Regiodivergent Halogenation of (E)-β-Chlorovinyl Ketones via Soft α-Vinyl Enolization Strategy

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S *Supporting Information*

**ABSTRACT:** The soft α-vinyl enolization of (E)-β-chlorovinyl ketones was investigated in the presence of various halogen electrophiles. Depending on the nature of halogen electrophiles, the selective formation of three products, namely α,α-dichloropropargyl ketones, α,γ-dihaloallenyl ketones, and 3-halofurans, was observed. The observed regiodivergent nucleophilic pathways of (E)-β-chlorovinyl ketones demonstrate the diversity-oriented synthesis strategy in which the nucleophilic reactivity of (E)-β-chlorovinyl ketones can be selectively modulated by the choice of suitable hard and soft electrophiles.
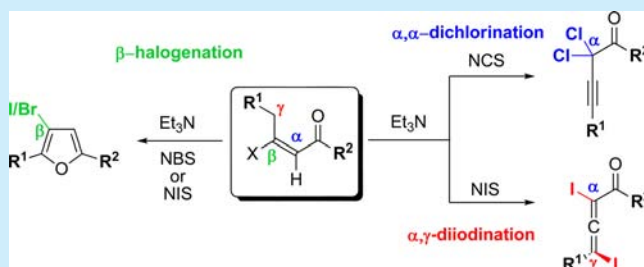
While the enolization of carbonyl compounds with α-C(sp³)−H bonds constitutes one of the pillars of synthetic chemistry,[1] the corresponding enolization of carbonyl compounds with α-C(sp²)−H bonds is virtually unknown. Accordingly, α,β-unsaturated (i.e., conjugated) carbonyl compounds are less prone to direct α-vinyl enolization except for a few limited cases of α-vinyl deprotonation under strong basic conditions using lithium amide bases.[2] With an aim of developing a general and direct α-vinyl enolization method, we recently disclosed a mild base-promoted dehydrohalogenation of (E)-β-halovinyl ketones that involved a preferential α-vinyl enolization over the α-C(sp³)−H bond (Scheme 1).[3] The fact that such α-vinyl enolizations are readily achieved by using a mild base, Et₃N, as opposed to the deprotonation conditions using hard lithium amide bases prompted us to investigate the chemo- and regioselective enol formations in a conjugated carbonyl system that otherwise would have been difficult, if not impossible, under other basic conditions.[4] Our studies subsequently demonstrated the synthetic utility of [3]cumulenolate intermediate species that displayed ambivalent reactivity; the intrinsically electrophilic (E)-β-chlorovinyl ketones acted as either nucleophiles[5] or electrophiles[6] under different Lewis acid conditions.

To further scrutinize the reaction pathways of (E)-β-chlorovinyl ketones under the soft α-vinyl enolization conditions, we investigated the nucleophilic character of enol intermediates using N-halosuccinimides. Herein, we report that the regiodivergent nucleophilic pathways of (E)-β-chlorovinyl ketones could be realized by using different halogen sources based on their hard−soft acid−base interactions with different nucleophilic species. This regiodivergent approach allows halogenation at either the α-, β-, or γ-carbon position of (E)-β-chlorovinyl ketones, leading to a facile formation of previously unknown α,α-dichloropropargyl ketones and α,γ-dihaloallenyl ketones as well as synthetically useful halofuran derivatives.

