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Stereoselective Halo-Succinimide Facilitated α-Halogenations of Substituted α-Trialkylsilyl-β-Substituted-α,β-Unsaturated Esters

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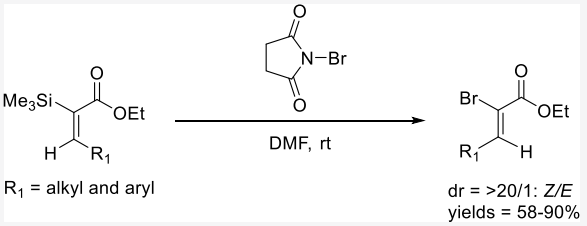
ABSTRACT: The NXS (X = Cl, Br)-mediated halogenation of a series of (*E*)-α-trimethylsilyl-β-alkyl(aryl)-α,β-unsaturated esters in dimethylformamide (DMF) has furnished (*Z*)-β-substituted-α-halogenated-α,β-unsaturated ester products in moderate to high isolated yields (58−90%) with dr values of >20:1 coupled with the inversion of olefin stereochemistry. The reaction process was hypothesized to include an initial halonium cation intermediate, followed by regioselective ring opening with DMF. Subsequent *anti*-E2-type concomitant elimination allowed for the stereoselective formation of the product vinylic bromo- and chloroesters.



INTRODUCTION

Facile stereoselective olefin formation remains an important area of research because of the boundless potential for further downstream synthetic operations.[1] More specifically, new methods for the rapid construction of stereodefined vinyl halides (i.e., Cl, Br, and I) containing additional reactive functional groups are enormously sought after owing to their ability to function as electrophilic coupling partners in a myriad of metal-catalyzed cross-couplings, mostly involving Pd complexes.[2] One approach to such compounds centers on a halogenation/desilylation process that ultimately provides a simple vinyl halide product with inverted stereochemistry relative to the organosilane starting material.[3] Because of the numerous advantages of organosilane reagents,[4−9] the development of methods that provide stereodefined vinylsilanes remains as a noteworthy area of research.[10]

Recent reports from our laboratory have described the stereoselective synthesis of α-trialkylsilyl-β-alkyl(aryl)-α,β-unsaturated esters and the subsequent utilization of said compounds for target-based synthetic applications (i.e., stereoselective deconjugations, conjugated silyl ketene acetal formations, tandem stereoselective deconjugation-stabilized Peterson olefinations, and diastereoselective conjugate additions/protonations), as shown in Figure 1.[11] Based on our interest in novel organosilane reagents, we sought to investigate α-ester-substituted vinylsilanes as general nucleophilic precursors to stereodefined α-halo-α,β-unsaturated esters. Herein, we wish to divulge a regio-and diastereoselective halosuccinimide-mediated α-halogenation of α-trialkylsilyl-β-alkyl(aryl)-α,β-unsaturated esters, which, in turn, affords tri-and tetrasubstituted stereodefined vinyl halide (Cl and Br) products with high levels of dr and in modest to excellent yields.

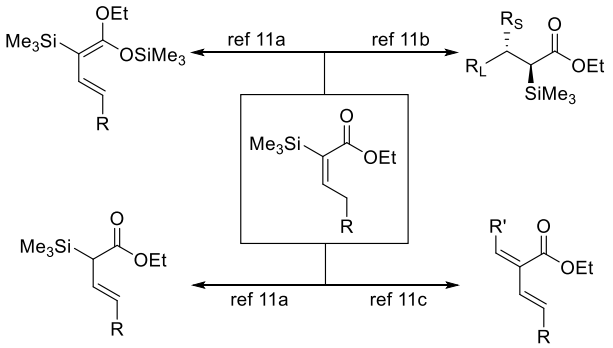


Figure 1. Diverse utility of α-trialkylsilyl-β-substituted-α,β-unsaturated esters in synthetic applications.

RESULTS AND DISCUSSION

Synthesis of Stereodefined α-Trialkylsilyl-β-Alkyl-(Aryl)-α,β-Unsaturated Esters. Before fully investigating the electrophilic halogenation of α-trialkylsilyl-β-alkyl(aryl)-α,β-unsaturated esters, there was a need to expand the synthetic scope of the catalytic carbocupration/silyl group migration of propiolate esters **3** and **4** to include new Grignard coupling reagents. Thus, using the previous reports as a guide,[11a,12] we examined the catalytic carbocupration of esters **3** and **4** with 5 mol % of CuI•2LiCl in the presence of

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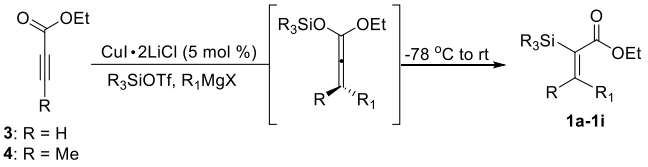
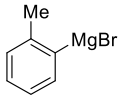
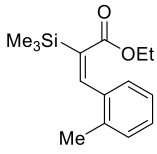
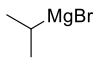
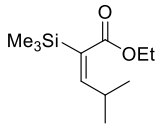
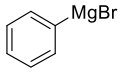
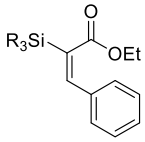
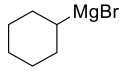
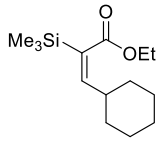
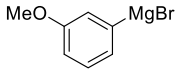
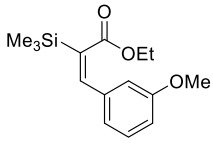
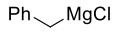
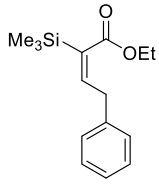
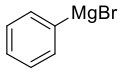
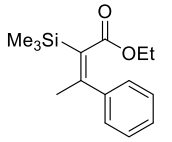
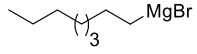
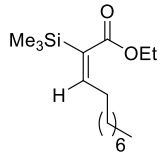
Table 1. Vicinal Functionalization of 3 and 4 via a Catalytic Carbocupration-Silicon Group Migration Sequence with Various Aliphatic and Aromatic Grignard Reagents and R_3SiOTf[a,b]



