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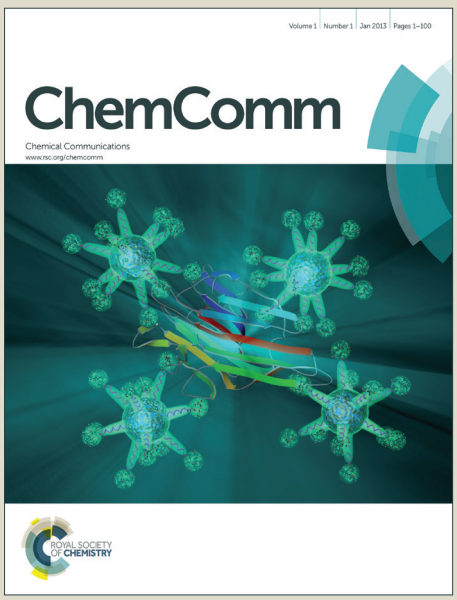

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Ru-catalyzed decarboxylative cyclization of mandelic acids with acrylates: facile access to phthalide skeleton

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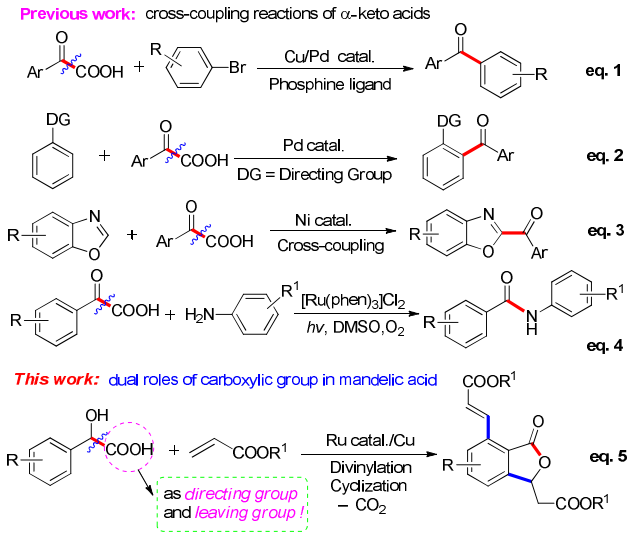
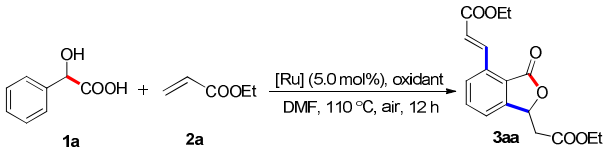
A new protocol for Ru-catalyzed decarboxylative cyclization of mandelic acids with acrylates was firstly established that allows the efficient construction of phthalide skeleton. Interestingly, this reaction underwent a decarboxylative process, in which only divinylation was observed and the subsequent cyclization led to the formation of phthalides.

Arguably, the decarboxylative couplings in recent years have emerged as one of the most attractive and powerful tools for the formation of C–C and C–heteroatom bonds in organic synthesis.[1] Generally, the decarboxylative reaction often employ carboxylic acids as substrates, and the new C–C bonds would be formed with extrusion of CO_2 gas.[2] Recently, much progress has been made on the transition metal-catalyzed decarboxylative couplings.[3-4] Of them, the transition metal catalysts, such as Pd, Ni, Cu, Ag and Rh salts,[4a-g] have been demonstrated high efficiency in the decarboxylative coupling reactions and similar to the bimetal catalysts including Pd/Cu and Pd/Ag.[4h-j] For instance, Myers et al. firstly reported a Pd-catalyzed decarboxylative Heck-type coupling of olefin with arene carboxylic acids.[5] Then Goossen, Glorius, Liu, Forgione, Crabtree, and others showed us a number of elegant results on the transition metal-catalyzed decarboxylative cross-coupling reactions.[3,6] In addition, we found that the acidic substrates used in the above catalytic system mainly includes activated carboxylic acids, such as oxoacids, diphenylacetic acids, and polyfluorobenzoic acids, heteroaromatic carboxylic acids. Among these, the decarboxylative couplings of α-keto acids with other reagents have been extensively studied.[7] For selected examples, Goossen et al. discovered the decarboxylative cross-coupling of α-ketone carboxylic acid with aryl bromides in Cu/Pd bimetalltic system (Scheme 1, eq. 1).[7a] In 2010, Ge and co-workers reported a Pd-catalyzed intermolecular decarboxylative dehydrogenative cross-coupling of *N*-phenylacetamides with α-keto acids (eq. 2).[7b] Then a Ni-catalyzed decarboxylative cross-coupling of α-ketone carboxylic acid with benzoxazoles was developed by the same group (eq. 3).[7c] Inspired by these works, some recent results reported by Kim, Duan, Tan, Wang and our group also showed the high activity of α-ketone acid, and which presented an alternative way to synthesize ketone derivatives.[7c-o] It should be noted that Lei and co-workers recently realized the first decarboxylation/oxidative amidation of α-keto acids with amines by taking the advantage of visible light with the assistance of photocatalyst (Scheme 1, eq. 4).[8] To our knowledge, the Ru and its complexes have been rarely studied in the decarboxylative coupling reactions.



