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Vanadium-Catalyzed Synthesis of Geometrically Defined Acyclic Tri- and Tetrasubstituted Olefins from Propargyl Alcohols

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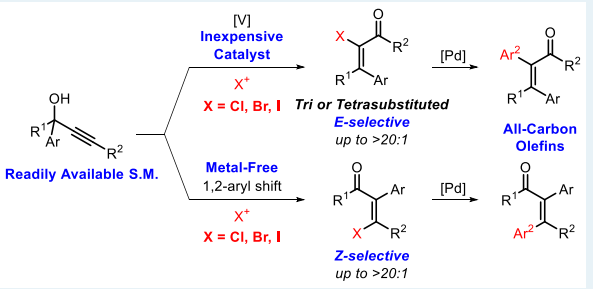
Supporting Information

ABSTRACT: A highly selective formation of geometrically defined acyclic tri- and tetrasubstituted alkenes from inexpensive and readily available propargyl alcohols is described. Through vanadium oxo catalysis, tri- and tetrasubstituted α-chloro-, bromo-, and iodo-enone olefins can be synthesized with the kinetic *E*-geometry. Complementary tetrasubstituted β-chloro-, bromo-, and iodo-enone olefins with *Z*-geometry can be accessed through a metal-free 1,2-aryl shift. The utility of these geometrically defined vinyl halides is demonstrated through cross-coupling reactions to form all-carbon tetrasubstituted olefins with near complete retention of starting olefin geometry as well as through the total synthesis of (±)-myodesmone.



KEYWORDS: *vanadium, tetrasubstituted olefins, alkenes, halogenation, vinyl halides, propargyl alcohols, Meyer−Schuster rearrangement*

INTRODUCTION

Enolate chemistry is perhaps the most fundamental and well-studied method for the generation of carbon bonds.[1] Despite the intensive research efforts in this area, the generation of enolates is still commonly plagued by the use of stoichiometric amounts of strong base, cryogenic temperatures, and/or stoichiometric additives that generate waste and lower atom economy.[2] Our group has devised a method for the mild, catalytic, and chemoselective generation of metal enolates starting from cheap and readily available propargyl alcohols. In this method, an inexpensive vanadium oxo complex catalyzes a 1,3-transposition of the propargyl alcohol to form a vanadium allenolate that can undergo trapping by a series of carbon-based electrophiles,[3] even in the presence of a competing simple protonation pathway that would lead to the Meyer−Schuster product. Such a general strategy, which can be termed "sigmatropic functionalization",[4] offers a very promising pathway for the rapid and economic generation of chemical complexity.

One chemical motif that remains a significant synthetic challenge in modern organic chemistry is the geometrically defined tetrasubstituted acyclic olefin.[5] While recent advances in this area have been made based upon the elimination of alcohols,[6] the functionalization of enolates,[7] conjugate addition to allenyl aldehydes,[8] carbometalaton of internal alkynes,[9] and the use of strongly electrophilic reagents to activate internal alkynes,[10] these methods generally suffer from issues related to regioselectivity, functional group tolerance, and/or the use of difficult to access starting materials.

In addition to serving as a valuable building block for a wide variety of asymmetric transformations,[11] the geometrically defined tetrasubstituted acyclic olefin motif is found in natural products[12] and commercialized pharmaceuticals,[13] and is of interest in materials science.[14] Within this class of compounds, tetrasubstituted vinyl halides are of particular interest due to their versatility as substrates for metal-catalyzed cross-coupling reactions, allowing for the rapid formation of libraries of tetrasubstituted all-carbon olefins. Our approach to synthesizing such valuable substrates involved the trapping of catalytically generated vanadium enolates, formed from tertiary propargyl alcohols, by an electrophilic halide (Figure 1, top). Control of this electrophilic trapping would provide ready access to geometrically defined tetrasubstituted olefins containing a valuable halide functional group handle. At the onset, we predicted the geometric selectivity to arise from a steric differentiation of the two vanadium enolate faces. Approach of the electrophile from the same face as the small R group (R^S) would be favored over approach from the face of the more sterically demanding large R group (R^L) (Figure 1, bottom). A result of this facial selectivity is the production of tetrasubstituted olefins with the difficult to obtain kinetic *E*-geometry, where the bulkier ketone and R^L group sit on the same side of the olefin. While there are a few scattered reports of such a process in the literature, they all suffer from poor geometric selectivity (generally less than 2:1) and require either the use of expensive gold catalysts or harsh acidic conditions that limit functional group tolerance (Scheme 1).[15] Successful use of our earth-abundant vanadium catalyst system

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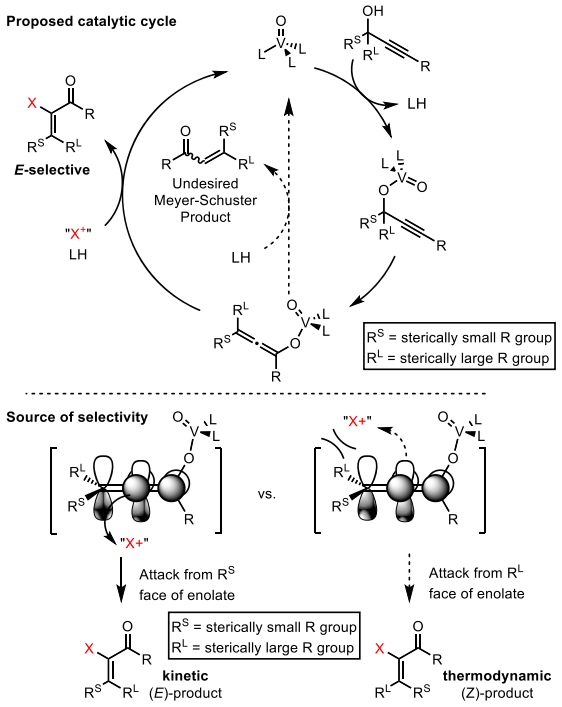
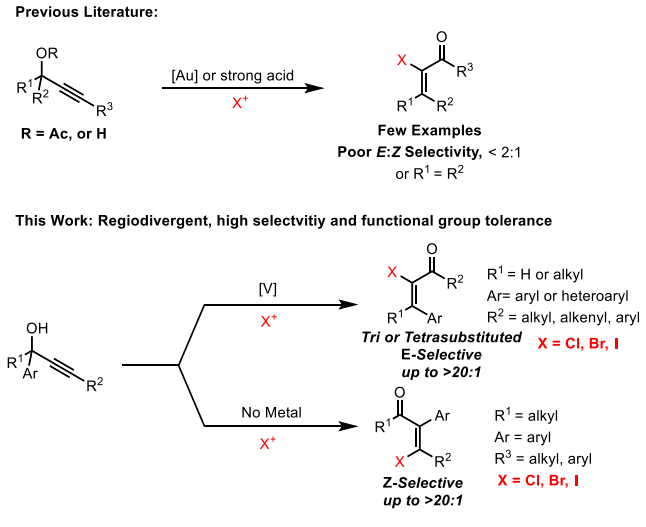


Figure 1. Proposed catalytic cycle (top) and source of selectivity (bottom).

