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Catalytic Intermolecular *C*-Alkylation of 1,2-Diketones with Simple Olefins: A Recyclable Directing Group Strategy

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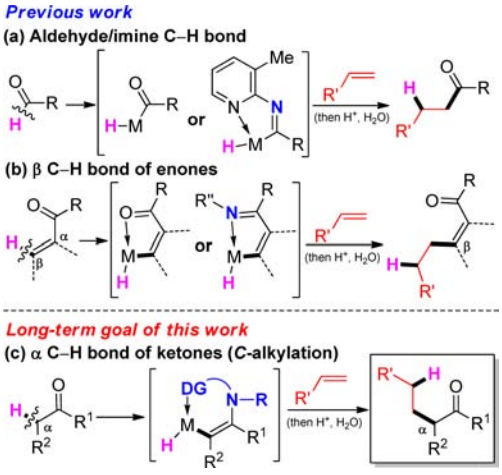
Supporting Information

ABSTRACT: We describe the first example of Rh-catalyzed intermolecular *C*-alkylation of cyclic 1,2-diketones using simple terminal olefins as alkylating agents. Aminopyridine is employed as a recyclable directing group. First, it reacts with ketones to give enamines and delivers Rh to activate the vinyl C−H bonds in the same pot; second, it can be cleaved off and recovered via hydrolysis. A broad range of olefins can be utilized as substrates, including aliphatic, aromatic olefins and vinyl esters. The efficiency of this method is also demonstrated in the synthesis of a natural flavoring compound, 3-ethyl-5-methyl-1,2-cyclopentadione (one-pot 53% yield vs a previous four-step route 16% yield from the same starting material). This work is expected to serve as a seminal study toward catalytic ketone α-alkylation with unactivated olefins.

Transition-metal-catalyzed addition of C−H bonds across olefins represents a powerful and economical way to construct C−C bonds;[1] in particular, carbonyl-involved C−H addition reactions are very attractive due to the pivotal role of the carbonyl group in organic synthesis. For example, aldehydes or imines can be catalytically transformed to functionalized ketones via oxidative addition of the C−H bonds (Scheme 1a).[2] The β C−H bonds in aryl ketones or enones are known to undergo carbonyl or imine-directed metalation, and addition reactions with olefins provide β-alkylated products (Scheme 1b).[1d−f] Addition of **α C−H bonds** of ketones across unactivated olefins would afford *formal enolate-alkylation products* but in a more atom-economical[3] and "greener" fashion compared to the typical enolate alkylation, because this catalytic process would eliminate the need for stoichiometric amounts of a strong base and relatively expensive and/or toxic alkylating agents. However, general strategies for such transformations remain underdeveloped.[4−6] The challenges are likely due to the inert nature of the α C−H bonds (sp^3 vs sp^2 for aldehyde and enone C−H bonds) and lack of suitable directing groups (DGs).

Scheme 1. Carbonyl-Involved C−H Additions Across Olefins



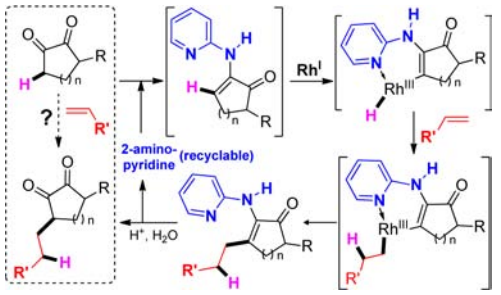


Figure 1. *C*-Alkylation of cyclic 1,2-diketones using simple olefins.

To address these challenges, we envisaged that *enamine formation would convert the ketone sp^3 α C−H bonds to sp^2 bonds, thus enhancing their reactivity toward oxidative addition* by a low-valent transition metal (Scheme 1c).[7] Meanwhile, if a proper DG is incorporated with the amine agent, metalation would be directed to the α C−H bonds upon enamine formation.[8] Subsequent olefin insertion−reductive elimination and enamine hydrolysis would lead to the desired α-alkylation product. Here, serving as an important proof of principle, we examine the feasibility of such a transformation in a 1,2-diketone system.

