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Mild Acylation of C(sp^3)−H and C(sp^2)−H Bonds under Redox-Neutral Rh(III) Catalysis

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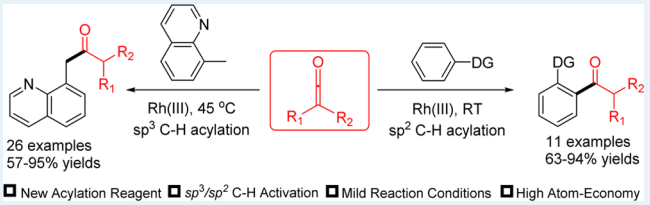
Supporting Information

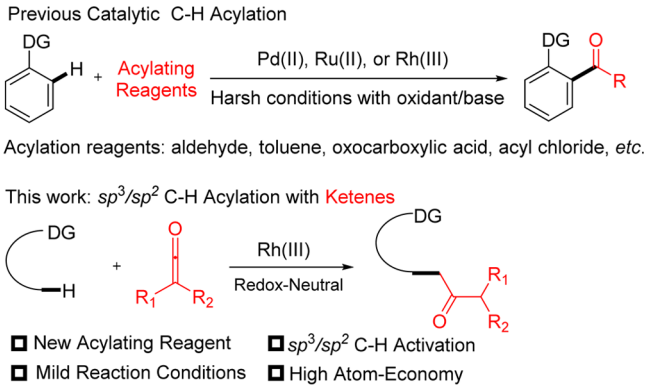
ABSTRACT: Carbonyl groups are ubiquitous in functional molecules. Although C−H bond acylation has been well-studied via different mechanisms, transition-metal-catalyzed redox-neutral C(sp^3)−H acylation under mild conditions is unprecedented. In this work, ketene is designed as a acylating reagent for both C(sp^3)−H and C(sp^2)−H bonds under Rh(III) catalysis, affording a diverse array of carbonyl compounds in high yields and high atom economy under mild conditions.



KEYWORDS: *acylation, C−H activation, rhodium, ketene, arene*

The carbonyl is a ubiquitous structural motif in natural products, dyes, and pharmaceuticals.[1] Rich chemistry of carbonyls allows the introduction of other diverse functional groups.[2] In this regard, the development of efficient methods that deliver molecules containing carbonyls has been of continuing interest. Among the well-established methodologies, transition-metal-catalyzed direct C−H acylation[3] has emerged as a valuable and atom-economical alternative to the traditional Friedel−Crafts acylation, because the latter generally suffers from the limitation of electron-rich arenes and stoichiometric amounts of corrosive Lewis acids.[4] Thus, the recent years have witnessed the significant progress in Pd-, Rh-, and Ru-catalyzed *ortho*-acylation of C(sp^2)−H bond using aldehydes,[5] toluenes,[6] benzyl alcohols,[7] α-oxocarboxylic acids,[8] and other[9] acyl sources (Scheme 1). However, such protocols are mostly limited to direct acylation of sp^2 C−H bonds and often require stoichiometric amounts of metals or explosive peroxide oxidants under harsh conditions, which may restrict the synthetic utility. To overcome these limitations and to realize acylation of a diverse array of sp^3 C−H bonds, a dual catalysis, merging photoredox with transition-metal/NHC catalysis, has been established in the acylation of the α-C(sp^3)−H bond of a tertiary amine under mild conditions by Doyle[10] and Rovis.[11] Despite the significant progress, concise, efficient, and mild catalytic systems that refer to direct C(sp^3)−H acylation are rare, because of the low reactivity of the resulting metal−alkyl species. Therefore, the development of a novel catalytic system for mild construction of carbonyl compounds with broader substrate generality in a more efficient and atom-economic fashion is highly desirable, especially for C(sp^3)−H substrates. Compared to the complicated dual catalysis, a challenging but potentially more facile approach would be the exploitation of more-reactive acylating reagents.

Scheme 1. Transition-Metal-Catalyzed Direct C−H Acylation



Ketene, a general synthon in cycloaddition reactions,[12] can be recognized as a readily available and highly reactive acylating reagent, because of its coordinating ability, together with the highly polarized and consequently reactive C═C and C═O bonds. However, to date, metal-catalyzed C−H acylation using ketene remains unprecedented and the following challenges might arise:

(1) A highly efficient and mild catalytic system is required to prevent the ready dimerization of ketenes at a high temperature;

(2) An operationally simple catalytic system is necessary, because ketenes are not compatible with most

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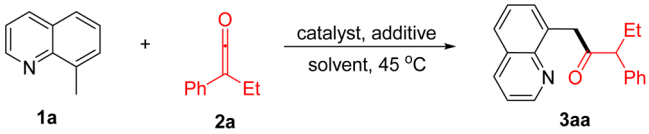
nucleophilic additives such as acids, bases, and protic solvents; and

(3) The substrate or the acylated product should not be too nucleophilic.