Scheme 1. Synthesis of Geometrically Defined Tetrasubstituted Enone Olefins

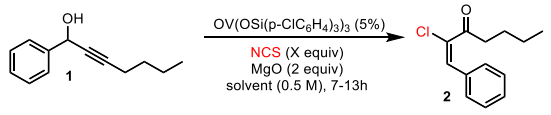


would provide an economical and functional group tolerant approach to overcome the significant issue of geometric selectivity.

RESULTS AND DISCUSSION

We began our studies with the use of secondary alcohol **1**. Initial screening was performed with a secondary alcohol due to the larger steric differentiation in the nucleophilic trapping step between hydrogen and an aryl group as compared to that of an alkyl and aryl group. Treatment of **1** with 5 mol % $OV(OSiPh_3)_3$, 2 equiv of *N*-chlorosuccinimide (NCS), and 2 equiv of MgO as a general base in acetonitrile at 80 °C resulted in 61% of the desired trisubstituted olefin **2** in a 2:1 *E*:*Z* ratio of olefin geometric isomers (Table 1, entry 1). The remainder

Table 1. Optimization of the Formation of *E*-Chloro-Trisubstituted Olefins



entry	solvent	X	T (°C)	*E*:*Z* ratio[a]	Yield (%)
1[b]	MeCN	2	80	2:1	61
2	MeCN	2	80	4:1	66
3	MeCN	2	65	6:1	87
4	MeCN	1.05	65	20:1	85
5[c]	MeCN	1.05	65	5:1	63
6	PhMe	2	65	10:1	81
7	PhMe	1.05	65	19:1	82
8	THF	2	80	1:3	<5

[a]*E*:*Z* ratio determined via ^{1}H NMR of the crude reaction mixture. [b]$OV(OSiPh_3)_3$ used as catalyst. [c]1.0 M, 2.5 mol % $OV(OSi(p\text{-}ClC_6H_4)_3)_3$.

of the mass balance was accounted for by the Meyer−Schuster product that results from simple protonation of the vanadium enolate. Switching to the more electron withdrawing catalyst $OV(OSi(p\text{-}ClC_6H_4)_3)_3$ resulted in an improvement of the *E*:*Z* selectivity to 4:1 (entry 2). This improvement in selectivity is thought to be attributed to the more electron deficient 4-chlorophenyl silanol vanadium complex forming a more stabilized enolate. As a result, a later transition state that incorporates more carbon-chloride bond character better accentuates the steric difference between the two faces of the enolate (see Figure 1). Dropping the reaction temperature from 80 to 65 °C led to a further improvement in selectivity and a large improvement in yield to 87% (entry 3).

A major improvement in selectivity was observed by decreasing the equivalents of electrophile from 2 to 1.05. Under these conditions, the desired product was isolated in 85% yield and with a 20:1 *E*:*Z* ratio (entry 4). Such a drastic improvement in selectivity, coupled with the observation of high *E*:*Z* selectivity at low conversion with 2 equiv of NCS (see the Supporting Information, Table S1), strongly suggests that the excess halide, perhaps through a radical intermediate, is acting to isomerize the kinetically formed *E* product into the thermodynamic *Z* product. Lowering the catalyst loading to 2.5 mol % while increasing the reaction concentration to 1.0 M resulted in a reduction of both the *E*:*Z* ratio and conversion (entry 5). While PhMe gave similar results to those of acetonitrile (entries 6 and 7), use of THF resulted in low conversion and provided the *Z*-olefin isomer as the major product (entry 8).

With a set of optimized conditions for the formation of *E*-chloro-olefins in hand (Table 1, entry 4), the scope of chlorination was explored (Table 2, part A). Both electron-rich and electron-poor aromatic groups on R^L performed well, giving high yields and selectivities (Table 2, **2**−**5**). In some cases, use of PhMe as solvent was beneficial to the *E*:*Z* ratio, but there was no general trend observed. Ortho substituted aromatic R^L groups required a slightly elevated reaction temperature of 75 °C, but did not impact yield or selectivity (**5**). Heteroaromatic groups were also well-tolerated at R^L under the reaction conditions (**6** and **7**), as was branching on

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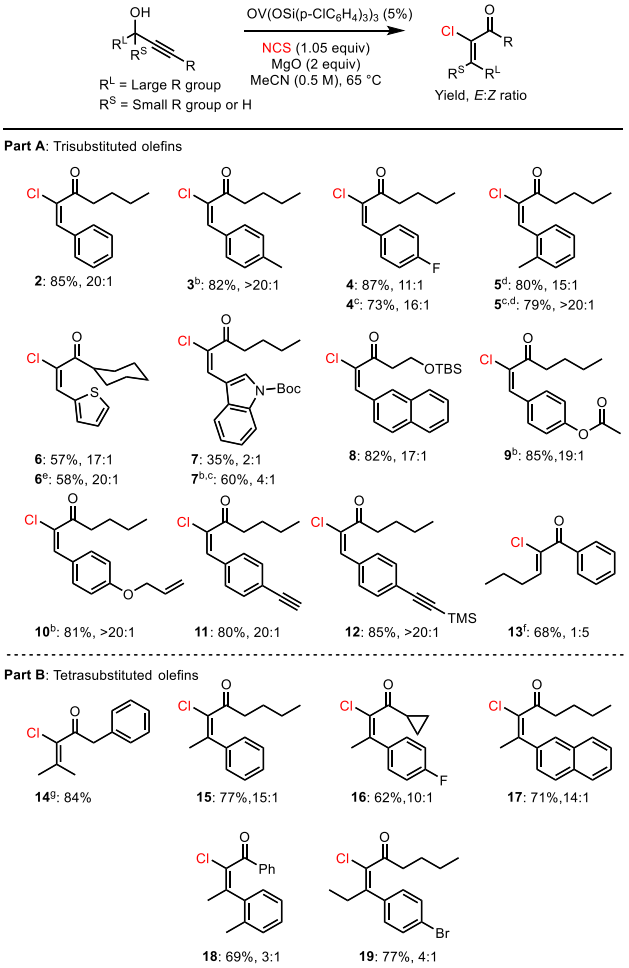
Table 2. Scope of the *E*-Selective Vanadium Chlorination Reaction[a]