3: R = H
4: R = Me

Grignard reagent	product yield, (*E*/*Z*)	Grignard reagent	product yield, (*E*/*Z*)
	 **1a**: 88% (*E*/*Z* > 20/1)		 **1f**: 82% (*E*/*Z* > 20/1)
	 **1b**: R = Me; 92% (*E*/*Z* > 20/1) **1e**: R = Et; 83% (*E*/*Z* > 20/1)		 **1g**: 60% (*E*/*Z* > 20/1)
	 **1c**: 88% (*E*/*Z* > 20/1)		 **1h**: 70% (*E*/*Z* > 20/1)
	 **1d**: 85% (*E*/*Z* > 20/1)		 **1i**: 65% (*E*/*Z* > 20/1)

[a]*E*/*Z* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b]Yields are of the isolated, pure compounds.

Me_3SiOTf and/or Et_3SiOTf (3.3 equiv) and 1.2 equiv of alkyl or aryl Grignard reagents.[13] As described in Table 1, catalytic carbocupration with all of the aromatic Grignard examples and propiolates **3** or **4** in the presence of Me_3-or Et_3SiOTf afforded products **1a**−**1e** with consistently high yields ranging from 83−92% with dr values >20:1 strongly favoring the *E* isomer.[11a] Likewise, catalytic carbocupration (5 mol %) of ethyl propiolate **3** with aliphatic Grignard reagents and Me_3SiOTf provided the vinyl silane products **1f**−**1i** in modest to good isolated yields (60−82%). Similarly, the dr values of the aliphatic product esters remained very high with a >20:1 ratio for the *E* isomer. As observed previously, the isolated yields for aliphatic esters **1f**−**1i** were consistently lower than those of the aromatic products when utilizing 5 mol % catalyst loading. However, the dr values for all the synthesized esters **1a**−**1i** remained very high (>20:1), irrespective of the catalyst loading. In order to improve the isolated yields for aliphatic Grignard reagents, a higher catalyst loading can be utilized, and it has been further described in a previous report.[11a]

NXS (X = Cl, Br)-Mediated Halogenation of Stereodefined α-Trialkylsilyl-β-Alkyl(Aryl)-α,β-Unsaturated Esters. Inspired by the Tamao report on the halogenolysis of simple vinyl silanes utilizing a variety of reagents (NBS, Br_2, and ICl) and the resultant stereochemical outcomes of the newly formed alkenyl halides, we chose to investigate the bromination of α-trialkylsilyl-β-alkyl(aryl)-α,β-unsaturated esters **1a**−**1i**, shown in Table 1, with the anticipation of being afforded with stereodefined α-bromo-β-substituted acrylate ester products.[3] The initial examination focused on the *N*-bromosuccinimide (NBS)-mediated halogenation of *o*-tolyl-ester **1a** in a variety of solvents at room temperature.

As described in Table 2, the bromination (2 equiv of NBS) of **1a** in non-Lewis-basic solvents such as toluene and CH_2Cl_2 (entries 1 and 2) did not proceed at room temperature, and unfortunately, it furnished the product alkenyl bromide **2a** in very low yields of <15%, with the majority of the remaining mass balance as the starting material ester **1a**. Because of the poor yields, the dr of **2a** was not determined by ^{1}H NMR. However, by exchanging the reaction medium to the more Lewis-basic solvents Et_2O, tetrahydrofuran (THF), and dimethoxyethane (DME), the bromination of **1a** readily progressed with 2 equiv of NBS and afforded ester **2a** with increasing isolated yields of 26, 53, and 75%, respectively, and a dr of >20:1 strongly favored the *Z*-isomer in entries 3−5. Much to our delight, the halogenation of **1a** in DMF at room temperature under the previous mentioned reaction conditions (NBS, 2 equiv) afforded ester **2a** in 90% isolated yield with a dr of >20:1 for the *Z*-olefin. Interestingly, lowering or

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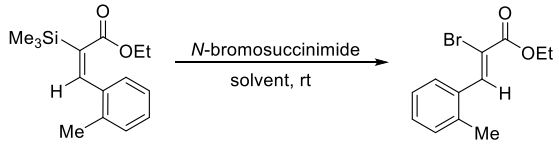
Table 2. Initial Bromination of Vinyl Silane 1a with NBS in Various Solvents



1a 2a

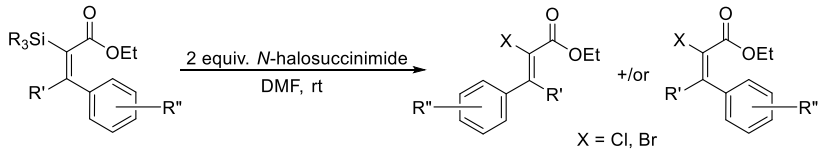
entry	NBS equiv	solvent	yield %[a,b]	Z/E[c]
1	2.0	CH_2Cl_2	<15	ND
2	2.0	toluene	<15	ND
3	2.0	Et_2O	26	>20/1
4	2.0	THF	53	>20/1
5	2.0	DME	75	>20/1
6	2.0	DMF	90	>20/1
7	1.0	DMF	55	>20/1
8	4.0	DMF	62	>20/1

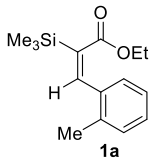
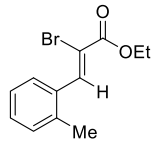
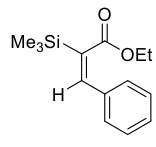
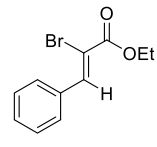
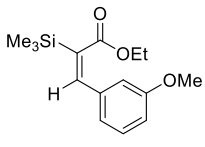
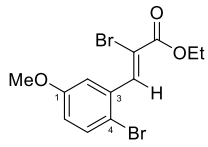
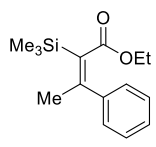
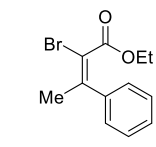
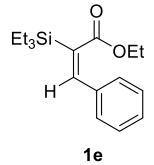
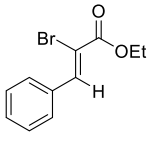
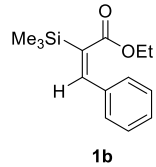
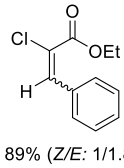
[a]Purified, isolated yield of vinyl bromide. [b]Remaining mass balance was a combination of the starting material and unidentifiable products. [c]Z/E ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture; ND = Not Determined.

