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Switchable C−H Alkylation of Aromatic Acids with Maleimides in Water: Carboxyl as a Diverse Directing Group

Fan Pu,[a] Zhong-Wen Liu,[a] Lin-Yan Zhang, [a] Juan Fan,[a] and Xian-Ying Shi*[a]

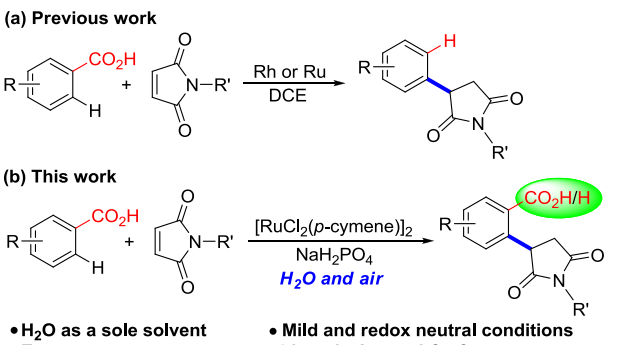
Dedication ((optional))

Abstract: A ruthenium-catalyzed protocol to access conjugate addition or decarboxylative conjugate addition of aromatic acids with maleimides has been developed. The reaction shows interesting chemoselectivity with different substituted benzoic acids. The reaction pathway of C−H alkylation is controlled by the intrinsic property of aromatic acids but not reaction conditions. Under almost the same reaction conditions, carboxyl can act as either a classical directing group or a traceless directing group, thereby generating two kinds of products, i.e., 2-alkyl substituted benzoic acids and alkyl substituted benzenes. These two reactions proceeded under mild and redox-neutral conditions in neat water under the atmosphere of air, and could be easily scaled up to grams. The decarboxylative conjugate addition, where carboxyl acts as a traceless directing group, can be realized without the addition of any ligand, silver or copper salt.

Introduction

Succinimides are important motif found in many natural products as well as pharmaceuticals with distinctive bioactivities such as phensuximide, ethosuximide, and mesuximide.[1] Succinimide moieties can be readily transferred to biologically relevant pyrrolidines, and synthetically useful derivatives.[2] Thus, much effort has been devoted to develop efficient methodologies synthesizing these compounds in the past decades.[3] Recently, the direct addition of Csp^2–H bonds onto polar C=C provides a more direct, atom- and step economical alternative to many important compounds because all of the substrates are incorporated into the target products.[4] As an easily available starting material and a highly electrophilic olefin, maleimides were frequently utilized in introducing the succinimide structures into organic molecules to construct complex structures.[5] In this context, Prabhu and his co-workers successively reported *N*-substituted carboxamide, pyrimidinyl, azo, ketone and benzoyl directed conjugate addition of C−H to maleimides catalyzed by ruthenium, cobalt and rhodium catalyst, respectively.[6] Moreover, rhodium- and cobalt-catalyzed carbonyl- or carbamoyl-directed conjugate additions of C−H to maleimides were developed by several research groups.[7] Ackermann and Li demonstrated (hetero)aryl and alkenyl C−H alkylation of maleimides with maleate esters under remarkably mild reaction conditions.[8] The manganese-catalyzed addition of C-2 position of indoles to maleimides has been developed by Gong and Song under additive-free conditions.[9] Cobalt(III)-catalyzed conjugate addition of C–H bonds in oximes and enamides to maleimides was illuminated by Zhang and Wu successively.[10] Shi and Kim reported Csp^3−H alkylation of 8-methylquinolines, amino acids and peptides with maleimides, respectively.[11]

Carboxylic acids with the following advantages have been applied extensively in C−H functionalization.[12] It widely exists in organic molecules and can be obtained from many other functional groups readily. The carboxyl group can be easily transformed into diverse functional groups or be removed via decarboxylation after directed C−H functionalization. Carboxyl directed hydroarylations were successively achieved by Gooßen's group, who employ *α,ß*-unsaturated carbonyl compounds, alkynes, and allyl amines as reaction partners, respectively.[13] Moreover, all the reported reactions between aromatic acids and maleimides delivered decarboxylative hydroarylation products. Prabhu disclosed a rhodium(III)-catalyzed C−H activation followed by conjugate addition to maleimides, using carboxylic acid as a traceless directing group.[14] Subsequently, Baidya and Ackermann demonstrated ruthenium(II)-catalyzed hydroarylation of maleimides with aryl carboxylic acids based on carboxyl-directed *ortho*-C−H alkylation and concomitant decarboxylation processes, fabricating 3-aryl succinimides, respectively (Scheme 1a).[15] However, these rhodium- or ruthenium-catalyzed decarboxylative alkylations have been realized only in the organic solvent of 1,2-dichloroethane. Thus, a more sustainable method is still highly desirable to accomplish these transformations in a more green manner.[16] Moreover, the non-decarboxylative hydroarylation of aromatic acids with



Scheme 1. Reactions between aromatic acids and maleimides.