It seems that it all boils down to the proper design of a highly efficient, simple, and mild catalytic system. Recently, Cp*Rh(III) complexes have emerged as useful and efficient catalysts for C−H bond activation[13] and insertion into various π bonds,[14] yet transition-metal-mediated unreactive sp^3 C−H bond mild insertion into alkenes[15] or carbonyls leading to alkylation or acylation products is still unprecedented. Inspired by the unique role of Rh(III) catalysts, we reasoned that the highly polarized C═C and C═O bonds in ketene should readily undergo insertion to a Rh−C bond to give a rhodium(III) enolate[16] en route to an acylation product. We now report our findings on the mild coupling of ketenes with both C(sp^3)−H and C(sp^2)−H bonds.

We initiated our studies by exploring the reaction conditions of C−H acylation of 8-methylquinoline (**1a**)[17] with ketene **2a** (Table 1). To our delight, the use of a 4 mol % loading of

Table 1. Optimization Studies[a]



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

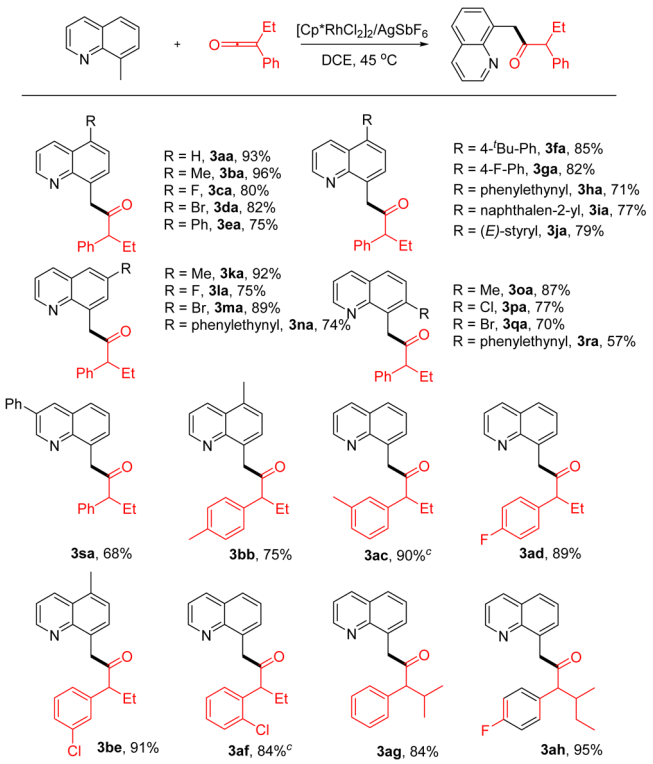
entry	catalyst/silver salt additive[b]	solvent	yield[c] (%)
1[d]	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	DCE	93
2	$[IrCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	DCE	trace
3	$CoCp^*(CO)I_2$ (8)/$AgSbF_6$ (20)	DCE	trace
4	$Pd(OAc)_2$/(10)	DCE	NR
5	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	DCM	91
6	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	THF	25
7	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	dioxane	76
8	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	PhCF3	23
9	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	acetone	34
10	$[RhCp^*Cl_2]_2$ (4)/ $AgSbF_6$ (20)	EtOAc	46
11[e]	$[RhCp^*Cl_2]_2$ (4)/ $AgSbF_6$ (20)	DCE	17
12[f]	$[RhCp^*Cl_2]_2$ (4)/ $AgSbF_6$ (20)	DCE	60
13	−/$AgSbF_6$ (20)	DCE	NR
14	$[RhCp^*Cl_2]_2$ (4)/−	DCE	NR

[a]Reaction conditions: 8-methylquinoline (**1a**, 0.2 mmol), ketene **2a** (0.4 mmol), catalyst, additive, and solvent (3 mL) at 45 °C for 20 h. [b]Values shown in parentheses represent the mole fraction of catalyst or salt additive. [c]GC yield with biphenyl as a standard. [d]Isolated yield. [e]At room temperature (RT). [f]0.2 mmol **2a** was used.