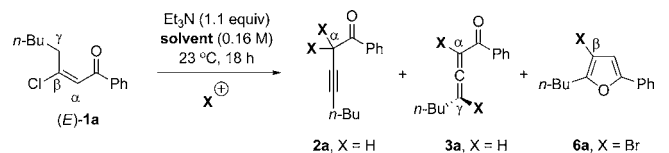**Scheme 1. Soft α-Vinyl Enolization of β-Halovinyl Ketones and Their Janus-like Reactivity**
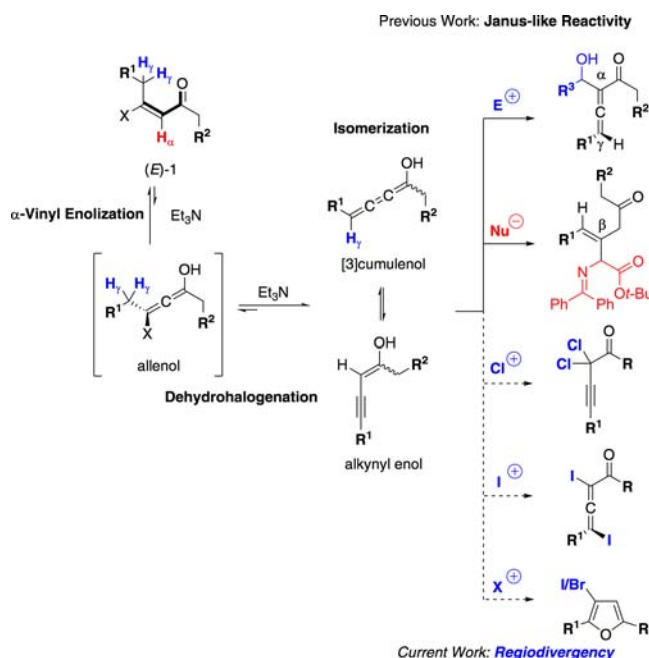
First, we employed a number of halogen electrophiles to see if selective reaction pathways between different enol species could be achieved (Table 1). Upon employing N-chlorosuccinimde (NCS) in the α-vinyl enolization of **1a** in CH₂Cl₂ (Table 1, entry 1), the formation of a new chemical entity, α,α-dichloropropargyl ketone **4a**, was observed in 45% yield along with a

Table 1. Optimization of the Regioselective Halogenation

entry	halogen (equiv)	solvent	4a/5a/6a or 7a[a]	yield[b] (%)
1	NCS (1.1)	CH$_2$Cl$_2$	1:0:0	45[c]
2	NCS (2.2)	CH$_2$Cl$_2$	1:0:0	88
3	NBS (1.1)	CH$_2$Cl$_2$	0:2:1	37[c]
4	NBS (2.1)	CH$_2$Cl$_2$	0:1:2	81
5	NIS (1.1)	CH$_2$Cl$_2$	0:1:2	38[c]
6	NIS (2.1)	CH$_2$Cl$_2$	0:1:0	85
7	Selectfluor (2.2)	[d]		nr[c]
8	TCCA (1.1)	[d]	1:0:0	<25
9[e]	NBS (1.1)	THF	0:0:1	73
10[e]	NBS (2.1)	THF	0:0:1	75
11[e]	NIS (1.1)	THF	0:0:1	75
12[e]	NIS (2.1)	THF	0:0:1	75

[a]Determined by crude ^{1}H NMR. [b]Isolated yield of products after column chromatography. [c]The remaining molecular mass balance accounts for a 1:2 mixture of 2a and 3a. [d]Reactions in THF, PhCH$_3$, CH$_3$COCH$_3$, CH$_3$CN. [e]Solvent switch from CH$_2$Cl$_2$ to THF before addition of halogen source.

mixture of elimination products **2a** and **3a**.[3] An increased amount of NCS (2.2 equiv) provided **4a** in 88% yield (Table 1, entry 2). The use of other *N*-halosuccinimides led to a mixture of another new chemical entity, α,γ-dihaloallenyl ketones **5**, and a known chemical entity, 3-halofurans **6a/7a** (Table 1, entries 3−5). Gratifyingly, the use of 2.1 equiv of NIS provided the exclusive formation of α,γ-diiodoallenyl ketone **5a** in excellent yields (Table 1, entry 6). While we also investigated other electrophilic fluorine (NFSI/Selectfluor) and chlorine sources (trichloroisocyanuric acid, TCCA), no satisfactory results were observed, possibly due to the different counter-cation effects (Table 1, entries 7 and 8). To optimize the formation of 3-halofurans, we screened different solvents and found THF to be a suitable solvent for the regioselective formation of 3-halofurans *in the absence of Et$_3$N* (Table 1, entries 9−12). Further control experiments of the reaction also showed that the 3-halofuran was less likely derived from the electrophilic halogenation of furans. Thus, the formation of 3-halofurans was not observed upon treating a nonhalogenated furan, 2-butyl-5-phenylfuran,[3] with NXS (1.2 equiv) in THF at ambient temperature.

The scope of α,α-selective chlorination of (*E*)-β-chlorovinyl ketones is summarized in Scheme 2. The reaction was readily applicable to a range of aryl ketones with good to excellent yields (72−94%). The electronic and steric nature of aryl substituents of (*E*)-**1** did not significantly affect the reaction outcome (**4a−h**). However, in the case of alkyl ketones, the chlorination did not work, resulting in the formation of elimination products **2** and **3** in 50% yield.[7] Aryl ketones with functional groups such as a halide, **4i**, an ester, **4j**, and a phthalyl group, **4k**, were also tolerated under the optimized α,α-dichlorination conditions.

