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Direct Decarboxylative *meta*-Selective Acylation of Arenes via *ortho*-Ruthenation Strategy

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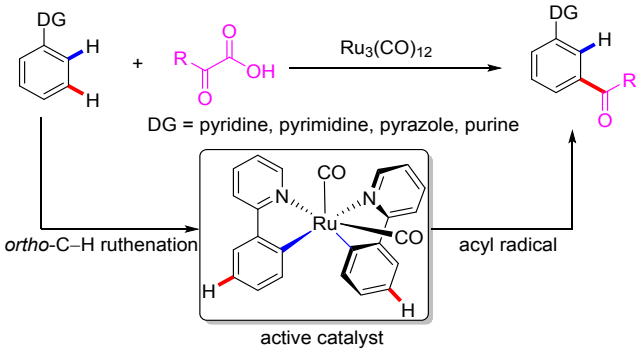
ABSTRACT: The direct decarboxylative *meta*-selective C–H acylation of a wide range of arenes is established via the ruthenium-catalyzed *ortho*-metalation strategy. This procedure, using $Ru_3(CO)_{12}$ as the catalyst and *α*-oxocarboxylic acids as the acylation source, featured broad substrate scope, good functional group tolerance, and high regioselectivity. Mechanistic studies demonstrated that a radical process and an 18e-octahedral ruthenium species were involved in this reaction. The present work provides a new strategy for the regioselective *meta*-acylation reactions and will be a powerful tool for the development of pharmaceutical and materials science.



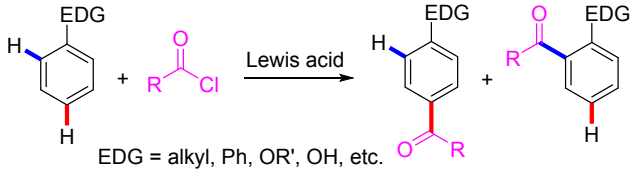
KEYWORDS: *meta* selectivity, decarboxylative acylation, ruthenium catalysis, *ortho*-metalation, α-oxocarboxylic acids, radical process

INTRODUCTION

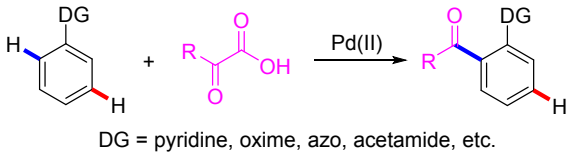
Aromatic ketones have practical applications in pharmaceuticals, agrochemicals, fragrances, flavors, dyes, and photosensitizers,[1] and substantially act as structural motifs or precursors of many natural products. The site-selective C–H bond functionalization of aromatic compounds is of crucial importance to synthetic organic chemistry and has versatile applications in drug discovery and materials science.[2] Therefore, regioselective introduction of carbonyl groups to the *ortho*-, *meta*-, and *para*-positions of aromatic ring to access distinctly substituted aryl ketones is extremely valuable in organic synthesis. The classic Friedel–Crafts acylation reactions usually give a mixture of products with poor *ortho*/*para* regioselectivity (Scheme 1a),[3] and generally suffer from the limitation of substrate scope to arenes bearing electron-donating groups (EDGs) as well as the requirement of a stoichiometric amount of Lewis acid. In addition, the associated disadvantages arising from the hydrolysis of the strong complex formed between the ketone product and the Lewis acid such as $AlCl_3$ during the workup process would result in the loss of the catalyst, substantial amount of waste, and corrosion problems. The past decade has witnessed tremendous development of the transition-metal-catalyzed directing group (DG)-assisted *ortho*-C–H acylation of aromatic compounds with various acyl sources.[4] Among them, the palladium-catalyzed decarboxylative *ortho*-acylation reactions with *α*-oxocarboxylic acids have emerged as valid tools to construct aromatic ketones for their efficient and environment-friendly advantages[5] (Scheme 1b). In stark contrast, the *meta*-selective C–H acyl-

