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Stereoselective halo-succinimide mediated γ-halogenations of substituted α-trialkylsilyl-β,γ-unsaturated esters

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ABSTRACT

The halogenation of various α-ester allylsilanes with halo-succinimides (NXS, X = Cl, Br, and I) has been investigated. It has been shown that these reactions readily allow for good yields and excellent diastereoselectivities (up to >20:1) for a series of α-ester allylsilanes and halo-succinimide reagents, thereby providing a straightforward approach of preparing γ-halo-(*E*)-α,β-unsaturated esters.

The nucleophilic reaction of allylsilanes with a variety of electrophilic coupling partners has afforded chemists the opportunity to build important synthetic intermediates with high levels of regio- and stereoselectivities in generally modest to excellent yields [1]. Unfortunately, α-ester substituted allylsilane reagents have received little attention most likely due in part to the historical lack of a general synthetic pathway to said compounds coupled with their diminished reactivity compared to that of most other allylsilanes [2,3]. Recently, we have reported on a very general synthesis of α-substituted allylsilanes by means of a highly stereoselective γ-deprotonation/kinetic protonation of α-trialkylsilyl-β-alkyl-α,β-unsaturated esters [4,5].

Initially disclosed in 1989 by Suzuki, the Pd-catalyzed cross coupling between an electrophilic α-bromo ester and nucleophilic aryl boronic ester afforded the α-arylated ester product in 74% yield via a proposed Pd-enolate intermediate [6]. This reaction represented an umpolung approach to nucleophilic Pd-enolate cross coupling as developed by Hartwig and Buchwald [7,8]. Subsequently, Gooßen expanded the Miyaura-Suzuki reaction scope to include a variety of aryl boronic acids and α-halo carbonyls [9]. Along this line, we reported on the syntheses of a variety of phenylacetic acid lactone (PAL) natural products utilizing Pd-enolates derived from a series of substituted α-bromo esters coupled with functionalized aryl boronic acids [10]. In addition to boronic acids, other nucleophilic coupling partners (i.e. potassium trifluoroboronates and alkynylstannanes) have been successful in cross-coupling under the umpolung approach to Pd-enolates derived from α-haloesters and amides [11,12].

Based on our interest in both novel organosilane reagents and broadening umpolung Pd-enolate chemistry to include extended enolates, we sought to investigate α-ester substituted allylsilanes as general nucleophilic precursors to γ-halo-α,β-unsaturated esters. Herein, we wish to disclose our results centered on a stereoselective halosuccinimide mediated γ-halogenation of α-trialkylsilyl-β,γ-unsaturated esters.

Unfortunately, a general stereoselective synthesis of γ-halo-(*E*)-α,β-unsaturated esters is lacking [13,14]. The approach outlined in this paper relied on the utilization of α-trialkylsilyl-β,γ-unsaturated esters coupled with *N*-halosuccinimides. With this in mind, we initially employed our recently reported synthesis of a variety of α-ester substituted allylsilane reagents by means of a γ-deprotonation/kinetic protonation of α-trialkylsilyl-β-alkyl-α,β-unsaturated esters.

As shown in Scheme 1, catalytic carbocupration (15 mol% CuI·2LiCl) of ethyl propiolate with an assortment of Grignard Reagents and a trialkylsilyl triflate (TMS-or TESOTf) provided vinyl silanes **1a-1e** in yields ranging from 44 to 82% post silyl group migration with ratios of >20:1 for the *E* isomer in all cases. Subsequently, a complex induced proximity effect (CIPE) mediated γ-deprotonation of esters **1a-1e** all readily proceeded through the proposed 8-membered transition state **2** to afford the transient lithium enolate which was then transformed in situ to the TMS silyl ketene acetal upon the addition of TMSCl [15]. Final kinetic protonation with 1.4 M HCl furnished the α-trialkylsilyl-β,γ-unsaturated esters **3a-3e** in 80–99% isolated yields (no purification was

