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Regio- and Stereoselective Synthesis of 1,2-Dihaloalkenes Using In-Situ-Generated ICl, IBr, BrCl, I2, and Br2

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SUMMARY

We describe a catalyst-free 1,2-*trans*-dihalogenation of alkynes with an unprecedented substrate scope and exclusive regio- and stereoselectivity. This versatile dihalogenation system—a combination of NX^1S electrophile and alkali metal halide (MX^2) in acetic acid—is applicable for diverse categories of alkynes (electron-rich or poor alkynes, internal and terminal alkynes, or heteroatoms such as O-, N-, S-substituted alkynes). The hydrogen bonding donor solvent acetic acid is essential for the *in-situ* generation of X^1X^2 electrophile, including ICl, IBr, BrCl, I_2, and Br_2.

Graphical abstract

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AUTHOR CONTRIBUTIONS

X.Z., G.B.H., and X.B. conceived the research. X.Z., S.L.,Yuhao Yang, and Yi Yang carried out experiments and analyzed results. X.Z., G.B.H., and X.B. wrote the manuscript with input from all the authors.

DATA AND CODE AVAILABILITY

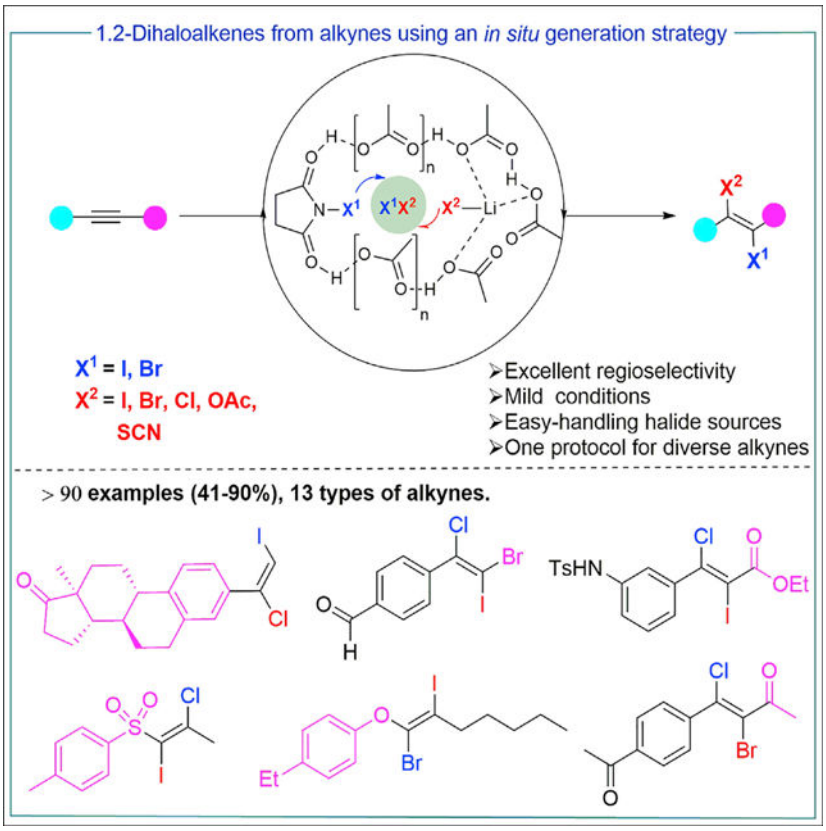
Crystal structure data of compounds **10** (CCDC: 1912785), **29** (CCDC: 1948339), **51** (CCDC: 1912792), **69** (CCDC: 1948338), **82** (CCDC: 1966560), **91** (CCDC: 1966562), **101** (CCDC: 1912791), and **105** (CCDC: 1966561) have been deposited in the Cambridge Structural Database.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.020.03.011.

DECLARATION OF INTERESTS

The authors declare no competing interests.