The scope of α,γ-selective iodination of (*E*)-β-chlorovinyl ketones is illustrated in Scheme 3. While the formation of α,γ-dibromoallenyl ketones could be achieved in >90% yields, the rapid decomposition of products upon isolation did not allow the full characterization (see the Supporting Information for ^{1}H NMR data). The stability of α,γ-diiodoallenyl ketones

Scheme 2. Scope of α,α-Selective Chlorination
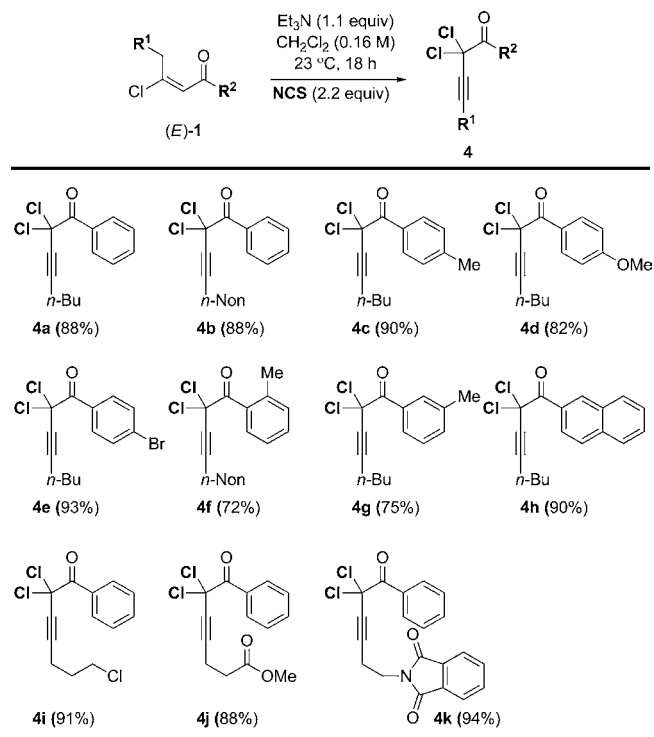
5 was greatly improved upon handling the materials in the absence of light. Thus, the α,γ-selective iodination was achieved with a range of aryl ketones with good to excellent yields (60−85%). Additionally, functionalized α,γ-diiodoallenyl ketones were produced under the optimized conditions (**5i−k**).

Scheme 4 shows the scope of β-selective halogenation of (*E*)-β-chlorovinyl ketones. While the vinyl enolization of (*E*)-**1** could be performed in THF, the reaction was sluggish and the presence of a residual Et$_3$N resulted in the formation of side products, α,γ-dihaloallenyl ketones **5**. Thus, we adopted a

Scheme 3. Scope of α,γ-Selective Iodination
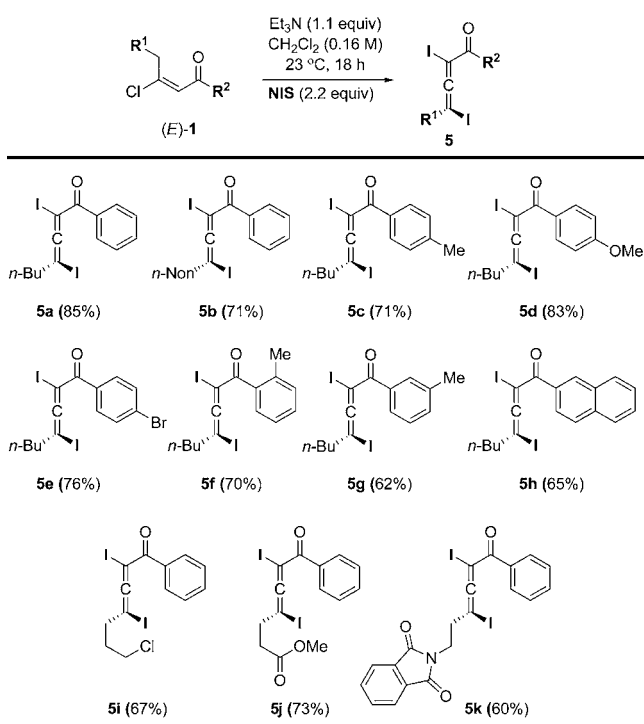
Scheme 4. Scope of β-Selective Halogenation
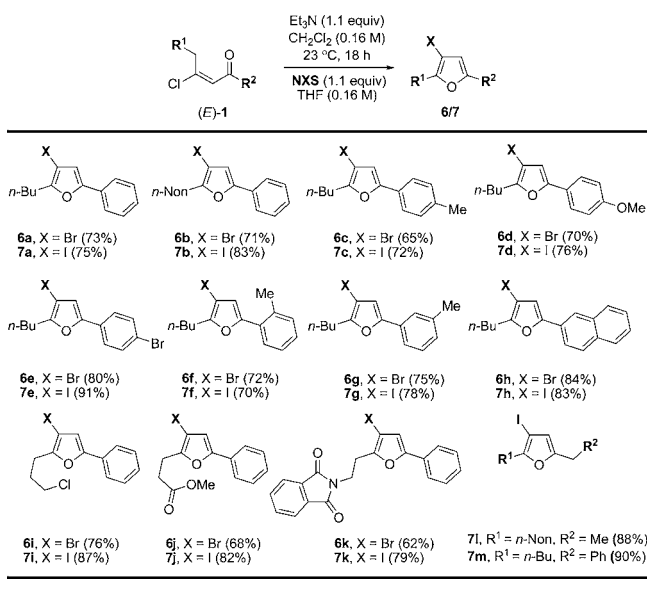
solvent-switch strategy before adding halogen sources. In this way, the β-selective halogenation efficiently proceeded to give the exclusive formation of 3-halofurans in good to excellent yields (62−91%). In general, the iodination using NIS was slightly higher yielding than bromination using NBS. Notably, the β-selective halogenation worked well for functionalized aryl (6/7i-6/7k) as well as alkyl ketones (7l,m).