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has also not been reported, which may be due to its high tendency towards the competitive transformations such as the cascade cyclization and the decarboxylation.

Water as an environmentally benign, nonflammable, and nontoxic reaction medium has been attracted considerable attention in sustainable C−H bond functionalizations.[17] A few examples of ruthenium-catalyzed hydroarylations in water have been demonstrated,[14] including the direct addition of amides and aromatic acids with conjugated alkenes, the intramolecular hydroarylation of arenes with olefins, and annulations of alkynes by benzamides and heteroaromatic acids.[13c, 18]

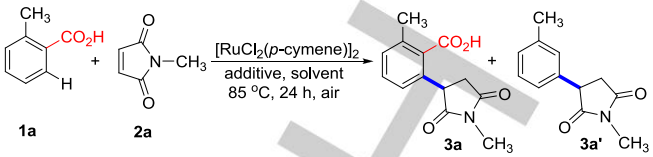
Based on these understandings and our continuous interest in C−H functionalizations in water,[18f] herein we describe a ruthenium(II)-catalyzed protocol to access conjugate addition or decarboxylative conjugate addition of aromatic acids with maleimides under mild and redox-neutral conditions in benign water as a reaction medium (Scheme 1b). Carboxyl can serve as either a classical directing group or a traceless directing group, which is controlled by the intrinsic property of aromatic acids but not reaction conditions. The reaction is environmentally friendly, operationally simple, and not sensitive to air. Noteworthy, although carboxyl as a classical or a traceless directing group has been extensively studied,[12] the reaction pathway controlled by the intrinsic property of aromatic acids but not reaction conditions has never been reported.

Results and Discussion

We initiated our study by reacting 2-toluic acid (**1a**) with *N*-methyl maleimide (**2a**) via the catalysis of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in neat water under atmosphere of air. The conjugate addition product **3a** was formed in 67% yield at 85 °C accompanied with 6% yield of decarboxylative product **3a'** (Table 1, entry 1). Then, the amount of the catalyst, reaction time and temperature were tested. Unfortunately, variation of these parameters did not enhance the yield of **3a**. Gratifyingly, it was found that the yield could be increased to 76% by the addition of NaH_2PO_4 (Table 1, entry 2). On the contrary, other alkali salts such as Na_2HPO_4, KH_2PO_4, K_2HPO_4, NaOAc, HCOONa, PivONa·H_2O, and KOAc are less efficient in this transformation (Table 1, entries 3-9). To our surprise, the utilization of commonly used organic solvents such as THF, 1,4-dioxane, DME, DCE, toluene, and CH_3CN afforded unsatisfactory yield of **3a** (Table 1, entries 10-15).

With the optimized reaction conditions in hand, the present conjugate addition reaction was then carried out between a series of substituted benzoic acids and *N*-methyl maleimide. As can be seen in Table 2, this methodology was applicable to diverse aromatic acids irrespective of the nature of their substituents. *Ortho*-substituted benzoic acids bearing electron-donating groups, such as C_2H_5, Ph, $PhCH_2$, $PhCH_2CH_2$, all delivered the addition products in moderate to good yields (**3b-3e**, 50-74%). 2-Iodobenzoic acid showed lower reactivity in this reaction affording **3f** in 39% yield. However, 2-ethoxybenzoic acid generated rather low yield of addition product (8% NMR yield). Strong electron-withdrawing groups such as CF_3 and NO_2

Table 1. Selected results for optimizing reaction conditions.[a]



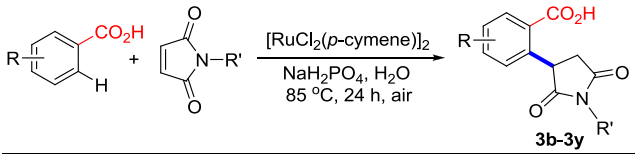
Entry	additive	Solvent	Yield (%)[b]	
			3a	3a'
1	-	H_2O	67	6
2	NaH_2PO_4	H_2O	76	9
3	Na_2HPO_4	H_2O	45	11
4	KH_2PO_4	H_2O	70	9
5	K_2HPO_4	H_2O	44	13
6	NaOAc	H_2O	54	14
7	HCOONa	H_2O	45	10
8	PivONa·H_2O	H_2O	58	11
9	KOAc	H_2O	61	13
10	NaH_2PO_4	THF	24	trace
11	NaH_2PO_4	1,4-dioxane	trace	0
12	NaH_2PO_4	DME	trace	0
13	NaH_2PO_4	DCE	0	0
14	NaH_2PO_4	toluene	0	0
15	NaH_2PO_4	CH_3CN	0	0

