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Ruthenium-catalyzed *meta*-C–H bond alkylation of aryl 2-pyridyl ketones†

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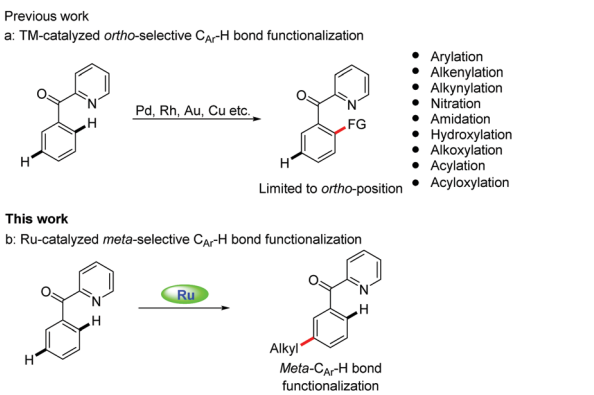
The first example of *meta*-selective C_{Ar}–H bond functionalization of aryl 2-pyridyl ketones has been developed using [Ru(*p*-cymene)Cl_2]$_2$ as the catalyst and alkyl bromide as the coupling reagent. This development provides an efficient strategy for modifying the *meta*-position of aryl 2-pyridyl ketone skeletons, which are found in various functional molecules.

Aromatic ketones and their derivatives are essential compounds that are not only present in various pharmaceutical chemicals, bioactive natural products, agricultural chemicals, and many newly developed functional materials, but also used as key intermediates for the synthesis of various functional molecules.[1] To date, numerous methods for synthesizing aromatic ketones have been reported. A classical method for preparing aromatic ketone derivatives involves introducing substituents into aromatic ketones *via* electrophilic aromatic substitution reactions. This approach is efficient and has been applied in laboratory synthesis and the chemical industry. As carbonyls are strong deactivating groups, electrophilic aromatic substitution is limited to methods such as nitration and sulfonation, while Friedel–Crafts alkylation and acylation cannot proceed.[2]

In recent years, in addition to the increase in TM-catalyzed C–H bond functionalization, arylation,[3] alkenylation,[3d,4] nitration,[5] amidation,[6] alkoxylation,[7] acylation,[8] and halogenation[9] of aryl 2-pyridyl ketones, C_{Ar}–H bonds have been achieved in the presence of various transition metals (Scheme 1). However, these approaches have been limited to the *ortho*-position of the pyridyl group. Meanwhile, a practical and efficient approach to remote *meta*-selective C_{Ar}–H functionalization of arenes remains challenging.

Ruthenium complexes are not only inexpensive and have high catalytic activity, but also have a unique catalytic character. Intriguingly, ruthenium can catalyze *meta*-selective C–H bond functionalization through the Ru–C_{Ar} bond *ortho*/*para*-directing effect,[10] in addition to *ortho*-C_{Ar}–H bond transformation.[11] Herein, we achieved the first example of *meta*-selective C_{Ar}–H bond functionalization of aryl 2-pyridyl ketones employing a ruthenium complex as a catalyst.

To explore the feasibility of Ru-catalyzed *meta*-selective C_{Ar}–H bond functionalizations of aryl 2-pyridyl ketones, commercially available phenyl(pyridin-2-yl)methanone (**1a**) and methyl 2-bromopropanoate (**2a**) were used as classical substrates for screening and optimizing the reaction conditions. The reaction was conducted at 110 °C for 24 h in a sealed thick-walled Schlenk reaction tube under a N_2 atmosphere, as shown in Table 1. Using [Ru(*p*-cymene)Cl_2]$_2$ as a catalyst, KOAc as a base, and toluene as a solvent, the product was obtained in 26% isolated yield (entry 1). When carboxylic acids were added into the system, the reaction efficiency improved dramatically (entries 2–5). In particular, when 1-AdCOOH was used as an



Scheme 1 TM-catalyzed C_{Ar}–H functionalization of aryl 2-pyridyl ketones.

