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Using Rh(III)-Catalyzed C−H Activation as a Tool for the Selective Functionalization of Ketone-Containing Molecules

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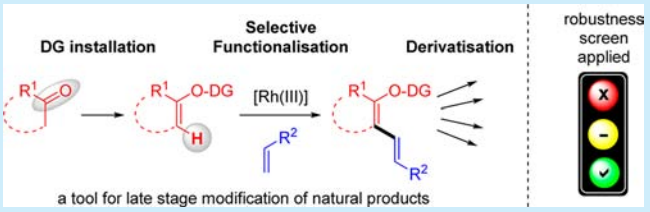
Supporting Information

ABSTRACT: Due to the strong potential of C−H activation in many areas of organic chemistry, the use of a pre-existing carbonyl group for the installation of a directing group to enable selective and predictable α-alkenylation with activated olefins as coupling partners is described. This Heck-type reaction would then lead either to β,γ-unsaturated ketones or to variously substituted 1,4-butadienes depending on the conditions used for the cleavage of the directing group.



Ketones are a very common motif in natural products and biologically active compounds, including polyketides, alkaloids, flavonoids, and steroids (Figure 1). The development

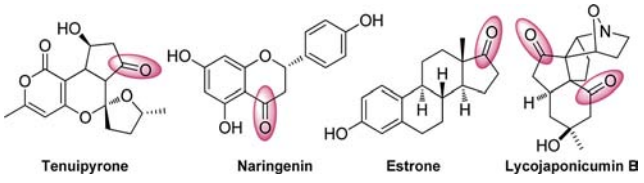


Figure 1. Structure of ketone-containing natural products.

of methods for the late-stage diversification of complex molecules or for the synthesis of biologically active compounds has attracted tremendous interest in the scientific community. In this regard, the activation of C−H bonds has led to significant advances in the field of organic chemistry over the past 15 to 20 years.[1] Based on all these facts, we focused our interest on the use of pre-existing functional groups for the selective and predictable functionalization of ketone-containing molecules.

More specifically, a pre-existing enolizable ketone would allow the installation of a directing group to perform selective C−H activation. While the α-functionalization of ketones by traditional methods (e.g., aldol chemistry or alkylation) is a well explored fundamental aspect of synthetic chemistry,[2] only recently have metal-catalyzed transformations been extensively developed.[3] Despite great advances in the transition-metal-mediated arylation of ketones, surprisingly little progress has been made using other coupling partners.[4] Over the past decade, palladium-catalyzed decarboxylative transformations such as allylations, propargylations, or allenylations of enolates have been developed.[5] However, the direct alkenylation of enolates has been rarely exploited.[6,7] We propose that by trapping enolates with a suitable directing group, C−H activation and functionalization of the vinylic position may be achievable (Figure 2). More precisely, we report herein the

Figure 2. Rh(III)-catalyzed alkenylation of stabilized enolates.

Rh(III)-catalyzed alkenylation of enol-carbamates followed by the derivatization of the obtained products and the application of this methodology to natural products.

As illustrated in Figure 2, the first step of the present work was the installation of the directing group.[8] Concerning the subsequent functionalization step, the initial experiments were performed with enol-carbamate **1a** derived from acetophenone and *n*-butyl acrylate (**2a**), in the presence of 2.5 mol % $[(Cp^*RhCl_2)_2]$, 10.0 mol % $AgSbF_6$, and 2.1 equiv of $Cu(OAc)_2$ as the catalytic system. The reaction optimization indicated that protic solvents were best suited for this transformation. Throughout this screening, MeOH gave the best results leading to the formation of **3aa** in 77% yield of the two double-bond isomers (*Z*,*E*)-**3aa** and (*Z*,*Z*)-**3aa** in a ratio of 88:12 (Figure 3). On a larger 2.5 mmol scale, the yield and the (*Z*,*E*)/(*Z*,*Z*) ratio improved to 95% and 92:8 respectively.

With the optimized conditions in hand, we examined the scope of this transformation with both coupling partners (Figures 3 and 4). Initially we studied the effect of the substitution pattern of the aromatic ring with various acetophenone-like enol-carbamates. The reaction proceeded with electron-rich and -poor substrates with high efficiency, leading to the desired conjugated dienes **3ba** to **3ga** with yields of 62% to 85%, the (*Z*,*E*) diastereomer being the expected major isomer in all cases. We were pleased to see that naphthalene-substituted enol-carbamate **1h** was suitable for this transformation, giving diene **3ha** in an excellent 95% yield.

