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Ruthenium pincer complex-catalyzed heterocycle compatible alkoxy carbonylation of alkyl iodides: substrate keeps the catalyst active†

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The electron pair of the heteroatom in heterocycles will coordinate with metal catalysts and decrease or even inhibit their catalytic activity consequently. In this work, a pincer ruthenium-catalyzed heterocycle compatible alkoxy carbonylation of alkyl iodides has been developed. Benefitting from the pincer ligand, a variety of heterocycles, such as thiophenes, morpholine, unprotected indoles, pyrrole, pyridine, pyrimidine, furan, thiazole, pyrazole, benzothiadiazole, and triazole, are compatible here.

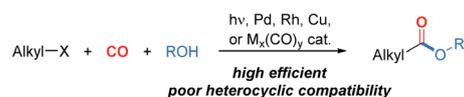
Since the pioneering work on the catalytic alkoxy carbonylation of unactivated alkyl halides reported by Heck and Breslow in 1963,¹ this transformation has attracted a great deal of interest due to its modularity and the direct employment of CO as a cheap and abundant C1 feedstock.² However, compared with aryl halides, the development of alkoxy carbonylation of alkyl halides has been much more gradual.^{2,3} This situation is due to both the slow oxidative addition of C(sp³)-X bonds to the metal center and the easy β-hydride elimination of the alkyl-metal intermediate, particularly in the presence of carbon monoxide.⁴ Several catalytic systems for this process have been successfully developed in recent years (Scheme 1A), such as pure radical-based systems,⁵ palladium-based systems,⁶ *hν*/palladium-based systems,⁷ rhodium-based systems,⁸ copper-based systems,⁹ and other metal carbonyl complex-based systems.¹⁰ Very recently, Neumann, Skrydstrup, and co-workers reported a nickel pincer-mediated alkoxy carbonylation for complete carbon isotope replacement, and this approach provided a procedure for generating carbon-labeled versions of potential simple carboxylate prodrug derivatives (Scheme 1B).¹¹ Besides their advantages, in these cases the heterocycles, particularly those containing multiple N atoms or NH groups, are hardly compatible, which is considered as a remaining challenge. We attribute this to the Lewis-basic atoms in heterocyclic motifs being particularly detrimental to catalyst activity and potentially quenching the radical intermediates.¹² Indeed, the development of heterocycle

compatible catalytic systems remains an exciting task in the field of alkoxy carbonylation.

On the other hand, heterocycles constitute important structural components of biologically active compounds and are ubiquitous in agrochemical and pharmaceutical industries.¹³ In a recent survey, 88% of small molecule drugs approved by the FDA between 2015 and June 2020 were found to contain at least one N-heterocycle.¹⁴ Specifically, heterocyclic subunits can modify the solubility, lipophilicity, polarity and hydrogen bonding ability of biologically active agents, thereby optimizing the corresponding ADME/Tox (absorption, distribution, metabolism, excretion, and toxicity) properties of drugs or drug candidates.¹⁵ Under this premise, the pursuit of new synthetic methods with good heterocycle compatibility is a worthwhile endeavor.

Herein we report a heterocycle compatible catalytic system for alkoxy carbonylation of alkyl iodides. With a ruthenium

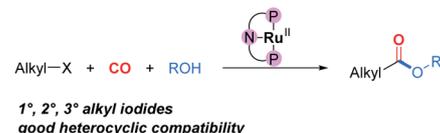
A. Previous work on alkoxy carbonylation of alkyl halides



B. Nickel pincer-mediated alkoxy carbonylation



C. This work: Ruthenium pincer-catalyzed heterocycle compatible alkoxy carbonylation



Scheme 1 Approaches to alkoxy carbonylation of alkyl halides.

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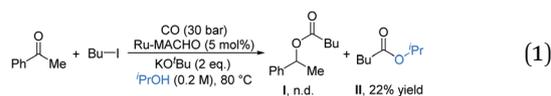
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pincer complex as the catalyst, the tight coordination of the pincer ligand can effectively prevent the ruthenium from deactivation by heterocycle coordination (Scheme 1C). To the best of our knowledge, this is the first example of a ruthenium pincer complex-catalyzed carbonylation reaction.¹⁶ This new catalytic system might lead to novel synthetic routes toward heterocyclic carbonyl-containing compounds.