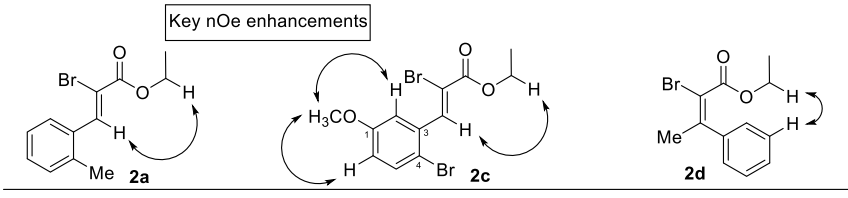
increasing the equivalence of NBS exhibited a deleterious effect on the overall yield of **2a** while maintaining the high levels of dr in entries 7 and 8.

Based on the results from Table 2, a single key point merits further discussion. Very similar to the Tamao report, a significant solvent effect for the NBS-mediated bromination of **1a** was observed. In our case, the halogenation of **1a** did not proceed in the non-Lewis-basic solvents toluene and CH_2Cl_2. However, ethereal solvents (Et_2O, THF, and DME) allowed for the production of **2a**, but the extent of product formation was dependent on the level of Lewis basicity.[14] For example, the bromination of **1a** with NBS in Et_2O provided the product **2a**, although with a low isolated yield of 26%, whereas more Lewis-basic solvents THF and DME afforded ester **2a** in 53 and 75% yields, respectively. Moreover, when the reaction was conducted in DMF (the most Lewis-basic solvent studied in Table 1), there was complete conversion of **1a** into product **2a**, with an isolated yield of 90% Thus, solvent dependency influenced the reaction rate and ultimately the isolated yield, but not the final stereochemistry of product **2a** (>20:1 in all cases), as shown in entries 3−6. Surprisingly, the lack of solvent dependence on the final stereochemistry of product **2a** (and others, vide infra) contrasted with Tamao's observations on less-complex vinyl silane substrates.[3]

Table 3. NXS (X = Cl, Br) Facilitated Halogenations of a Variety of α-Trialkylsilyl-β-Aryl-α,β-Unsaturated Esters[a,b]



vinyl silane	product yield, (Z/E)	vinyl silane	product yield, (Z/E)
 **1a**	 **2a**: 90% (*Z/E:* > 20/1)	 **1b**	 **2b**: 73% (*Z/E:* > 20/1)
 **1c**	 **2c**: 61% (*Z/E:* > 20/1)	 **1d**	 **2d**: 70% (*E/Z:* > 20/1)
 **1e**	 **2b**: 91% (*Z/E*: 3/1)	 **1b**	 **2e**: 89% (*Z/E:* 1/1.8)



[a]Z/E ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b]Yields are of the isolated, pure compounds.

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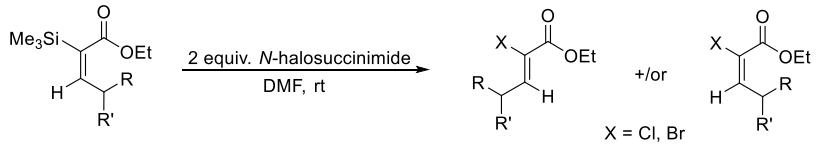
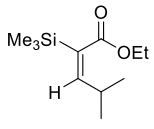
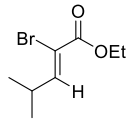
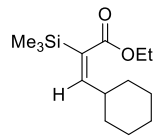
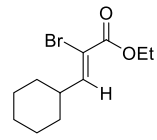
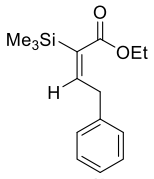
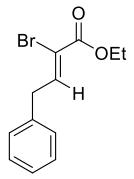
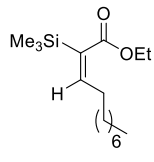
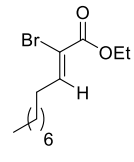
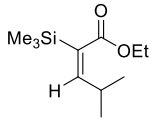
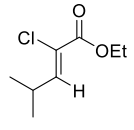
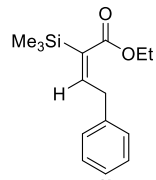
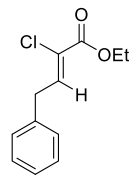
Table 4. NXS (X = Cl, Br) Facilitated Halogenations of a Variety of α-Trialkylsilyl-β-Alkyl-α,β-Unsaturated Esters[a,b]



vinyl silane	product yield, (*Z*/*E*)	vinyl silane	product yield, (*Z*/*E*)
 **1f**	 **2f:** 67% (*Z*/*E*: > 20/1)	 **1g**	 **2g**: 90% (*Z*/*E*: > 20/1)
 **1h**	 **2h**: 82% (*Z*/*E*: > 20/1)	 **1i**	 **2i**: 58% (*Z*/*E*: > 20/1)
 **1f**	 **2j**: 82% (*Z*/*E*: > 20/1)	 **1h**	 **2k**: 80% (*Z*/*E*: > 20/1)

[a]*Z*/*E* ratio determined by ^{1}H NMR (360 or 500 MHz) from the crude reaction mixture. [b]Yields are of the isolated, pure compounds.