Cyclic 1,2-diketones represent an important structural motif in various natural products,[9] such as bruceantin (anticancer)[10] and terpestacin (anti-HIV),[11] and are also widely used as perfumery and flavoring materials in cosmetics and food industries respectively.[12] This functional group possesses unique reactivity where one of the ketones often exists in enol form. However, their usage as synthetic building blocks has received limited attention, likely because direct and regioselective alkylation to form C−C bonds is difficult and *O*-alkylation is generally favored under normal alkylation

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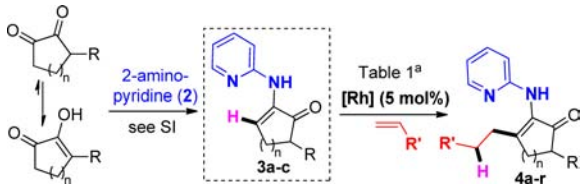
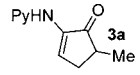
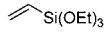
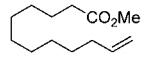
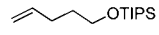
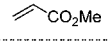
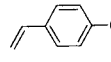
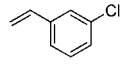
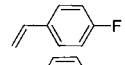
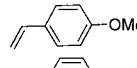
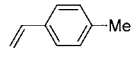
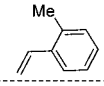
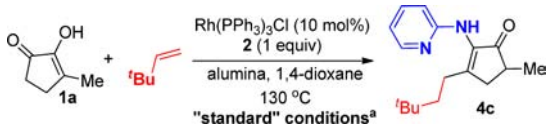
Table 1. Investigation of the C−H/Olefin Coupling Step



Entry	Enamine	Olefin	Rh catalyst[b]	Yield[c]
1	 **3a**		A	**4a**, 99%
2	**3a**		A	**4b**, 90% 87%[e]
3	**3a**		A	**4c**, 99%
4	**3a**		A	**4d**, 89%(99%)
5	**3a**		A	**4e**, 82%(98%)
6	**3a**		A	**4f**, 74%
7	**3a**		A[d]	**4g**, 45%
8	**3a**		A[d]	**4h**, 55%(99%)
9	**3a**		A	**4i**, 96%
10	**3a**		A **B**	**4j**, 82% **4j**, **95%**
11	**3a**		B	**4k**, 90%
12	**3a**		B	**4l**, 89%
13	**3a**		B	**4m**, 71%
14	**3a**		B	**4n**, 71%
15	**3a**		B	**4o**, 74%
16	**3a**		B	**4p**, 88%
17	 **3b**		A	**4q**, 82%
18	 **3b**		A	**4r**, 61%
19	 **3c**		A	**4s**, 78%

[a]General reaction conditions: **3a−c** (1 equiv), olefin (10 equiv), Rh catalyst (5 mol %) in 1,4-dioxane (0.4 M), 130 °C in a sealed vial. TIPS, triisopropylsilyl. Py, pyridyl group. [b]Catalyst A: $Rh(PPh_3)_3Cl$ 5 mol %, Catalyst B: $[Rh(coe)_2Cl]_2$ 2.5 mol %. [c]Isolated yields of the C−H functionalization step; the number in parentheses represents the yield based on recovered starting material (brsm). [d]5 equiv of the olefin are used. [e]2 equiv of the olefin are used.

Table 2. Selected Optimization of the Tandem Enamine Formation/C−H Olefin Coupling Reaction



entry	variation from the "standard" conditions	yield[b]
1	none	65%
2	no alumina	7%
3	4 Å MS, instead of alumina	0%[c]
4	half the amount of alumina	37%
5	no $Rh(PPh_3)_3Cl$	0%[d]
6	$Rh(PPh_3)_3Cl$ (5 mol %)	48%
7	$[Rh(coe)_2Cl]_2$ (5 mol %), instead of $Rh(PPh_3)_3Cl$	<1%[d]
8	toluene, instead of 1,4-dioxane	39%
9	aniline (1 equiv), instead of **2**	0%[e]

[a]Standard conditions: **1a** (0.2 mmol, 1 equiv), **2** (0.2 mmol, 1 equiv), 3,3-dimethyl-1-butene (2 mmol, 10 equiv), neutral alumina (200 mg), $Rh(PPh_3)_3Cl$ (0.02 mmol, 10 mol %) in 1,4-dioxane (0.4 mL), 130 °C in a sealed vial. [b]Isolated yield. [c]**1a** remained unreacted. [d]Enamine **3a** was the major product. [e]Only enamine formation and no alkylation products were observed.

conditions.[13−15] In this communication, we report the first example of a Rh-catalyzed intermolecular *C*-alkylation of cyclic 1,2-diketones using simple terminal olefins as alkylating agents.

Our strategy is depicted in Figure 1. 2-Aminopyridine is employed as a DG for selective activation of the *less hindered α C−H bond* of cyclic 1,2-diketones.[16] It would first generate the enamine with the less hindered ketone and then deliver Rh insertion into the resulting vinyl C−H bond. Note that a *six-membered metallocycle* is expected in contrast to the more common five-membered ones (see Scheme 1a,b). Subsequently, the *C*-alkylation product would be generated via migratory insertion of an olefin and reductive elimination. Finally, the aminopyridine DG would be cleaved off and recycled via acid-mediated hydrolysis.

