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Vanadium-Catalyzed Coupling of Allenols with Electrophilic Halide Sources for the Formation of α -Halo- α',β' -unsaturated Ketones

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Supporting Information

ABSTRACT: A vanadium-catalyzed coupling of allenvlic alcohols with electrophilic halide sources to form α -halo- $\alpha'_{,\beta}\beta'$ -unsaturated ketones is described. The process proceeds through a metal enolate formed from the 1,3-transposition of an allenol that is initiated by a cheap and earth-abundant vanadium oxo catalyst. Fluorine, chlorine, and bromine electrophiles can be utilized, and the resulting products can give rise to the introduction of nitrogen, oxygen, sulfur, and



iodine nucleophiles α to the ketone through substitution chemistry.

he α -halo- α',β' -unsaturated ketone motif, especially those adorned with fluorine, have begun to receive significant attention in the patent literature as key intermediates in the synthesis of biologically active targets.¹ However, their synthesis is generally plagued by multistep reaction sequences and/or the need to use specialized reagents that are often difficult to access.² While the direct electrophilic halogenation of α_{β} -unsaturated ketones is an appealing method, the use of enolate chemistry is particularly challenging due to issues associated with overhalogenation that occur because of the increased acidity of α -protons following the first halogenation.³ While judicious choice of stoichiometric strong base and the use of cryogenic reaction temperatures can help to limit overhalogenation, most approaches rely upon the use of stoichiometric silyl or boron activating agents that typically necessitate cryogenic reaction temperatures in addition to stoichiometric strong base.⁴

Our group has developed a very mild and regioselective method for the in situ, catalytic generation of enolates starting from allenyl⁵ or propagyl⁶ alcohols that negates the need for stoichiometric activation, strong base, and cryogenic reaction temperatures. In this method, which can be termed "sigmatropic functionalization", a vanadium oxo complex catalyzes the 1,3-transposition of the alcohol to form a metal enolate that can undergo trapping by a series of electrophiles in preference to a competing simple protonation pathway that would lead to the Meyer-Schuster product. Given the mild reaction conditions and high functional group tolerance previously observed, we wondered whether the vanadium enolates generated from readily available allenyl alcohols' would be able to successfully trap electrophilic halide sources to generate α -halo- α',β' -unsaturated ketones and overcome the issues of regioselectivity and overhalogenation typically observed in base-promoted processes (Figure 1).

Previous attempts to utilize allenylic alcohols as precursors for α -halo- α',β' -unsaturated ketones have been plagued by the need to utilize a three-step reaction sequence, the use of an



Figure 1. Proposed catalytic cycle.

expensive gold catalyst, and the inability to install halides other than fluorine (Scheme 1).⁸ Use of our group's earth-abundant vanadium catalyst would provide an economical method for the generation of a wide range of α -halo- α' , β' -unsaturated ketones.

We began our studies with allenol 1. Treatment with 5 mol % of $OV(OSiPh_3)_3$, 1.2 equiv of N-fluorobenzenesulfonimide (NFSI), and 3 equiv of freshly ground sodium carbonate in 1,2-dichloroethane (DCE) at 65 °C for 19 h resulted in clean formation of monofluorinated product 2 in 68% isolated yield (Table 1, entry 1). No difluorinated adduct 3 was observed, and the remaining material could be accounted for by formation of the Meyer-Schuster product. Increasing the amount of electrophile was beneficial, with 2 equiv of NFSI yielding the desired product in 84% yield (entry 2). The

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Scheme 1. Use of Allenols for the Synthesis of α -Halo- α',β' unsaturated Ketones





= F CL B

Table 1. Optimization for the Formation of α -Fluoroenones^{*a*}

Ph H		OV(OSiPh ₃) ₃ (5 mol %) NFSI (Y equiv) Base (X equiv) Pl DCE (0.5M)		$\frac{1}{2} + \frac{1}{2} + \frac{1}$	
entry	base	X	temp (°C)	Y	yield of 2^{b} (%)
1	Na_2CO_3	3	65	1.2	68
2	Na_2CO_3	3	65	2	84
3	Na_2CO_3	2	65	2	80
4	Na ₂ CO ₃	1.05	65	2	26
5	K_2CO_3	2	65	2	$60^{c} (10)^{b}$
6	Cs ₂ CO ₃	2	65	2	$19^{d} (4)^{b}$
7	NaHCO ₃	2	65	2	11
8	MgO	2	rt	2	22
9 ^e	Na_2CO_3	2	65	2	28

^{*a*}Experiments run at a 0.2 mmol scale. The base was freshly ground before use. ^{*b*}Isolated yield of **2**. If observed, isolated yield of **3** is given in parentheses. The remainder of the mass balance could be accounted for by Meyer–Schuster product. ^{*c*}80% conversion. ^{*d*}25% conversion. ^{*c*}Reaction run in toluene.