Dihaloalkenes are important raw materials for pharmaceutical and chemical industries. However, existing preparation methods suffer from a limited substrate scope as well as poor regio- and stereoselectivity. Furthermore, these methods often necessitate highly toxic reagents, such as Cl_2, ICl, and BrCl. Our environmentally friendly 1,2-*trans*-dihalogenation is based on easy-handling halide sources, such as alkali metal halides. What is more, our method offers an unprecedented substrate scope, the regio- and stereoselectivity for the synthesis of 1,2-dihaloalkenes.

INTRODUCTION

Halogenated organic compounds are among the most important structural motifs as they are ubiquitous in natural products,[1,2] materials,[3] and pharmaceuticals.[4] They are also among the most versatile building blocks.[5,6] More specifically, 1,2-dihaloalkenes are reliable cross-coupling partners, which have been extensively utilized to construct a wide range of multisubstituted alkenes and other complex molecules.[7–14] Compared with 1,2-dihaloalkenes containing only one kind of halogen (e.g., dichloroalkenes), dihaloalkenes containing two different halogens are more exciting and have broader applications.[15] For example, dihaloalkenes containing two different halogens could undergo cross-coupling reactions in a step-wise manner for the installment of two different molecular fragments.[7,16–27] In this regard, significant efforts have been devoted to the construction of dihaloalkenes. However, the regio- and stereoselective, yet environmentally friendly synthesis of dihaloalkenes with a broad scope is still challenging.[28–34]

As taught in any introductory organic chemistry course, the electrophilic addition of X_2, such as Br_2 or Cl_2, to alkynes is a straightforward method for the synthesis of 1,2-dihaloalkenes. The electrophilic dihalogenation of alkynes suffers from limited substrate scope as well as poor regio- and stereoselectivity. Furthermore, these methods need highly toxic reagents, such as Cl_2, ICl, and BrCl.[35,36] For example, many electrophilic additions of permanent dipole reagents, such as ICl and Ibr, to alkynes deliver a mixture of *cis*- and *trans*-products with poor regioselectivity[37,38] or, in other cases, ionic liquids[39] are required (Scheme 1A). Chalifoux and co-workers[23] described a *trans*-addition of ICl to trialkysilyl-substituted alkynes via neighboring group participation at −78 °C (Scheme 1B). However, this strategy is limited to silyl-substituted alkynes. Many other dihalogenation systems based on combinations of N-halosuccinimide (NXS),[21,40] I_2,[41] or Cl_2 [42] together with TMSBr,[22] TMSCl, $HgCl_2$,[43] or HCl[33] have been developed (Scheme 1C). A Bu_4NI/DCE system [19,20] has also been explored (Scheme 1D). All these approaches generally need harsh reaction conditions and are case-specific for a given type of alkyne substrate. Alternatively, 1,2-dihaloalkenes could also be accessed via hydrohalogenations of haloalkynes, where pre-installment of a halogen to an alkyne is needed. For instance, the nucleophilic addition of alkali metal halides to haloalkynes leads to Z-dihaloalkenes[44] (Scheme 1E), but unfriendly reaction conditions are indispensable and regio-isomer formation is common[45] (Scheme 1F). Zhu's group (Scheme 1G) reported a Pa-catalyzed hydrohalogenation of haloalkynes,[46] a reaction that exclusively gives anti-addition products but their method is limited to the synthesis of iodoalkenes. Recently our group developed the synthesis of (*Z*)- and (*E*)-1,2-chlorohaloalkenes via gold catalysis and hydrogen bonding catalysis, respectively[47] (Scheme 1H). However, these methods were only applicable to hydrochlorination. Hitherto, the efficient regio- and stereoselective synthesis of diverse dihaloalkenes from a wide range of categories of alkynes (electron-rich or -poor alkynes, internal and terminal alkynes, heteroatoms such as O, N, S-substituted alkynes) by using a unified yet straightforward and environmentally friendly protocol remains an unsolved challenge in synthesis.