Pincer complexes of ruthenium are among the most effective catalysts for hydrogen transfer reactions between alcohols and unsaturated compounds.¹⁷ We initially used it to attempt the carbonylative coupling of acetophenone with iodobutane, as shown in eqn (1). Although we did not get the desired product **I**, the ester **II** could be obtained in 22% yield. By literature survey, we found there was no example showing that alkyl halides could be activated by ruthenium in previous reports on carbonylation reactions.^{3,16,18} We thus envisioned that the ruthenium pincer complex played a key role in this transformation.^{11,19}



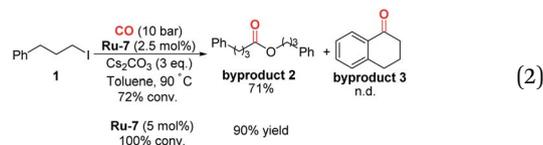
With this discovery in mind, we started the investigation of this ruthenium-catalyzed alkoxy carbonylation of alkyl halides

Table 1 Optimization of the alkoxy carbonylation of **1**^a

| Entry | [Ru] | Conv. ^b (%) | Yield ^b (%) |
|-------|---|------------------------|------------------------|
| 1 | Ru(acac) ₃ | 60 | 15 |
| 2 | RuH(Cl)(CO)(PPh ₃) ₃ | 21 | 11 |
| 3 | Ru-1 | 100 | 24 |
| 4 | Ru-2 | 93 | 41 |
| 5 | Ru-3 | 53 | 4 |
| 6 | Ru-4 | 49 | 5 |
| 7 | Ru-5 | 100 | 32 |
| 8 | Ru-6 | 100 | 38 |
| 9 | Ru-7 | 100 | 81 |
| 10 | Ru-7 | 100 | 63 ^c |
| 11 | Ru-7 | 100 | 82 ^d |
| 12 | Ru-7 | 100 | 72 ^e |
| 13 | Ru-7 | 100 | 86 ^{d,f} |

^a Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), [Ru] (5 mol%), Cs₂CO₃ (0.6 mmol), toluene (0.5 mL), CO (10 bar), 100 °C, 12 h. ^b Determined by GC with hexadecane as the internal standard. ^c CO (1 bar), N₂ (9 bar). ^d [Ru] (2.5 mol%) was used. ^e [Ru] (1 mol%) was used. ^f 90 °C, average yield of two independent reactions.

by examining the reaction of (3-iodopropyl)benzene (**1**) with isopropanol (**2**) at 100 °C under a CO atmosphere (10 bar) in the presence of a catalytic amount of various readily available ruthenium pincer complexes (Table 1). Ordinary ruthenium catalysts, when used alone or in combination with monodentate/bidentate ligands, barely allow the reaction to proceed (Table 1, entries 1–3; for more details, see the ESI†). The improved yield of the desired product **3** was obtained when utilizing Milstein's catalyst **Ru-2**²⁰ (Table 1, entry 4). SNS or NNS-type pincer/Ru complexes **Ru-3,4** afforded moderate conversions and poor selectivity (Table 1, entries 5 and 6). Meanwhile, Ru-MACHO-BH (**Ru-5**) and Ru-MACHO (**Ru-6**)²¹ were applied in the reaction; however, the selectivity obtained was unsatisfactory (Table 1, entries 7 and 8). Encouragingly, a significant improvement in the yield of **3** was achieved when employing **Ru-7** as the catalyst precursor (Table 1, entry 9). The reaction could also be successfully performed under low CO pressure (1 bar), although with slightly lower yield (Table 1, entry 10). When using **Ru-7**, we were able to decrease the catalyst loading to 2.5 mol% without affecting the yield (Table 1, entries 11 and 12). Finally, after a judicious choice of the reaction temperature, optimal reaction conditions were constituted, delivering **3** in 86% yield (Table 1, entry 13). In most of these reactions, the formation of **byproduct 1–3** was observed. As shown in eqn (2), when we removed isopropanol from the reaction, **byproduct 2** which was produced by carbonylative homocoupling of the alkyl halide could be obtained in 71% yield.²² However, the reduced conversion and the absence of **byproduct 3** implied that the alcohol plays more than a nucleophile role in this reaction. It is important to mention that the addition of water had no effect on the yield of **byproduct 2**. Concerning the effects from bases, organic bases, such as NEt₃ and DBU, were tested, but no desired ester could be detected. Inorganic bases, including K₂CO₃ and K₃PO₄, were also tested, but very low yield of the ester was obtained. Notably, comparable yield of ester **3** can be obtained when LiO^tBu was used as the base.