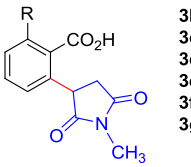
[a] Reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), additive (0.5 equiv), solvent (0.5 mL) at 85 °C for 24 h, under air. [b] Determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

were also tolerated. 2-(Trifluoromethyl)benzoic acid produced moderate yields (**3g**, 55%). While 2-nitrobenzoic acid afforded addition products in a lower yield of 25% (NMR yield). For *meta*-substituted substrates such as 3-toluic acid and 3-(trifluoromethyl)benzoic acid, better regioselectivity occurring in a less hindered C−H bond was observed (**3h-3i**). However, when *para*-substituted benzoic acids including CH_3, CH_3O, Cl, Br, I, CF_3 and NO_2 were employed, a trace amount of addition products was detected. Moreover, all cyano substituted benzoic acids including 2-, 3- or 4-cyanobenzoic acids showed a poor reactivity. Disubstituted aromatic acids, such as 2,3- and 2,4-disubstituted benzoic acids, were also applicable in this transformation affording the target products in moderate to good yields (**3j-3o**, 50-70%).

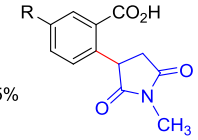
Several maleimides were used to examine the compatibility of this on water conjugate addition with 2-toluic acid, 2-ethylbenzoic acid and 2-benzylbenzoic acid, respectively. Unprotected maleimide, i.e., N−H maleimide, led to the desired products in good isolated yields (**3p** of 60% and **3q** of 70%). Substrates with protecting groups of ethyl afforded the expected products in moderate to good yields (**3r-3t**, 56-74%). To our delight, *N*-substituted maleimides bearing bulky protecting groups such as tertiary butyl and benzyl, also delivered the corresponding products in moderate to good yields (**3u-3y**, 50-70%). As for this transformation, decarboxylative addition products were observed as side products (see Supporting

Table 2. Substrate scope for conjugate addition. [a]

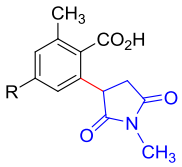




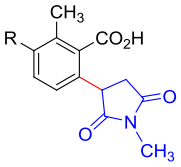
3b: R = C_2H_5, 72%
3c: R = Ph, 50%
3d: R = $PhCH_2$, 74%
3e: R = $PhCH_2CH_2$, 55%
3f: R = I, 39%
3g: R = CF_3, 55%



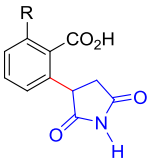
3h: R = CH_3, 54%
3i: R = CF_3, 50%



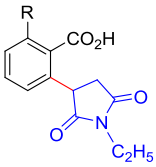
3j: R = CH_3, 57%
3k: R = Br, 58%



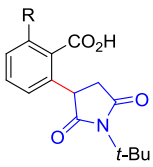
3l: R = CH_3, 70%
3m: R = CH_3O, 58%
3n: R = Cl, 50%
3o: R = F, 50%



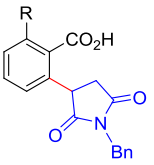
3p: R = CH_3, 60%
3q: R = C_2H_5, 70%



3r: R = CH_3, 56%
3s: R = C_2H_5, 65%
3t: R = Bn, 74%



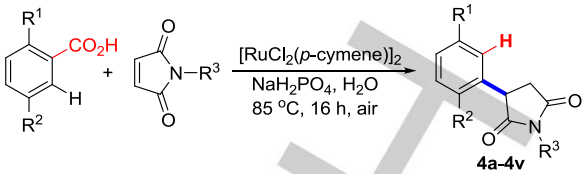
3u: R = C_2H_5, 50%
3v: R = Bn, 70%

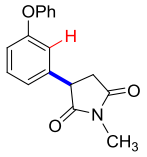


3w: R = CH_3, 50%
3x: R = C_2H_5, 60%
3y: R = Bn, 62%

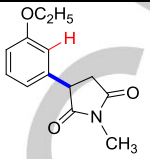
[a] Reaction conditions: aromatic acids (0.2 mmol), maleimides (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaH_2PO_4 (0.1 mmol), deionized water (0.6 mL), 85 °C, 24 h, isolated yield.