Recently, we developed easily handled and reactive N,N′-Dimethylpropyleneurea (DMPU)-HX reagents that enable the *regio*- and stereoselective synthesis of haloal-kenes.[47–51] Nevertheless, the high acidity of HX was incompatible with some functional groups.[52,53] An *in-situ* generated reactive halogenation reagent could be advantageous in such instances.[54–59] Recently, Oestreich and co-workers reported the hydroiodination of C–C multiple bonds by using *in-situ*-generated HI or HBr driven by the aromatization of cyclohexa-1,4-dienes.[60,61] We are now glad to report a versatile dihalogenation system—a combination of NX^1S and LiX^2 that arises in the presence of an H-bonding solvent, such as AcOH. This system slowly generates reactive ICl, IBr, BrCl, Br_2, and I_2 *in situ*. Because of the mild conditions, our dihalogenation of alkynes has demonstrated unprecedented substrate scope, yielding products with remarkably high regio- and stereoselectivity (Scheme 1, bottom).

RESULTS

We used the iodochlorination of alkyne 1a as our model reaction (Table 1). We first evaluated this reaction by using an extensively used iodochlorination reagent—ICl (Table 1, entry 2). Not surprisingly, a mixture of regioisomers was detected; this result was consistent with the reported literature.[31] Another reported dihalogeneration system (Bu_4NI-

dichloroethylene (DCE), 80 °C)[20] gave a complex mixture of products (Table 1, entry 2). An additional dihalogenation system [N-Iodosuccinimide (NIS)-Trimethylsilyl chloride (TMSCl)][16] gave only the hydrochlorinated product (Table 1, entry 3). We found that neither NIS/PhCOCl nor NIS/AcCl gave the desirable product (Table 1, entries 4–5), suggesting that hydrochlorination occurs before iodochlorination. Remarkably, the hydrochlorination products could be inhibited when LiCl was used (Table 1, entries 6–7) but because of the limited solubility of LiCl, employing solvents like CH_3CN or HFIP led to very low yields. We envisioned that a hydrogen bond donor solvent, such as HOAc not only would be able to dissolve LiCl, but would also increase the reactivity of the electrophile. As expected, a high yield of iodochlorinated product was observed with HOAc, albeit with low stereoselectivity (Table 1, entry 8). Interestingly, using dichloromethane (DCM) as the co-solvent significantly improved both the yield and the regioselectivity of the product (Table 1, entry 9). We tested another electrophilic iodide source (DIH), but it did not improve the reaction (Table 1, entry 10). Because AcOH might play an important role in the selectivity of this reaction, we investigated the reaction of Icl by using AcOH/DCM as the solvent, but we found the E/Z selectivity was still not good (Table 1, entry 11). Similarly, IOAc gave poor EZ selectivity (Table 1, entry 12). When more equivalents of LiCl were employed, we obtained a lower yield and stereoselectivity (Table 1, entry 12). Recently, Ishihara and co-workers[34] reported an efficient thiourea-I_2-NCS system for iodochlorination of alkenes. However, the same condition showed poor E/Z selectivity in the iodochlorination of alkyne 1a when using Ishihara and co-workers' thiourea catalyst (Table 1, entry 14). Next, weswitched the solvent to DCM/HOAc, We found that it could slightly improve the stereoselectivity, but offered a lower chemical yield (We then explored the substrate scope under the optimized conditions (Figure 1). First, we evaluated the scope of terminal aromatic alkynes (Figure 1, **2**–**12**), obtaining good yields and excellent regioselectivities. The efficiency of the reaction was not affected by electron-withdrawing groups (e.g., ester-) or electron-donating groups (e.g., MeO^-, Ph). Even an unprotected phenol group was well tolerated (Figure 1, **9**). Heteroaromatics such as pyridine and thiophene were not affected by the reaction conditions (Figure 1, **11** and **12**). We next evaluated the scope of terminal aliphatic alkynes and found that at lower temperatures (−25 °C) the reaction showed high *trans*-selectivity[62] (Figure 1, **13**–**22**). It should be noted that unprotected hydroxyls (Figure 1, **14** and **17**), alkene (Figure 1, 15), sulfonate (Figure 1, **18**), benzotriazoles (Figure 1, **20**), indazole(Figure 1, 20), thiophene (Figure 1, **21**), or the nitro group (Figure 1, **22**) did not hinder the efficiency of the reaction.

