethylformamide (DMF) at 50 °C for 12 h.[4a] Unfortunately, no desired 2(3*H*)-furanone derivative **3a** was formed in any of the cases (Table 1, entries 1–3). A mass balance study of the reaction in aqueous acetonitrile was carried out, and only 11% yield of **1a** was recovered, along with isolation of less than 5% yield of bisdecarboxylative alkynylation product **4a**, which suggested that decomposition of starting material **1a** occurred. Given the elusive chemistry of malonic acids in RDFs, the generation of **4a** is exciting, implying the feasibility of the radical decarboxylative alkynylation of malonic acids. However, to achieve monodecarboxylative C–C bond coupling, a compatible set of reaction conditions between Ag-catalyzed decarboxylative alkynylation and 5-*endo-dig* cyclization has to be exploited.

Recently, the Nicewicz group and our group demonstrated that bases played a substantial role in the hydrodecarboxylation[5] and decarboxylative fluorination[6] of malonic acids, respectively. Accordingly, the influence of different bases on the reaction was examined in the present study. To our delight, after the addition of PhCOOK to the reaction (entry 4), product **3a** was obtained for the first time, albeit in a low yield. Further screenings revealed that with increasing basicity of the additive, the yield of product **3a** also increased (entries 5–9). When KOH or K_3PO_4 was employed, **3a** was produced in 42% yield (entries 8 and 9). With K_3PO_4 as the optimal base, changing the mixed solvent to acetone/H_2O, DMF/H_2O or *n*-hexane/H_2O decreased the yield (entries 10–12). Silver catalysts such as Ag_2O, $AgClO_4$, Ag_2CO_3 and AgF were also examined in aqueous acetonitrile with K_3PO_4 as the base, and the product **3a** was obtained in yields ranging from 32–40% (see ESI† for details). Furthermore, replacement of the alkynylating agent **2a** with phenylethynyl halides (Cl or Br), or phenyl phenylethynyl sulfone compromised the reaction efficiency dramatically, and only trace amounts of product were observed. Ultimately, careful examinations of the substrate ratio, solvent and temperature revealed that the yield of **3a** could be increased to 72% (entry 13); meanwhile, only a trace amount of bisalkynylation product **4a** was observed. A control experiment showed that $AgNO_3$ was essential for this reaction (entry 14).

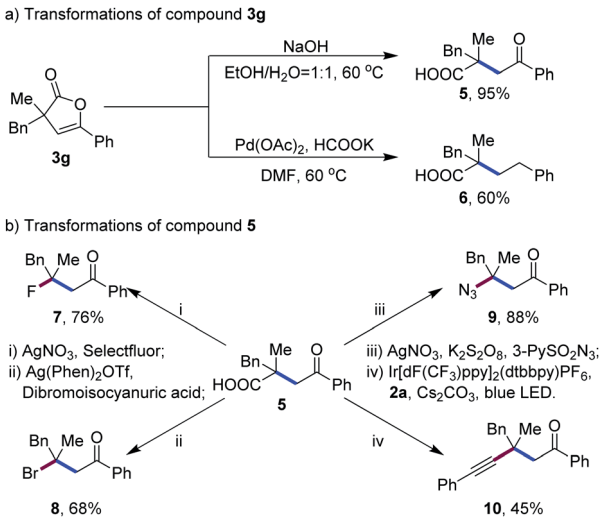
With the optimized conditions in hand, the diversity of malonic acids was first evaluated (Scheme 1). Various dialkyl-substituted malonic acids served as viable C–C bond coupling precursors for this Ag-catalyzed tandem decarboxylative alkynylation and 5-*endo-dig* cyclization, efficiently affording 2(3*H*)-furanones containing quaternary carbon centers in moderate to good yields. Even malonic acid with steric hindrance at the α-position was applicable for this reaction, delivering product **3c** in 62% yield. Aryl- and alkyl-substituted malonic acids are



Scheme 1 Reaction scope. Unless otherwise noted, all experiments were performed with **1** (0.2 mmol), **2** (0.3 mmol), $AgNO_3$ (0.02 mmol), $K_2S_2O_8$ (0.2 mmol), K_3PO_4 (0.4 mmol), CH_3CN (1.0 mL), H_2O (3.0 mL), and *n*-hexane (4.0 mL), 65 °C, under N_2 for 12 h. Yields of isolated products are listed. [a]Gram-scale reaction. [b]30 mol% AgF was used instead of $AgNO_3$. [c]0.1 mmol $K_2S_2O_8$ was used, and the reaction time was reduced to 6 h.