Scheme 1. Decarboxylation of α-keto acid and mandelic acids

Table 1. Optimization of Ru catalyst, oxidant and additive[a]



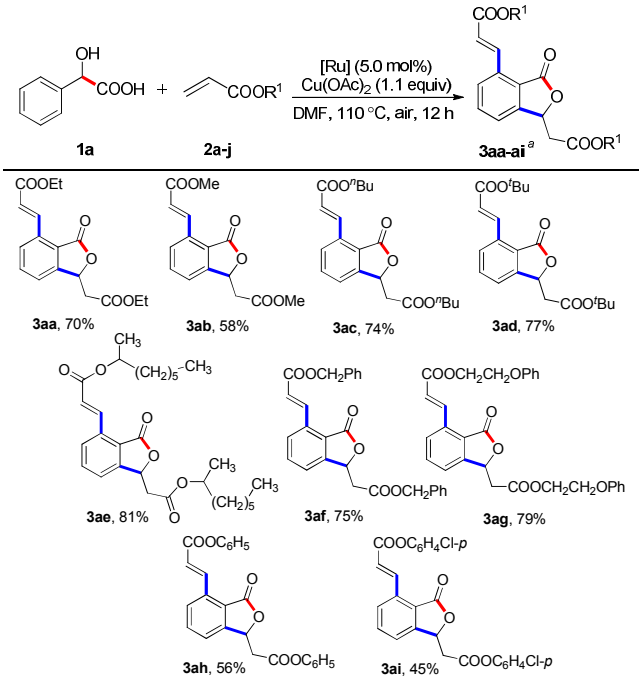
1a 2a 3aa

entry	Ru source	oxidant	additive	yield(%)[b]
1	$RuCl_3 \cdot nH_2O$	$Cu(OAc)_2$	/	0
2	$Ru(PPh_3)_3Cl_2$	$Cu(OAc)_2$	/	0
3	$[Cp^*RuCl_2]_n$	$Cu(OAc)_2$	/	48
4	*$[RuCl_2L]_2$*	*$Cu(OAc)_2$*	*/*	*70*
5	$[RuCl_2L]_2$	$Cu(OAc)_2$	/	n.r.[c]
6	$[RuCl_2L]_2$	$Cu(OAc)_2 \cdot nH_2O$	/	33
7	$[RuCl_2L]_2$	$Cu(OAc)_2$	$AgSbF_6$	64
8	$[RuCl_2L]_2$	$Cu(OAc)_2$	K_3PF_6	50
9	$[RuCl_2L]_2$	$Cu(OAc)_2$	$NaBF_4$	43
10	$[RuCl_2L]_2$	/	/	n.r.
11	$[RuCl_2L]_2$	TBHP	/	n.r.
12	$[RuCl_2L]_2$	BQ	/	n.r.
13	$[RuCl_2L]_2$	Ag_2CO_3	/	n.r.
14	$[RuCl_2L]_2$	AgOAc	/	n.r.
15	$[RuCl_2L]_2$	Ag_2O	/	n.r.
16	$[RuCl_2L]_2$	$PhI(OAc)_2$	/	n.r.
17	$[RuCl_2L]_2$	$Cu(OAc)_2$	/	55[d]
18	$[RuCl_2L]_2$	$Cu(OAc)_2$	/	37[e]
19	$[RuCl_2L]_2$	$Cu(OAc)_2$	/	68[f]
20	$[RuCl_2L]_2$	$Cu(OAc)_2$	/	36[g]