Haloalkynes are versatile, yet readily available, building blocks, [46,47,63–69] with which our highly regioselective iodochlorination protocol should enable to access extremely valuable trihalogenated alkenes.[70] To our delight, both aromatic and aliphatic haloalkynes gave excellent regioselectivity and chemical yields of trihalogenated alkenes. Diverse functional groups, such as acid-sensitive esters (Figure 1, **24**), aldehyde (Figure 1, **25**), methoxyl (Figure 1, **26**), and nitrile (Figure 1, **27**) survived the reaction conditions. Compared with bromoalkynes and iodoalkynes (Figure 1, **28**, **30**), chloroalkynes (Figure 1, **31** and **32**) were less reactive and required a longer time as well as more equivalents of NIS / LiCl, but the products were, never-theless, obtained in good yields and excellent *trans*-selectivity.

Encouraged by the broad scope of haloalkynes that tolerated our reaction conditions, we examined the scope of electron-deficient alkynes, such as alkynyl ketones (Figure 1, **33**–**41**). The substitution pattern (*ortho*, *meta*, and *para*) and electronic properties of aromatic substituents (electron-deficient or electron-rich) played a small role; good yields were obtained regardless (Figure 1, **33**–**38**). In general, substrates containing electron-rich substitution gave slightly higher yields than those containing electron-deficient substitutions (Figure 1, **36** and **37**). The substitution groups attached to the carbonyl group played a negligible role in the reactivity; even the sterically hindered cyclohexyl and tertiary butyl groups were well tolerated (Figure 1, **39** and **40**). A dialkyl ynone was also a suitable substrate (89%, Figure 1, **41**). We were pleased to find that the same protocol worked well for alkynyl esters (Figure 1, **42**–**49**). Moreover, phenylamine (Figure 1, **47**) and alkyl alkynyl esters (Figure 1, **48** and **49**) were good substrates for this reaction. It should be noted that our protocol displayed much better regioselectivities compared with the reported method.[20] Our iodochlorination system could be extended to other diverse alkyne types such as highly electron-deficient sulfonyl alkynes (Figure 1, **50**–**57**),[71] electron-rich alkynyl thioethers (Figure 1, **55**–**57**), electron-deficient alkynyl aldehydes (Figures 1, 65), electron-deficient alkynyl acid (Figure 1, **66**), electron-deficient alkynyl nitrile (Figure 1, **67**), electron-rich ynol ether (Figure 1, **68**), and ynamide (Figure 1, **69**). Most of the highly functional dihaloketenes prepared using our protocol were hitherto unknown.

Despite the wide structural diversity of the above alkynes, our dihalogenation afforded products with exclusive or very high regioselectivity. We investigated the regioselectivity of internal alkynes that exhibited small structural biases (R^1 and R^2) on each end of the triple bond (Figure 1, **58**–**64**). We were pleased to find that for alkynes substituted with an aryl group and an aliphatic group (R^1 = aryl, R^2 = aliphatic) (Figure 1, **58**–**60**), the reaction was regiospecific. To our delight, even very challenging unsymmetrical aryl alkynes (R^1 = phenyl substituted with a withdrawing group—ester or ketone, and R^2 = phenyl substituted with an electron-donating group) furnished regiospecific products (Figure 1, **61** and **62**). As expected, our protocol worked very well for symmetric diaryl and dialkyl alkynes (Figure 1, **63** and **64**). To corroborate the functional group tolerance and wide applicability of our methodology, we conducted late-stage dihalogenation of alkynes containing natural product motifs (Figure 1, **70**–**73**). Alkynes tethered to complex structures such as zaltoprofen (Figure 1, **70**), diacetone-D-glucose (Figure 1, **71**), hiestrone (Figure 1, **72**) and L-menthol (Figure 1, **73**) gave desired products in excellent yields and selectivity. The structure assignments of our obtained products were further confirmed by single-crystal X-ray diffraction (see the ORTEP drawings of **10**,[72] **29**,[73] **51**,[74] and **69**,[75] Figure 2).