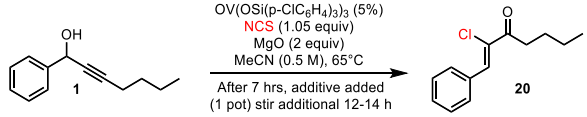
[a]Reactions performed at 0.2 mmol scale. *E*:*Z* ratio determined via ^{1}H NMR of the crude reaction mixture. [b]Slow addition of the alcohol to the reaction. [c]PhMe used as solvent. [d]75 °C. [e]40 °C. [f]110 °C. [g]80 °C.

the alkyne at R (**6**). In the case of indole substitution, a slow addition of the alcohol was required to obtain a higher yield and *E*:*Z* selectivity. The lower selectivity of this substrate (4:1) was due to the proclivity of the product to undergo isomerization: a pure sample of the *E*-product was observed to isomerize to a 1:1 mixture of *E*:*Z* isomers simply by standing in $CDCl_3$ overnight. Functional group tolerance of this process was found to be very high. Silyl-protected alcohols, enolizable esters, and even olefins, terminal alkynes, and silyl-protected alkynes were all well-tolerated by the reaction conditions (**8**–**12**). All of these functional groups, known to be sensitive to electrophilic halide sources, were not observed to undergo any halide incorporation. Switching R^L from an aryl group to an alkyl group required a significantly elevated reaction temperature (110 °C) due to less stabilization of the developing partial positive charge at the carbinol carbon during the transition state of the 1,3-transposition.[16] While a good yield was obtained, the higher reaction temperature resulted in significant product isomerization, with the isolated product having a 1:5 *E*:*Z* ratio favoring the thermodynamic *Z* product (**13**). For several of the secondary alcohol substrates containing electron-rich aromatic groups at R^L, a slow addition of the alcohol was required to prevent ethereal dimerization of the propargyl alcohol starting material (**3**, **9**, and **11**).

We next investigated the use of tertiary propargyl alcohols that would result in the formation of tetrasubstituted olefins (Table 2, part B). For dimethyl substitution at the propargylic position (R^S = R^L = Me), a higher reaction temperature was required (**14**). Even though product **14** contains readily enolizable protons alpha to the ketone, further acidified by their benzylic nature, no chlorine incorporation at that position was observed, highlighting the mild nature of the reaction conditions. Excellent selectivity for the kinetic *E*-product was obtained when R^L was aryl, and R^S was methyl (10:1 to 15:1, **15**–**17**). For this class of substrates, both electron-rich and electron-poor aryl groups were tolerated at R^L, as were aryl and branched alkyl groups on the alkyne at R. When R^L and R are both large aromatic groups, as in the case of **18**, the *E*:*Z* selectivity begins to drop. This decrease in selectivity is a result of an increase in steric crowding between R^L and R during the allenolate sp carbon rehybridization in the enolate trapping transition state that begins to compete with the steric differentiation between the electrophile and R^S/R^L (Figure 1, *vide supra*). Finally, switching R^S from methyl to a larger ethyl group resulted in a modest reduction in *E*:*Z* selectivity to 4:1 (**19**).

Having observed the ability of excess NCS to isomerize the kinetically formed *E*-olefin to the thermodynamic *Z*-olefin, we sought to develop one-pot conditions to both form the initial *E*-product and then isomerize it via an addition−elimination mechanism to the *Z*-product. To do so, a series of additives were added to the reaction mixture after complete consumption of the starting propargyl alcohol was observed. Use of phosphines, added neat or in solution, led to only small amounts of isomerization and complete conversion of the phosphine to the phosphine oxide (Table 3, entries 1–3).

Table 3. Optimization for the One-Pot Synthesis of Thermodynamic *Z*-Chloro-olefins



entry	additive	*E*:*Z* ratio[a]	Yield (%)
1	10% PPh_3	11:1	82
2	25% PPh_3	10:1	85
3	20% PBu_3 in 0.1 mL MeCN	6:1	81
4	20% DABCO in 0.1 mL MeCN	8:1	82
5	20% DMAP in 0.1 mL MeCN	1:2	84
6	20% DMAP in 0.1 mL DMF	1:21	79

[a]*E*:*Z* ratio determined via ^{1}H NMR of the crude reaction mixture.

While addition of 20 mol % 1,4-diazabicyclo[2.2.2.]octane (DABCO) in MeCN resulted in minimal isomerization, addition of 20 mol % 4-(dimethylamino)pyridine (DMAP) in MeCN resulted in the isolation of the desired product in a promising 2:1 *Z*:*E* ratio and with an 84% yield (Table 3, entries 4 and 5). Using the same 20 mol % DMAP but switching the addition solvent from MeCN to the more polar

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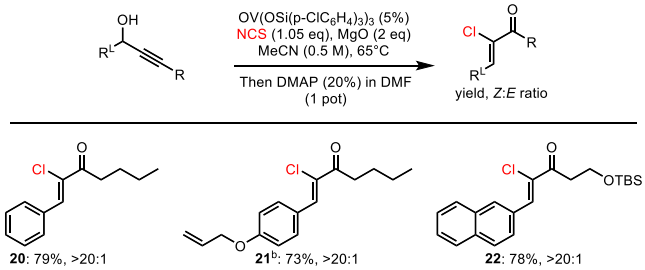
DMF resulted in near complete isomerization of the product to the thermodynamic *Z*-olefin (>20:1 *Z*:*E*) in 79% isolated yield.

With a set of conditions for the one-pot synthesis of *Z*-chloro-olefins (Table 3, entry 6), a very brief scope was explored. In each case, the desired product was obtained in good yield and in >20:1 *Z*:*E* selectivity (Table 4, **20**–**22**). In these substrates, no halogenation of a terminal allyl double bond or loss of a silyl alcohol protecting group was observed. With access to both *E*- and *Z*-trisubstituted olefins, NOE analysis was able to definitively assign the olefin geometry for both sets of products (Figure 2).

