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Highly Regio- and Diastereoselective Formation of Tetrasubstituted (*Z*)-1,2-Dihaloalkenes from the Halogenation of Trimethylsilyl Alkynes with ICl

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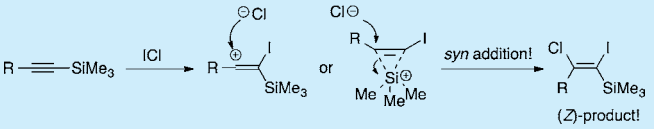
Supporting Information

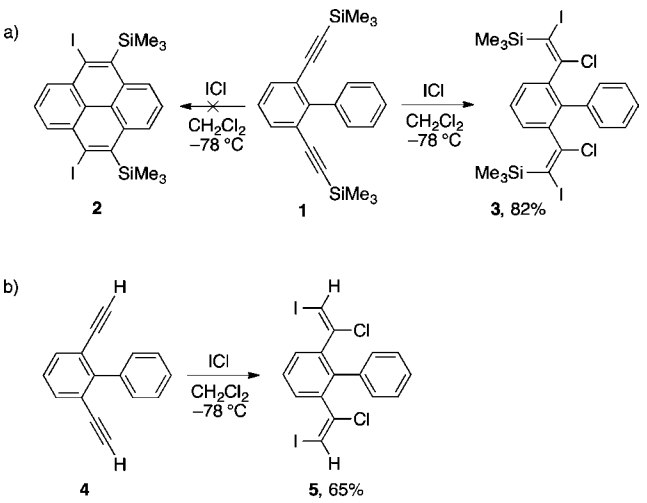
ABSTRACT: The stereoselective *anti* addition of diatomic halogens to alkynes has been well studied. A method is reported that utilizes the β-silyl effect to override this typically observed *anti* selectivity and provides halogenation products that result from *syn* addition. The reaction involves the addition of iodine monochloride to trialkylsilyl-substituted alkynes to produce tetrasubstituted (*Z*)-dihaloalkenes in good to excellent yields and with excellent regio- and diastereoselectivity.



The synthesis of 1,2-(*E*)-dihaloalkenes has been shown to occur readily by the treatment of alkynes with molecular halogen reagents.[1−4] As taught in many introductory organic chemistry textbooks, the stereochemistry observed in the products is usually the result of *anti* addition, providing (*E*)-dihaloalkene products.[5] The importance and utility of dihaloalkenes as coupling partners has also been well demonstrated.[6−10] Therefore, the ability to generate (*Z*)-dihaloalkenes in an analogous manner would be of great utility by providing access to a host of isomeric cross-coupling partners. Some methods to produce (*Z*)-dihaloalkenes include haloboration/halogenation of alkynes,[11] halogenation in the presence of tetraalkylammonium iodide salts,[12] halogenation of alkynes in ionic liquids,[13] addition of KI to haloalkynes,[14] or the substitution of iodonium salts with tetraalkylammonium iodide.[15] Some impressive work by Zhu and co-workers was recently reported where they were successful in producing (*Z*)-dihaloalkenes via a palladium-catalyzed hydrohalogenation of alkynyl halides.[16,17] In 2004, there was an interesting report by Selina et al. where (*Z*)-iodochloroalkenes were furnished when silyl- and germylphenylacetylenes were treated with $KICl_2$.[18] During the preparation of this manuscript an analogous (*Z*)-halogenation of TIPS-ethynylarenes by the addition of BrCl was reported by Iwasawa and co-workers.[19] The Iwasawa group developed an excellent way to generate the volatile and toxic BrCl reagent in situ from a mixture of excess NBS and excess trimethysilyl chloride. Since they generate an excess of BrCl under these conditions, they must utilize a bulky and very stable TIPS group to prevent desilylation/halogenation. Here, we report an analogous method that not only is atom economical but also utilizes commercially available iodine monochloride (ICl) in a metal-free *syn* halogenation of TMS-substituted alkynes. This reaction overrides the textbook-taught stereoselective *anti* addition, where ICl reacts with TMS-substituted alkynes in a *syn* addition manner with very high regio- and diastereoselectivity to provide tetrasubstituted (*Z*)-dihaloalkenes.