amount of base could be reduced to 2 equiv without any significant impact on yield (entry 3). Further reducing the amount of base to 1.05 equiv led to a significant increase in the formation of the Meyer-Schuster product (entry 4). Choice of base was very important to the outcome of the reaction. Switching from sodium carbonate to potassium carbonate resulted in lower conversion as well as the formation of 10% of the difluorinated adduct 3 (entry 5). Cesium carbonate led to an even lower conversion (25%) and also resulted in the formation of a small amount of difluorinated adduct 3 (entry 6). While full conversion was obtained using sodium bicarbonate and magnesium oxide, the desired product was obtained in only 11 and 22% yield, respectively, with the remainder of the material being composed of the Meyer-Schuster product (entries 7 and 8). The ability of the reaction to proceed at rt with magnesium oxide while requiring elevated temperatures of 65 °C to obtain reactivity with carbonate bases indicates that the carbonates are likely acting as Lewis bases to the vanadium catalyst, reducing the Lewis acidity of the catalyst and impacting its ability to ionize the allenylic alcohol during the 1,3-transposition. Finally, solvent was found to play a large role in the outcome of the reaction, with the use of toluene yielding the desired product in just 28% yield.

A control experiment was performed to ensure that the fluorination reaction was not simply the result of a vanadiumcatalyzed Meyer–Schuster rearrangement followed by a general base-promoted fluorination (Scheme 2). In this experiment, the allenol and vanadium oxo catalyst were stirred





in DCE at rt until complete conversion to the Meyer–Schuster product was observed. At this point, NFSI and freshly ground sodium carbonate were added to the reaction flask, and the mixture was allowed to stir at 65 °C for 23 h. Under these conditions, only 3% of fluorinated product **2** was obtained. This control clearly supports the reaction pathway presented in Figure 1.

With a set of optimized conditions in hand (Table 1, entry 3), the scope of the process was explored (Scheme 3). Steric





^{*a*}Reactions performed at 0.2 mmol scale. The base was freshly ground before use. In all cases, >20:1 *E/Z* olefin geometry is observed. ^{*b*}10 mol % of OV(OSiPh₃)₃. ^{*c*}5 mol % of OV(OSi[*p*-ClC₆H₄]₃)₃ used. ^{*d*}10 mol % of OV(OSi[*p*-ClC₆H₄]₃)₃ used. ^{*c*}Reaction run in acetonitrile*d*₆. NMR yield based upon mesitylene internal standard. ^{*f*}7.5 mol % of OV(OSiPh₃)₃.

bulk on \mathbb{R}^2 was well tolerated, with an isopropyl group at that position resulting in only a slight decrease in yield compared to a methyl group (4). Both electron-deficient aryl (5 and 6) and electron-rich aryl (7–9) and heteroaryl (10) groups were tolerated at \mathbb{R}^1 , although a modest decrease in yield is generally seen in the case of electron-rich aryl groups. The functional group tolerance of the reaction was found to be remarkably high for a process that involves the trapping of a metal enolate with an electrophilic halide under Lewis acidic and Brønsted basic conditions. An allenol containing a methyl alkynyl ketone underwent the desired transformation, with the alkynyl ketone acting as neither an acceptor for the vanadium enolate nor a nucleophile toward the NFSI (6). Silyl-protected alcohols remained intact, as did free alcohols (8 and 9). Distal alkenes, silyl protected alkynes, and terminal alkynes were all well tolerated and showed no undesired fluorine incorporation (7, 11, and 12). Aryl substitution at R^1 was not required for reactivity. Using the more electron-deficient $OV[OSi(p-ClC_6H_4)_3]_3$ catalyst, a phenethyl-substituted allenol gave the desired product in good yield (13). In addition to secondary allenylic alcohols, tertiary allenols also participated cleanly to give trisubstituted double bonds (14–16). When a cyclic allenol is utilized, exocyclic enones can be produced (15). Likewise, when the two R^1 substituents are sterically differentiated, the resulting enone is formed exclusively with the thermodynamic *E*-double-bond geometry (16).

We next turned our attention to expanding the scope of electrophiles to include electrophilic chlorine sources. Treating allenol 1 under the previously optimized fluorination conditions (Table 1, entry 3) but switching the electrophile from NFSI to *N*-chlorosuccinimide (NCS) resulted in the formation of a 1:2 mixture of the desired chlorination product 17 and the overhalogenated product 18 (Table 2, entry 1).



Ph	ОН 	OV(OSiPh ₃) ₃ NCS (X e base (2 e solvent (C	(5 mol %) quiv) quiv) 9.5M)	Ph 17	+ CI CI Ph 18
entry	base	solvent	X	temp (°C)	yield of 17 $(\%)^b$
1	Na_2CO_3	DCE	2	65	$20 (46)^{b}$
2	MgO	DCE	3	65	96
3	MgO	DCE	2	45	92
4	MgO	DCE	2	rt	88
5	MgO	DCE	1.2	45	93
6	MgO	DCE	1.0	45	94
7	MgO	THF	1.0	45	51
8	MgO	PhMe	1.0	45	93
9 ^c	MgO	PhMe	1.0	45	84

^{*a*}Experiments run at a 0.2 mmol scale. The base was freshly ground before use. ^{*b*}Isolated yield of 17. If observed, the isolated yield of 18 is given in parentheses. The remainder of the mass balance could be accounted for by Meyer–Schuster product. ^{*c*}Reaction run at 1.0 M.