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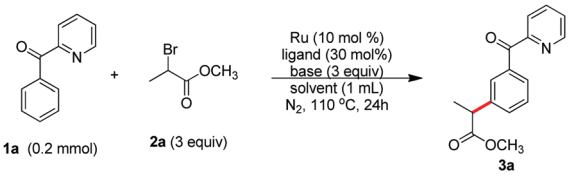
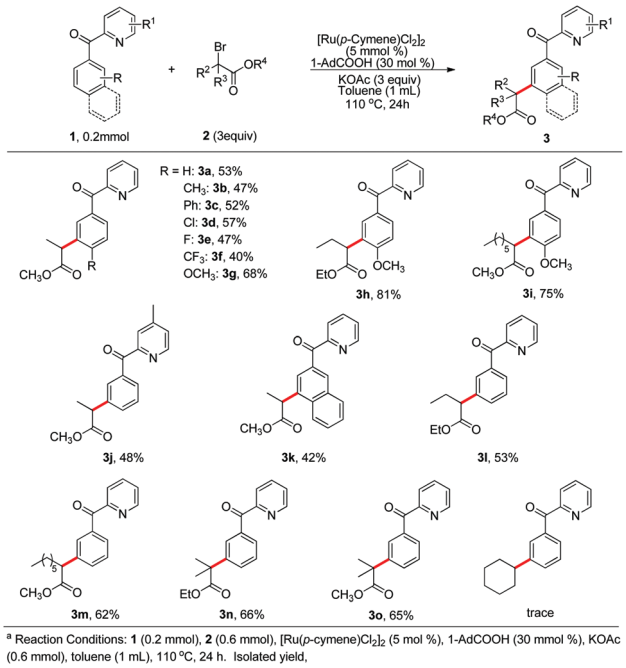
Table 1 Optimization of the reaction conditions for *meta*-selective C_{Ar}–H alkylation of aryl 2-pyridyl ketones



Entry	Catalyst	Base	Ligand	Solvent	Yield (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	—	Toluene	26
2	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	Ac-Leu-OH	Toluene	35
3	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	MesCOOH	Toluene	34
«	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	1-AdCOOH	Toluene	53
5	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	PivOH	Toluene	43
6	$[Ru(p\text{-cymene})Cl_2]_2$	K_2CO_3	1-AdCOOH	Toluene	37
7	$[Ru(p\text{-cymene})Cl_2]_2$	Na_2CO_3	1-AdCOOH	Toluene	12
8	$[Ru(p\text{-cymene})Cl_2]_2$	CS_2CO_3	1-AdCOOH	Toluene	32
9	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc	1-AdCOOH	Toluene	27
10	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	1-AdCOOH	Benzene	43
11	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	1-AdCOOH	Xylene	18
12	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	1-AdCOOH	Acetonitrile	0
13	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	1-AdCOOH	DMF	0
14	$RuCl_3$	KOAc	1-AdCOOH	Toluene	19
15	$Ru_3(CO)_{12}$	KOAc	1-AdCOOH	Toluene	0
16	$Pd(OAc)_2$	KOAc	1-AdCOOH	Toluene	0
17	—	KOAc	1-AdCOOH	Toluene	0

additive, the desired product was obtained in 53% isolated yield (entry 4). Base screening indicated that K_2CO_3, Na_2CO_3, Cs_2CO_3, and NaOAc were also effective for Ru-catalyzed *meta*-selective C_{Ar}–H bond functionalization (entries 6–9), but gave the desired product in lower yields. The solvent also played an important role. The desired product was also obtained in aromatic solvents other than toluene, such as benzene and xylene (entries 10 and 11). However, acetonitrile and DMF were ineffective solvents for the transformation (entries 12 and 13). A small amount of the product was obtained when $RuCl_3$ was used as a catalyst (entry 14). When $Ru_3(CO)_{12}$, $Pd(OAc)_2$, or no metal catalyst was added to the system, the reaction did not proceed (entries 15–17).