[a] *Reaction conditions:* 2-hydroxy-2-phenylacetic acid (**1a**, 0.20 mmol, excess), ethyl acrylate (**2a**, 0.20 mmol), Ru complex (0.01 mmol, containing Ru 5.0 mol% based on **2a**), oxidant (0.22 mmol), additive (20 mol%), DMF (1.0 mL) at 110 ºC in air for 12 h. [b] Isolated yield. [c] N_2. [d] 90 ºC. [e] 130 ºC. [f] **1a/2a** = 1:2. [g] **1a/2a** = 2:1. Cp* = pentamethylcyclopentadienyl, L = *p*-cymene. n.r. = no reaction.

Mandelic acid and its derivatives are widely distributed in nature.[9] As important materials, they have been broadly used as pharmaceuticals, agrochemicals, dyeing and flavouring agent in industry.[10] Up to date, multiple methods have been established for the synthesis of mandelic acids, including traditional chemical synthesis,[11] isolation from natural sources[9] and preparation by using an enzymatic biochemical process.[12] However, there is not enough literature to know about the chemical transformation of mandelic acids, especially in organic synthesis.[13] In light of the above facts, we envision that mandelic acids may undergo a normal decarboxylative process in particular environment,[7] and the formed intermediate would react with other appropriate agents to realize some possible cross-coupling reactions. Based on our recent work on the transition metal-catalyzed decarboxylations,[7m-n,14] herein we will firstly report a Ru-catalyzed decarboxylative cyclization of mandelic acids with activated acrylates to generate phthalide derivatives in good yields (Scheme 1, eq. 5). It is important to note that the carboxylic group in mandelic acid *acts as directing group, and subsequently as leaving group* in the reaction.

Firstly, 2-hydroxy-2-phenylacetic acid (**1a**) and ethyl acrylate (**2a**) were chosen as model substrates for the optimization of reaction conditions, described in Table 1 (*DMF should be dried and distilled prior to use in this investigation*). It was found that the Ru salts, such as $RuCl_3 \cdot nH_2O$ and $Ru(PPh_3)_3Cl_2$, did not work under the standard reaction conditions (entries 1 and 2). To our delight, employing $[Cp^*RuCl_2]_n$ as catalyst allows the efficient reaction of **1a** with

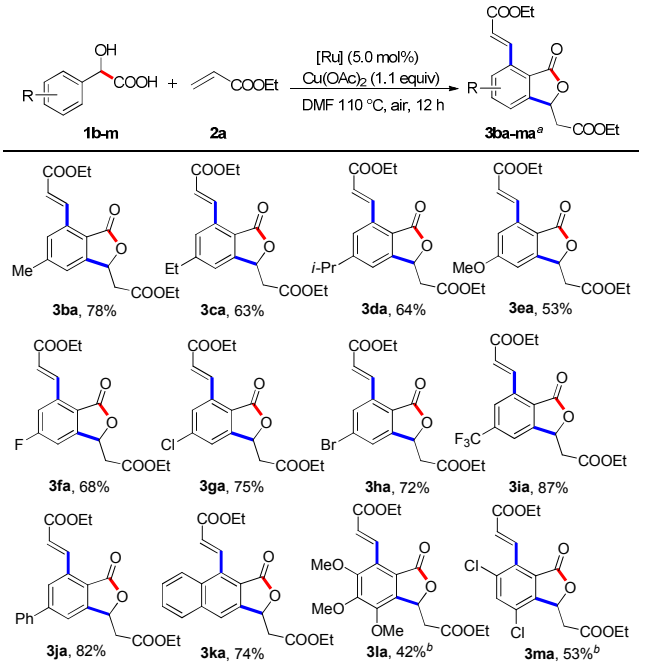


Reaction conditions: 2-hydroxy-2-phenylacetic acid (**1a**, 0.20 mmol), acrylate (**2**, 0.20 mmol), [Ru] = $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol, containing Ru 5.0 mol%), $Cu(OAc)_2$ (0.22 mmol, 1.1 equiv), DMF (1.0 mL), 110 ºC, air, 12 h. [a] Isolated yields.