$[RhCp^*Cl_2]_2$, together with $AgSbF_6$ (20 mol %) as an additive in DCE was found to be optimal, affording acylation product **3aa** in 93% yield (entry 1). Switching the rhodium catalyst to Ir(III), Co(III), and Pd(II) catalysts, however, all led to essentially no desired product, indicating the superiority of Rh(III) catalysis in this transformation (entries 2−4). Screening of the solvent gave DCE as an optimal medium (entries 5−10). Lowering the reaction temperature from 45 °C to room temperature (RT) resulted in a much lower yield (entry 11). Lowering the amount of the ketene to 1 equiv still afforded **3aa** in 60% yield (entry 12). Our control experiments revealed that no desired product was detected when either the catalyst or the silver salt additive was omitted (entries 13 and 14).

By following the optimized conditions, the scope of 8-methylquinoline was explored first (Scheme 2). Gratifyingly,

Scheme 2. Acylation of C(sp^3)−H Bonds[a,b]



[a]Reaction conditions: 8-methylquinoline (0.2 mmol), ketene (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (20 mol %), and DCE (3 mL), 45 °C, 20 h. [b]Isolated yield. [c]At 60 °C. [b]Isolated yield. [c]At 60 °C.

differently substituted 8-methylquinolines are generally all viable, and the acylation products were isolated in 57%−95% yields. 8-Methylquinolines bearing both electron-donating and electron-withdrawing groups at the 5- and 6-positions of the quinoline ring all coupled in good to excellent yields (**3aa**−**3na**). Moreover, reactions with diverse 7-substituted substrates also gave the corresponding acylation product in high yields (57%−87%), indicating the tolerance of steric hindrance. With phenyl group at 3-position of quinoline ring, the reaction also proceeded smoothly (**3sa**). Of note, some reactive groups such as alkynyl and alkenyl are fully compatible. Unfortunately, 8-ethylquinoline is not an effective substrate in the current catalytic system. In addition to ketene **2a**, a series of alkylphenylketenes were investigated under the optimized conditions. Variation of a series of ethylarylketenes has been made by incorporation of both electron-withdrawing and electron-donating substituents, providing acylation products in 75%−91% yields (**3bb**−**3af**). Besides an ethyl substituent, other alkyl substituents such as *iso*-propyl and *sec*-butyl were compatible (**3ag** and **3ah**). In contrast to these couplings, poor reactivity was observed for diphenylketene, likely due to steric effects.

The C−H substrate of the acylation reaction was not restricted to 8-methylquinolines. The acylation substrate was successfully extended to arenes (Scheme 3). The acylation of *ortho* C(sp^2)−H bonds of arenes assisted by an pyridine, pyrimidine, pyrazole, and quinoline all proceeded smoothly at room temperature in good to high yields (**5aa**−**5da**).

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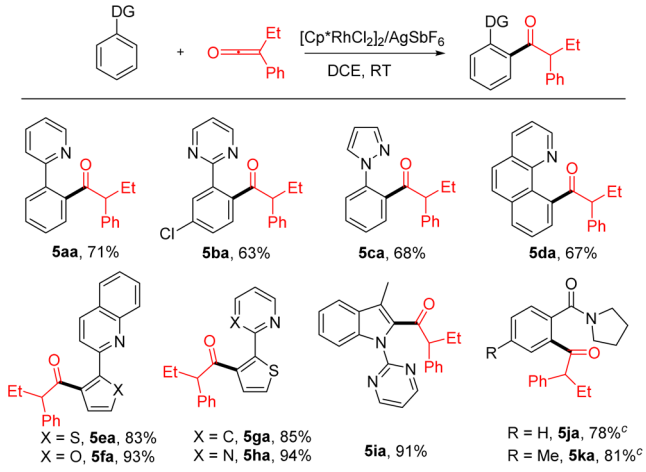
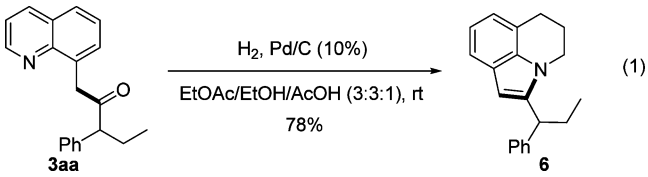
Scheme 3. Acylation of C(sp²)−H Bonds[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (20 mol %), and DCE (3 mL) at RT for 20 h. [b]Isolated yield. [c]At 60 °C.