Table 3. Substrate scope for decarboxylative conjuage addition. [a]

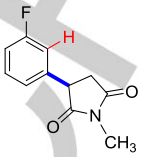




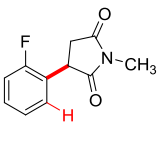
4a 74%



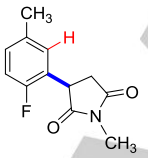
4b 51%



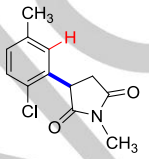
4c 65%



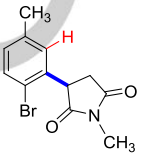
4d 66%



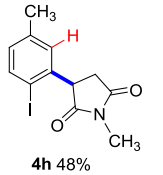
4e 70%



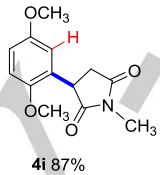
4f 84%



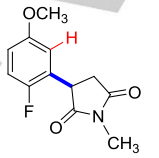
4g 84%



4h 48%



4i 87%



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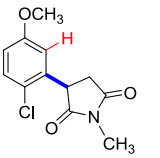

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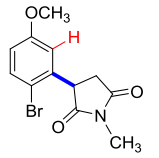
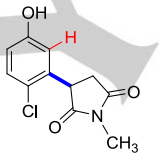
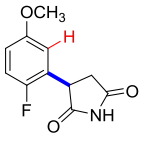


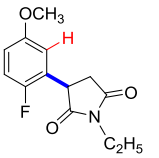
4l 81%



4m 86%



4n 75%



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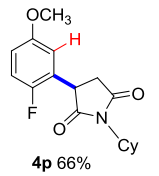
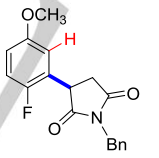
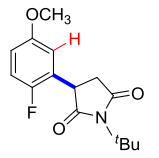


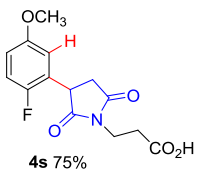
4p 66%



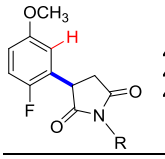
4q 75%



4r 80%



4s 75%



4t: R = Ph 81%
4u: R = 4-PhOH, 50%
4v: R = 4-PhBr, 80%

[a] Reaction conditions: aromatic acids (0.2 mmol), maleimides (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaH_2PO_4 (0.1 mmol), deionized water (0.6 mL), 85 °C, 16 h, isolated yield.

Information Table S1).

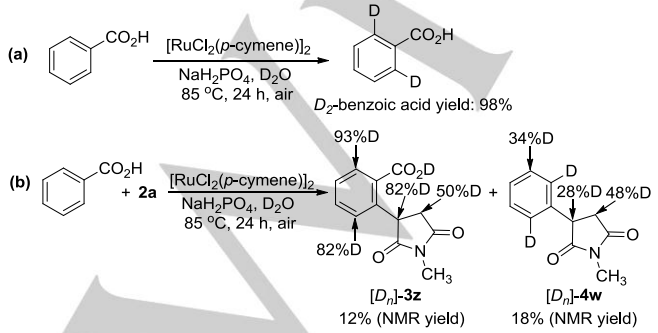
Surprisely, the reaction between 2-phenoxybenzoic acid and *N*-methyl maleimide under this catalytic system generated 1-methyl-3-(3-phenoxyphenyl)pyrrolidine-2,5-dione (**4a**) in a 74% isolated yield in water and air. The process involves carboxyl-directed conjugate addition of C−H bond to the polar double bond of maleimide with concerted decarboxylation, in which carboxyl acts as a traceless directing group. Although the rhodium or ruthenium-catalyzed decarboxylative hydroarylation of maleimides were demonstrated by Ackermann, Ramaiah and Mahiuddin Baidya,[14-15] respectively, the reactions all proceeded in the organic solvent of DCE. Baidya also used $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst, however, phosphorus ligand of Cy_3PO is required in catalytic system.[15b] In viewing that water is the most abundant compound on the earth surface, and is regarded as a green solvent, various conditions including the amount of catalyst, additive, reaction time and reaction temperature were examined to further improve the yield of **4a**. Shortening the reaction time to 16 h, the isolated yield of **4a** was still 74%. No improved yield was observed in other reaction conditions. Then, the applicability of this decarboxylative hydroarylation of maleimides to establish 3-aryl succinimides in water and air was investigated.

Firstly, the substrate scope was examined with respect to the aromatic acids and *N*-methyl maleimide. It was found that this decarboxylative conjugate addition depended greatly on the substituent and its position. 2-Ethoxylbenzoic acid proceeded smoothly to afford the desired product in a moderate yield accompanied by 40% unreacted 2-ethoxybenzoic acid (**4b**, 51%).