Table 4. Brief Scope of the One-Pot Synthesis of *Z*-Chloro-olefins[a]



[a]Reactions performed at 0.2 mmol scale. [b]Slow addition of the alcohol to the reaction.

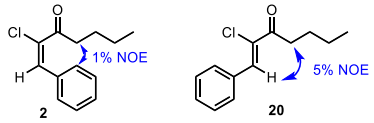
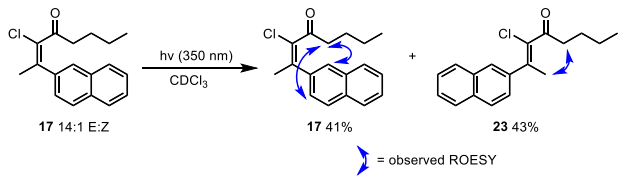


Figure 2. Confirmation of olefin geometry through ^{1}H NOE analysis.

While DMAP in DMF was successful at the isomerization of trisubstituted olefins, it was unable to isomerize the kinetic *E*-tetrasubstituted olefins to their thermodynamic *Z*-configuration. After screening a number of addition–elimination and radical-based isomerization conditions, we eventually found that irradiation of *E*-tetrasubstituted-choloro-olefin **17** with 350 nm wavelength light resulted in a 1:1 photoequilibrium of *E* and *Z* products, separable via silica chromatography (Scheme 2). With access to both *E* and *Z* products, use of ROESY ^{1}H NMR data allowed for confirmation of the assigned olefin geometry.

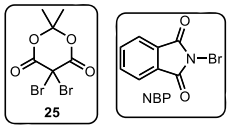
Scheme 2. Photoequilibrium of Tetrasubstituted Enone 17



Having established the ability of our vanadium system to provide selective access to geometrically defined *E*- and *Z*-trisubstituted as well as *E*-tetrasubstituted chloro-olefins, we turned our attention to the corresponding bromination process. Treatment of tertiary propargyl alcohol **24** with 5 mol % OV(OSi(p-ClC$_6$H$_4$)$_3$)$_3$, 1.05 equiv of dibromo-Meldrum's acid (**25**), and 2 equiv of MgO as a general base in acetonitrile at 65 °C resulted in isolation of 80% of the tetrasubstituted olefin **26** in a 6:1 *E*:*Z* ratio (Table 5, entry 1).

Table 5. Optimization of the Formation of *E*-Bromo-Tetrasubstituted Olefins

entry	Solvent (concn)	"Br$^+$"	T (°C)	*E*:*Z* ratio[a]	Yield (%)
1	MeCN (0.5 M)	**25**	65	6:1	80
2	MeCN (0.5 M)	**25**	50	7:1	81
3	MeCN (0.5 M)	NBP	65	8:1	84
4	MeCN (0.5 M)	NBP	40	7:1	78
5	DCE (0.25 M)	NBP	40	12:1	83
6	PhMe (0.25 M)	NBP	40	20:1	82
7[b]	PhMe (0.25 M)	NBP	40	N/A	< 5



[a]*E*:*Z* ratio determined via ^{1}H NMR of the crude reaction mixture. [b]Reaction performed without any catalyst.

Lowering the temperature to 50 °C had little impact on reactivity or selectivity (entry 2). Switching electrophilic bromine sources from **25** to *N*-bromophthalimide (NBP) resulted in a slight improvement in *E*:*Z* ratio at 65 and 40 °C (entries 3 and 4). Switching to less polar solvents, such as 1,2-dichloroethane (DCE) and PhMe, led to significant improvements in selectivity, with PhMe resulting in an isolated yield of 82% and an *E*:*Z* ratio of 20:1 (entries 5 and 6). Finally, a control experiment run without use of the vanadium catalyst led to recovery of the starting alcohol (entry 7).

The developed conditions worked well for a wide range of tertiary propargyl alcohols, yielding geometrically defined *E*-tetrasubstituted bromo-olefins (Table 6). Both electron-rich and electron-poor substituents on the aromatic R^L give rise to good reactivity and high olefin selectivity (**27**–**33**). Ortho substitution on R^L gave rise to a slight reduction in selectivity (**29**), while branching on the alkyne R group is well-tolerated with no impact on the reaction outcome (**31** and **32**). Functional group tolerance was found to be remarkably high for a process that involves the trapping of a metal enolate with an electrophilic bromine reagent. A propargyl alcohol bearing a methyl aryl ketone was found to undergo the desired transformation, with the methyl ketone acting as neither an electrophile to the catalytically generated enolates nor as a nucleophile to the NBP, successfully yielding diketone **33** in good yield and olefin selectivity. Protected amines and alcohols, free alcohols, and alkyl halides were all well-tolerated (**34**–**37**). Conjugated alkenes at R posed no issues and generated divinyl ketones (**32** and **38**). Remarkably, no Michael-addition of either the vanadium enolate or starting propargyl alcohol was observed with unsubstituted vinyl ketone product **38**. Distal alkenes were also tolerated by the reaction, showing no bromine incorporation (**39**).

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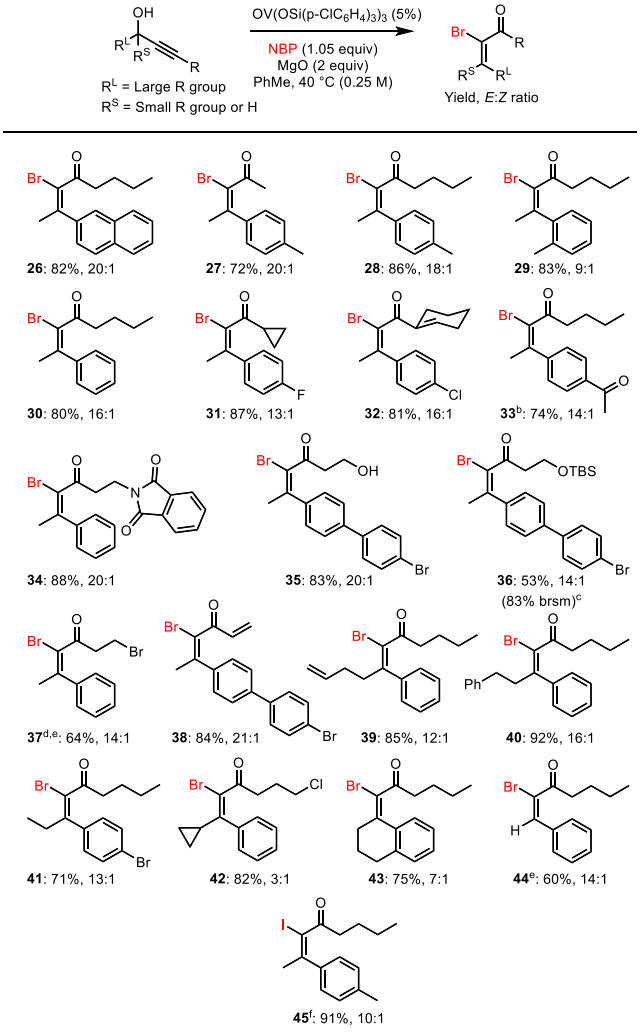
Table 6. Scope of the *E*-Selective Vanadium Bromination Reaction[a]