With the optimized conditions in hand, the generality and scope of the Ru-catalyzed *meta*-C–H alkylation of aryl 2-pyridyl ketones was examined using various aryl 2-pyridyl ketones and alkyl bromides as substrates, as shown in Scheme 2. Initially, various aryl 2-pyridyl ketones bearing different substituents on the phenyl ring were used as substrates under the optimized conditions. Phenyl(pyridin-2-yl)methanones bearing a methyl or phenyl group on the benzene ring were suitable substrates for the Ru-catalyzed *meta*-C_{Ar}–H alkylation, affording the corresponding products in moderate yields (**3b** and **3c**). Notably, halogen substituents were tolerated well in the process, providing the opportunity for further transformations to produce highly functionalized derivatives (**3d** and **3e**). Further experimental results indicated that the electronic nature markedly affected the reaction efficiency. Although the desired products were obtained using substrates bearing both electron-withdrawing substituents (–CF_3, **3f**) and electron-donating substituents (–OCH_3, **3g–3i**), electron-donating substituents were better suited to Ru-catalyzed *meta*-C_{Ar}–H alkylation compared with electron-withdrawing substituents. A 2-pyridyl-bearing methyl group was also an efficient



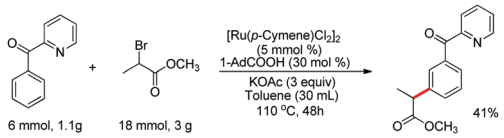
[a] Reaction Conditions: **1** (0.2 mmol), **2** (0.6 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), 1-AdCOOH (30 mmol %), KOAc (0.6 mmol), toluene (1 mL), 110 °C, 24 h. Isolated yield,

Scheme 2 Scope and generality of Ru-catalyzed *meta*-C_{Ar}–H alkylation of aryl 2-pyridyl ketones with alkyl bromides.

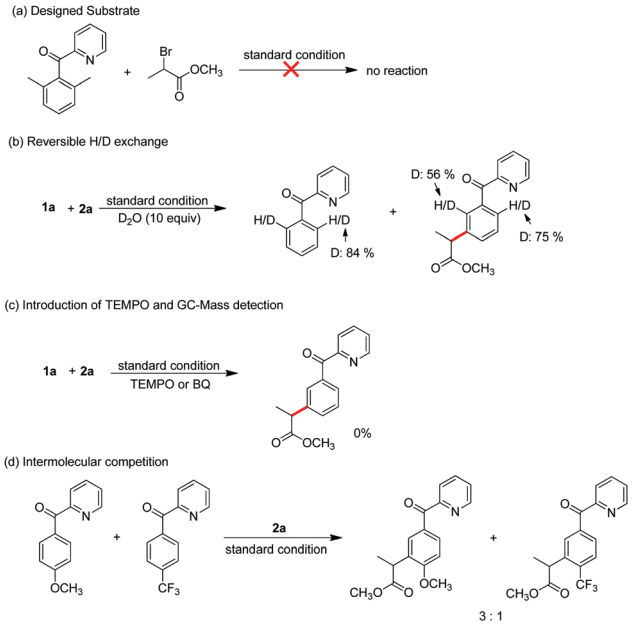
directing group in the process (**3j**). To our delight, when 2-(2-naphthyl)pyridine was used as a reactant, the desired product was obtained (**3k**). Various other alkyl bromides were also subjected to the optimized conditions, with the results indicating that the other 2-bromocarboxylates were suitable alkylation reagents, affording the desired products in good isolated yields (**3h**, **3i**, **3l–3o**). Unfortunately, the other brominated alkanes were not tolerated in the process.

In a gram-scale experiment, the desired product was only obtained by extending the reaction time (Scheme 3). Therefore, the present Ru-catalyzed *meta*-C_{Ar}–H alkylation provided an efficient and practical approach to modification and functionalization at the *meta*-position of aryl 2-pyridyl ketones.