Regioselective C−H acylation was observed at the less-hindered site for substrate **5b** bearing a meta-Cl group, as only product **5ba** was isolated. Besides C−H acylation in benzene rings, the acylation reaction can be smoothly extended to heterocyclic substrates including pyridyl-, quinolyl-, and pyrimidyl-functionalized thiophene, furane, and indole in 85%−94% yields (**5ea**−**5ia**). Furthermore, weak directing groups also proved viable as in the efficient acylation of benzamides (60 °C), affording the corresponding products in good yields (**5ja** and **5ka**).

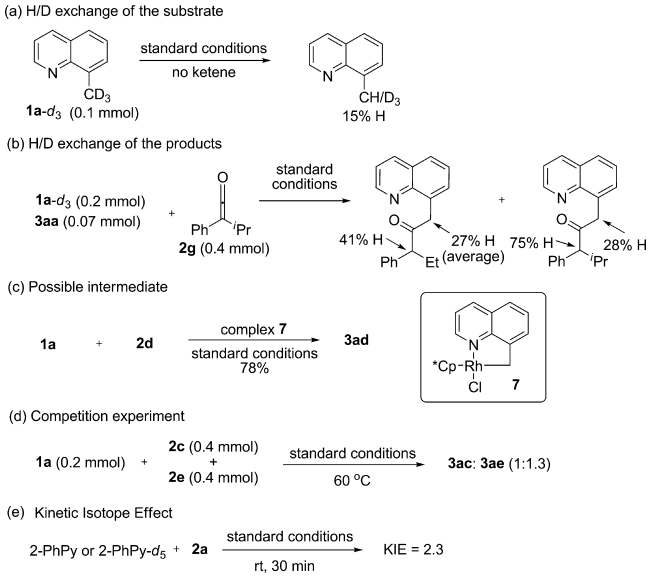
With the readily prepared product **3aa** in hand, derivatization of this product has been performed to demonstrate the synthetic utility. Hydrogenation of **3aa** using Pd/C as a catalyst in a mixed solvent (EtOAc/EtOH/AcOH = 3:3:1) led to the formation of a polycyclic skeleton **6** in 78% yield (eq 1), which is ubiquitous in natural products and bioactive molecules.[18]



(1)

To gain insight into the mechanism of the acylation reaction, several related deuterium experiments were conducted (Scheme 4). H/D exchange experiment of **1a**-d_3 under the standard conditions indicated the reversibility of the C−H cleavage process. Coupling of **1a**-d_3 with **2g** under the standard conditions in the presence of **3aa** afforded both **3ag**-d_n with extensive H/D exchange (75% H) and **3aa**-d_n with extensive H/D exchange (41% D) at the methyne position, suggesting that the α-C(sp^3)−H protons are sufficiently acidic to allow facile H/D exchange under the catalytic conditions. Application of rhodacyclic complex **7** as a catalyst precursor for the coupling of **1a** and **2d** afforded product **3ad** in 78% yield, suggesting that the reaction proceeds via a C−H activation pathway. In addition, a competition reaction using **1a** and electronically differentiated **2c** and **2e** afforded **3ae**/**3ac** in a ratio of 1.3:1, which suggests that the Rh−C bond of rhodacyclic intermediate insertion more favorably into a more

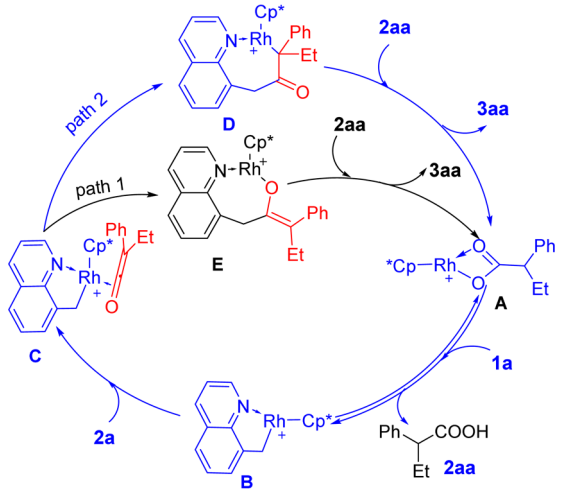
Scheme 4. Experimental Mechanistic Studies



electrophilic ketene in the catalytic system.[19] We also attempted but failed in the isolation of a reaction intermediate by stoichiometric reaction between rhodacyclic complexes and **2a**. Furthermore, a kinetic isotope effect was measured on the basis of two side-by-side reactions using 2-phenylpyridine and 2-phenylpyridine-d_5. The obtained value of k_H/k_D = 2.3 indicates that cleavage of the C−H bond is probably involved in the turnover-limiting step.