Building on the observations from Table 2, attention was paid toward examining the scope and limitations of the NXS (X = Cl, Br)-mediated halogenations of a variety of α-trialkylsilyl-β-aryl-α,β-unsaturated esters (**1a**−**1e**) utilizing DMF as the reaction medium at room temperature. Thus, the treatment of **1b** under the standardized reaction conditions from Table 2 (2 equiv NBS in DMF) afforded the α-bromo-ester product **2b**[15] in 73% isolated yield, with a dr of >20:1 with the *Z*-olefin geometry, as delineated in Table 3. Interestingly, the attempted bromination of the *m*-substituted methoxy aryl ester (**1c**) did not furnish the expected stereodefined α-bromo-β-substituted acrylate ester product. However, the halogenation with NBS of ester **1c** provided the *bis*-brominated ester **2c**, while maintaining the high level of dr for the newly formed vinylic bromide (>20:1 for the Z-product) in 61% yield. In addition, the electron-rich aromatic ring of **1c** was concomitantly brominated at the C4-position (*para* to the methoxy directing group) during the reaction, as noted in Table 3.[16] Unfortunately, lowering the equivalents of NBS did not afford the monosubstituted vinylic bromo-ester product and resulted in a lower overall yield of **2c** with most of the starting material **1c** remaining. The geometry of the olefin and aromatic substitution pattern of **2c** was elucidated by 1D NOE (see Table 3). Surprisingly, the replacement of the Me_3Si (TMS) group of **1b** for the Et_3Si (TES) moiety (**1e**) led to an inferior dr (3:1 versus 20:1 for the *Z*-geometry) but greater yield of the newly formed vinylic bromide product **2b** under identical halogenation conditions. This result was suggestive that a trivial disparity in the substate structure (TMS versus TES) could have deleterious effects on the levels of dr for the halogenated product **2b**.

With the observations in Table 3 of complete olefin inversion in products **2a**−**2c** during the NBS-mediated halogenation of the three α-trimethylsilyl-β-aryl-α,β-unsaturated esters **1a**-**1c**, we opted to investigate the geometrical outcome of a potential tetrasubstituted vinyl bromide product derived from the α-trimethylsilyl-β,β-aryl,alkyl-α,β-unsaturated ester **1d**. Hence, the treatment of **1d** under the standard bromination conditions (2 equiv of NBS in DMF) for esters **1a**−**1c** furnished the tetrasubstituted vinylic bromide product **2d** as a single isomer (>20:1) in 70% isolated yield. After a close inspection of the 1D NOE (Table 3), it was determined that the stereochemistry of the olefinic moiety of **2d** was indeed the *E* isomer. As a result, the olefinic stereochemistry of **2d** was retained with respect to the starting material **1d**. This observation was surprising and stood in stark contrast to that of the three previous examples of **1a**−**1c** leading to **2a**−**2c** from an olefinic geometry perspective (*Z* versus *E* stereochemistry), thus suggesting that a different mechanism was in operation for the NBS-mediated halogenation of ester **1d** versus that of **1a**−**1c**, vide infra.

The final example of Table 3 investigated the chlorination of **1b** with *N*-chlorosuccinimide (NCS) under similar conditions to the bromination process with NBS. Thus, the reaction of **1b** with NCS (2 equiv) in DMF at 60 °C for 24 h afforded the vinylic chloride ester **2e**[17] with a 1.8:1 dr (slightly enriched in the *E* isomer, as determined by ^{1}H NMR) and 89% isolated yield. Unfortunately, the chlorination of **1b** with NCS did not proceed at room temperature. Frankly, we were quite surprised by the lack of stereochemical control of the reaction process leading the chloro-olefin product, considering the only variation was the usage of NCS in place of NBS. Once

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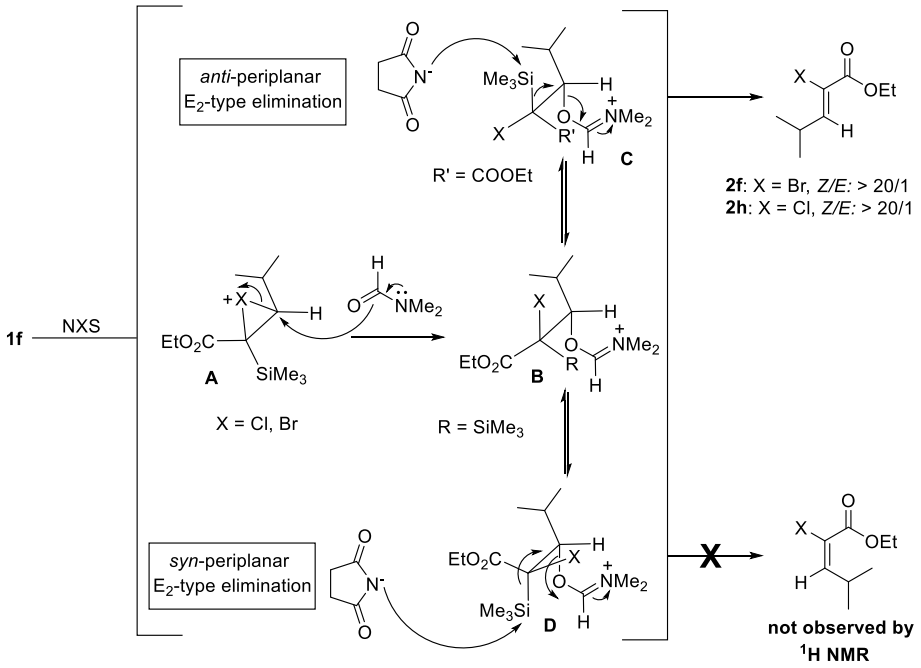

Figure 2. Proposed mechanism to account for the complete geometrical olefin inversion of aliphatic esters **1f**−**1i** during NXS-mediated halogenation in DMF.