Our study initiated from a serendipitous discovery that the reaction of 2,6-dialkynylbiphenyl **1** with 2 equiv of ICl failed to undergo the expected double cyclization reaction to generate diiodopyrene **2**,[20] but instead provided the double ICl addition product **3** in good yield (Scheme 1). What was most interesting about this result was that the addition of ICl happened in a *syn* fashion to give exclusively the bis(*Z*)-alkene product. The stereochemistry of **3** was confirmed by X-ray crystallographic analysis (Figure 1a). When we subjected desilylated compound **4** to the ICl reaction conditions, we observed the selective

Scheme 1. Addition Reaction of ICl To Generate (a) Bis(*Z*)-dihaloalkene 3 and (b) Bis(*E*)-dihaloalkene 5



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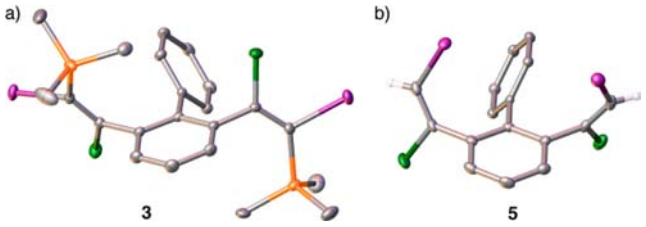


Figure 1. X-ray crystal structures of (a) compound **3** resulting from double *syn* addition of ICl to **1** and (b) compound **5** resulting from double *anti* addition of ICl to **4** (nonessential H's removed for clarity; orange = Si; green = Cl; purple = I).

formation of the bis(*E*)-alkene product **5**, where the stereochemistry was also confirmed by X-ray crystallographic analysis (Figure 1b). One can imagine the utility of these diversely functionalized tetrasubstituted alkene products that contain an iodide, a chloride, and a TMS group. The halogen functional groups provide excellent handles for further chemical manipulation, such as selective cross-coupling reactions.[9,21−24] Also, the ease in which a TMS group can be chemically transformed to other useful functionality is particularly attractive, compared to the more robust TIPS group. The TMS group can be readily converted to halides,[25,26] alcohols,[27−30] and a hydrogen (protodesilylation),[31,32] undergo electrophilic substitution,[33] and be utilized as a cross-coupling partner.[34]

We hypothesized that the stereochemistry seen in product **3** was the result of the TMS substitution on the alkynes. It seems reasonable to propose that the β-silyl effect is disrupting the formation of the iodonium intermediate **A** to produce either stabilized cationic intermediate **B**, or perhaps something in-between **B** and a 3-centered 2-electron bonded intermediate such as **C** (Figure 2). Both intermediates (**B** and **C**) could

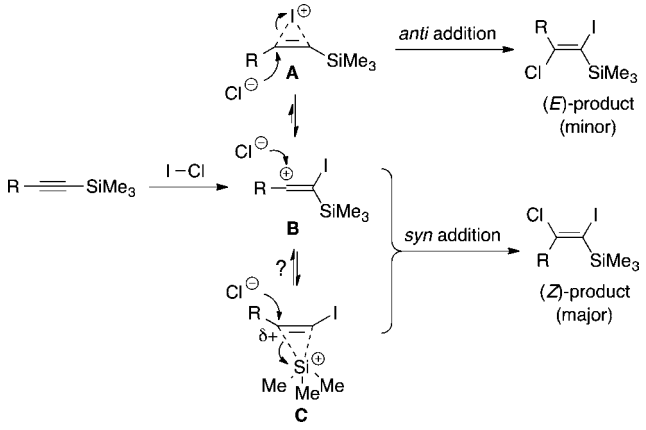
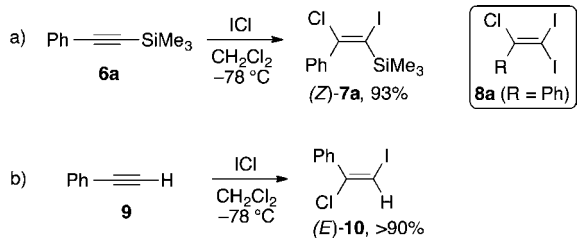


Figure 2. Proposed cationic intermediates **B** and/or **C**.

explain the observed selectivity. In intermediate **B**, nucleophilic attack of the chloride anion would be favored from the less hindered face, away from the larger TMS group, to provide the (*Z*)-dihaloalkene products. In intermediate **C**, backside attack would be favored, which would also explain the formation of (*Z*)-dihaloalkene products.