2- and 3-fluorobenzoic acid also worked well in the decarboxylative reaction and provided moderate yields of products (**4c**-**4d**, 65-66%). To our surprise, in the case of 3-fluorobenzoic acid, the decarboxylative alkylation occurred at the sterically hindered position. Moreover, 5-halogen substituted 2-toluic acids, 2,5-dimethoxyl benzoic acid, and 5-halogen substituted 2-methoxylbenzoic acids performed well under the reaction conditions providing the product in moderate to excellent yields regardless of steric hindrance effect (**4e**-**4l**, 48-93%). The reaction is compatible with sensitive functional group, such as hydroxyl (**4m**, 86%). However, benzoic acid proved to be a poor substrate for decarboxylative reaction, providing decarboxylative product in a rather low NMR yield of 18% (**4w**) accompanied by 6% NMR yield of conjugate addition product (**3z**). Very interestingly, when 2-alkyl benzoic acids, 3-toluic acid, 2,3-disubstituted benzoic acids, and 4-disubstituted benzoic acids were utilized to react with *N*-methyl maleimide under almost the same reaction conditions, non-decarboxylative conjugate addition products were isolated as main products but not decarboxylative products. These results illuminate that the main product under the present catalytic system is determined by the intrinsic property of aromatic acids but not reaction conditions. Moreover, the good to excellent selectivity of non-decarboxylative or decarboxylative products was observed in these two transformations (See Supporting Information Table S1 and S2).

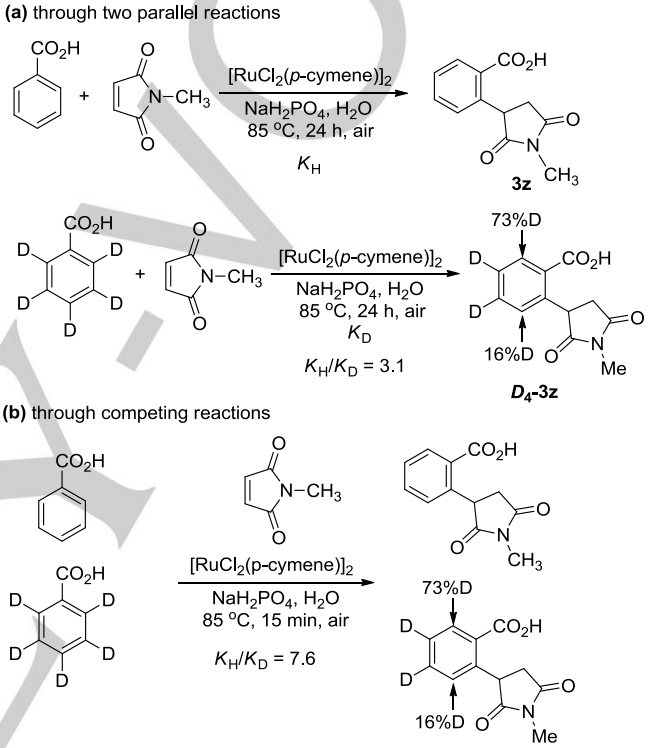
We next examined the scope of maleimides in decarboxylative conjugate addition with 5-fluoro-2-methoxybenzoic acid in neat water. Similar to conjugate addition, maleimide, *N*-ethyl, *N*-cyclohexyl, *N*-2-carboxyethyl and *N*-benzyl maleimide could be efficiently converted into the corresponding decarboxylative products in good to excellent yields (**4n**-**4q**, **4s**, 66-84%). Unexpectedly, *N*-*tert*-butyl maleimide displayed good activity despite steric hindrance (**4r**, 80%). In addition to *N*-alkyl maleimide, phenyl and substituted phenyl such as 4-hydroxyphenyl and 4-bromophenyl, employed in place of alkyl groups did not affect the outcome of the reaction (**4t**-**4v**, 50-81%). In most cases, the high conversion of aromatic acids was observed. Moreover, almost no conjugate addition product was detected (see Supporting Information Table S2).

Further experiments were carried out to probe the possible reaction mechanism. First, experiments were performed with D_2O as the solvent. 98% Deuterium incorporation was observed at the two *ortho* positions of the carboxyl when the benzoic acid

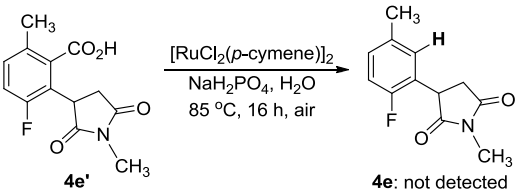


Scheme 2. Probing the reversibility of the C–H activation step.

was treated in the absence of *N*-methyl maleimide (Scheme 2a). The same reaction conducted in the presence of *N*-methyl maleimide displayed a significant H/D scrambling in the product [*Dn*]-**3z** and [*Dn*]-**4w** (Scheme 2b). These results suggest that a reversible cyclometalation mode was involved.[19] The kinetic isotope effect was investigated via competition and parallel experiments within 15 min, respectively. A KIE of 3.1 (parallel experiment and k_H/k_D= 7.6 (competition experiment) were observed (Scheme 3a and 3b), which illuminates that the C–H bond cleavage might be related with the rate determining step.[20]



Scheme 3. The experiments to determine the kinetics isotopic.