Scheme 1. Regioselectivity Control in Acylation Reactions

a) Classic Friedel-Crafts acylation

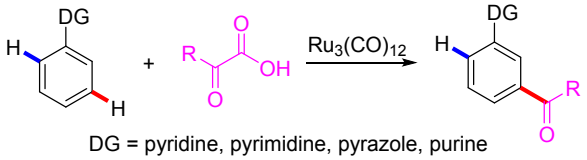


b) Pd-catalyzed *ortho*-C_{Ar}-H acylation with α-oxocarboxylic acids



c) ***This work:***

Ru-catalyzed *meta*-C_{Ar}-H acylation with α-oxocarboxylic acids



ation of arenes is still limited and remains a challenging task. In 1998, the Buchwald group reported a directed *meta*-selective acylation of aromatic compounds by combining an *ortho*-lithiation procedure with zirconocene–benzyne chemistry to afford a series of 3-acyl-1-substituted benzene derivatives.[6] However, this method is limited in organic synthesis due to its multi-step process and requirement of tedious preparation of organometallic intermediates. 3-Acyl-1-substituted aromatic compounds represent an important class of subunits in many natural products and drugs, such as Ketoprofen,[7] Rubialatins B,[8] and Nepafenac.[9] Therefore, it is highly desirable to develop more efficient methodologies for the *meta*-selective C–H acylation of aromatic compounds with high regioselectivities.

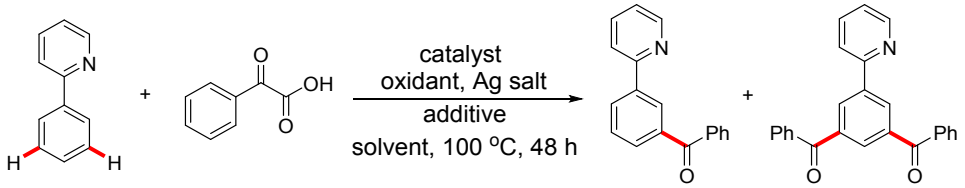
Recently, the ruthenium-catalyzed σ-activation was utilized to realize the *meta*-C–H functionalization of arenes, in which the *ortho*-cycloruthenation was exploited to influence the aromatic ring electronically and to enable *para*-sulfonation to the Ru–C bond.[10] This protocol demonstrates advantages of obviating complex templates/ligands or additional transient mediators and cheaper ruthenium catalysts for remote C–H functionalizations.[11] As a consequence, many other *meta*-selective functionalizations using the Ru-catalyzed *ortho*-metalation strategy have been developed to date, including alkylation,[12] halogenation,[13] nitration,[14] difluoro- and monofluoroalkylation[15] and benzylation.[16] It is noteworthy that the Ru-catalyzed indirect *meta*-carboxylation with carbon tetrabromide (CBr_4) as the C1 source was described very recently.[17] The CO_2Me group was introduced via further methanolysis of the incipient tribromomethyl adduct, which was essentially an alkylation process with CBr_4. Despite of these indisputable advances, many other new types of functional groups remain to be introduced to the *meta*-position of arenes with this powerful Ru-catalyzed *meta*-selective functionalization regime.

Inspired by the above-mentioned ruthenium-catalyzed *meta*-C–H functionalizations, we envisioned that the switch of regioselectivity from the *ortho*- to *meta*-position might be realized by changing the Pd catalyst to a Ru species. Herein, we disclose the first ruthenium-catalyzed direct decarboxylative *meta*-selective acylation of arenes with α-oxocarboxylic acids (Scheme 1c). In this strategy, the decarboxylative C_{Ar}–H acylation occurred at the *meta*-position of arenes exclusively, and a variety of common functional groups, such as halogen (F, Cl, Br, and I), cyano, trifluoromethyl, ether, and thioether, were well tolerated.