We decided to test the hypothesis that silyl substitution inverts the typical *anti* selectivity seen with halogen addition to alkynes and provide (*Z*)-products by looking at more simple systems. First, we examined the result of ICl addition to 1-(TMS)-2-phenylacetylene **6a** at −78 °C (Scheme 2a). The

Scheme 2. (a) *Syn* Addition of ICl Provide (*Z*)-7a; (b) Stereospecific *anti* Addition of ICl To Provide (*E*)-10[35]



result was that of *syn* addition of ICl across the triple bond with high regio- and stereoselectivity to generate (**Z**)-**7a** in excellent yield. Only a trace (0.6%) amount of the iodine−silane exchange product **8a** was detected by GCMS analysis. The stereochemistry of **7a** was determined by NOESY NMR analysis, which showed the presence of a NOE correlation between the hydrogens on the TMS group and the *ortho*-hydrogens of the benzene ring. It has been shown that the treatment of phenylacetylene **9** (no TMS substitution) with ICl results in the exclusive formation of (**E**)-**10** as a single regioisomer (Scheme 2b).[35]

Kamieńska-Trela[36] and co-workers have reported that bromination of trimethylsilylacetylene provides exclusively the *trans* halogenation product in the absence of light and that, in the presence of catalytic Br_2 and light, the product is isomerized to a mixture of *E* and *Z* products. To ensure that our isolated (**Z**)-**7a** product was not the result of isomerization, we carried out some control reactions. We began by carrying out the reaction of **6a** with ICl in the dark, which still resulted in a >99:1 ratio of *Z*/*E* products. Even upon standing in ambient light for days, we saw no change in the ratio of products. We also carried out the reaction using 0.7 equiv of ICl (limiting) in the dark to remove the possibility of excess ICl catalyzing the isomeration, as was proposed by Kamieńska-Trela and co-workers.[36] Again, we saw >99:1 *Z*/*E*-selectivity for the formation of **7a**. These control reactions suggest that (**Z**)-**7a** is obtained initially in high selectivity and not the result of either photoisomerization or halogen catalyzed isomerization from the (*E*)-product to the (*Z*)-product. To rule out a radical mechanism, the reaction was carried out in the presence of radical scavengers (10 mol % of TEMPO or BHT). The ratio of *Z*/*E* products was not affected and still provided (**Z**)-**7a** almost exclusively in 84% (TEMPO) and 85% (BHT) yields after purification.

We explored the scope of this stereoselective halogenation reaction. The reaction resulted in *syn* addition products for electron-rich and electron-poor 1-(TMS)-2-arylacetylenes (Table 1, entries 2−8). The *Z*-selectivities resulting from ICl addition to the thiophene (**6b**) and *p*-methoxyphenyl (**6c**) derivatives were significantly lower at 27:1 and 7:1, respectively, but all other aryl substituents were very high. Even electron-deficient substrates (entries 4 and 7) worked well, a problem that was reported in Iwasawa's work with the addition of BrCl to electron-deficient substrates.[19] The ICl addition to alkyl derivatives such as 1-(TMS)-hexyne (**6i**) to produce **7i** also worked, where BrCl fails,[19] resulting in only a modest 3:1 selectivity in favor of the *Z*-isomer (entry 9). The ester (**6k**) proved to be unreactive to ICl, even at room temperature (entry 10). Halogenation of ketone (**6l**) was sluggish at low temperature and needed longer reaction times (24 h) at room temperature but did provide *Z*-product with excellent

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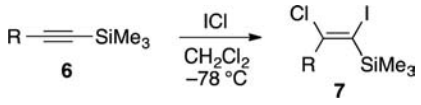
Table 1. Substrate Scope of ICl Addition to TMS Substituted Alkynes 6