Because the iodochlorination of alkynes using ICl is the most commonly used method in the literature, we compared the reactivity of the ICl method with our new *in-situ* method for various types of alkynes (see Supplemental Information, Section 23). In general, possibly due to the high reactivity of ICl, a mixture of regioisomers was obtained in most cases, and we also detected dichlorinated and diiodinated products in some cases.

Having demonstrated the scope of the iodochlorination of alkynes, we switched our attention to other dihalogenation systems (Figure 3). Diiodination (NIS/LiI/AcOH), iodobromination (NIS/LiBr/AcOH), dibromination (NBS/LiBr/AcOH) and chlorobromination (NBS/LiCl/

AcOH) gave the desired products with exclusive *trans*-stereochemistry and in good chemical yields (Figure 3). Aromatic and aliphatic terminal alkynes, haloalkynes, sulfonyl alkynes, alkynyl thioether, alkynyl ether, alkynyl ketone, alkynyl ester as well as functionalized internal alkynes proved to be suitable substrates. Moreover, acid-sensitive groups such as tert-butyldiphenylsilyl ether (Figure 3, **80**), and phenolic ether (Figure 3, **83**) were compatible with our mild conditions. A lower temperature (−40 °C) was needed for chlorobromination (NBS/LiCl/AcOH), possibly because of the high reactivity of BrCl generated *in situ*. Our protocol is a safer and more selective alternative to literature methods that rely on the use of toxic Br_2, Ibr, and BrCl. The structure assignments of our obtained products were further confirmed by single-crystal X-ray diffraction (see the ORTEP drawings of **82**[76] and **91**[77]).

Recently, the haloacetoxylation of alkenes[78–81] and alkynes[82] employing electrophilic X^+ and HOAc was reported. We did not detect any competitive acetate addition reactions in our experiments possibly because HOAc is a weaker nucleophile than LiX in our dihalogenation reaction. We took solace in finding that the iodoacetoxylated alkene **98**[83] (Scheme 2, Equation 2a) was cleanly prepared using NaOAc as the nucleophile. Encouraged by our success, we investigated other common nucleophiles. Although LiSCN delivered the desirable product **99**[84] in a moderate yield (Scheme 2; Equation 2b), other nucleophiles such as LiSeCN, KF, TMSCN and NaN_3 only gave a trace amount of desired products (Scheme 2, Equations 2c–2f). To demonstrate the general applicability of our developed robust methods, a commercially available phenylacetylene was extended up to gram-scale under the optimized conditions, which offered desirable products in 80% yield (Scheme 2, Equation 2g), and maintain excellent selectivity (E/Z> 20/1).

Figure 4 shows our proposed mechanism. We and others have reported that linear H-bond aggregates[85] of $(AcOH)_n$ are the dominant species in neat AcOH or a highly concentrated AcOH solution, and $(AcOH)_n$ is a strong and tunable hydrogen bond donor system. We postulated that the interaction of $(AcOH)_n$ with NIS and LiCl led to the generation of ICl and succinimide A; the strong H-bond interaction between succinimide A, ICl and $(AcOH)_n$ was the driving force that displaced the equilibrium to the right. The textbook mechanism for dihalogenation of an alkyne is the formation of a cyclic iodonium intermediate, followed by an S_N2-like backside attack of chloride nucleophile to obtain the *trans*-addition product.[86]

Usually, steric and electrophilic factors determine the regioselectivity of electrophilic addition to unsymmetric alkynes. However, most literature protocols have only showcased a narrow alkyne substrate scope; thus, a comprehensive yet rational study of the regioselectivity of electrophilic additions to unsymmetric alkynes is lacking. Because our protocol works for unprecedently diverse categories of unsymmetric alkynes, we now have a rare opportunity to conduct a systematic study of the regioselectivity of the addition. We speculated that the geometry of the cyclic iodonium intermediate is the determining factor of the regioselectivity seen. For an alkyne with R^1 and R^2 on each end of the triple bond, an unsymmetrical iodonium intermediate will form, and the nucleophilic chloride anion will prefer to attack the carbon with the weaker (longer) bond with the iodine atom.[32] As a result, we predicted that the regioselectivity would be determined by the equilibrium geometry of