Furthermore, a series of experiments were designed and conducted to explore the mechanism of the Ru-catalyzed *meta*-C_{Ar}–H alkylation of aryl 2-pyridyl ketones, as shown in Scheme 4. First, (2,6-dimethylphenyl)(pyridin-2-yl)methanone, bearing two methyl groups blocking both *ortho*-positions on the phenyl ring, did not react with the alkyl bromide under the optimized condition (Scheme 4a), supporting that the directing group-assisted *ortho*-C_{Ar}–H metalation was indispensable in the Ru-catalyzed alkylation process. Next, significant H/D-exchange at the *ortho*-position was observed when D_2O was added to the model reaction, indicating that *ortho*-C_{Ar}–H metalation was a reversible



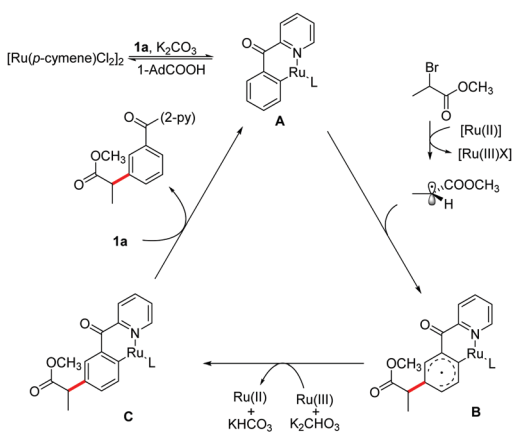
Scheme 3 Gram-scale synthesis.



Scheme 4 Preliminary mechanistic studies.

process and that the Ru-catalyzed *meta*-C_{Ar}–H functionalization was water-tolerant (Scheme 4b). Furthermore, when radical inhibitors, such as TEMPO and BQ, were separately added to the model reaction, the desired product was not obtained, indicating that Ru-catalyzed *meta*-C_{Ar}–H alkylation involved a radical mechanism *via* a single electron transfer (SET) process (Scheme 4c). Finally, to investigate the impact of electronic nature on the alkylation, a competitive reaction of (4-methoxyphenyl)(pyridin-2-yl)methanone, bearing an electron-donating group, and pyridin-2-yl(4-(trifluoromethyl)phenyl)methanone, bearing an electron-withdrawing group, with methyl 2-bromopropanoate provided mainly product **3g** under the optimized conditions (Scheme 4d). This result showed that this Ru-catalyzed alkylation was an electrophilic process.

Based on the above experimental results and previous reports related to Ru-catalyzed *meta*-C_{Ar}–H bond functionalization,[10] a plausible mechanism was proposed, as shown in Scheme 5. The aryl 2-pyridyl ketones react with $[Ru(p\text{-cymene})Cl_2]_2$ to provide a



Scheme 5 Proposed catalytic cycle.

key active six-membered ruthenacycle species (**A**) *via* reversible *ortho*-C_{Ar}–H bond metalation. Next, aided by the C_{Ar}–Ru σ-bond *ortho*/*para*-directing effect, an alkyl radical, formed from alkyl bromide *via* a ruthenium-mediated SET process, attacks species **A** at the *meta*-position to the pyridyl group, providing an active species **B**. The deprotonation of species **B** assisted by ruthenium(III) and K_2CO_3 generates a stable species **C**. Finally, the species **C** exchanged a ligand with the aryl 2-pyridyl ketone to provide the final product and recycle the active catalyst species.

In conclusion, we have achieved the first *meta*-C_{Ar}–H functionalization of aryl 2-pyridyl ketones using alkyl bromides in the presence of a ruthenium complex catalyst. Mechanistic studies suggested that this *meta*-C_{Ar}–H bond functionalization might involve a ruthenium-mediated SET. This method provides an efficient approach to the modification and functionalization at the *meta*-position of aryl 2-pyridyl ketones.

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Conflicts of interest

There are no conflicts to declare.

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