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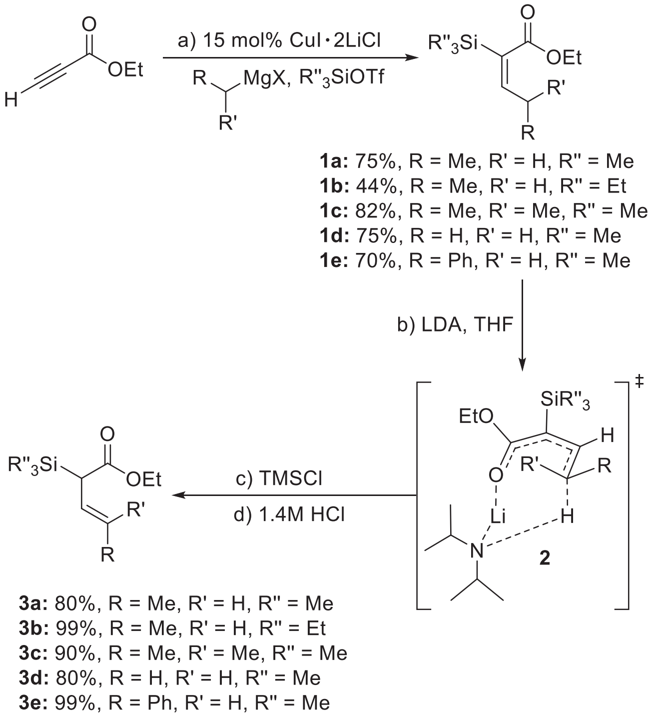


Scheme 1.

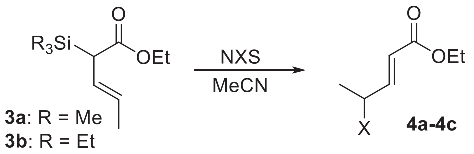
required) with dr values of >20:1 (where applicable) for the *E* alkenes as determined by ^{1}H NMR.

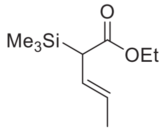
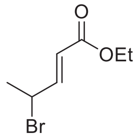
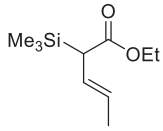
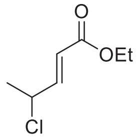
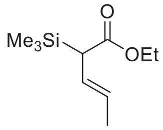
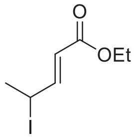
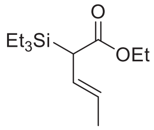
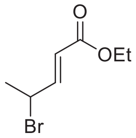
With the requisite nucleophiles **3a-3e** in hand, we commenced our investigation by initially examining the halogenation of methyl substituted allylsilanes **3a** and **3b** with NXS (X = Cl, Br, I) as described in Table 1. Thus, treatment of **3a** with NBS (1.1 equiv.) in MeCN for 3 h at 0 °C afforded the γ-brominated ester **4a** in 92% yield with a >20:1 dr for the *E* isomer as determined by ^{1}H NMR (J = 15.6 Hz) [14,16]. The stereochemistry of the newly formed alkene moiety of **4a** was further assigned as the *E*-isomer by 1D NOE based on the observed cross-peaks shown in Table 1. Similar to **3a**, the bromination of the TES variant (**3b**) with NBS in entry 4 provided product **4a** in a nearly identical yield (90 versus 92%) with a >20:1 dr for the newly formed alkene as well. Similarly, the iodination of **3a** with NIS (1.1 equiv.) readily proceeded at 0 °C in MeCN to furnish **4c** in 78% yield with an identical olefin dr of >20:1 for the *E* isomer [14]. It is worth noting that iodo ester **4c** was unstable and fully decomposed at rt within 24 h post purification, which most likely led to a lower yield of **4c** versus that of **4a**. Surprisingly, chlorination of **3a** with NCS did not proceed under the previous reaction conditions and only starting material was recovered. However, heating the reaction of **3a** with NCS (1.1 equiv.) to 50 °C in MeCN for 12 h afforded the chlorinated ester **4b** in 87% isolated yield with a dr of >20:1 for the newly formed *E* alkene [14]. As noted above, the olefin geometries of esters **4a-4c** were assigned as *E* by analysis of the coupling constants in ^{1}H NMR (J = 15.5–15.6 Hz) of the crude and subsequently isolated and purified products.