We next performed DFT studies to gain detailed mechanistic profiles of our reported reaction (Schemes 5 and 6), and two possible pathways have been evaluated.[20] The ketene is proposed to undergo hydration to Ph(Et)CHCOOH **2aa** by the adventitious water.[21] Anion exchange with the Rh(III) catalyst affords the carboxylic intermediate **A**. C−H activation of **1a** occurs via a concerted metalation−deprotonation mechanism with a calculated activation free energy of 24.7 kcal/mol. The resulting rhodacyclic species **B** could undergo migratory insertion of the Rh−C bond into the ligated ketene via two possible pathways (Scheme 5). In path 1, insertion into

Scheme 5. Two Possible Reaction Pathways



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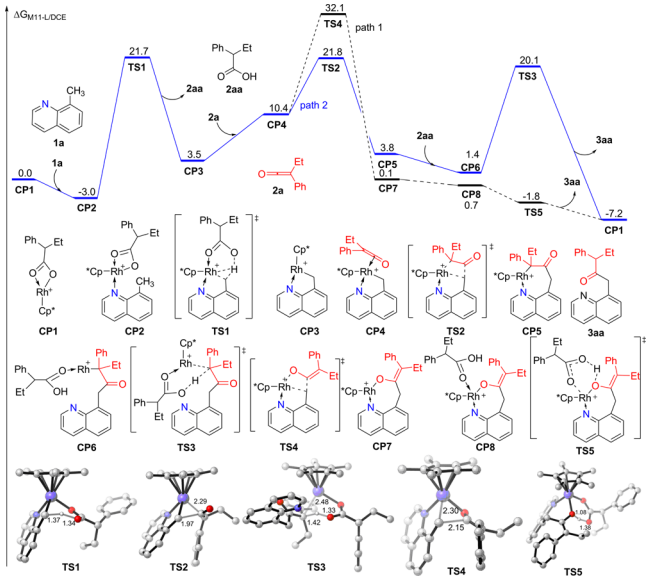
the C═O bond gives an *O*-bound enolate (*Z*)-**E** (**CP7** in Scheme 6) with a calculated activation free energy of 21.7 kcal/

Scheme 6. Calculated Energy Profiles of the Two Possible Pathways (See the Supporting Information for Details)



mol for this single step, and the energetics of generation of the (E)-**E** isomer has also been examined, which carries an even higher barrier. We also considered the slippage of **E** to the 18-electron η^3-enolate isomer.[12c,22] However, we failed to locate it, likely because it is highly twisted in a sterically rigid setting. In path 2 (Scheme 5), the C═C bond is involved in the migratory insertion and a 16-electron C-bound enolate **D** (**CP5** in Scheme 6) is generated with an activation free energy of only 11.4 kcal/mol for this single step. In subsequent steps, the Rh−C (**D**) and the Rh−O bonds (**E**) were protonolyzed by carboxylic acid **2aa** to afford the acylation product with the regeneration of the active Rh(III) catalyst.[23] Clearly, formation of **D** requires a lower barrier, although it is less thermodynamically stable than **E**. In path 1, the highest barrier corresponds to the coordination of ketene and subsequent migratory insertion, while the C−H activation was established as the rate-determining step in path 2. Thus, consistency in terms of the rate-determining step of the catalytic cycle also indicated the likelihood of path 2. We noted that the Rh−C and Rh−O bond might also be protonolyzed by a $HSbF_6$ in the catalytic cycle, but for reliability of calculated energies of protonolysis, the carboxylic acid and the corresponding Rh(III) carboxylate were evaluated.

In summary, we have developed the first Rh(III)-catalyzed mild acylation of both C(sp^3)−H bonds and C(sp^2)−H bonds under redox-neutral conditions, using readily available ketene as a novel acylation reagent, leading to the efficient synthesis of multisubstituted carbonyl compounds. A broad scope of the reaction substrate has been demonstrated, and further derivatization of the acylation product has been performed to synthesize a biological active polycyclic skeleton. This protocol for accessing complex carbonyl compounds may be useful in the synthesis of various biologically active compounds and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02668.

Detailed experimental procedures, characterization data, copies of NMR spectra, and DFT data of optimized structures (PDF)

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Notes

The authors declare no competing financial interest.

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