Given that the C−H/olefin coupling is the key to the success of the proposed strategy, we investigated the viability of this step directly using enamine adducts (**3a−c**) as substrates (Table 1). After optimizing the reaction conditions, we found the vinyl C−H bonds of the enamines were effectively coupled with a broad range of terminal olefins, providing adducts **4a−s** in good to excellent yields.[17] Wilkinson's catalyst (5 mol %) proved to be most effective for aliphatic olefins, including both sterically hindered olefins, such as *tert*-butyl ethylene and vinyl silanes, and less hindered ones, such as 1-hexene and ethylene gas (entries 1−9, Table 1). Both the alkylation product (**4a**) and its starting material (**3a**) were unambiguously identified by ^1H and ^{13}C NMR, IR, HRMS, and X-ray crystallography (see Supporting Information). Notably, Michael acceptors, such as methyl acrylate, also serve as a good substrate (entry 9, Table 1). Although aromatic olefins also react under the same reaction conditions, $[Rh(coe)_2Cl]_2$ (coe = cyclooctene) was found to be a more efficient catalyst (entry 10). *Para-*, *meta-*, and *ortho*-substituted styrenes coupled smoothly (entries 11−16, Table 1).[18] In addition, *a number of functional groups are tolerated under the C−H/olefin coupling conditions*, including silanes, ethers, silyl ethers, aryl chlorides, aryl fluorides, and esters. Importantly, all these reactions proceeded with excellent regioselectivity offering only the linear products likely due to the preference of formation of the less hindered Rh-alkyl species (see Figure 1),[1e,f] while the potential branched products were not observed.

With the success of the Rh-catalyzed α-alkylation reaction, we then attempted to combine the enamine formation and C−H activation into one pot. Toward this end, the optimal conditions were discovered: when *tert*-butyl ethylene was used as the olefin partner, alkylation product **4c** was isolated in 65% yield (entry 1, Table 2). Subsequently, we examined the role of each reactant through a series of control experiments. Neutral

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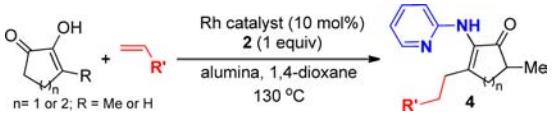
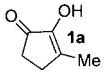
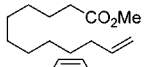
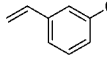
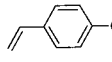
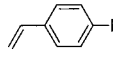
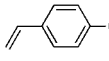
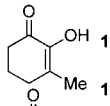
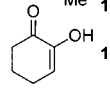
Table 3. Direct Alkylation with Cyclic 1,2-Diketones[a]



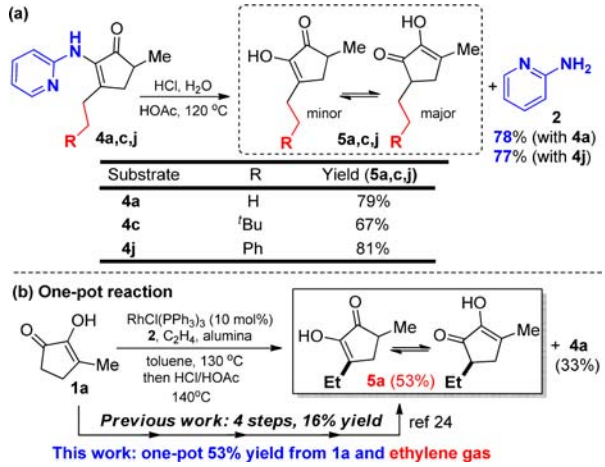
Entry	Ketone	Olefin	Rh catalyst[b]	Yield[c]
1	 **1a**		A	80%
2	**1a**		A	75%
3	**1a**		A	65%
4	**1a**		A	65%
5	**1a**		A	51%
6	**1a**		A	48%
7	**1a**		A	35%
8	**1a**		B	61%
9	**1a**		B	73%
10	**1a**		B	64%
11	**1a**		B	53%
12	**1a**		B	54%
13	**1a**		B	47%
14	 **1b**		A	30%[d]
15	 **1b**		A	24%[d]
16	**1c**		A	19%[e]

[a]General reaction conditions: **1a** (0.2 mmol, 1 equiv), **2** (0.2 mmol, 1 equiv), olefins (2 mmol, 10 equiv), neutral alumina (200 mg), Rh catalyst (0.02 mmol, 10 mol %) in 1,4-dioxane (0.4 mL), 130 °C in a sealed vial. [b]Catalyst A: $Rh(PPh_3)_3Cl$, 10 mol %; Catalyst B: $[Rh(coe)_2Cl]_2$ 5 mol %. [c]Isolated yield. [d]2 equiv of **2** were used. [e]No alumina is used.