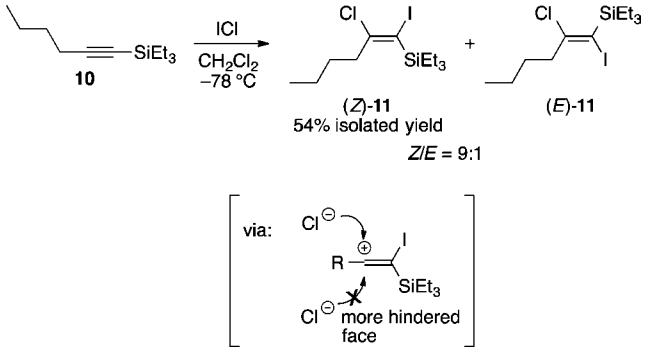
entry	R	product	Z:E[a]	yield (%)[b]
1	Ph	**7a**	>99:1	93
2		**7b**	27:1	56[cd]
3	*p*-MeOC$_6$H$_4$	**7c**	7:1	69[cd]
4	*p*-CF$_3$C$_6$H$_4$	**7d**	>99:1	87
5	*p*-BrC$_6$H$_4$	**7e**	>99:1	91
6	*o*-MeOC$_6$H$_4$	**7f**	>99:1	85
7	*o*-CF$_3$C$_6$H$_4$	**7g**	>99:1	73
8	*o*-BrC$_6$H$_4$	**7h**	>99:1	92
9	C$_4$H$_9$	**7i**	3:1	68[cd]
10[e]	CO$_2$Et	**7k**	N/A	0
11[e]	PhCO	**7l**	>99:1	54

[a]Z:E ratio determined by GCMS analysis of the crude product solution immediately upon quenching the reaction. [b]Isolated yields. [c]These reactions produced larger amounts of the iodine−silane exchange product **8**. [d]Yield corrected for purity by GCMS analysis. [e]Reaction started at 0 °C and warmed to rt.

selectivity, albeit, in modest yield along with some intractable baseline material (entry 11).

The low selectivities seen in entries 3 and 9 (Table 1) suggest that the reaction may not be going via a concerted *syn* addition if ICl is used, at least with more electron-rich substrates. If this is true, then one of the intermediates shown in Figure 2 is more likely and therefore the size of the silyl group would affect the diastereoselectivity of the reaction. To test this, we carried out the halogenation reaction on substrate **10**, which was substituted with the more bulky TES group, to provide crude **11** as a 9:1 Z/E mixture (Scheme 3). Pure (**Z**)-**11** could be isolated after chromatography in a moderate 54% yield. This result supports the idea that more sterically demanding silanes provide better Z-selectivity, as can be seen by comparison of this result to the smaller TMS derivative **7i**

Scheme 3. Increase in Z-Selectivity Is Observed in Product 11 When Substituted with a Larger Triethylsilyl Group



(Table 1, entry 9). While sterics imparted by the silyl group clearly play a large role in the diastereoselectivity, as was also demonstrated by Selina et al.,[18] we cannot rule out that stereoelectronic effects from a slightly more electron-rich TES group could also explain the observed increase in selectivity. If sterics is indeed the major contributor to our observed increase in selectivity, then the intermediate in this reaction likely resembles **B** (see Figure 2) since the outcome from a pseudo-3-centered 2-electron bonded intermediate **C** would be less affected by the size of the silyl group. This would also explain why we do not detect any 1,1-dihaloalkene products being formed, accompanied by TMS or TES migration, which would be a minor product expected from intermediate **C**. Studies are ongoing regarding the steric and electronic contribution to selectivity and will be reported in due course.

In conclusion, we have demonstrated a reversal of stereoselectivity in the addition of iodine monochloride to trialkylsilyl-substituted alkynes. The reaction results in the formation of tetrasubstituted (Z)-alkenes with high diastereoselectivity. The reaction of trialkylsilyl-substituted alkynes with iodine monochloride provides highly functionalized tetrasubstituted Z-alkenes in an atom-economical manner with high stereo- and regiocontrol. This reaction will provide a beneficial addition to existing methods of alkyne halogenation by providing products with highly useful functional handles that can be utilized for further chemical elaboration.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, crystallographic data, and CIF files. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01558.

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Notes

The authors declare no competing financial interest.

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