With the successfully regioselective γ-halogenations coupled with the diastereoselective formation of α,β-unsaturated esters derived from γ-methyl-substituted allylsilanes **3a** and **3b**, attention was turned to investigating structurally related γ,γ-disubstituted, γ-phenyl, and unsubstituted allyl silanes **3c-3e**. Based on the results from Table 1, we chose to replicate the reaction conditions for esters **3c** and **3d** with the three NXS reagents. As shown in Table 2, treatment of the γ,γ-dimethyl allylsilane **3c** with NBS (1.1 equiv.) at 0 °C in MeCN for 3 h afforded the 3°-allylic bromide ester **4d** in 89% yield after purification [17]. The dr of the newly constructed olefin was >20:1 strongly favoring the *E* isomer (J = 15.7 Hz) as determined by ^{1}H NMR of the crude reaction mixture. Similarly, the iodination of **3c** proceeded with NIS under identical reaction conditions to provide the γ-iodo-ester **4f** with a dr of >20:1 for the *E* isomer in 79% yield as noted in entry 3.

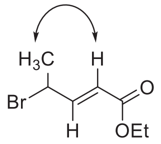
Analogous to entry 3 in Table 1, the chlorination of ester **3c** with NCS was quite sluggish at rt and furnished only the recovered starting material. Much to our delight, heating to 50 °C and allowing the reaction to take place over a 12hr period afforded the γ-chlorinated ester **4e** in 67% yield with an identical *E/Z* ratio of >20:1 to that of **4d** and **4f** [18]. In addition to the γ,γ-dimethyl

Table 1
NXS-mediated γ-Halogenations of Allylsilanes **3a** and **3b**.[a,b]



Entry	Allyl silane	Product Yield, (*E/Z*)
1[c]	 **3a**	 **4a** 92%, *E/Z*:>20/1
2[d]	 **3a**	 **4b** 87%, *E/Z*:>20/1
3[c]	 **3a**	 **4c** 78%, *E/Z*:>20/1
4[c]	 **3b**	 **4a** 90%, *E/Z*:>20/1

Key NOE Enhancement



4a

(a) *E/Z* ratio determined by ^{1}H NMR (500 MHz) from the crude reaction mixture. (b) Yields are of the isolated, pure compounds. (c) Reaction ran with 1.0 equiv of **3a/3b**, and 1.1 equiv of NXS (X = Br or I) for 3 h at 0 °C. (d) reaction ran with 1.0 equiv of **3a/3b**, and 1.1 equiv of NCS for 12 h at 50 °C.

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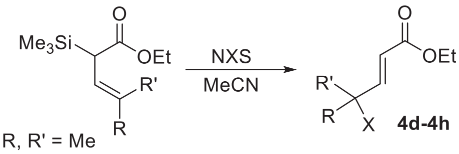
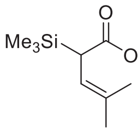
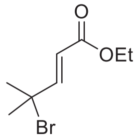
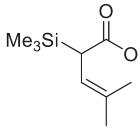
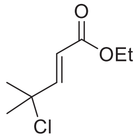
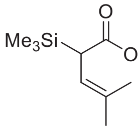
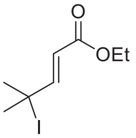
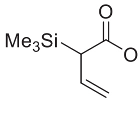
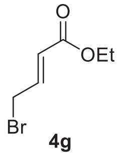
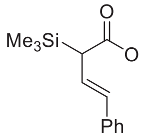
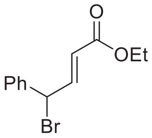
Table 2
NXS-mediated γ-Halogenations of Allylsilanes **3c-3e**.[a,b.]