alumina was found to promote the enamine formation effectively; in contrast, only a 7% yield was obtained in the absence of alumina (entry 2, Table 2). Use of 4 Å molecule sieves did not lead to enamine formation (entry 3, Table 2). No alkylation occurred without Wilkinson's catalyst, while a 48% yield was obtained with a 5 mol % catalyst loading. Use of $[Rh(coe)_2Cl]_2$ as a catalyst proved to be inefficient for *tert*-butyl ethylene insertion (entry 7, Table 2). 1,4-Dioxane served as a more effective solvent than toluene (entry 8, Table 2). Finally, replacement of aminopyridine with aniline led only to enamine formation; however, no alkylation product was observed, suggesting a critical role for the pyridine group as a DG for C−H activation.[19]

Next, we investigated the scope of the tandem enamine formation/alkylation reaction (Table 3). Similar to the C−H/olefin coupling with preformed enamines, a broad scope of olefins can be coupled under the tandem-reaction conditions.

Scheme 2. Cleavage and Recovery of Aminopyridine DG



By properly choosing the Rh catalysts, both aliphatic and aromatic olefins reacted and provided good yields of substituted enamines.[20] The six-membered diketones (**1b** and **1c**) are more challenging substrates for this tandem reaction, likely caused by their tendency to decompose to aromatic compounds during the enamine-formation step (entries 14−16, Table 3),[21] as their yields are much higher when using the corresponding enamines as the starting materials (entries 17−19, Table 1). Note that only monoalkylation was observed with nonsubstituted cyclcohexan-1,2-dione (**1c**) (entry 16, Table 3).

With success of the tandem enamine formation/C−H olefin coupling, we continued to explore the feasibility to remove and recycle the aminopyridine auxiliary. Preliminary hydrolytic-cleavage experiments were conducted: treatment with acetic acid and HCl at elevated temperatures provided the alkylated 1,2-diketones in high yields, which exist as enol tautomers (Scheme 2a).[22] In addition, the pyridine was recovered in 77−78% yield. Further study suggested that the enamine formation, C−H/olefin coupling, and enamine cleavage can all be operated in one pot! Reaction of diketone **1a** with ethylene gas at ca. 1 atm pressure followed by hydrolysis afforded diketone **5a** in 53% yield along with enamine **4a** in 33% yield (Scheme 2b). Notably, 3-ethyl-5-methyl-1,2-cyclopentadione (**5a**) is a natural flavoring compound isolated in a trace amount from roasted coffee and cigarette smoke condensate.[23,24] A previous synthetic route required four steps from diketone **1a** and provided **5a** in 16% yield.[24] *Our method prepared the same compound in 53% yield via a one-pot procedure from the same diketone intermediate using ethylene gas as the alkylating agent.*

In summary, we developed the first Rh-catalyzed intermolecular α-alkylation of cyclic 1,2-diketones via coupling with simple olefins. This reaction exhibits excellent regioselectivity to give linear products. Aminopyridine was employed as a recyclable DG for this transformation, and a broad range of terminal olefins can be coupled in good to excellent yields. This preliminary work should have broad implications and serve as a seminal study toward catalytic ketone alkylation with unactivated olefins. Future work will focus on achieving milder cleavage and catalytic turnover of the DG through its structural modification and expanding the scope of C−H donors, such as 1,3-diketones, enones, and regular ketones, as well as the scope of C−H acceptors, such as alkynes, allenes, and dienes. In addition, mechanistic studies and development of the related intramolecular reactions are currently ongoing.

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■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, spectral data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) Excess olefins were generally used in this study to enhance the reaction rate because they are often volatile under these reaction conditions; however, when 2 equiv of vinyl trimethylsilane reacted with enamine **3a**, an 87% yield was obtained (see SI).

(18) 1,1-Disubstituted styrenes, cyclohexene, and cyclopentene do not react under current reaction conditions.

(19) Further control experiments were conducted: using the aniline-derived enamine with added pyridine (either 10 mol% or 1 equiv) under the standard reaction conditions (5 mol% catalyst) did not provide any coupling products.

(20) Two challenging substrates: (a) Reaction with TIPS-protected 4-penten-1-ol proceeded sluggishly under the tandem conditions and provided the alkylated enamine product in 12% yield. (b) Reaction with methyl acrylate gave a complex mixture, likely due to the background reaction between methyl acrylate (Michael acceptor) and the diketones (OH as the nucleophile).

(21) For example, condensation between six-membered diketone **1b** and **2** in the presence of alumina generated a significant amount of aromatic oligomers (see SI), while use of five-membered diketone **1a** experiences no such problem.

(22) Enamine hydrolysis has been attempted with substrates **4b** and **4i**; unfortunately, the silane and ester groups are not tolerated under the aqueous acidic conditions: protodesilylation and ester hydrolysis were observed.

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