RESULTS AND DISCUSSION

In our initial investigation, we chose 2-phenylpyridine (**1a**) as the model substrate and phenylglyoxylic acid (**2a**) as the acylation reagent to identify the optimal reaction conditions, and selected results are summarized in Table 1 (For details, see Table S1 in the Supplemental Information). At first, the commonly used $[RuCl_2(p\text{-cymene})]_2$ was employed as the catalyst, but no desired product was detected (entry 1). Screening of alternative ruthenium catalysts showed that the desired *meta*-acylated product **3aa** was obtained in 27% yield in the presence of $Ru_3(CO)_{12}$ (entry 2). To our delight, when $Na_2S_2O_8$ was added, the yield of **3aa** was increased to 48%, along with a small amount of di-*meta*-acylated product **3aa'** (the structure of **3aa'** was confirmed by the single-crystal X-ray diffraction, for details, see Figure S134 and Table S2 in the Supplemental Information) (entry 3). Several additives such as *D*-camphorsulfonic acid (*D*-CSA), trifluoacetic acid (TFA), CH_3SO_3H, and *p*-toluenesulfonic acid (PTSA) were examined, and it was found that the addition of *D*-CSA led to a higher isolated

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa** **3aa'**

Entry	Catalyst	Oxidant	Ag salt	Additive	Solvent	Yield, %[b] (**3aa**/**3aa'**)
1	$[RuCl_2(p\text{-cymene})]_2$	-	Ag_2CO_3	-	DCM	0

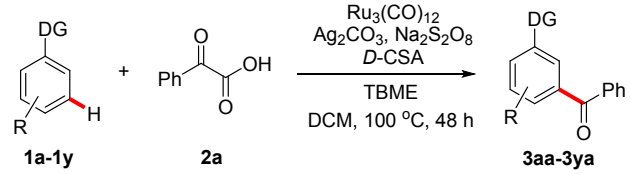
2	$Ru_3(CO)_{12}$	-	Ag_2CO_3	-	DCM	27/trace
3	$Ru_3(CO)_{12}$	$Na_2S_2O_8$	Ag_2CO_3	-	DCM	48/<5
4	$Ru_3(CO)_{12}$	$Na_2S_2O_8$	Ag_2CO_3	*D*-CSA	DCM	55/<5
***5*[c]**	***$Ru_3(CO)_{12}$***	***$Na_2S_2O_8$***	***Ag_2CO_3***	***D*-CSA**	***DCM***	***72*/*6***
6[c]	-	$Na_2S_2O_8$	Ag_2CO_3	*D*-CSA	DCM	0
7[c]	$Ru_3(CO)_{12}$	$Na_2S_2O_8$	-	*D*-CSA	DCM	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst (5 mol%), oxidant (2.0 equiv), Ag salt (2.5 equiv), and additive (0.5 equiv) in DCM (6 mL) at 100 ° C for 48 h in a sealed thick-walled tube. [b]Isolated yields based on **1a**. [c]150 μL TBME was added.

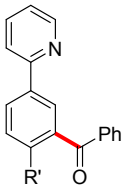
yield (55%) (entries 4). To our great delight, dramatically improved yield of **3aa** (72%) was obtained when *tert*-butyl methyl ether (TBME) was added as the co-solvent (entry 5), which may favour the dissolution of the reaction mixture or the formation of the active catalytic intermediate. Control experiments revealed that $Ru_3(CO)_{12}$ and Ag_2CO_3 were essential for this reaction (entries 6 and 7). Therefore, the optimized reaction conditions of the Ru-catalyzed decarboxylative *meta*-acylation were as shown in entry 5.