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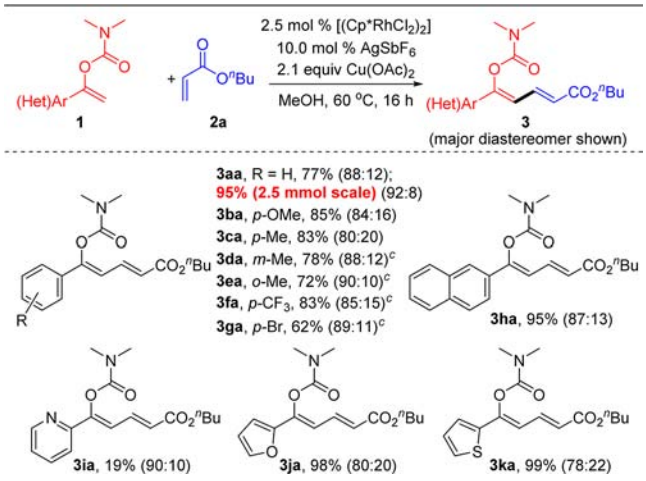


Figure 3. Variation of the aromatic ring of the enol-carbamate moiety.[a,b] [a] Conditions: **1** (0.20−0.50 mmol), **2a** (0.30−1.5 mmol), 2.5 mol % $[(Cp^*RhCl_2)_2]$, 10 mol % $AgSbF_6$, 2.1 equiv of $Cu(OAc)_2$, solvent (0.2 M), 16 h, under Ar. [b] Isolated yields of a mixture of double bond isomers (ratio of major (*Z*,*E*) isomer/minor isomers given in brackets). [c] At 100 °C.

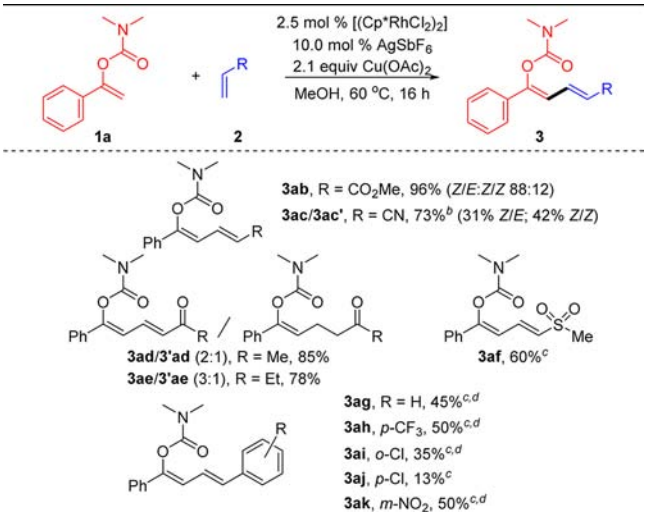


Figure 4. Variation of the olefin.[a,b] [a] For conditions, see Figure 3. [b] Isolated yields unless otherwise stated. [c] Using 5.0 mol % $[Cp^*RhCl_2]_2$, 20.0 mol % $AgSbF_6$, in 1,4-dioxane at 100 °C. [d] NMR yield using CH_2Br_2 as standard.

Moreoever, heteroaromatic rings were also well tolerated. Indeed, 2-acetyl furan and 2-acetyl thiophene derived enol-carbamates **1j** and **1k** promoted the formation of the desired products **3ja** and **3ka** in excellent yields although 2-acetyl pyridine derived substrate **1i** led to an expected lowered yield, presumably due to competitive complexation of the pyridine nitrogen atom.

Subsequently, we investigated the scope of the second coupling partner (Figure 4). The reaction of enol-carbamate **1a** with methyl acrylate (**2b**) afforded product **3ab** in a very good 96% yield. Other activated olefins such as acrylonitrile, vinyl ketones, and methyl vinyl sulfone were also compatible in the reaction. The reaction with acrylonitrile (**2c**), performed in 1,4-dioxane at 100 °C, provided a separable stereoisomeric mixture of products **3ac** (*Z*,*E*) and **3ac′** (*Z*,*Z*) in 73% combined yield. Methyl vinyl ketone (**2d**) and ethyl vinyl ketone (**2e**) led to high conversions as well, affording mixtures of the expected products **3ad** and **3ae** with the reduced products **3′ad** and **3′ae** in 85% and 78% combined yield respectively. Methyl vinyl sulfone (**2f**) underwent coupling with **1a** to give the alkenylated product **3af** as a single isomer in 60% yield. Use of styrenes as coupling partners was also feasible, albeit leading to moderate to low yields due to partial conversion of the starting material and difficult separation.