Scheme 2. Substrate scope of acrylates

2a, and **3aa** as a only product was isolated in 48% yield (entry 3). Instead of $[Cp^*RuCl_2]_n$, the use of $[Ru(p\text{-cymene})Cl_2]_2$ led to a significant increase in the yield of **3aa** to 70% (entry 4). Additionally, we found that the reaction of **1a** with **2a** almost did not proceed in the nitrogen atmosphere (entry 5). When $Cu(OAc)_2 \cdot nH_2O$ was tested in the above reaction conditions, lower yield of **3aa** was obtained (entry 6). Moreover, the addition of some common additives, such as $AgSbF_6$, K_3PF_6 and $NaBF_4$, did not help promoting this process (entries 7–9). The reaction did not proceed without $Cu(OAc)_2$ (entry 10). Subsequently, the screening of oxidants, including *tert*-butyl hydroperoxide (TBHP), 1,4-benzoquinone (BQ), Ag_2CO_3, AgOAc, Ag_2O and $PhI(OAc)_2$, showed that no reaction occurred (entries 11–16). Then we found that reaction temperature had an obvious effect on the reaction of **1a** with **2a** (entries 17 and 18). Interestingly, we noticed that changing the molar ratio of **1a/2a** from 1:2 to 2:1 did not affect the components of the product, but resulted into decreased yield of **3aa** (entries 19 and 20). Finally, we observed that this reaction behaved strong dependence on the solvent and DMF was demonstrated as the best reaction medium (Table S1, ESI†).

After establishing the optimized conditions for the model reaction, several acrylates and mandelic acid derivatives were synthesized[15] and applied to explore the substrate scope under the optimized conditions, as shown in Scheme 2. Generally, acrylates with low boiling point, such as ethyl acrylate and methyl acrylate, reacted with 2-hydroxy-2-phenylacetic acid (**1a**), providing the lower yields of corresponding products (**3aa** and **3ab**). In contrast, most of the acrylates with high boiling point gave the satisfactory yields of the desired products (**3ac–ag**). Unfortunately, the reaction of phenyl acrylate and 4-chlorophenyl acrylate with **1a** gave **3ah** in 56%, and **3ai** in 45% yields, respectively.

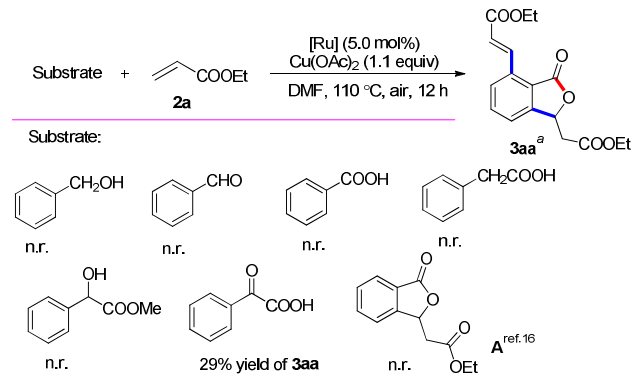


Reaction conditions: 2-hydroxy-2-arylacetic acid (**1**, 0.20 mmol), ethyl acrylate (**2a**, 0.20 mmol, excess), [Ru] = [Ru(*p*-cymene)Cl_2]$_2$ (0.01 mmol, containing Ru 5.0 mol%), Cu(OAc)$_2$ (0.22 mmol, 1.1 equiv), DMF (1.0 mL), 110 ºC, air, 12 h. [a] Isolated yields. [b] 24 h.