We next turned our attention to study the scope and the limitation of this transformation, as shown in Fig. 1. At the first stage, a variety of alcohols containing different functional groups and structural blocks were tested. In general, moderate to excellent yields were obtained under the standard conditions. For primary alcohols, the length of the carbon chain did not affect the good yield (4–7). The reaction tolerated the presence of ethers (**8**, **9**), thioether (**10**), alkene (**11**), chlorine (**12**), trimethylsilyl (**13**), and amide (**21**). Benzyl alcohols and secondary alcohols were afterwards tested in this system and successfully transformed into the corresponding esters in good yields (**14–17**). With the further increase of the steric hindrance, tertiary alcohols hardly provided the desired products (**18**, **19**). Phenol was also employed as the substrate in our attempt, and not



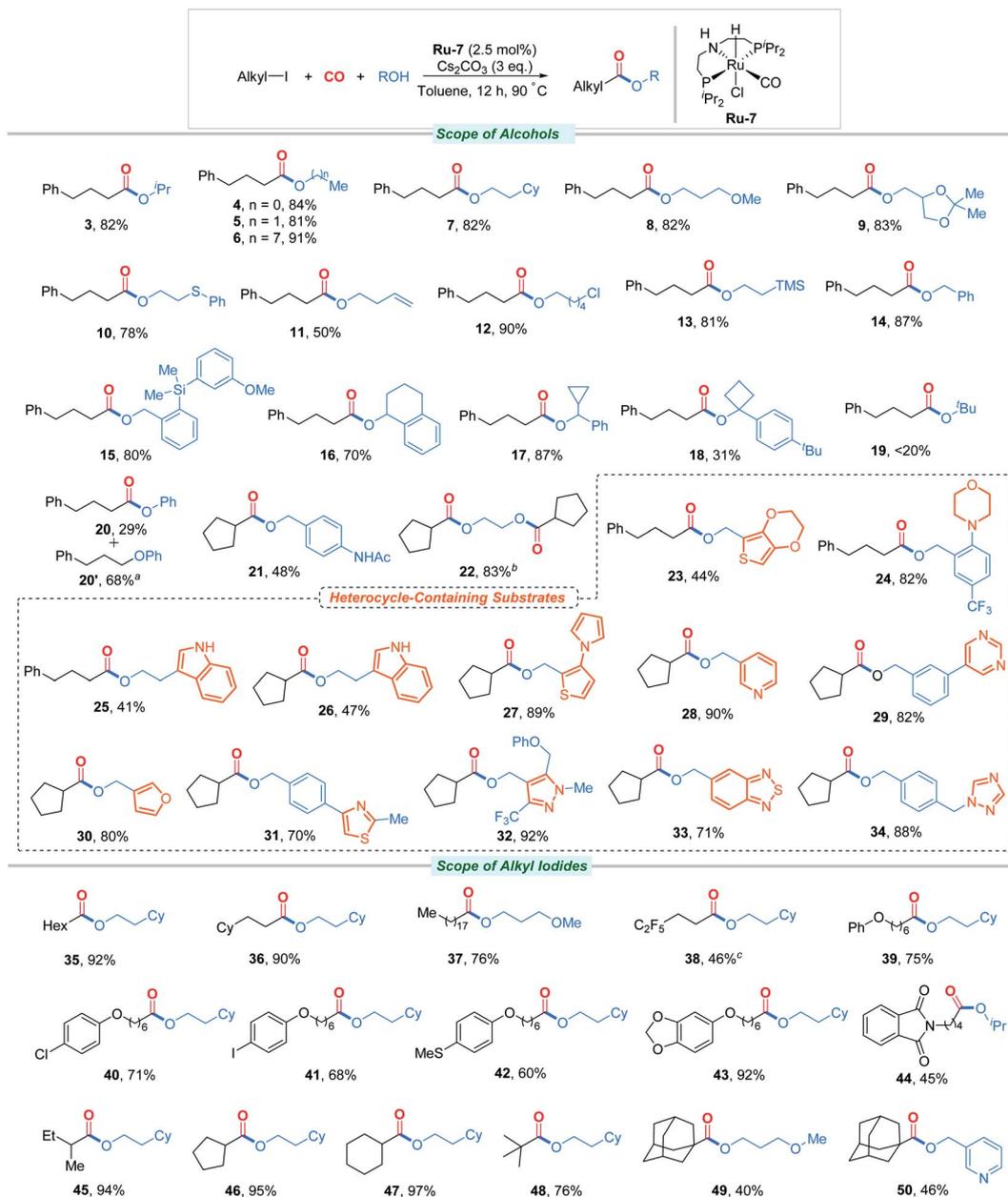


Fig. 1 Scope of Ru pincer complex-catalyzed alkoxy carbonylation. Reactions run with 0.2 mmol of alkyl iodide and 3 equiv. of alcohol. Yield of the isolated product. ^aTogether with a 68% yield of the S_N reaction product (phenyl 3-phenylpropyl ether). ^bEthylene glycol (3 equiv.) was used. ^cReduced yield of the isolated product because of the volatility of the product.

surprisingly, phenyl 3-phenylpropyl ether (S_N reaction product) was isolated as the main product (20).²³ Interestingly, ethylene glycol could be converted to diester 22 in 83% yield, and no monocarbonylation product was detected, even though the alcohol was three equivalents. This suggests an interaction between the alcohol and the catalytic center, resulting in a higher rate of intramolecular reaction than intermolecular reaction. Subsequently, the excellent heterocycle compatibility of the method is nicely illustrated by the fact that thiophenes (23, 27), morpholine (24), unprotected indoles (25, 26), pyrrole (27), pyridine (28), pyrimidine (29), furan (30), thiazole (31), pyrazole (32), benzothiadiazole (33), and triazole (34) were

perfectly tolerated under our protocol. The broad synthetic applicability of the reaction was also reflected in the successful alkoxy carbonylation of various primary iodides (35–44), secondary iodides (45–47), and even sterically hindered tertiary iodides (48–50).

In particular, the secondary iodides generated the corresponding esters in near quantitative yields. We also evaluated a substrate containing the C(sp²)-I bond to probe the chemoselectivity of our process (41). No trace of arylate was detected in the crude mixture by GC-MS, hence illustrating the good chemoselectivity of this catalytic system and offering opportunities for further structure modification. While this new methodology