Having established the optimal reaction conditions, then we investigated the scope and functional group tolerance with respect to 2-arylheterocycles **1**. As shown in Scheme 2, the reactions proceeded smoothly to afford *meta*-acylated products **3aa**–**3ya** in moderate to good yields, with slight modification of reaction conditions in some cases. The *para*-substituted 2-phenylpyridines were well tolerated with our standard conditions, regardless of electron-rich or electron-deficient functional groups. The arylpyridines **1b**–**1g** with *para*-substituted electron-donating groups gave the corresponding products **3ba**–**3ga** in 42–76% yields. Substrates with halogen substituents worked well and furnished products **3ha**–**3ja** in moderate to good yields (52–75%), which provided the opportunity for further functionalization via cross coupling reactions. Substrates **1k** and **1l** with strong electron-withdrawing groups (CF_3 and CN) also proceeded well and delivered the desired products **3ka** and **3la** in 51% and 44% yields, respectively. Nevertheless, the substrate with very strong electron-withdrawing nitro group failed to provide the desired *meta*-acylated product, probably due to the increased electron-deficiency of the aryl ring. To our delight, when one of the two *meta*-positions on the phenyl was occupied by fluorine, the acylation occurred on the other *meta*-position, and the corresponding product **3ma** was isolated in 52% yield. It is worth noting that when *ortho*-substituted substrate **1n** was employed, the acylation occurred on both *meta*-positions (m/m' = 2.9:1), which may result from the steric effect of fluorine atom. In addition, 2-(naphthalen-2-yl)pyridine also participated in this protocol well, and the corresponding product **3oa** was obtained in 59% yield. Furthermore, substrates bearing a substituent on the pyridine moiety were also examined, and the desired products **3pa**–**3ra** were isolated in 47–66% yields. Other directing groups were also explored to survey the scope and limitation of our protocol. When the pyrimidyl moiety was used as the directing group, the desired products **3sa**–**3va** were obtained in yields of 51–71%. The pyrazolyl group was also well tolerant under the optimized conditions, providing the *meta*-acylated product **3wa** in 52% yield, and the regioselectivity directly contrasts with classic Friedel–Crafts acylation reaction of 1-phenylpyrazole with benzoyl chloride, where the acylation took place on the 4-position of the pyrazole ring.[18] To demonstrate the utility of our methodology, bioactive purine derivatives were employed, and to our great delight, the desired *meta*-acylated products **3xa** and **3ya** were successfully obtained in 55% and 54% yields, respectively. The above-mentioned results indicate that our methodology may be useful for the preparation of many bioactive compounds.

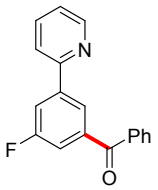
Scheme 2. Scope of Substituted Arenes[a]



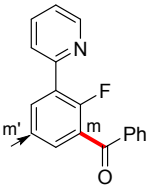
1a-1y **2a** **3aa-3ya**



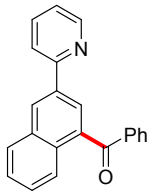
3aa, R' = H, 78% (12:1)
3ba, R' = Me, 76% (4:1)[b]
3ca, R' = ^{t}Bu, 42%
3da, R' = OMe, 67%[c]
3ea, R' = SMe, 61%[c]
3fa, R' = OBn, 63%
3ga, R' = OPh, 46%
3ha, R' = F, 75%
3ia, R' = Cl, 66%
3ja, R' = Br, 52%
3ka, R' = CF_3, 51%
3la, R' = CN, 44%



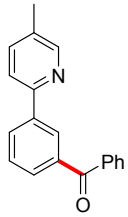
3ma, 52%



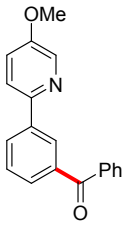
3na, 58%
(m/m' = 2.9:1)



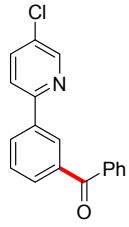
3oa, 59%



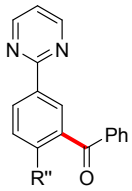
3pa, 66%
(10:1)



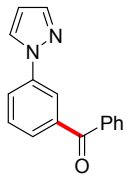
3qa, 63%
(5:1)



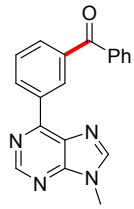
3ra, 47%



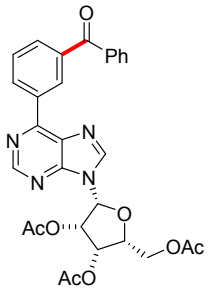
3sa, R'' = H, 71% (9:1)
3ta, R'' = Me, 70% (6:1)
3ua, R'' = OMe, 65%
3va, R'' = Cl, 51%



3wa, 52%



3xa, 55%[b,d]

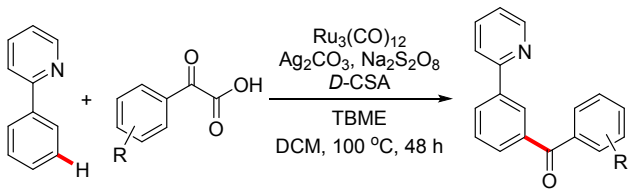


3ya, 54%[b,d]