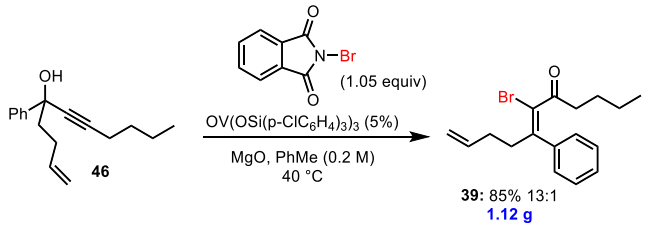
[a]Reactions performed at 0.2 mmol scale. *E*:*Z* ratio determined via ^{1}H NMR of the crude reaction mixture. [b]55 °C. [c]Yield based on recovered starting material (brsm). [d]10 mol % OV(OSi(*p*-C_6H_4)$_3$)$_3$. [e]1.05 equiv of **25** used as Br^+ source, 65 °C. Product reduced at completion of the reaction and characterized as the alcohol. [f]NIS (1.05 equiv) used.

In the case of bromination, changing R^S from methyl to longer chain alkyl groups had little impact on selectivity (12:1 to 16:1, **39**–**41**). Even adding branching to the alkyl group at R^S resulted in an impressive 3:1 *E*:*Z* ratio (**42**). Exocyclic geometrically defined tetrasubstituted olefins could also be formed starting from cyclic propargyl alcohols, albeit with a slightly diminished *E*:*Z* ratio of 7:1 (**43**). Geometrically defined *E*-trisubstituted bromo-olefins could also be selectively generated starting from secondary propargylic alcohols (**44**). The analogous iodination process proceeded cleanly by simply switching the electrophile from NBP to *N*-iodosuccinimide (NIS) (**45**). Finally, these reactions proved to be scalable and could be run at gram-scale with no impact on yield or selectivity (Scheme 3).

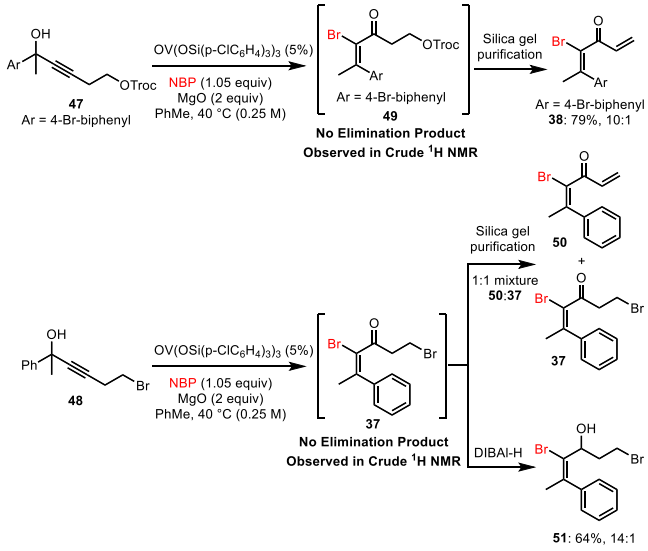
The remarkably mild nature of this transformation is highlighted by the reactivity of propargyl alcohols **47** and **48** (Scheme 4). Both of these ketone products (**49** and **37**) have the ability to undergo an E1cb elimination. In each case, the crude reaction mixtures showed no evidence for the presence of any elimination products. However, silica gel purification of Troc-protected alcohol product **49** resulted in complete elimination of the protected alcohol to give diene **38**, while silica gel purification of alkyl bromide product **37** resulted in an inseparable 1:1 mixture of **37** and elimination product **50**. Clean alkyl bromide **51** could be isolated from the crude reaction mixture following a reductive quench with diisobutylaluminum hydride (DIBAl-H) prior to chromatography. The proclivity of these sensitive products to readily undergo elimination during mild silica gel chromatography while remaining intact during the Lewis acidic (OV(OSi(*p*-ClC_6H_4)$_3$)$_3$) and Brønsted basic (vanadium enolate and MgO) reaction conditions is notable.

To definitively characterize both the bond connectivity and the geometric selectivity of the products, a single crystal suitable for X-ray diffraction was grown of biphenyl alcohol **35**. Indeed, the X-ray structure confirmed both our assignment of bond connectivity as well as *E*-olefin geometry (Figure 3).

Scheme 3. Gram-Scale Synthesis



Scheme 4. Mild Conditions of the Vanadium Bromination Reaction



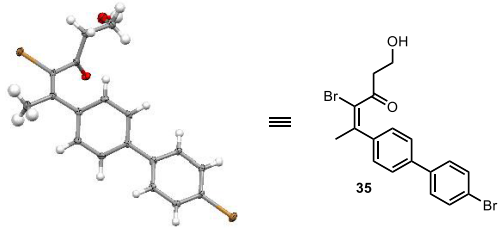


Figure 3. X-ray crystal structure of **35**.