To delineate the reaction pathways of active enol species under halogenation conditions, we performed control experiments (Scheme 5). The use of both NXS and Et$_3$N under the α-vinyl enolization conditions of (E)-1a did not produce halogenated products. The failure of halogenation might be attributed to the inherent redox reactions between NXS and Et$_3$N,

Scheme 5. Regiodivergent Halogenations of Allenyl and Propargyl Ketones
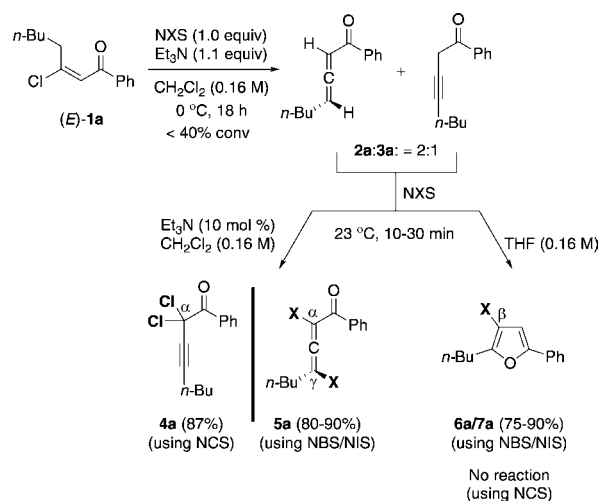

eliminating electrophilic halogen sources.[8] Next, we subjected a mixture of allenyl and propargyl ketones **2a** and **3a** under the halogenation conditions in the presence and absence of Et$_3$N. No reaction was observed when NCS was used in the absence of Et$_3$N; however, the use of NBS and NIS provided the exclusive formation of 3-halofurans **6a/7a**. In the presence of a catalytic amount of Et$_3$N (10 mol %), the reaction of **2a** and **3a** with NXS led to the formation of α,α-dichloropropargyl ketone **4a** and α,γ-dihaloallenyl ketones **5a**, respectively, in high yields.

On the basis of the halogenation reaction profile of (E)-β-chlorovinyl ketones, it is tempting to speculate that the thermodynamic (Z)-alkynyl enol is responsible for the regioselective formation of α,α-dichloropropargyl ketones **4** and α,γ-dihaloallenyl ketones **5** (Scheme 6a).[9] The formation of alkynyl enols from allenyl ketones **2** is believed to involve the γ-enolization by Et$_3$N, given that the pK$_a$ values of γ-substituted allenyl ketones range from 13.3−13.9.[10] Likewise, the alkynyl enols should have been generated from the α-enolization of propargyl ketones **3** by Et$_3$N.[11] While allenyl ketones can, in principle, be directly converted to [3]cumulenolates without the intermediacy of alkynyl enolates, such α-deprotonation of allenyl ketones requires either hard base[12] or Lewis acid as we recently showed in the Ti(O-i-Pr)$_4$-promoted aldol condensation of allenyl ketones in the absence of base.[5] While more studies are needed to analyze structure−reactivity relationships (i.e., using Marcus theory by a combination of intrinsic and product stability effect),[13] on the basis of our data we propose a possible mechanism for the regiodivergent halogenation pathways of (E)-β-chlorovinyl ketones that involves the α-halogenation of thermodynamic enol species followed by the interactions between hard (NCS)−soft electrophiles (NBS/NIS) and hard (α-carbon)−soft nucleophiles (γ-carbon of α-haloalkynyl enols).