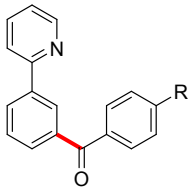
[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $Ru_3(CO)_{12}$ (5 mol%), $Na_2S_2O_8$ (2.0 equiv.), Ag_2CO_3 (2.5 equiv.), *D*-CSA (0.5 equiv.), and TBME (150 μL) in DCM (6 mL) at 100 °C for 48 h. Isolated yields based on **1**. Data in parentheses are the ratios of mono- to diacylation products. Unless otherwise noted, mono/di > 20:1. [b]$Ru_3(CO)_{12}$ (10 mol%). [c]$Na_2S_2O_8$ (2.5 equiv.), 110 °C. [d]PPh_3 (30 mol%) was added.

To further survey the substrate scope and generality, a variety of α-oxocarboxylic acids **2b**–**2w** were employed to react with **1a** (Scheme 3). It was found that both electron-rich and -deficient substituents on the phenyl ring of phenylglyoxylic acids were widely tolerated, and the desired *meta*-acylated products were obtained in moderate to good yields. The *para*-substituted phenylglyoxylic acids proved

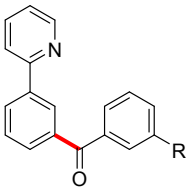
Scheme 3. Scope of Substituted α-Oxocarboxylic Acids[a]



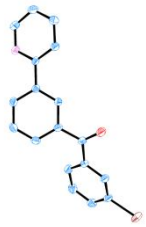
1a **2b-2w** **3ab-3aw**



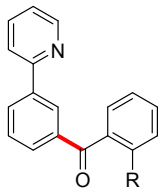
3ab, R = Me, 67% (16:1)
3ac, R = F, 72% (11:1)
3ad, R = Cl, 75%[b] (10:1)
3ae, R = Br, 65%
3af, R = I, 61%
3ag, R = Ph, 60%[b,c]



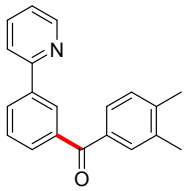
3ah, R = Me, 62%[b]
3ai, R = OMe, 63%
3aj, R = Cl, 73% (11:1)
3ak, R = Br, 76% (17:2)



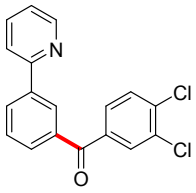
3ak
CCDC 1829341



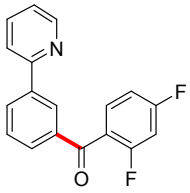
3al, R = Me, 58%
3am, R = OMe, 48%
3an, R = Cl, 48%



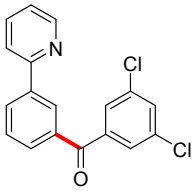
3ao, 60%[b]



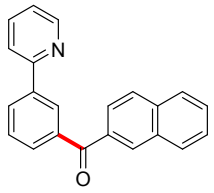
3ap, 76%
(12:1)



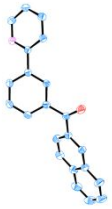
3aq, 67%
(10:1)



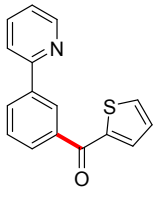
3ar, 67%[b]
(12:1)



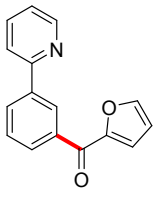
3as, 69%



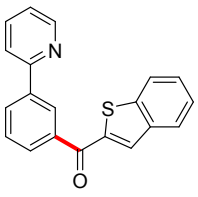
3as
CCDC 1829342



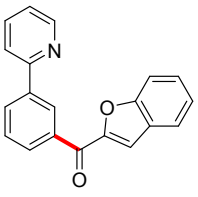
3at, 41%



3au, 24%



3av, 30%



3aw, 27%

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $Ru_3(CO)_{12}$ (5 mol%), $Na_2S_2O_8$ (2.0 equiv.), Ag_2CO_3 (2.5 equiv.), *D*-CSA (0.5 equiv.), and TBME (150 μL) in DCM (6 mL) at 100 °C for 48 h. Isolated yields based on **1a**. Data in parentheses are the ratios of mono- to diacylation products. Unless otherwise noted, mono/di > 20:1. [b]$Ru_3(CO)_{12}$ (10 mol%). [c]36 h.