In order to validate the concept of the present work, the scope of nonaromatic and/or cyclic enol-carbamates was also investigated with *n*-butyl acrylate (**2a**) as the coupling partner (Figure 5). The alkyl substituted enol-carbamates **4a**, **4b**, and

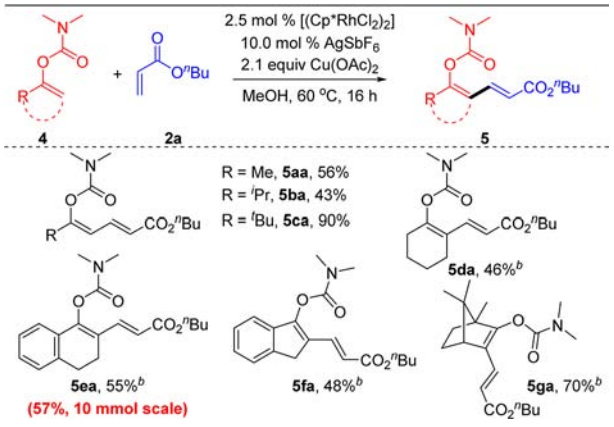
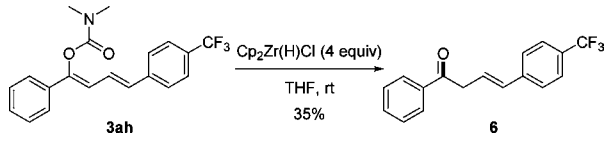


Figure 5. Extension of the substrate scope to nonaromatic and/or cyclic enol-carbamates.[a,b] [a] For conditions, see Figure 3. [b] Using 5.0 mol % $[Cp^*RhCl_2]_2$, 20.0 mol % $AgSbF_6$, in 1,4-dioxane at 100 °C.

4c were coupled with **2a** under the standard conditions to give the desired conjugated dienes **5aa**, **5ba**, and **5ca** in 56%, 43%, and 90% yield respectively. Interestingly, although these conditions led to very poor conversion in the case of cyclic enol-carbamates, the alkenylated products could be obtained using our modified conditions. Thus, enol-carbamate **4d** derived from cyclohexanone gave the expected product **5da** in 46% yield. Coupling of enol-carbamates **4f** and **4g**, derived from 1-indanone and camphor respectively, led to the alkenylated products **5fa** and **5ga** in 48% and 70% yield respectively. Finally, we were very pleased to establish that the reaction was readily scalable, with compound **5ea** being obtained in a comparable 57% yield on a 10 mmol scale.

Aiming to develop a new method for the late-stage selective functionalization of complex ketone-containing molecules, we then focused our interest on the derivatization of these enol-carbamates. First, it was important to show that the directing group could be cleaved leading to the α-alkenylated ketone (Scheme 1). However, this transformation proved particularly challenging and could only be performed by use of the Schwartz reagent.[9] Thus, enol-carbamate **3ah** was converted into β,γ-unsaturated ketone **6** in 35% yield.

Scheme 1. Cleavage of the Carbamate to the β,γ-Unsaturated Ketone



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Inspired by the numerous reports on Ni-catalyzed C−O bond cleavage of aryl carbamates from the groups of Garg, Snieckus, and Shi,[10] we then attempted similar transformations on our system. As cyclic ketones are much more prevalent in naturally occurring or biologically relevant compounds than terminal methyl ketones, we decided to carry out this study on the cyclic enol-carbamate **5ea** (Figure 6). Surprisingly, the reaction of **5ea** in the presence of $Cp_2Zr(H)Cl$ led to the quantitative formation of **7** after selective reduction of the ester over the carbamate moiety.

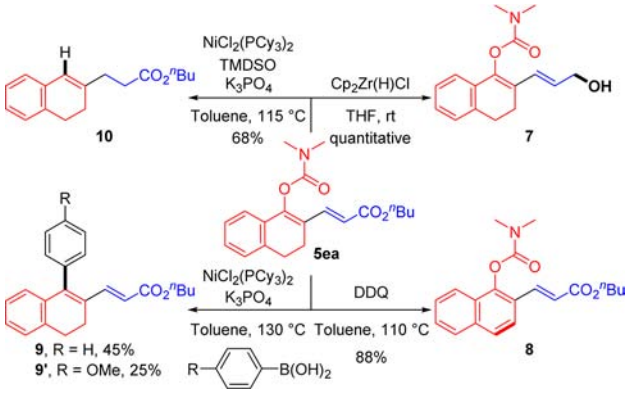
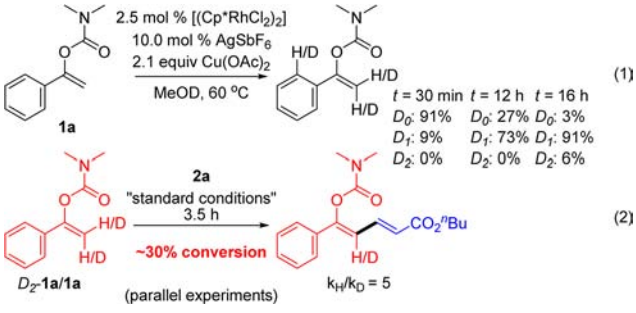


Figure 6. Derivatization of the alkenylated enol-carbamates.