susceptible to bisdecarboxylative functionalizations due to stabilization of the corresponding benzylic radicals generated under oxidative conditions,[6] but with the present *in situ* masking strategy, 2(3*H*)-furanones (**3h** and **3y**) instead of bisdecarboxylative alkynylation products were produced exclusively. Additionally, the performance of cyclic malonic acids was examined, and the reaction of cyclohexane-1,1-dicarboxylic acid under the optimized conditions produced rigid spiro-β,γ-unsaturated-γ-lactone **3k** in 20% yield, along with a 20% yield of the bisdecarboxylative alkynylation product. This is the first time that we isolated a bisalkynylated product in an appreciable amount. However, simply changing the reaction conditions improved the yield of **3k** to 45%, accompanied by a 10% yield of the bisdecarboxylation product. In contrast to the reaction with the six-membered cyclic malonic acid, the reactions of five- and seven-membered cyclic malonic acids proceeded smoothly, delivering the corresponding spiro products **3j** and **3l** in 58% and 57% yields, respectively; only trace amounts of bisalkynylated products were observed. It is worth noting that the spiro-β,γ-unsaturated-γ-lactone unit is widely present in natural products.[14] Furthermore, this mild transformation could accommodate a number of functional groups, including aryl halide (**3a–3c**, **3i**), ether (**3n** and **3o**), phthalimide (**3q**), distal alkyne (**3u**), amide (**3r** and **3s**), sulfone (**3m**), ester (**3p**) and ketone (**3t**) groups. Notably, functionalities such as alkenyl and hydroxyl groups susceptible to oxidative conditions remained intact in the system (**3v** and **3w**). The excellent functional group compatibility of this reaction encouraged us to test this protocol in complex molecular settings. Gratifyingly, malonic acids derived from clofibrate and dehydroepiandrosterone were also suitable, producing products **3y** and **3z** in 65% and 42% yields, respectively. At the present stage, the substrate scope with respect to malonic acid derivatives is restricted mainly to *gem*-disubstituted derivatives. The reason is presumably that the *gem*-disubstituents can not only stabilize the α-carboxylic acid radical but also promote 5-*endo-dig* cyclization *via* the Thorpe–Ingold effect.[17] The reaction of monosubstituted malonic acid with **2a** was also examined, but only those with sterically encumbered groups at the α-position could afford product **3x**.

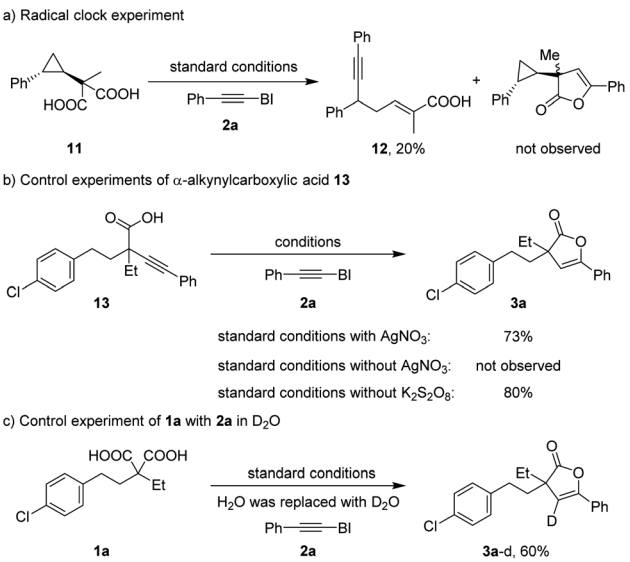
Subsequently, ethynylbenziodoxolones (EBXs) with various aryl substituents were investigated (Scheme 1, **3aa–3ah**). It was found that electron-donating (Me, OMe) and electron-withdrawing (Br, Cl, CN) substituents on the aryl ring were well tolerated, affording products in yields ranging from 50–62%. Additionally, the position of the substitution on the phenyl ring had no obvious effect on the reaction efficiency (**3ac**, **3af** and **3ag**). It should be noted that the good compatibility of chloro- and bromo-substituents provides additional opportunities for further derivatizations through cross-coupling techniques. Naphthyl-substituted EBX was also a viable reaction partner, yielding 2(3*H*)-furanone **3ah** in 44% yield. EBXs with alkyl (*n*-C_4H_9) and silyl (TIPS) groups were also examined; unfortunately, no desired products were obtained. To demonstrate the scalability of this approach, gram-scale reactions of malonic acids **1a**, **1g** and **1q** were carried out; to our delight, desired products **3a**, **3g** and **3q**, respectively, were produced in yields similar to those obtained on smaller scales (Scheme 1).



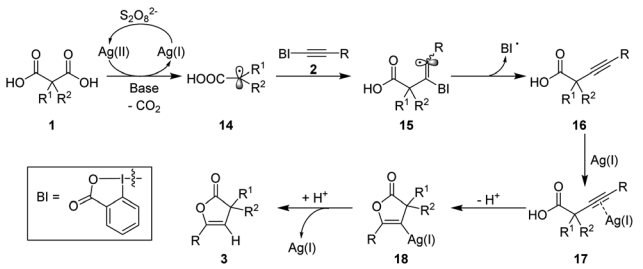
Scheme 2 Synthetic applications.