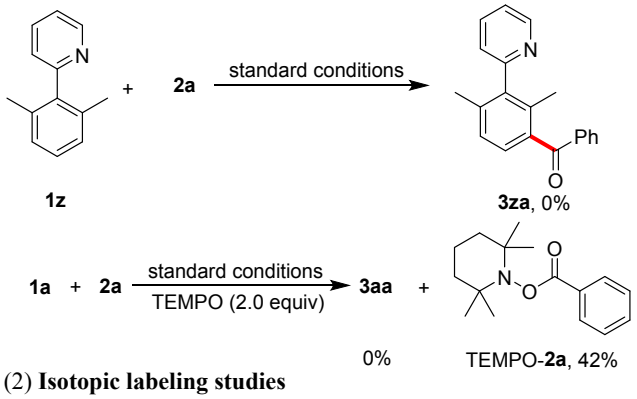
to be suitable substrates for this transformation, affording the corresponding products **3ab**–**3ag** in good yields (60–75%). Similarly, the *meta*-substituted phenylglyoxylic acids **2h**–**2k** also worked well to give the desired products **3ah**–**3ak** in 62–76% yields. Moreover, this reaction could also be extended to *ortho*-substituted phenylglyoxylic acids to produce **3al**–**3an** in moderate yields (48–58%). When disubstituted phenylglyoxylic acids were employed, the corresponding products **3ao**–**3ar** were obtained in 60–76% yields. 2-(Naphthalene-1-yl)-2-oxoacetic acid (**2s**) was well tolerant to this acylation reaction conditions, providing the *meta*-acylated product **3as** in 69% yield. What is more, heteroaryl glyoxylic acids were also examined, and to our delight, the corresponding products **3at**–**3aw** were obtained, albeit in relatively lower yields (24–41%). It should be noted that phenylglyoxylic acids with a very strong electron-deficient nitro group at *meta*- or *para*-position and alkylglyoxylic acids such as pyruvic acid and 3,3-dimethyl-2-oxobutanoic acid gave disappointing results, even with higher temperatures or more additives. In addition, the attempts to replace the arylglyoxylic acids with other possible radical precursors such as aromatic carboxylic acids, and aromatic aldehydes failed. The structures of products **3** were unambiguously established by the single-crystal X-ray diffraction analyses of representative **3ak** and **3as** (see Figures S135–S136 and Tables S3–S4 in the Supplemental Information).[19]

It is noteworthy that electron-deficient arenes are usually not suitable for the classic Friedel-Crafts acylation reactions due to the electrophilic nature of the acylating agents. In fact, our attempts to realize the acylation reactions of the representative substrates **1a** and **1s** containing electron-withdrawing pyridine and pyrimidine groups with benzoyl chloride in the presence of $AlCl_3$ failed, reflecting the superiority and uniqueness of our *meta*-selective acylation methodology.