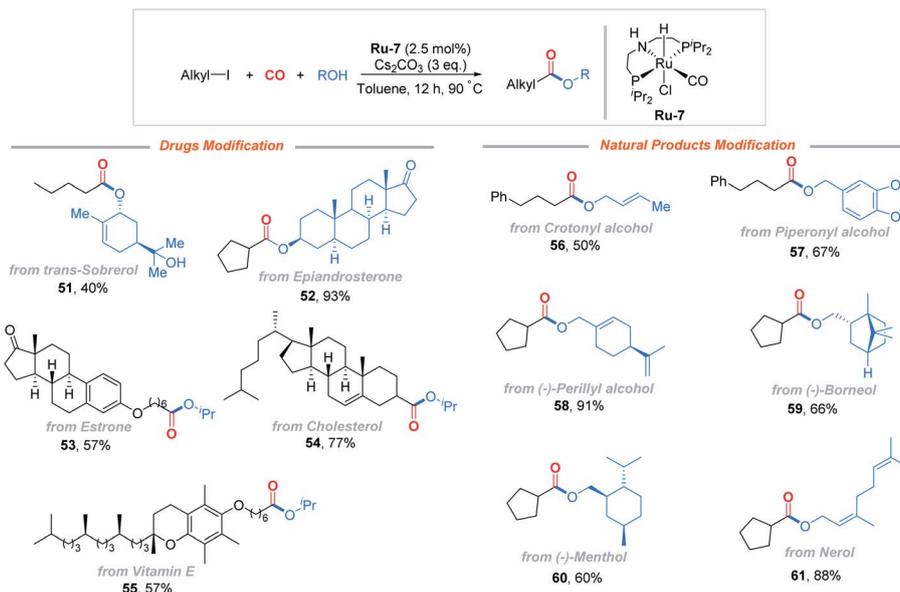


Fig. 2 Modification of drugs and natural products. Reactions run with 0.2 mmol of alkyl iodide and 3 equiv. of alcohol. Yield of the isolated product.

allows for the formation of a wide range of heterocycle-containing esters, some limitations still remain in terms of substrate scope. Bromoalkanes and chloroalkanes cannot be successfully converted under these conditions, even with the addition of equivalent amounts of NaI.

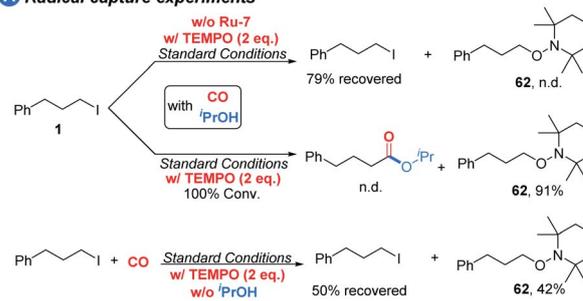
The alkoxy-carbonylation could be applied to late-stage modification of a range of drugs and natural products, as shown in Fig. 2. *trans*-Sobrerol, a mucolytic, was successfully transformed, while the tertiary C–OH group was retained (51). A weak androgen, epiandrosterone, which is widely recognized to inhibit the pentose phosphate pathway and to decrease intracellular NADPH levels, provided 52 in 93% yield. Derivatives of estrone, cholesterol, and vitamin E also delivered the corresponding esters 53–55 in moderate to good yields. Common alcohol natural products, such as crotonyl alcohol, piperonyl alcohol, (–)-perillyl alcohol, (–)-borneol, (–)-menthol, and nerol, were tested as well and applicable to the reaction (56–61), which illustrated the utility of this method.

To gain more mechanistic insight into the reaction pathway, several experiments were conducted (Scheme 2). Under the standard conditions, the addition of TEMPO (radical capture agent) to the reaction led to the termination of the target reaction; meanwhile, the intermediate was captured (62) in 91% isolated yield (Scheme 2A, middle). In the control experiment, only limited conversion and no 62 was observed in the absence of the pincer catalyst (Scheme 2A, top), thus suggesting that the pincer/Ru activates the alkyl iodides to radicals. To ensure the radical pathway, we subsequently conducted radical inhibition experiments with BHT (butylated hydroxytoluene) as the radical inhibitor (Scheme 2B) and radical clock experiments (Scheme 2C). The model reaction was gradually suppressed with the addition of BHT. Furthermore, (iodomethyl)cyclopropane and 6-iodohex-1-ene under our optimized reaction conditions provided the corresponding ring-opening expansion product 64

and the cyclization product 65, respectively, with high selectivity.²⁴

Based on the above results, we believe that the reaction involves a radical intermediate. In addition to this, as noted