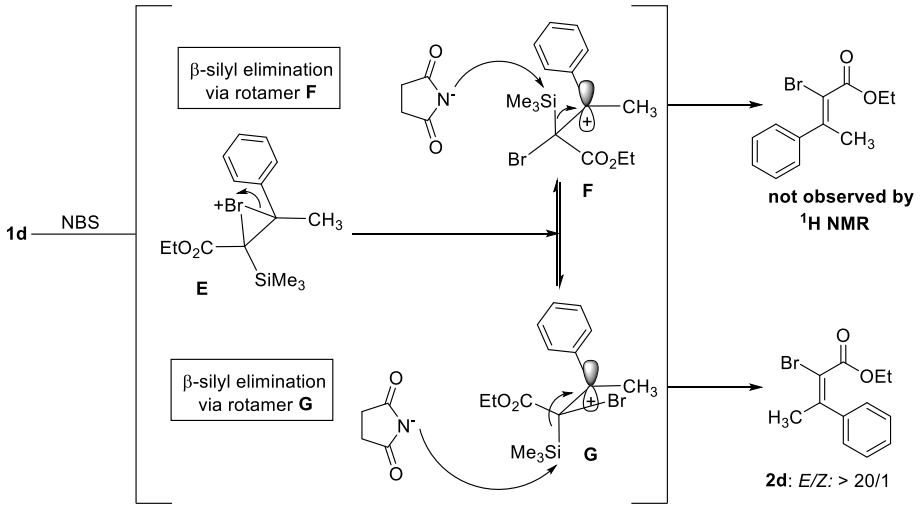

Figure 3. Proposed mechanism to account for the stereochemical olefin retention of the tetrasubstituted ester **1d** during NBS-mediated halogenation in DMF.

again, this example underscores the notion that an alteration in reaction conditions (reagent choice, reaction temperature, or subtle differences in the substrate) can have a dramatic effect on the outcome of the halo-olefin dr.

With the observations from Table 3 in hand, we sought to expand the reaction scope of the NXS (X = Br or Cl)-mediated halogenation to include α-trimethylsilyl-β-alkyl-α,β-unsaturated esters. As delineated in Table 4, the standardized reaction conditions (2 equiv of NXS and DMF) were duplicated from Table 3 for all the substrates **1f**−**1i**. Thus, the bromination of the isopropyl-substituted vinyl trimethylsilane ester **1f** with NBS in DMF afforded the expected halogenated product **2f**[18] in 67% isolated yield with a >20:1 dr favoring the *Z*-olefin geometry, as determined by ^{1}H NMR. In addition, the treatment of the cyclohexyl variant **1g** with NBS also furnished the predicted brominated product **2g**[18] with a greater isolated yield (90 versus 67% for **2f**) and identical dr (>20:1 for the *Z*-isomer). The more sterically encumbered β-isopropyl-and cyclohexylesters **1f** and **1g** selectively provided the Z-olefin geometry of the newly formed vinyl bromides **2f** and **2g**. We were interested in expanding the aliphatic reaction scope by examining the stereochemical outcomes of NBS-mediated halogenation of less-hindered α-trimethylsilyl-β-alkyl-α,β-unsaturated esters. Accordingly, the bromination of the β-benzyl substituted TMS ester **1h** readily proceeded with NBS in DMF at room temperature and afforded the bromo-ester product **2h** after the standard workup with an 82% isolated yield and a >20:1 dr favoring the *Z*-olefin.

Comparably, the treatment of the β-*n*-octyl TMS ester **1i** with NBS furnished the corresponding vinyl bromo-ester **2i** in 58% yield, with a continued dr of >20:1 for the Z-isomer. Similar to the aromatic esters **1a**−**1c** shown in Table 3, the

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aliphatic counterparts (**1f−1i**) underwent NBS-mediated bromination in DMF at room temperature, allowing for the stereoselective formation of vinylic bromide products **2f−2i** with complete inversion of the olefin geometry, as determined by ^{1}H NMR in modest to excellent yields.

The final two entries shown in Table 4 investigated the chlorination of **1f** and **1h** with NCS under conditions similar to those of the NBS bromination process. Hence, the reaction of **1f** with NCS (2 equiv) in DMF at 60 °C for 24 h provided the product vinylic chloride ester **2j** with a >20:1 dr (enriched in the *Z*-isomer, as determined by ^{1}H NMR of the crude material) and an 82% isolated yield. Likewise, the benzyl derivative **1h** readily underwent chlorination in the presence of NCS to afford the product halogenated ester **2k** in 80% isolated yield with a very similar >20:1 dr for the *Z*-olefin. We were extremely pleased by the high level of stereochemical control of the reaction process leading the chloro-olefin products **2j** and **2k** during the NCS-mediated chlorination of the precursor *α*-trimethylsilyl-*β*-alkyl-*α*,*β*-unsaturated esters **1k** and **1h**. Two important observations merit a brief discussion. The first is that the *β*-alkyl TMS esters afforded very high levels of dr (>20:1), as opposed to the *β*-aryl counterpart from Table 3 (1.8:1 dr). This suggests that different mechanisms might be in operation, depending upon the starting material during the NCS halogenation. The second key point is that the NCS reaction mirrors the NBS process with respect to the complete geometrical olefin inversion of the alkene starting material *α*-trimethylsilyl-*β*-alkyl-*α*,*β*-unsaturated esters, leading to the newly formed *β*-alkyl-*α*-haloesters shown in Table 4.

Based on the vinyl halide products obtained from the halogenation of (*E*)-*α*-trimethylsilyl-*β*-alkyl(aryl)-*α*,*β*-unsaturated esters **1a−1i**, we envisioned two possible mechanisms that would account for the observed high levels of dr (>20:1), as highlighted in Figures 2 and 3. The *β*-aliphatic ester examples (**1f−1i**) from Table 4 provided the halogenated (Br and Cl) products **2f−2k** with dr levels of >20:1 for the Z-olefin geometry coupled with the complete olefin inversion in all cases. A proposed mechanism is outlined in Figure 2, which is constructed from the previously reported Tamao model.[3]