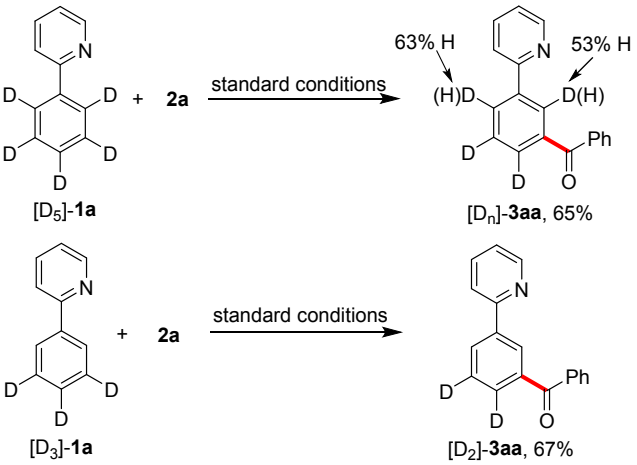
To gain insight into the reaction mechanism of this transformation, some control experiments were performed (Scheme 4). First, substrate **1z** bearing two methyl groups to block the two *ortho* positions of the phenyl ring failed to give the desired product under the standard conditions, indicating the importance of the *ortho*-C_{Ar}–H metalation in the *meta*-acylation process. Second, the reaction between **1a** and **2a** was retarded completely in the presence of 2.0 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and the TEMPO-**2a** adduct was isolated in 42% yield, suggesting that a radical process might be involved in this transformation. Third, experiments with the isotopically labeled substrates were conducted to investigate the D/H exchange during this reaction. It was found that a significant D/H exchange was observed at the *ortho*-position of **3aa** when [D_5]-**1a** was treated with **2a** under the standard conditions, while no D/H exchange occurred when [D_3]-**1a** was used as the substrate. These results suggested that the *ortho*-C_{Ar}–H activation was a reversible process in this transformation, whereas the *meta*-C_{Ar}–H cleavage was not. Finally, the intermolecular competition experiment with **1a** and [D_3]-**1a** showed a kinetic isotopic effect (KIE) of k_H/k_D = 4.0, indicating that the *meta*-C–H cleavage might be kinetically relevant in our catalytic system.

Scheme 4. Preliminary Mechanistic Studies

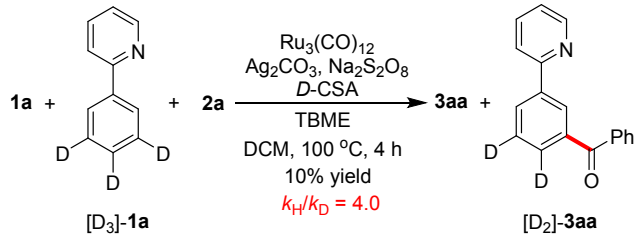
(1) **Control experiments**



(2) **Isotopic labeling studies**



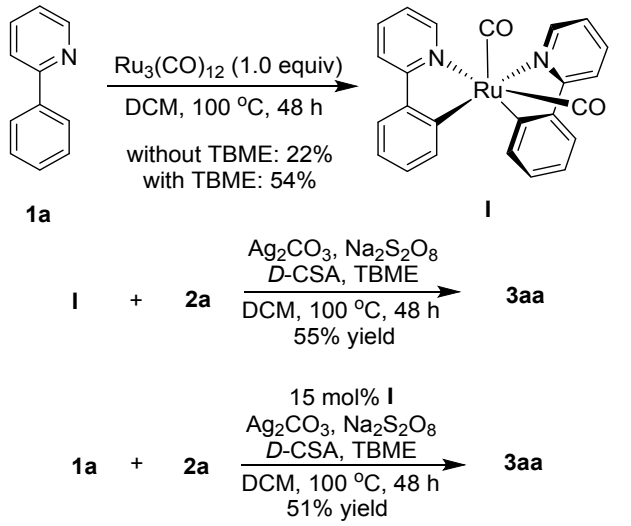
(3) **Kinetic isotope effect study**



In order to obtain the active ruthenium intermediate, the stoichiometric reaction of **1a** with 1.0 equiv. of $Ru_3(CO)_{12}$ was conducted in DCM at 100 °C for 48 h, and an 18e-octahedral ruthenium complex **I**[14a] was isolated in 22% yield. Interestingly, a better yield of 54% was obtained in the presence of TBME, indicating that the mixed solvents of DCM and TBME favoured the formation of the active ruthenium intermediate in our *meta*-C–H acylation reaction. Furthermore, the stoichiometric and catalytic experiments utilizing the complex **I** worked well and produced product **3aa** in 55% and 51% yields, respectively. These results implied that **I** might be the active catalyst intermediate in this reaction (Scheme 5).