Scheme 3. Substrate scope of mandelic acids

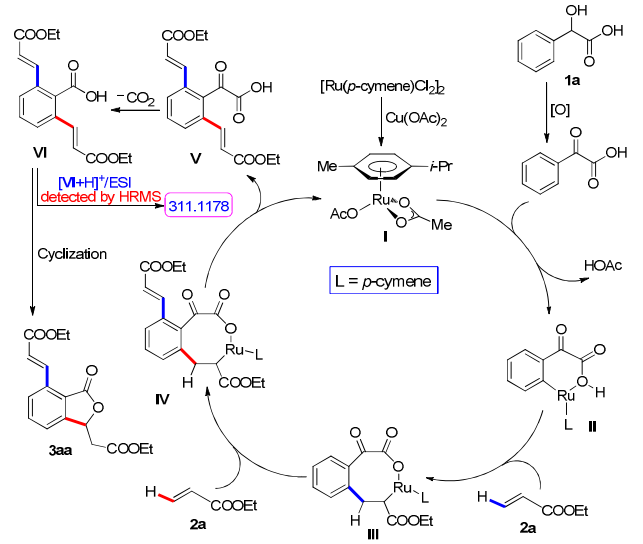
Subsequently, the scope of mandelic acids was investigated under the above reaction conditions. We found that the substitutes on the aromatic ring of mandelic acids had a significant influence on the chemical process, as summarized in Scheme 3. In general, the electron-donating groups on the aromatic ring, such as Me, Et, *i*-Pr and MeO, led to inferior yields of corresponding products (**3ba** *vs* **3ea**). The introduction of halogens into mandelic acids, including F, Cl and Br, behaved similar reactivity in this catalytic system (**3fa–3ha**). As expected, the presence of strong electron-withdrawing group CF_3 contributed to good yield of **3ia**. Although we did not figure out the effect of the conjugated aryl group in mandelic acids, the good yields of **3ja** and **3ka** were also obtained. For the mandelic acids bearing disubstitued or trisubstitued aromatic group, prolonging reaction time to 24 h is necessary to generate **3la** and **3ma** in acceptable yields.

To gain insight into the reaction mechanism of this decarboxylative process, some control experiments were conducted. As can be seen from Scheme 4, the substrates, such as benzyl alcohol, benzaldehyde, benzoic acid and 2-phenylacetic acid were used to react with ethyl acrylate, and we found that neither of them participates in the decarboxylative process and the starting materials were recovered. Similarly, the reaction of methyl 2-hydroxy-2-phenylacetate with ethyl acrylate did not proceed under standard conditions, too. However, employing 2-oxo-2-phenylacetic acid as substrate led to the generation of **3aa** in 29% isolated yield. Furthermore, substrate **A** was specially synthesized[16] and was used to react with ethyl acrylate, and no desired product **3aa** was obtained. These experiments reveal that intramolecular combination of carboxylic and hydroxyl group is extremely important to realize this decarboxylative cyclization. In addition, we successfully detected the in situ formed CO_2 gas[2] that released from the reaction of 2-hydroxy-2-phenylacetic acid with ethyl acrylate (Fig. S1, ESI†).



Reaction conditions: substrate (0.20 mmol), ethyl acrylate (**2a**, 0.20 mmol), [Ru] = [Ru(*p*-cymene)Cl_2]$_2$ (0.01 mmol, containing Ru 5.0 mol%), Cu(OAc)$_2$ (0.22 mmol), DMF (1.0 mL) at 110 ºC in air for 12 h. [a] Isolated yields. n.r. = no reaction.

Scheme 4. Control experiments



Scheme 5. Proposal reaction mechanism

Thus, a possible mechanism for the reaction was proposed in Scheme 5. 2-Hydroxy-2-phenylacetic acid (**1a**) was initially oxidized into 2-oxo-2-phenylacetic acid,[4b] which next coordinated to Ru-species **I**, forming Ru-complex **II**. The migratory insertion of ethyl acrylate (**2a**) with **II** and reductive elimination twice led to the formation of intermediate **III**, **IV**, **V** and **I** [Ru(O_2CMe)$_2$(*p*-cymene)]. On the other hand, the **V** lost CO_2 and resulted into the formation of **VI**.[4a] Although **VI** was not isolated, a significant molecular ion peak presented the possible structural information (Fig. S2, ESI†). Finally, intramolecular cyclization of **VI** afforded the product **3aa**.

We have demonstrated a new route to construct the phthalide skeleton from the reaction of mandelic acids with acrylates. To the best of our knowledge, this work is a first example referring to Ru-catalyzed decarboxylative reaction, which features the only divinylation and final cyclization. Control experiments, CO_2 detection by IR and trapping intermediate by high resolution mass spectrum support this decarboxylative cyclization process. Further application of decarboxylative reactions is currently underway.

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Notes and reference

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