Using ester **1f** as a representative example, it was deemed that the NXS addition in DMF to the olefin moiety should have produced the halonium ion intermediate **A**. An ensuing S_N2-type addition of DMF to the *β*-carbon of intermediate **A** would have subsequently afforded intermediate **B** and set the stage for the final elimination en route to the observed halogenated products. Thus, intermediate **B** included two possible rotamers (**C** and **D**), both of which could undergo the elimination of the TMS moiety concomitantly with DMF via an E2-type pathway. Based on the ^{1}H NMR of the crude reaction mixture, we detected only products **2f** (X = Br) and **2h** (X = Cl) with dr values of >20:1. These observations strongly suggest that the *anti*-periplanar rotamer **C** was in operation along the E2-elimination pathway, leading to the final halogenated ester products. While elimination via the *syn*-periplanar rotamer **D** was a possibility, we did not detect any of the resultant *E*-haloester. Moreover, it appeared that the bromination of aromatic esters **1a−1c** followed the identical (or very similar) elimination pathway (rotamer **C**) based on the very high levels of dr and the overall inversion of the olefin geometry of the halogenated products **2a−2c**. In addition to the proposed mechanism, as described Figure 2, one could suggest an alternative mechanistic pathway by means of an E1cB process.[19] However, this elimination route seems unlikely because of the complete geometrical inversion of olefin stereochemistry, and because typically, it is only in operation when a much stronger base (i.e., tetra-n-butylammonium fluoride, TBAF) is employed with respect to the substituted *α*-TMS esters with an appropriate leaving group resident at the *β*-carbon.

While we illustrated multiple examples of the complete geometrical olefin inversion during the NBS-mediated bromination of *α*-trimethylsilyl-*β*-alkyl(aryl)-*α*,*β*-unsaturated esters (>20:1 dr) in Tables 234, the tetrasubstituted congener **1d** afforded the vinylic bromo-ester product **2d** with a complete retention of the alkene geometry, as determined by 1D NOE.

As delineated in Figure 3, we envisioned an initial reaction pathway similar to that shown in Figure 2 using the bromonium cation intermediate **E** post-NBS addition to **1d**. An ensuing regioselective ring opening of the bromonium cation **E** would have afforded the highly stabilized *β*-trimethylsilyl-3°-benzylic carbocation intermediate in which two possible rotamers (**F** and **G**) could undergo elimination of the TMS moiety via an E1-type pathway.[20] Based on the high dr in favor of product **2d**, it would seem sensible that rotamer **G** would have been the preferred conformation prior to the *β*-silyl elimination process. Similar to Figure 2, elimination from rotamer **F** was a possibility, but we did not observe any of the ensuant *Z*-haloester product from the crude reaction mixture by ^{1}H NMR.

Unfortunately, the chlorination of **1b** with NCS in DMF lacked stereochemical control and afforded the resultant ester product with a 1.8:1 dr. We surmised that both rotamers similar to **C** and **D**, shown in Figure 2, might very well be in operation based on the low dr of product **2e** and the higher reaction temperature (60 °C versus room temperature). However, one cannot discount the possibility of a *β*-silyl-stabilized carbocation intermediate (akin to the one proposed and shown in Figure 3), followed by nonstereoselective TMS elimination.[20] Irrespective of the mechanistic pathway, the NCS-mediated chlorination of an *α*-trimethylsilyl-*β*-aryl-*α*,*β*-unsaturated ester was nonstereoselective and accentuated the notion that a slight alteration in reagents (NBS versus NCS) and ultimately reaction intermediates (bromonium versus chloronium cations) can have a considerable effect on the outcome of the halo-olefin dr. In support of the previous statement, Lee and Jung recently reported that an NXS [X = Br (100 °C), I (room temperature)]-mediated halogenation in MeCN of a *Z*-*α*-trimethylsilyl-*β*-phenyl-*α*,*β*-unsaturated amide afforded the corresponding *Z*-*α*-bromo/iodo-*α*,*β*-unsaturated amide with complete retention of configuration, whereas this work provided most ester products with a complete inversion of the olefin geometry.[21]

CONCLUSIONS

In conclusion, we have examined the NXS (X = Cl, Br)-mediated halogenation of a series of *α*-trimethylsilyl-*β*-alkyl(aryl)-*α*,*β*-unsaturated esters in DMF and observed the *β*-substituted-*α*-halogenated-*α*,*β*-unsaturated ester products in moderate to high isolated yields with dr values of >20:1 coupled with the inversion of olefin stereochemistry in most instances. Based on the observed products, a mechanistic model was suggested, which included an initial halonium cation intermediate, followed by regioselective ring opening with DMF via an S_N2 reaction mechanism. An ensuing *anti*-E2-type concomitant elimination of the TMS moiety and DMF

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allowed for the stereoselective formation of the product vinylic bromo-and chloroesters. Future directions of investigation will include further utilization of α-trimethylsilyl-β-alkyl(aryl)-α,β-unsaturated esters in the methodological development and target-driven natural product synthesis. Results from these studies will be reported in due course.

EXPERIMENTAL SECTION

All the reactions were performed under Ar in flame-dried glassware. All starting materials, solvents, reagents, and catalysts were commercially available and used without further purification, except for NBS, which was recrystallized in H_2O. NMR spectra were recorded with either a 360 or 500 MHz Bruker spectrometer. ^1H spectra were obtained using $CDCl_3$ as the solvent with chloroform ($CHCl_3$: δ = 7.26 ppm) as the internal standard. ^{13}C spectra were obtained using $CDCl_3$ as the solvent with chloroform ($CDCl_3$: δ = 77.0 ppm) as the internal standard. High-resolution mass spectra were recorded on an electric-magnetic-electric (EBE) sector instrument using electron ionization (EI) at 70 eV. Column chromatography was performed using 60−200 μm silica gel. Analytical thin layer chromatography was performed on silica-coated glass plates with the F-254 indicator. Visualization was accomplished using ultraviolet (UV) light (254 nm) and $KMnO_4$.