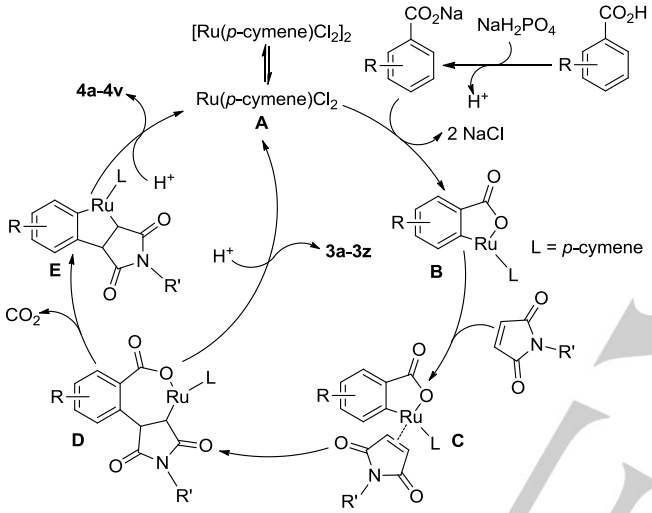


Scheme 4. Reaction of 3-aryl succinimde under standard reaction conditions.

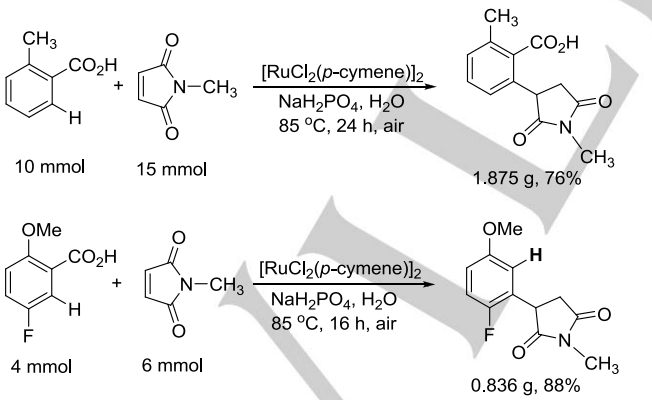
To test whether direct conjugate addition product is an intermediate to form decarboxylative product, we prepared 3-fluoro-6-methyl-2-(1-methyl-2,5-dioxopyrrolidin-3-yl)benzoic acid (**4e'**) and treated it under standard reaction conditions (Scheme 4). However, **4e** was not detected after the reaction, indicating that the decarboxylative conjugate addition product are not produced via a sequence of conjugate addition followed by protodecarboxylation.

On the basis of these observations as well as previous reports

about ruthenium-catalyzed carboxyl-directed C–H activation and carboxyl as a traceless directing group,[21-22] a plausible mechanism for the present conjugate addition and decarboxylative conjugate addition was depicted in Scheme 5. Firstly, the dimer $[RuCl_2(p\text{-cymene})]_2$ catalyst dissociates to a coordinatively unsaturated monomer **A**, which undergoes cyclometallation with carboxyl to generate five-membered ruthenium-cyclic intermediate **B**. Ru species in **B** coordinates to the maleimides followed by migratory insertion affording ruthenacycle **D**. Ruthenacycle **D** could proceed by two pathways. Direct protonolysis of **D** releases conjugate addition products **3a**-**3z.** The alternative pathway affords decarboxylative conjugate products **4a**-**4v** via decarboxylation of **D** and subsequent protonolysis. Under this catalytic system, the substrates determine the main reaction pathway of intermediate **D**.

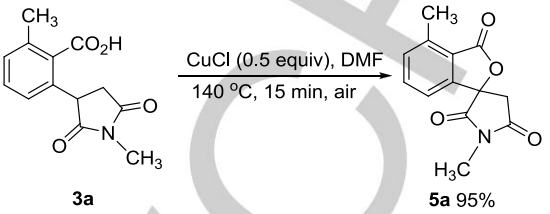


Scheme 5. A plausible reaction mechanism.



Scheme 6. Gram-scale preparation of **3a** and **4j**.