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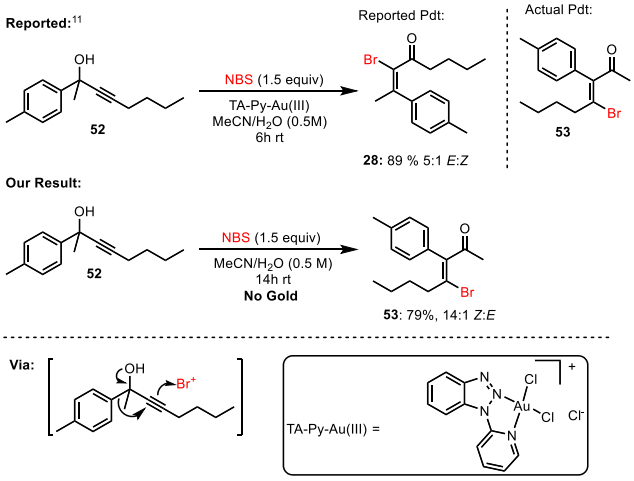
During the course of our work, a very similar reportedly gold-catalyzed process to obtain tetrasubstituted α-chloro-, bromo-, and iodo-enone olefins with *E*-geometry was published.[17] However, when we compared the reported products with those obtained from our process, the spectroscopic data did not match. Theorizing that their products might be arising from a halide induced pinnacol/Meerwein 1,2-aryl migration, we subjected propargyl alcohol **52** to the reported reaction conditions but omitted the gold catalyst (Scheme 5). Under these conditions, we obtained β-

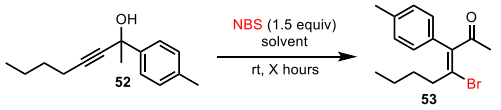
Scheme 5. Gold-Free Formation of β-Haloenones



bromo-enone **53** in 79% yield and with an improved 14:1 *Z*:*E* ratio compared to the 5:1 ratio reported with gold present. Importantly, the structure of **53** was confirmed via 2-D NMR (HMBC, HSQC, ROESY, see the Supporting Information), and its characterization data matched that erroneously assigned in the original report to α-bromo-enone **28**. While such a metal-free rearrangement is known for the ring expansion of cyclic propargyl alcohols,[18] as well as for specialized propargyl alcohols bearing haloalkynes,[19] there is little in the literature about simple acyclic propargyl alcohols participating. Just one publication containing only two examples of iodination with I_2 in periodic acid is reported.[20] Seeing the utility of developing a general process that would result in enones with geometrically defined tetrasubstituted olefins bearing a range of halides at the β-carbon, complementary to the vanadium process that places the halide at the α-position, we decided to further optimize the reaction.

Lengthening the reaction time from 14 to 23 h resulted in a complex mixture of products (Table 7, entries 1 and 2). Adding 2 equiv of K_2CO_3 to the reaction resulted in complete recovery of starting material, even at 40 °C, highlighting the importance of a mildly acidic reaction environment (entry 3). Doubling the reaction concentration resulted in an improved *Z*:*E* ratio of 20:1 and a yield of 95% (entry 4). Water was found to be important for reactivity, as running the reaction under anhydrous conditions led to a mere 6% conversion after 20 h (entry 5). While switching the organic solvent from MeCN to DMF resulted in both lower yield and selectivity (entry 6), use of hexafluoroisopropanol (HFIP) as the organic solvent resulted in a large improvement in rate with the reaction reaching completion within 2 h (entry 7). This large rate enhancement likely results from the increased hydrogen-bond donation of HFIP and its corresponding ability to better

Table 7. Optimization of the Metal-Free Synthesis of *Z*-Tetrasubstituted Halo Olefins



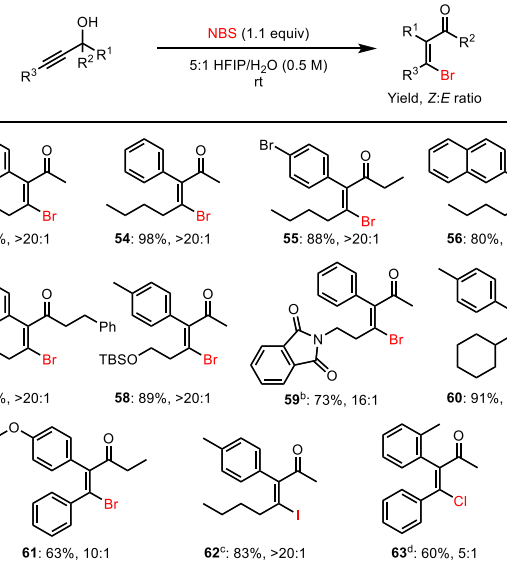
entry	Solvent	Concn (M)	X	*Z*:*E* ratio[a]	Yield (%)
1	MeCN/H_2O 5:1	0.17	14	14:1	79
2	MeCN/H_2O 5:1	0.17	23	N/A[b]	N/A
3[c]	MeCN/H_2O 5:1	0.17	24	N/A	No Rxn
4	MeCN/H_2O 5:1	0.34	14	20:1	95
5	MeCN	0.20	20	20:1	6[d]
6	DMF/H_2O 5:1	0.34	14	5:1	67
7	HFIP/H_2O 5:1	0.34	2	20:1	96
8[e]	HFIP/H_2O 5:1	0.34	2	20:1	92
9[e]	HFIP/H_2O 5:1	0.50	1	20:1	91

[a]Reactions performed at 0.2 mmol scale. *Z*:*E* ratio determined via ^{1}H NMR of the crude reaction mixture. [b]Complex reaction mixture. [c]2 equiv of K_2CO_3, 40 °C. [d]Conversion measured via ^{1}H NMR of crude reaction mixture. [e]1.1 equiv of NBS.

stabilize partial positive charges developing in the transition state. Finally, the loading of NBS could be decreased to 1.1 equiv, and the reaction concentration could be increased to 0.5 M with no impact on yield or selectivity (entries 8 and 9).

Both electron-rich and electron-neutral aromatic groups were capable of undergoing the halogen-initiated 1,2-aryl shift (Table 8, **53**−**57**). While 4-bromophenyl was shown to undergo clean migration, most electron withdrawing aromatic groups led to rapid decomposition. Silyl-protected alcohols

Table 8. Scope of the Metal-Free Synthesis of *Z*-Tetrasubstituted Halo Olefins



[a]Reactions performed at 0.2 mmol scale. *Z*:*E* ratio determined via ^{1}H NMR of the crude reaction mixture. [b]65 °C. [c]NIS used (1.1 equiv). [d]TCICA (1.5 equiv), 5:1 MeCN/H_2O (0.17 M), room temperature (rt).