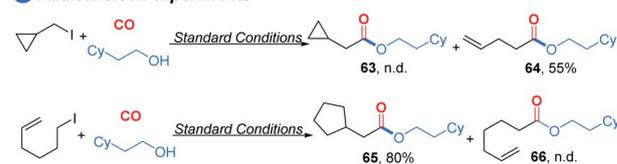
A Radical capture experiments



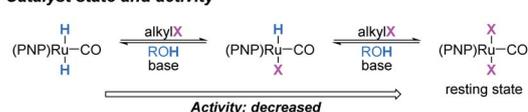
B Radical inhibition experiments



C Radical clock experiments



D Catalyst state and activity

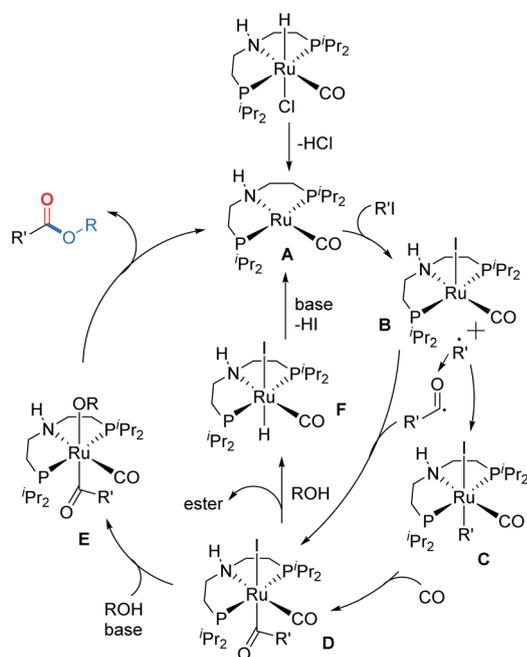


Scheme 2 Mechanism studies.



earlier, the alcohol appears to interact with the catalytic center and plays a role in promoting the activation of the alkyl halide. To probe this hypothesis, we removed the isopropanol from the reaction and utilized TEMPO to capture the radical intermediate (Scheme 2A, below). Compared with the reaction in the middle of Scheme 2A, the conversion and the yield of **62** significantly decreased in the absence of isopropanol. We explained that the (PNP)Ru(CO)X₂ type complex is the catalyst resting state, and the alcohol may help it to return to the active state by hydrodehalogenation (Scheme 2D).²⁵ Moreover, we could observe acetone during the optimization process, and when we subjected isopropanol alone to our optimized conditions, 57% yield of acetone could be detected,²⁶ which suggests that (PNP)Ru(CO)HX can also undergo hydrodehalogenation to form (PNP)Ru(CO)H₂.

Based on the above results and previous reports,^{16–18} a plausible mechanism is proposed (Scheme 3). Initially, the active 16 electron ruthenium complex **A** will be formed under the assistance of the base. Through a SET process, alkyl iodide will be activated and a 17 electron ruthenium complex **B** will be formed together with the corresponding alkyl radical which will immediately react with **B** to give 18 electron ruthenium complex **C**. The acylruthenium complex **D** will be produced after a CO insertion step. The possibility that the acylruthenium complex **D** might also be produced from complex **B** and the *in situ* formed acyl radical cannot be excluded. After X ligand exchange, ruthenium complex **E** will be formed which will provide the final ester product after a reductive elimination step and regenerate the active ruthenium catalyst **A** to finish the catalyst cycle. Alternatively, the direct nucleophilic attack at the acyl carbonyl of complex **D** by alcohol to give the ester product and complex **F** is also possible. Then complex **F** will be transformed into complex **A** under the assistance of the base.



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, we have developed a pincer ruthenium-catalyzed heterocycle compatible alkoxy carbonylation of alkyl iodides. By utilizing the tight coordination of the pincer ligand to effectively prevent the activity reduction of Ru, a variety of heterocycles are compatible. Remarkably, our approach also represents the first example of a pincer ruthenium-catalyzed carbonylation reaction. The excellent heterocycle compatibility, wide substrate scope, and generality of the protocol suggest that it can be a powerful tool for preparing heterocyclic carbonyl-containing compounds.

Author contributions

XFW directed this project and revised the manuscript. HJA performed all the experiments and prepared the draft and ESI.† YY prepared a part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- 23 This situation can mainly be explained from two aspects: (i) in the presence of a base, haloalkanes and phenols are prone to a nucleophilic substitution reaction to produce ethers; (ii) carbonylation of haloalkanes usually proceeds *via* free radical intermediates, which tend to be quenched by phenols. For solution, see ref. 8a.
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- 26 See the ESI for details.