To further explore the practicality of these two on water reactions, 10 mmol and 4 mmol scale reactions of 2-toluic acid and 5-fluoro-2-methoxybenzoic acid were carried out with *N*-methyl maleimide, respectively. We were pleased to find that the expected products of **3a** and **4j** was obtained in satisfactory isolated yields of 76% and 88%, respectively (Scheme 6). In addition, the synthesis of spirosuccinimide (**5a**), which is of potent interest in medicinal chemistry, was successfully demonstrated in a short time via intramolecular dehydrogenation of **3a** (Scheme 7)**.**



Scheme 7. Synthesis of spirosuccinimide.

Conclusions

In summary, we have developed a ruthenium-catalyzed switchable reaction to obtain either a conjugate addition product or a decarboxylative conjugate addition product from easily accessible aromatic acids and maleimides. A variety of different aryl substituted succinimides were obtained in moderate to excellent yields. It is interesting to note that aromatic acid plays a pivotal role in the chemoselectivity but not reaction conditions. The use of water as solvent under atmosphere of air makes this approach very environmentally friendly and practical. Given the mild and redox-neutral conditions in neat water, operational simplicity, easily scale-up to gram level, these methods may find applications in the synthesis of related complex structures.

Experimental Section

General Information

^{1}H NMR spectra and ^{13}C NMR spectra were measured on a 400 MHz spectrometer or 600 MHz spectrometer (^{13}C NMR 100 MHz or 150 MHz), with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ relative to TMS, with the coupling constants J given in Hz. High-resolution mass spectra (HRMS) were obtained from a Bruker Compass-Maxis instrument (ESI). All solvents were dried and/or distilled by standard methods. All reagents were purchased from commercial sources and used without further purification. All work-up and purification procedures were carried out with analytical reagent solvents. D_5-benzoic acid was prepared according to previous report.[23]

General procedure for ruthenium-catalyzed conjugate addition of aromatic acids with maleimides

An oven-dried reaction vessel was charged with $[RuCl_2(p\text{-cymene})]_2$ (Ru*, 6.1 mg, 5 mol%, 0.01 mmol), aromatic acids (0.2 mmol), maleimides (0.3 mmol), NaH_2PO_4 (12.0 mg, 0.1 mmol), deionized water (0.6 mL). The mixture was stirred under air at 85 °C (oil bath temperature) for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (5 mL) and filtered through a short silica gel pad. The filter cake was further flushed with EtOAc (3 × 5 mL). The combined solution was concentrated under vacuum, and the residue was purified by a preparative thin-layer chromatography to afford the corresponding product.

General procedure for ruthenium-catalyzed decarboxylative conjugate addition of aromatic acids with maleimides

An oven-dried reaction vessel was charged with $[RuCl_2(p\text{-cymene})]_2$ (Ru*, 6.1 mg, 5 mol%, 0.01 mmol), aromatic acids (0.2 mmol), maleimides (0.3 mmol), NaH_2PO_4 (12.0 mg, 0.1 mmol), deionized water (0.6 mL). The mixture was stirred under air at 85 °C (oil bath temperature) for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc (5 mL) and filtered through a short silica gel pad. The filter cake was further flushed with EtOAc (3 × 5 mL). The combined solution was concentrated under vacuum, and the residue was purified by a preparative thin-layer chromatography to afford the corresponding product.

Ortho deuteration experiment

$[RuCl_2(p\text{-cymene})]_2$ (Ru*, 3.1 mg, 5 mol%, 0.005 mmol), benzoic acid (12.2 mg, 0.1 mmol), NaH_2PO_4 (6.0 mg, 0.05 mmol), deuterium water (0.3 mL), were successively added to a reaction vessel equipped with a stir bar. The mixture was stirred at 85 °C (oil bath temperature) for 24 h. The resulting mixture was cooled to room temperature, filtered through a short column of silica gel. The solvent was removed under reduced pressure and the amount of *ortho*-deuterated benzoic acid was determined by the relative ratio of peak area.

KIE experiment (parallel experiments)

$[RuCl_2(p\text{-cymene})]_2$ (Ru*, 3.1 mg, 5 mol%, 0.005 mmol), benzoic acid (12.2 mg, 0.1 mmol), *N*-methyl maleimide (16.7 mg, 0.15 mmol), NaH_2PO_4 (6.0 mg, 0.05 mmol), deionized water (0.3 mL), were successively added to a reaction vessel equipped with a stir bar. In another reaction vessel, D_5-benzoic acid (12.7 mg, 0.1 mmol) was used instead of benzoic acid. The two reactions were stirred at 85 °C (oil bath temperature) for 5 min, 7.5 min, 10 min 12.5 min, 15 min respectively. Then the two reaction mixtures were filtered through a short column of silica gel. The solvent was then removed under reduced pressure and ^{1}H NMR used 1,3,5-trimethoxybenzene as the internal standard. Thus the KIE was found to be 3.1.