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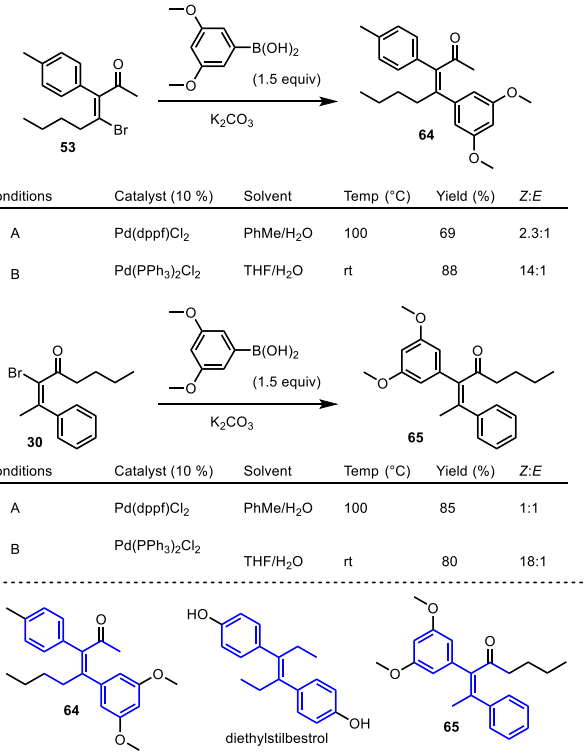
remained intact during the course of the reaction (**58**), as did protected amines (**59**). Branching (**60**) or aromatic substitution (**61**) on the alkyne at R^3 was well-tolerated, although a slight decrease in *Z*:*E* selectivity was observed in the case of R^3 = aryl. The corresponding iodination process could be performed simply by switching the electrophilic halide source from NBS to NIS (**62**), while chlorination could be achieved utilizing trichloroisocyanuric acid (TCICA) in an acetonitrile/water mixed solvent system (**63**).

To illustrate the synthetic utility of both halogenation methods, we sought to utilize the geometrically defined vinyl halides for cross-coupling. Treatment of both *β*-bromo-enone **53** and *α*-bromo-enone **30** under more "standard" Suzuki cross-coupling conditions (Scheme 6, condition A) led to a

Scheme 6. Suzuki Cross-Coupling Conditions



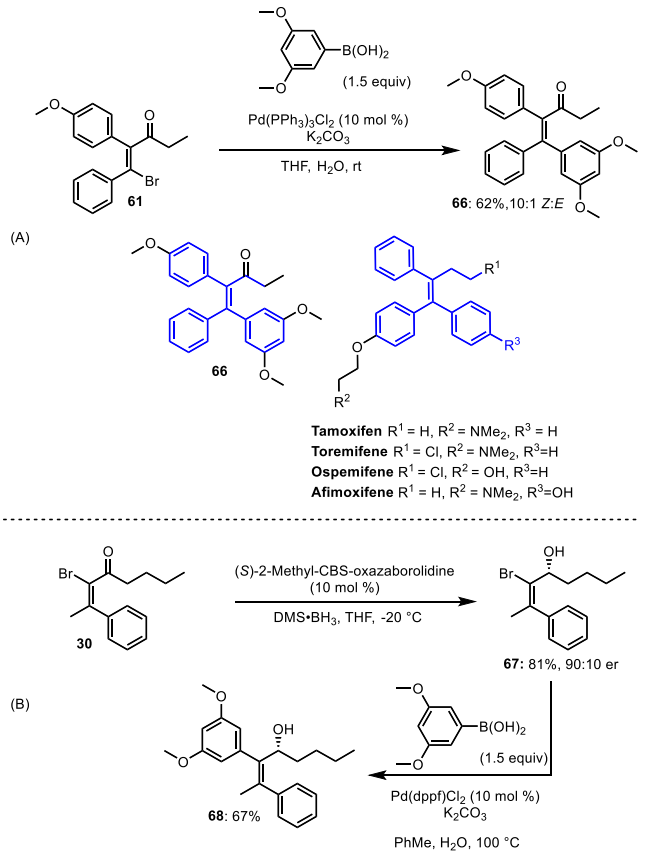
Conditions	Catalyst (10 %)	Solvent	Temp (°C)	Yield (%)	*Z*:*E*
A	$Pd(dppf)Cl_2$	$PhMe/H_2O$	100	69	2.3:1
B	$Pd(PPh_3)_2Cl_2$	THF/H_2O	rt	88	14:1

Conditions	Catalyst (10 %)	Solvent	Temp (°C)	Yield (%)	*Z*:*E*
A	$Pd(dppf)Cl_2$	$PhMe/H_2O$	100	85	1:1
B	$Pd(PPh_3)_2Cl_2$	THF/H_2O	rt	80	18:1

significant scrambling of olefin geometry. However, we were delighted to find that conditions initially reported by Lipschutz (condition B),[21] utilizing $Pd(PPh_3)_2Cl_2$ with K_2CO_3 in a THF/water solvent system at room temperature, gave rise to the desired all-carbon tetrasubstituted products in high yields and with near complete conservation of starting olefin geometry (**64** and **65**). Both of these cross-coupling products containing geometrically defined 1,2-diaryl substituted olefins share a similar carbon backbone with diethylstilbestrol, a former drug used for the treatment of prostate[22] and breast cancer.[23]

These cross-coupling conditions could also be utilized on vinyl bromide **61**, giving triaryl tetrasubstituted olefin **66** in good yield and with excellent conservation of original olefin geometry. The geometrically defined acyclic triaryl olefin motif is an important scaffold in medicinal chemistry and shared by a number of FDA approved and clinical phase drugs for the treatment of breast cancer,[13a,b] dyspareunia,[13c] and cyclical mastalgia[24] (Scheme 7A). Chiral allylic alcohols containing a

Scheme 7. Suzuki Coupling for the (A) Formation of Triaryl Olefins and (B) Formation of Tetrasubstituted Chiral Allylic Alcohol



geometrically defined tetrasubstituted olefin (**67**) could also be generated in high er (enantiomeric ratio) through the CBS reduction of the corresponding ketone.[25] Subsequent Suzuki coupling allows access to chiral allylic alcohols bearing an all-carbon, geometrically defined tetrasubstituted acyclic olefin (Scheme 7B). In all of the Suzuki couplings performed, 3,5-dimethoxyphenylboronic acid was utilized as the nucleophilic donor to ensure sufficient resolution of the newly installed aryl proton peaks in the ^1H NMR spectrum to allow for the definitive assignment of *E*/*Z* stereochemistry in the final products.