Believing the dichlorinated product to be arising from a general base-promoted chlorination of desired product 17, we switched the base from sodium carbonate to a milder magnesium oxide base. Under these conditions, the desired product was isolated in 96% yield and with no evidence of overchlorination (entry 2). Lowering the reaction temperature from 65 to 45 °C had no impact on reactivity (entry 3). While the reaction could be run at rt with only a very small reduction in yield, 45 °C was picked as the optimized temperature due to the observation of consistently higher yields at this slightly elevated temperature (entry 4). In the case of chlorination, the amount of electrophile could be dropped all the way down to 1.0 equiv without impacting yield (entries 5 and 6). While use of THF resulted in the formation of significant amounts of Meyer–Schuster product (entry 7), use of toluene gave nearly identical results as that of DCE (entry 8). Finally, attempts to increase the reaction concentration from 0.5 to 1.0 M resulted in a small 9% reduction in isolated yield (entry 9).

To determine the scope of the process, a series of allenols were subjected to our optimized conditions (Table 2, entry 8).

Both secondary and tertiary allenyl alcohols successfully participated in the process (Scheme 4A, 17, 19–22). Both

Scheme 4. Scope of the Vanadium-Catalyzed Chlorination and Bromination of Allenols a



"Reactions performed at 0.2 mmol scale. The base was freshly ground before use. In all cases, >20:1 E/Z olefin geometry is observed. ^b5 mol % of OV(OSi[p-ClC₆H₄]₃)₃ used. ^c15 mol % of OV(OSiPh₃)₃ used.

aryl and alkyl substitution at R¹ were well tolerated. As was the case with fluorination, no halogen incorporation into a terminal alkyne was observed (20). Monoalkyl substitution at R¹ required use of the more electron-deficient OV(OSi[p- $ClC_6H_4]_3$ catalyst (21). Of note, benzyl substitution at \mathbb{R}^2 was well tolerated, and no overhalogenation was observed (22). This result highlights the mild nature of these reaction conditions, as the benzylic nature of the α proton of 22 makes it particularly activated toward enolization that would lead to overhalogenation. The corresponding bromination process could also be performed utilizing slightly modified conditions: 1.2 equiv of dibromo-Meldrum's acid as the electrophilic bromine source in DCE at room temperature (see the Supporting Information, Table S1). The scope of bromination was equally broad, with secondary and tertiary allenyl alcohols participating (Scheme 4B, 23-27). Once again, no undesired halogenation of a pendant methyl alkynyl ketone was observed under the mild reaction conditions (24).

To showcase the scalability of the reaction, the fluorination of 1 was run on a gram scale, and its corresponding chlorination was run at 1 mmol scale (Scheme 5). No impact on yield was observed, but the heterogeneous nature of the

Scheme 5. Gram-Scale Fluorination and Millimole Scale Chlorination Reactions



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reaction mixture required an increase in the amount of base utilized to minimize formation of the Meyer–Schuster product at the larger scale.

The unique ability of our method to access α -bromo ketones was exploited to obtain a wide range of α -heteroatom substituted α',β' -unsaturated ketones. Starting from bromo ketone **23**, treatment with nitrogen, oxygen, sulfur, and iodine nucleophiles all led to the desired S_N2 products (**28–31**) in high yields (Scheme 6).

Scheme 6. $S_N 2$ Reactions To Form α -Heteroatom α',β' -Unsaturated Ketones



A final demonstration of the utility of our products was the palladium-catalyzed hydrogenation of **2** into the saturated ketone **32**. Direct access to such fluorinated ketones is unknown in the literature due to issues of regioselectivity arising from the similar steric and electronic properties of the two α methylene groups (Scheme 7).

Scheme 7. Hydrogenation To Access Saturated Ketones



In summary, we have developed an efficient method for the formation of α -halo α',β' -unsaturated ketones from readily available allenyl alcohols. This method utilizes a cheap and earth-abundant vanadium catalyst and shows remarkable functional group tolerance for a method involving the trapping of an electrophilic halide by a metal enolate under Lewis acidic and Brønsted basic conditions. Quite remarkable is the ability of the vanadium-catalyzed process to outcompete halogenation of the allene starting material, which is present in stoichiometric amounts at the start of the reaction. The reaction can be run at gram scale, and the products obtained can be converted into a variety of valuable α -heteroatom α',β' -unsaturated ketones or hydrogenated to their fully saturated α -halo ketone products.

ASSOCIATED CONTENT

S Supporting Information

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Experimental details, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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