KIE experiment (intermolecular competition)

$[RuCl_2(p\text{-cymene})]_2$ (Ru*, 3.1 mg, 5 mol%, 0.005 mmol), benzoic acid (6.1 mg, 0.05 mmol), D_5-benzoic acid (6.4 mg, 0.05 mmol), *N*-methyl maleimide (16.7 mg, 0.15 mmol), NaH_2PO_4 (6.0 mg, 0.05 mmol), deionized water (0.3 mL), were successively added to a reaction vessel equipped with a stir bar. The mixture was stirred at 85 °C (oil bath temperature) for 15 min. Then the reaction mixtures were filtered through a short column of silica gel. The solvent was then removed under reduced pressure and ^{1}H NMR used 1,3,5-trimethoxybenzene as the internal standard. Thus the KIE was found to be 7.6.

Experimental procedure for the synthesis of 3a on 10 mmol scale

An oven-dried 100 mL Schlenk tube was charged with 2-methylbenzoic acid (1.3600 g, 10 mmol), *N*-methyl maleimide (1.6665 g, 15 mmol), $[RuCl_2(p\text{-cymene})]_2$ (Ru*, 0.3062 g, 0.5 mmol), NaH_2PO_4 (0.5999 g, 5 mmol), and deionized water (30 mL). The mixture was stirred at 85 °C (oil bath temperature) in air for 24 h. Then, the reaction mixture was concentrated to give a crude product, which is purified by silica-gel column chromatography using hexanes/EtOAc/AcOH (2/1/0.05) to yield compound **3a** (1.875 g, 76%).

Experimental procedure for the synthesis of 4h on 4 mmol scale.

An oven-dried 50 mL Schlenk tube was charged with 5-fluoro-2-methoxybenzoic acid (0.6802 g, 4 mmol), *N*-methyl maleimide (0.6666 g, 6 mmol), $[RuCl_2(p\text{-cymene})]_2$ (Ru*, 0.1225 g, 0.2 mmol), NaH_2PO_4 (0.2400 g, 2 mmol), and deionized water (12 mL). The mixture was stirred at 85 °C (oil bath temperature) in air for 16 h. Then, the reaction mixture was concentrated to give a crude product, which is purified by silica-gel column chromatography using hexanes/EtOAc (5/1) to yield compound **4j** (0.836 g, 88%).

Experimental procedure for the synthesis of 4e'.

An oven-dried reaction vessel was charged with $[RuCl_2(p\text{-cymene})]_2$ (Ru*, 3.1 mg, 5 mol%, 0.005 mmol), 5-fluoro-2-methylbenzoic acid (0.0154 g, 0.1 mmol), *N*-methyl maleimide (0.0166 g, 0.15 mmol), deionized water (0.5 mL). The mixture was stirred under air at 85 °C (oil bath temperature) for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (5 mL) and filtered through a short silica gel pad. The filter cake was further flushed with EtOAc (3 × 5 mL). The combined solution was concentrated under vacuum, and the residue was purified by a preparative thin-layer chromatography to afford **4e'**.

Experimental procedures for the synthesis of spirosuccinimide.

An oven-dried reaction vessel was charged with **3a** (24.7 mg, 0.1 mmol), CuCl (4.9 mg, 0.05 mmol), *N,N*-dimethylformamide (0.6 mL). The vessel was heated at 140 °C (oil bath temperature) for 15 min under air. When the reaction was complete, the resulting mixture was cooled to room temperature, and filtered through a short silica gel pad. Then, the mixture was concentrated in vacuo to give a residue, which was purified by preparative thin-layer chromatography (TLC) on silica gel to afford the corresponding product.

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Keywords: on water reaction • ruthenium catalysis• conjugate addition •

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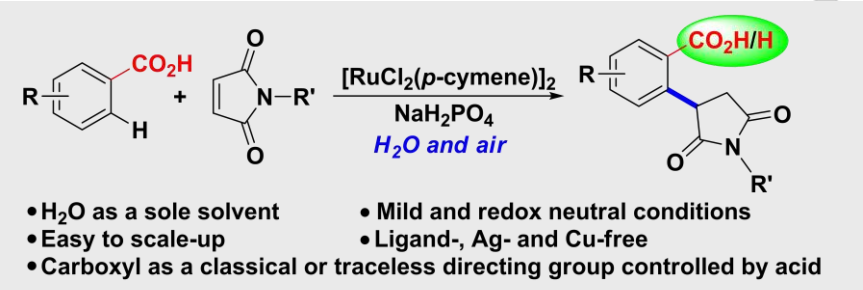

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