3c: R, R' = Me
3d: R, R' = H
3e: R = Ph, R' = H

Entry	Allyl silane	Product Yield, (*E/Z*)
1[c]	 **3c**	 **4d** 89%, *E/Z*:>20/1
2[d]	 **3c**	 **4e** 67%, *E/Z*:>20/1
3[c]	 **3c**	 **4f** 79%, *E/Z*:>20/1
4[c]	 **3d**	 **4g** 73%, *E/Z*:>20/1
5[c]	 **3e**	 **4h** not observed, *E/Z*: N/A

(a) *E/Z* ratio determined by ^{1}H NMR (500 MHz) from the crude reaction mixture. (b) yields are of the isolated, pure compounds. (c) reaction ran with 1.0 equiv of **3c/3d**, and 1.1 equiv of NXS (X = Br or I) for 3 h at 0 °C. (d) reaction ran with 1.0 equiv of **3c** and 1.1 equiv of NCS for 12 h at 50 °C.

silane reagent **3c**, the bromination of the unsubstituted allylsilane **3d** was accomplished upon addition of 1.1 equiv. of NBS in MeCN at 0 °C to afford γ-bromo ester **4g** in 73% isolated yield. Unfortunately, the attempted NBS mediated bromination of the γ-phenyl allylsilane **3e** did not proceed as desired and only decomposed starting material was observed after 3 h at 0 °C.

The high level of selectivity for the *E*-olefin can be rationalized by means of two possible reactive conformations/rotamers as shown in Fig. 1. It was assumed, based on literature precedence, that the parent allylsilane **3a** nucleophilically added to the electrophilic halogenating reagent to afford a subsequent secondary carbocation [19a]. The intermediate cation was stabilized via hyperconjugation as the adjacent C-Si bond was either *anti*-or *syn*-periplanar to the empty p-orbital. While elimination of either rotamer A or B was possible, the one that minimized $A^{1,3}$-strain should have been favored (i.e. rotamer A) and ultimately provided the *E*-olefin product. The other possible conformation, rotamer B, would maximize $A^{1,3}$-strain and would have consequently led to the *Z*-alkene [19b]. Based on examination of the crude reaction mixture by ^{1}H NMR, no Z-olefins were observed and we concluded that rotamer A was favored *en route* to the highly selective formation of the *E* isomer of the newly created alkenes in esters **4a-4g**.

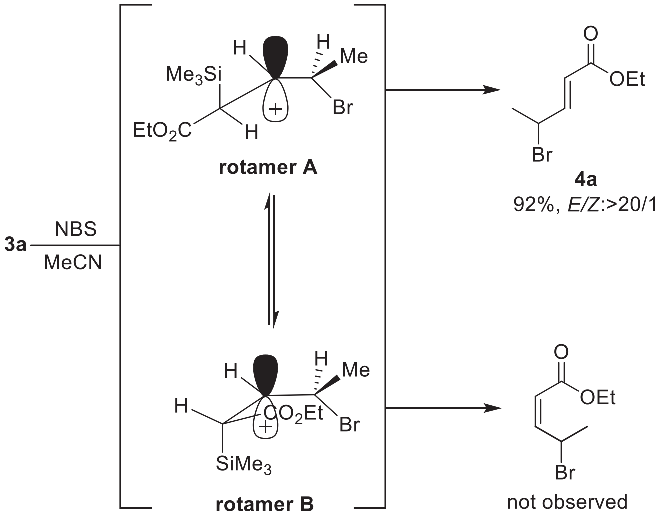


Fig. 1. Stereochemical rationale for selective *E*-olefin formation.

In conclusion, we have described a general reaction sequence that highlights regio-and stereoselective additions of a series of α-ester allylsilanes to halosuccinimides resulting in the formation of γ-halo-(*E*)-α,β-unsaturated ester products in modest to high yields with dr values of >20:1. The straightforward nature and enhanced scope of the described synthetic process should enable for the broadening of umpolung Pd-enolate chemistry to include extended enolates. Results from these studies will be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

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(b) D. De Joarder, M.P. Jennings, Tetrahedron Lett. 54 (2013) 3990.

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