Notably, the masked carboxylic acid group in the furanone products could be easily released. Simple treatments of **3g** under basic conditions or under Pd(II)/HCOOK produced γ-ketoacid **5** and trialkylacetic acid **6** in 95% and 60% yields, respectively (Scheme 2a). The unmasked carboxylic acid group could function as a useful platform for further elaborations, which was exemplified by facile transformations of γ-ketoacid **5** to β-fluoro-,[3b] bromo-,[3g] azido-[3d,n] and alkynyl-ketones[4] (**7**–**10**) *via* radical decarboxylative functionalizations (Scheme 2b). Thus, both carboxylic acid groups in the malonic acid derivatives have been well utilized for the rapid buildup of molecular complexity on the basis of this radical monodecarboxylative C–C bond coupling reaction enabled by an *in situ* masking strategy.

To obtain further insights into the reaction pathway, mechanistic studies were carried out (Scheme 3). Although the generation of alkyl radicals from a monocarboxylic acid in



Scheme 3 Mechanistic experiments.



Scheme 4 Proposed mechanism.

a Ag(I)/$S_2O_8^{2-}$ system has been well-documented,[1f,18] the oxidation of malonic acids to produce α-carboxylic acid radicals by Ag(I)/$S_2O_8^{2-}$ is unknown. Thus, the radical clock experiment was carried out. Exposing radical clock substrate **11** to **2a** under standard conditions afforded ring-opening product **12**, albeit in a low yield, supporting the intermediacy of the α-carboxylic acid radical (Scheme 3a). Moreover, the successful cyclization of **13** to 2(3*H*)-furanone **3a** suggested that α-alkynylcarboxylic acid was the intermediate in the formation of 2(3*H*)-furanones. Additionally, no cyclized product **3a** was found in the absence of $AgNO_3$, but **3a** could be obtained in 80% yield under standard conditions without $K_2S_2O_8$, implying the involvement of the Ag(I) catalyst in the 5-*endo-dig* cyclization (Scheme 3b). The control experiment of model substrate **1a** under standard conditions with D_2O instead of H_2O as the cosolvent delivered the vinyl position fully deuterated product **3a–d** in 60% yield, indicating that the vinyl proton of furanones originated from water (Scheme 3c).

On the basis of the above experimental results and literature precedents,[4,10,13] a reaction mechanism for this novel transformation of malonic acids has been tentatively proposed (Scheme 4). Initially, Ag(I) is oxidized by persulfate to give Ag(II).[18] Then, a single-electron transfer between the resulting Ag(II) and the malonic acid carboxylates occurs, followed by rapid CO_2 extrusion, affording the α-carboxylic acid radical **14**. Subsequent trapping of the newly generated radical **14** with EBX yields adduct **15**, which undergoes radical elimination to generate α-alkynylcarboxylic acid **16** along with the formation of a benziodoxolonyl radical.[4,19] The remaining carboxylate can be quickly masked by the Ag-activated alkynyl group *via* 5-*endo-dig* cyclization to produce vinyl silver species **18**.[13] Finally, hydrolysis of the vinyl silver species gives rise to the 2(3*H*)-furanone product and regenerates the silver catalyst.

Conclusions

In summary, we have accomplished radical monodecarboxylative C–C bond coupling of malonic acid derivatives with alkynylating reagents enabled by a masking strategy, which provides practical entry to synthetically useful 2(3*H*)-furanone derivatives. The key elements for this *in situ* masking strategy include (1) the dual role of the silver catalyst as a single-electron transfer catalyst to drive radical decarboxylative alkynylation and as a Lewis acid catalyst to promote 5-*endo-dig* cyclization and (2) the dual function of the alkynyl reagent as a radical trapper and as an *in situ* masking group. This reaction features the use of readily available starting materials, excellent functional group compatibility and gram-scale synthetic capability as well as versatile transformations of the latent carboxylate group in the furanone products. Mechanistic studies suggest that α-carboxylic acid radical and α-alkynylcarboxylic acid species are two key intermediates in this transformation. Ultimately, we believe that the successful utilization of malonic acid derivatives as novel C_{sp^3} coupling partners *via* a radical decarboxylation process will open up a new dimension of application of malonic acids in organic synthesis.

Data availability

All experimental procedures, characterization, copies of NMR spectra for all new compounds related to this article can be found in the ESI.†

Author contributions

H.-L. C. performed the experiments and prepared the ESI. X.-H. X., J.-Z. C., and Z. W. prepared some substrates and repeated some experiments. J.-P. C. supervised the research and wrote the manuscript with contributions from all authors.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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