The formation of 3-halofurans from both allenyl and propargyl ketones can be explained by invoking the electrophilic halogenation with assistance of the internal carbonyl oxygen atom without involving the intermediacy of alkynyl enols (Scheme 6b). The formation of 3-halofurans from allenyl ketones in the absence of base strongly argues against the possible involvement of alkynyl enol intermediates. In addition, the fact that Selectfluor and NCS do not work in the current 3-halofuran synthesis illustrates the soft nature of NBS and NIS toward allenyl and propargyl ketones, demonstrating the subtle difference between hard and soft acid/base interactions.[14]

Scheme 6. Proposed Reaction Mechanisms for Regiodivergent Halogenation Pathways

a) Electrophilic Halogenation of Alkynyl Enols

b) Soft Electrophilic Halogenation of Allenyl and Propargyl Ketones
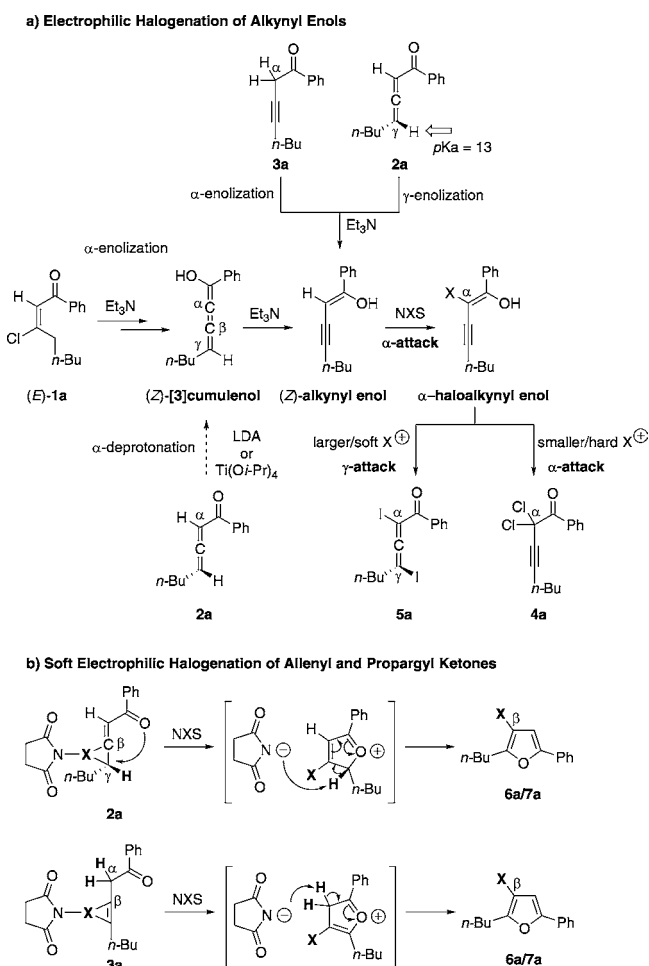
Notably, while the formation of 3-halofurans from propargyl ketones has been previously utilized,[15] the use of allenyl ketones for 3-halofurans has not been observed prior to our investigation.[16] The observed electrophilic cyclization reactions of both allenyl and propargyl ketones should be applicable to other soft electrophiles.[17]

In summary, we have developed the regiodivergent nucleophilic modes of (E)-β-chlorovinyl ketones under the soft α-vinyl enolization conditions. These newly observed reaction pathways of multiple chemical species, simultaneously generated in situ, allow complementary halogenations at respective α-, β-, and γ-carbon of (E)-β-chlorovinyl ketones. We are currently exploring the regiodivergent reactivity modes of enols derived from the soft α-vinyl enolization of (E)-β-chlorovinyl ketones using other hard/soft electrophiles. These results will be the subject of future publications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, computational studies, and characterization 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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