General Experimental Procedure for the Formation of α-Trialkylsilyl-β-Alkyl(Aryl)-α,β-Unsaturated Esters. CuI (0.029 g, 0.15 mmol) and LiCl (0.013 g, 0.30 mmol) were placed in a 100 mL round-bottom flask (flame-dried under vacuum) under Ar. Dry THF (20 mL) was added, and the mixture was stirred at room temperature for a period of 0.5 h until complete dissolution was achieved. The clear, light yellow homogeneous solution was cooled to −78 °C, and ethyl propiolate (0.294 g, 3.0 mmol) was added, followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) (3.3 equiv, 1.8 mL, 9.9 mmol). After 5 min at −78 °C, the aryl or alkyl Grignard reagent (1.2 equiv, 3.6 mmol) was added dropwise via a syringe, and the solution was stirred at −78 °C for 1 h and allowed to warm to room temperature. The reaction was quenched with H_2O, and the product was extracted with Et_2O (3 × 25 mL), and the combined organic layers were washed with deionized H_2O, followed by saturated NH_4Cl. The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo to provide the crude product, which was then analyzed by ^1H NMR spectroscopy to determine diastereoselectivity. Column chromatography of the crude material (3% ethyl acetate in hexanes) afforded pure vinyl silane products.

*Ethyl (E)-3-(o-Tolyl)-2-(Trimethylsilyl)Acrylate (**1a**).* Yield: 0.692 g, 88%; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.22−7.08 (m, 4H), 7.03 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 2.31 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H), 0.25 (s, 9H).[11a]

*Ethyl (E)-3-Phenyl-2-(Trimethylsilyl)Acrylate (**1b**).* Yield: 0.684 g, 92%; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 6.77 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H), 0.19 (s, 9H).[11a]

*Ethyl-(E)-3-(3-Methoxyphenyl)-2-(Trimethylsilyl)Acrylate (**1c**).* Yield: 0.734 g, 88%; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.89 (s, 1H), 6.83 (dd, J = 8.3, 3.0 Hz, 1H), 6.78 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.24 (s, 9H).[11a]

*Ethyl-(E)-3-Phenyl-2-(Trimethylsilyl)but-2-Enoate (**1d**).* Yield: 0.668 g, 85%; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.21 (m, 5H), 3.86 (q, J = 7.2 Hz, 2H), 2.19 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H), 0.28 (s, 9H).[11a]

*Ethyl-(E)-3-Phenyl-2-(Triethylsilyl)Acrylate (**1e**).* Yield: 0.722 g, 83%; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (360 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 6.79 (s, 1H), 4.18 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.6 Hz, 9H), 0.75 (q, J = 7.6 Hz, 6H).[11a]

*Ethyl-(E)-4-Methyl-2-(Trimethylsilyl)Pent-2-Enoate (**1f**).* Yield: 0.702 g, 82%; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (360 MHz, $CDCl_3$) δ 5.89 (d, J = 9.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.96−2.86 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H), 1.00 (d, J = 6.6 Hz, 6H), 0.13 (s, 9H).[11a]

*Ethyl (E)-3-Cyclohexyl-2-(Trimethylsilyl)Acrylate (**1g**).* Yield: 0.46 g, 60%, light yellow oil; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (d, J = 9.3 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.66−2.60 (m, 1H), 1.71−1.64 (m, 5H), 1.30 (t, J = 7.1 Hz, 2H), 1.29−1.24 (m, 2H), 1.20−1.04 (m, 3H), 0.12 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.6, 156.4, 133.8, 59.8, 40.3, 32.5, 25.9, 25.6, 14.4, −1.3. IR (NaCl): 2977, 2927, 1713, 1606, 1448, 1263, 1192, 855 cm^{-1}. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{14}H_{26}O_2Si$ 254.1696; found 254.1702. R_f = 0.50, 3% EtOAc in hexanes.

*Ethyl-(E)-4-Phenyl-2-(Trimethylsilyl)but-2-Enoate (**1h**).* Yield: 0.734 g, 70%; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (360 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 6.30 (t, J = 7.0 Hz, 1H), 4.27 (q, J = 7.0 Hz, 2H), 3.74 (d, J = 7.0 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 0.18 (s, 9H).[11a]

*Ethyl (E)-2-(Trimethylsilyl)Undec-2-Enoate (**1i**).* Yield: 0.56 g, 65%, yellow oil; flash column chromatography: 3% ethyl acetate in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (t, J = 7.3 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.37−2.33 (m, 2H), 1.48−1.38 (m, 2H), 1.31−1.26 (m, 10H), 1.27 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H), 0.13 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.6, 151.8, 135.9, 59.9, 31.9, 31.7, 29.4, 29.3, 29.2, 29.1, 22.7, 14.4, 14.1, −1.3. IR (NaCl): 2956, 2925, 2871, 2855, 1715, 1464, 1247,1191, 1033, 840, 754. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{16}H_{32}O_2Si$ 284.2160; found 284.2172. R_f = 0.62, 4% EtOAc in hexanes.

General Experimental Procedure for the α-Halogenated-α,β-Unsaturated Esters. In a room with the overhead and fume hood lights turned off, NBS or NCS (0.80 mmol, 2.0 equiv) was added to a (flame-dried under vacuum) round-bottom flask under Ar. The flask was then covered in aluminum foil, and a solution of vinyl silane (**1a−1i**) (0.40 mmol, 1.0 equiv) in anhydrous DMF (1.00 mL) was added in one portion. The mixture was stirred at room temperature (for NBS) or 60 °C (for NCS, oil bath) for a minimum of 24 h, where it was then quenched with saturated Na_2CO_3 (1.00 mL), and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with deionized H_2O (3 × 10 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to yield the crude product. Column chromatography of the crude material (3% Et_2O in pentane) afforded the pure halogenated products **2a−2k** in yields ranging from 58 to 91%.

*Ethyl (Z)-2-Bromo-3-(o-Tolyl)Acrylate (**2a**).* Yield: 0.092 g, 90%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.31−7.22 (m, 4H), 4.35 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.1, 140.6, 137.0, 133.7, 130.1, 129.4, 128.6, 125.6, 115.7, 62.8, 19.9, 14.2. IR (NaCl): 1720, 1481, 1257, 865, 482 cm^{-1}. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{12}H_{13}BrO_2$ 268.0099; found 268.0105. R_f = 0.39, 3% Et_2O in pentane.