The utility of the halo-olefin products was further highlighted in the total synthesis of (±)-myodesmone (**69**), a furanoid sesquiterpene ketone isolated from *Myoporum deserti* and *Myoporum acuminatum*.[26] Starting from 3-acetylfuran, *α*-allylation under conditions developed by Negishi resulted in ketone **70** in 78% yield (Scheme 8).[27] Nucleophilic addition of lithium acetylide **71** gave rapid access to propargyl alcohol **72** in 73% yield. Treatment of this electron-rich propargyl alcohol under the standard bromination conditions (Table 5, entry 6 *vide supra*) resulted in the isolation of less than 15% of the desired vinyl bromide **68**. It was found that a rapid electrophilic bromine-initiated background decomposition pathway associated with the furan was funneling the starting material away from the vanadium-catalyzed process. By switching the electrophilic bromine source to dibromo-Meldrum's acid **25** and utilizing the lithium alkoxide in place of the free alcohol, the vanadium-catalyzed sigmatropic functionalization process could become more competitive

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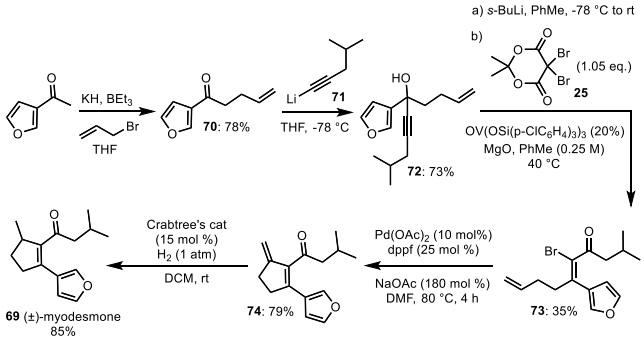
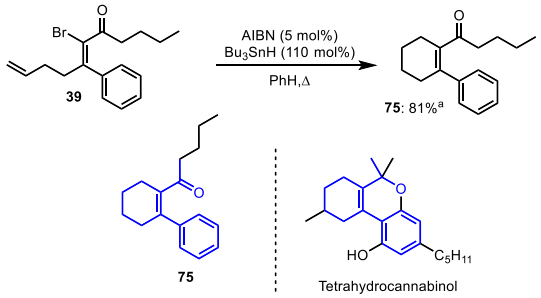
Scheme 8. Total Synthesis of (±)-Myodesmone



with the background decomposition pathway, giving vinyl bromide **73** in an improved 35% yield. Subsequent intramolecular Heck coupling followed by chemoselective Crabtree hydrogenation resulted in (±)-myodesmine in 67% yield over two steps.

In the course of our model studies toward the synthesis of myodesmone, we came across a couple of noteworthy observations. When the radical cyclization of **39** was explored, the 6-endo-trig cyclization product **75** was preferred 4:1 to the expected 5-exo-trig product (Scheme 9). While not the desired transformation, this type of cyclohexene scaffold maps onto the structure of a subclass of tetrahydrocannabinol natural products.

Scheme 9. Intramolecular Cyclization of 39



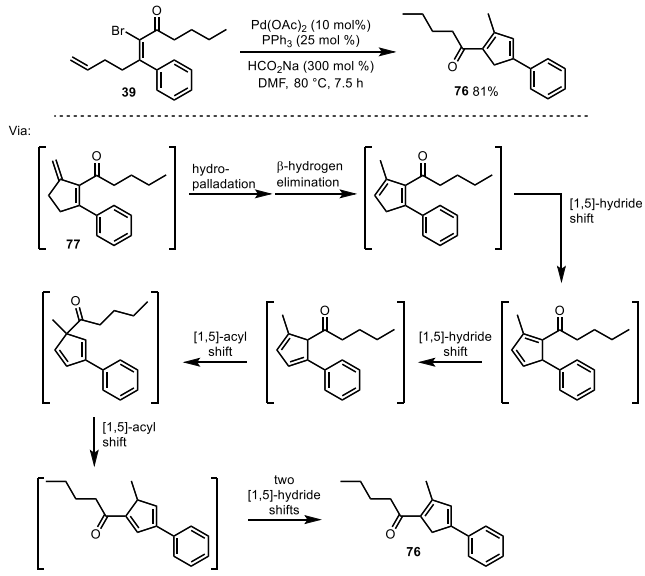
[a]81% isolated yield of a 4:1 mixture of 6-endo-trig and 5-exo-trig cyclization products.

Additionally, in the course of our unsuccessful exploration of reductive-Heck conditions for the cyclization of **39**, we observed an unexpected carbon-bond rearrangement. By utilizing a slight modification of the Heck conditions reported above (PPh_3 instead of dppf and HCO_2Na instead of NaOAc), cyclopentadiene product **76** was isolated in preference to either the Heck or the reductive-Heck products. Formation of this product is thought to proceed through simple Heck product **77** that, upon internal migration of the exocyclic double bond, undergoes a series of 1,5-hydride and 1,5-acyl shifts to arrive at the thermodynamic carbon skeleton (Scheme 10). This unexpected behavior highlights the unique and underexplored reactivity that these geometrically defined tetrasubstituted olefins possess.

CONCLUSION

In summary, we have developed a highly efficient method for the formation of both tri- and tetrasubstituted geometrically defined chloro, bromo, and iodo acylic olefins starting from

Scheme 10. Unusual Rearrangement to Cyclopentadiene Products



cheap and readily available propargyl alcohols. The economic and earth-abundant vanadium-catalyzed process results in the kinetically controlled formation of *E*-α-halo-enones and shows remarkable functional group tolerance, while a metal-free process results in complementary *Z*-β-halo-enones. These halo olefins have been shown to undergo cross-coupling reactions with retention of olefin configuration to construct biologically relevant, geometrically defined di- and triaryl acyclic olefin scaffolds. Additionally, the utility of these products has been demonstrated through the total synthesis of the sesquiterpene myodesmone. The importance of these tetrasubstituted products and the need for further exploration of these olefin structures are highlighted by the unexpected palladium-catalyzed formation of a rearranged cyclopentadiene ring.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b04567.

Additional experimental details, characterization data, spectra, and X-ray analysis (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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