Moreover, reaction of **5ea** with DDQ afforded the fully aromatized product **8** in a very good 88% yield. We were very pleased to see that the C−O bond of the carbamate moiety could be cleaved under nickel catalysis in the presence of arylboronic acids, giving the corresponding arylated products **9** and **9′**. The same nickel catalyst was also used in combination with TMDSO (tetramethyldisiloxane) leading in this case to reduced compound **10** in 68% yield. A robustness screen was also undertaken in order to investigate the applicability of this method in the presence of several functional groups and heterocycles (see Supporting Information (SI)).[11]

To gain insight into the mechanism of this transformation, deuteration experiments and kinetic isotope effect (KIE) studies were conducted (Scheme 2). When the reaction was

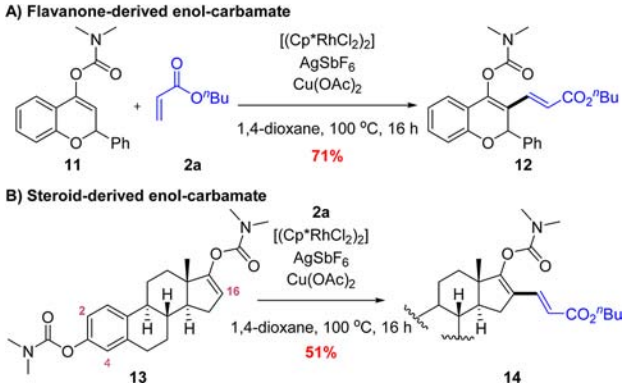
Scheme 2. Deuteration Experiments and KIE Studies



performed in $[D_4]$methanol in the absence of the olefinic coupling partner, the incorporation of deuterium increased from 10% after 30 min to 90% after 16 h [eq 1]. These results may be attributed to the fact that either the C−H activation process is slow or/and the intermediate rhodacycle is thermodynamically stable in these conditions. Control experiments were carried out in the absence of $Cu(OAc)_2$ or $[(Cp^*RhCl_2)_2]$, showing in both cases no incorporation of deuterium after 16 h (see SI). For a better understanding, we then studied the KIE of the reaction [eq 2]. Parallel experiments were performed with **1a** and D_2-**1a** and a KIE of 5 was measured, suggesting that the C−H bond activation is the rate-determining step.

Finally, in order to prove the concept described in the present work, we decided to apply this methodology to biologically relevant compounds (Scheme 3). Thus, the reaction of flavanone derived enol-carbamate **11** and bis-protected estrone **13** with *n*-butyl acrylate (**2a**) was investigated.

Scheme 3. Application to Natural Products



In the former case, the desired alkenylated product **12** was obtained in a very good 71% yield in the conditions previously optimized for cyclic enol-carbamates (Scheme 3A). In the case of bis-protected estrone **13**, this reaction afforded exclusively the C16 monoalkenylated product **14** in 51% yield and no C2−C16 bis-alkenylated product was observed. Alkenylation at the C4 position was not envisaged due to steric reasons as described in the literature (Scheme 3B).[7b]

In summary, we have developed the first example of a Rh-catalyzed alkenylation of enolates. This transformation allows the construction of linear 1,3-dienes from aryl, alkyl, and cyclic enolates. The cleavage of the carbamate moiety then enables the formation of either (*E*)-3-alkenones or various interesting products by C−O bond activation under Ni catalysis. Finally, the application of this methodology to natural products demonstrates the potential of this strategy.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. 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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(8) Although the formation of enol-carbamates has often proved challenging in this work, it should be noted that the unreacted ketone could readily be recovered and retreated after the reaction in all cases. Moreover, although we used a standard procedure for the installation of the directing group, without any further optimization, other protocols found in the literature seemed to be suitable for our substrates (see ref 12). This was indeed recently demonstrated, as enol-carbamate **4f** derived from 1-indanone was formed in 82% yield instead of the 40% obtained using the general procedure (see Supporting Information).

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