*Ethyl (Z)-2-Bromo-3-Phenylacrylate (**2b**).* Yield: 0.074 g, 73%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.86−7.84 (m, 2H), 7.44−7.42 (m, 3H), 4.36 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).[15]

*Ethyl (Z)-2-Bromo-3-(2-Bromo-3-Methoxyphenyl)Acrylate (**2c**).* Yield: 0.060 g, 61%, yellow solid. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 3.0 Hz, 1H), 6.83 (dd, J = 8.8, 3.0 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.8, 158.4, 140.4, 135.2, 133.6, 117.1, 116.7, 115.8, 114.8, 63.0, 55.6, 14.2. IR (NaCl): 1720, 1463, 1280, 1234, 908, 729. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{12}H_{12}Br_2O_3$ 361.9153; found 361.9164. R_f = 0.29, 3% Et_2O in pentane.

*Ethyl (E)-2-Bromo-3-Phenylbut-2-Enoate (**2d**).* Yield: 0.075 g, 70%, clear oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H

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NMR (500 MHz, $CDCl_3$) δ 7.33−7.31 (m, 3H), 7.19−7.17 (m, 2H), 3.95 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 0.91 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.9, 147.0, 141.2, 128.3, 128.0, 126.8, 111.1, 61.7, 25.9, 13.4. IR (NaCl): 1288, 1277, 1042, 700. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{12}H_{13}BrO_2$ 268.0099; found 268.0090. R_f = 0.18, 3% Et_2O in pentane.

*Ethyl (Z) and (E)-2-Chloro-3-Phenylacrylate (**2e**).* Yield: 0.040 g, 89%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. (*Z*)-product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.63 (d, J = 7.5, 1H), 7.44−7.39 (m, 4H), 4.36 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H); (*E*)-product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 7.21 (s, 1H), 4.21 (q, J = 7.2, 2H), 1.18 (t, J = 7.1, Hz, 3H).[17]

*Ethyl (Z)-2-Bromo-4-Methylpent-2-Enoate (**2f**).* Yield: 0.069 g, 67%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 9.3 Hz, 1H), 4.27 (q, J = 7.1 Hz, 1H), 2.88−2.83 (m, 1H), 1.33 (t, J = 7.1 Hz, 2H), 1.09 (d, J = 6.7 Hz, 3H).[18]

*Ethyl (Z)-2-Bromo-3-Cyclohexylacrylate (**2g**).* Yield: 0.083 g, 90%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 9.2 Hz, 1H), 4.27 (q, J = 7.1 Hz, 1H), 2.60−2.54 (m, 1H), 1.76−1.67 (m, 5H), 1.34−1.32 (m, 2H), 1.33 (t, J = 7.1 Hz, 2H), 1.21−1.16 (m, 3H).[18]

Experimental Procedure for the Synthesis of 2h @ 2.5 Mmol. In a dark room, NBS (5.00 mmol, 0.890 g, 2.0 equiv) was added to a (flame-dried under vacuum) round-bottom flask under Ar. The flask was then covered in aluminum foil, and a solution of **1h** (2.50 mmol, 0.656 g, 1.0 equiv) in anhydrous DMF (10.00 mL) was added in one portion. The mixture was stirred at room temperature for 24 h, where it was then quenched with saturated Na_2CO_3 (10.00 mL), and the product was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with deionized H_2O (3 × 30 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to yield the crude product. Column chromatography of the crude material afforded the pure halogenated product **2h** (0.551 g) in 82% yield as pale yellow oil. Ethyl (*Z*)-2-bromo-4-phenylbut-2-enoate (**2h**); flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, J = 7.3 Hz, 1H), 7.34−7.31 (m, 2H), 7.27−7.23 (m, 3H), 4.28 (q, J = 7.1 Hz, 2H), 3.70 (d, J = 7.3 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.4, 144.0, 137. 2, 128.8, 128.6, 126.9, 117.0, 62.5, 38.4, 14.1. IR (NaCl): 2360, 2341, 1652, 1255, 992, 799. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{12}H_{13}BrO_2$ 268.0099; found 268.0096. R_f = 0.42, 3% Et_2O in pentane.

*Ethyl (Z)-2-Bromoundec-2-Enoate (**2i**).* Yield: 0.059 g, 58%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 7.2 Hz, 1H), 4.28 (t, J = 7.1 Hz, 2H), 2.36−2.31 (m, 2H), 1.54−1.47 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.35−1.28 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.6, 146.3, 116.3, 62.3, 32.1, 31.8, 29.3, 29.3, 29.2, 27.5, 22.6, 14.2, 14.1. IR (NaCl): 2926, 1730, 1718, 1235. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{13}H_{23}BrO_2$ 290.0881; found 290.0882. R_f = 0.45, 3% Et_2O in pentane.

*Ethyl (Z)-2-Chloro-4-Methylpent-2-Enoate (**2j**).* Yield: 0.068 g, 82%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, J = 9.4 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.94−2.86 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 6.7 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.8, 148.3, 122.8, 62.2, 29.1, 21.1, 14.2. IR (NaCl): 1734, 1721, 1251, 1145, 1041, 754 cm^{-1}. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_8H_{13}ClO_2$ 176.0604; found 176.0601. R_f = 0.40, 3% Et_2O in pentane.

*Ethyl (Z)-2-Chloro-4-Phenylbut-2-Enoate (**2k**).* Yield: 0.052 g, 80%, yellow oil. Flash column chromatography: 3% Et_2O in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.27 (m, 2H), 7.26−7.20 (m, 3H), 7.22 (t, J = 7.4 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.71 (d, J = 7.4 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.4, 140.2, 137.4, 128.8, 128.6, 126.8, 125.2, 62.30, 35.6, 14.1. IR (NaCl): 1730, 1268, 1043 cm^{-1}. HRMS (EI-EBE Sector) m/z: [M] + Calcd for $C_{12}H_{13}ClO_2$ 224.0604; found 224.0605. R_f = 0.27, 3% Et_2O in pentane.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00876.

Full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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