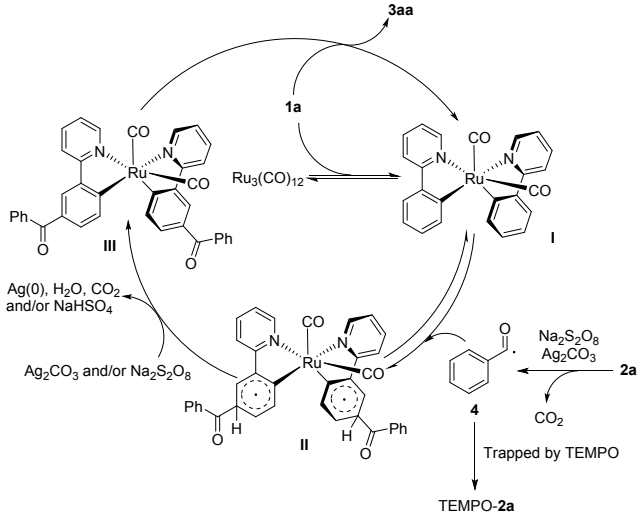
On the basis of the above results and previous literature, a plausible mechanism for this *meta*-selective acylation is

Scheme 5. Synthesis and Verification of Active Ruthenium Intermediate



proposed, as shown in Scheme 6. At first, the active ruthenium intermediate **I** is formed from **1a** and $Ru_3(CO)_{12}$ through the reversible *ortho*-ruthenation step.[14a] Subsequently, **I** undergoes electrophilic attack at the *para*-position of the Ru-C bond with the acyl radical **4**, which is produced by decarboxylation of **2a** with the aid of $Na_2S_2O_8$ and Ag_2CO_3,[5h,i] leading to the intermediate **II**, and subsequent oxidative deprotonation of **II** by Ag_2CO_3 and/or $Na_2S_2O_8$ furnishes the ruthenacycle **III**. Finally, the protonation and ligand exchange of **III** with **1a** release the desired *meta*-acylated product **3aa** and regenerate the intermediate **I** to complete the catalytic cycle. Trace amounts of biaryl byproducts[20] resulted from the homo-couplings of **I** and **III** could be detected in the reaction mixtures by mass spectroscopy, indicating that $Na_2S_2O_8$ and Ag_2CO_3 are not the suitable oxidants for this homo-coupling process, and thus preferably afford the *meta*-acylated products.

Scheme 6. Plausible Reaction Mechanism



CONCLUSION

In summary, we have developed the first ruthenium-catalyzed direct decarboxylative *meta*-selective C–H acylation of a wide range of arenes, using $Ru_3(CO)_{12}$ as the catalyst and *α*-oxocarboxylic acids as the acylation source. This procedure possesses advantages of broad substrate scope, good functional group tolerance, and high regioselectivity. Mechanistic studies demonstrated that an 18e-octahedral ruthenium intermediate as the active catalyst and a radical process were involved in this reaction. The present work extends the existing paradigm of the recently popular ruthenium-catalyzed *meta*-selective C–H functionalization regime and provides a new strategy for the regioselective *meta*-acylation reactions. We anticipate that this strategy should also be valuable for the development of pharmaceutical and materials science.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.

Detailed information on experimental procedures, characterization data, and crystallographic data.

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Notes

The authors declare no competing financial interest.

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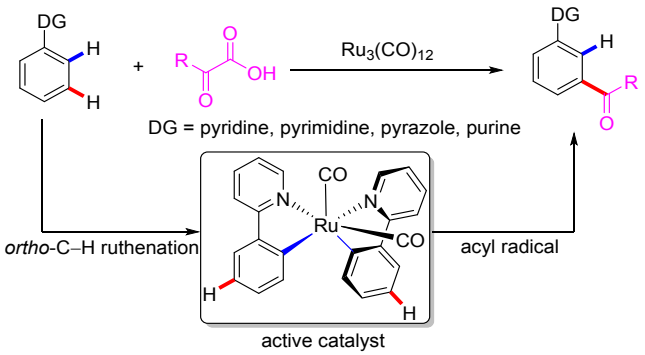

Meta-selective acylation of arenes has been achieved via the Ru-catalyzed *ortho*-metalation strategy and a radical process, featuring broad substrate scope, good functional group tolerance, and high regioselectivity.