the corresponding iodonium, which could be easily be obtained using DFT calculations (Figure 4). From these calculations, the geometry of the unsymmetrical iodonium depended on R^1 and R^2's relative ability to stabilize the neighboring positive charge, which, in turn, is determined by a combination of conjugation and hyperconjugation effects. According to the calculations (Figure 4), the neighboring positive charge stabilization ability of groups follows this approximate order: R_2N-, OR, SR >> Ar > Alkyl > H> I > Br > Cl > CHO, COOR, COR > RSO_{2-}. Thus, if the neighboring positive charge stabilization ability of R^1 is higher, in an alkyne substituted with R^1, and R^2 that reacts with NIS/LiCl/AcOH, the nucleophilic chloride will bind to the carbon closer to the R^1. From our calculations of LUMOs and geometries of unsymmetrical iodonium (Figure 4), this model explained the regioselectivity very well. We also found that the reaction system with a higher LUMO (iodonium) has a faster reaction rate in general. As a general rule, the iodine atom is added to the alkynyl carbon substituted with an electron-withdrawing group (e.g., ester and ketone) and the chlorine atom is added to the alkynyl carbon substituted with an electron-donating group (e.g., RS-, RO-, and R_2N-). It should be noted that for electron-deficient alkyne substrates, the reaction might also go through a Michael addition of a chloride followed by electrophilic iodination. But we think that this pathway is relatively unlikely. For example, the addition of LiCl in acetic acid to sulfonyl alkynes needs a very high temperature (100 °C)[56] and our reaction is conducted at 0 °C or lower temperatures.

To further verify our proposed mechanism, we studied the activating role of HOAc by using NMR spectroscopy. Figure 5A shows that the peak marked with H_a corresponded to the CH_2 signal of NIS, located at 3.03 ppm in $CDCl_3$. There was a small upfield shift of the methylene group, from 3.03 to 2.97 ppm, when HOAc was added (Figure 5B), indicating an H-bond interaction between the HOAc and NIS. Interestingly, the signal corresponding to CH_2 was completely shifted to 2.77 ppm when LiCl was added (Figure 5C) and succinimide was detected in a quantitative yield (Figure 5D). To follow up this result, we carried out two control experiments. When NIS (0.3 mmol) was added to the mixture solvent DCM/HOAc (0.5/0.5 mL) and stirred vigorously for 10 min at room temperature, however, the bench stable NIS was undissolved (Figure 5E). Surprisingly, the reaction mixture turned to a brownish color immediately after LiCl (0.4 mmol) was added (Figure 5F); this color is very similar to the color of a solution of ICl in DCM/HOAc. The formation of succinimide and the color change was a strong indication of ICl formation *in situ*.

To illustrate the synthetic potential of the products that we obtained using our protocol, we conducted eight representative *trans*formations of our dihaloalkene products (Scheme 3). Taking advantage of the reactivity difference between alkenyl chloride and iodide, we were able to synthesize *E*-enynes **100**, β-chloro-α, β-unsaturated nitriles **102**, phenylhexa-3,5-diyn-1-ol **103**, and 2-ethynylbenzofurans **104** by using a sequence of cross-coupling reactions. Our dihaloalkene products also could be reduced to alcohol which is consistent with our reported compound **58**. Moreover, the halothioalkane products enable oxidant to sulfone **101** or sulfoxide **105** with the dihaloalkene functionality untouched. The structural assignments of products **101**[87] and **105**[88] were further confirmed by single-crystal X-ray diffraction.

In summary, we have discovered an efficient method for the regio-selective dihalogenation of 14 different classes of alkynes. The *in-situ* generated electrophilic X^1X^2 reagents replaced toxic alternatives such as ICl, IBr. We transformed the dihalogenated products into synthetically useful *tri-* or *tetra* substituted alkenes via tandem cross-coupling reactions. Further exploration of the *in-situ* generated X^1X^2 electrophiles is currently under investigation in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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75. Its crystallographic data have been deposited to Cambridge Crystallographic Data Centre (CCDC 1948338).
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The Bigger Picture

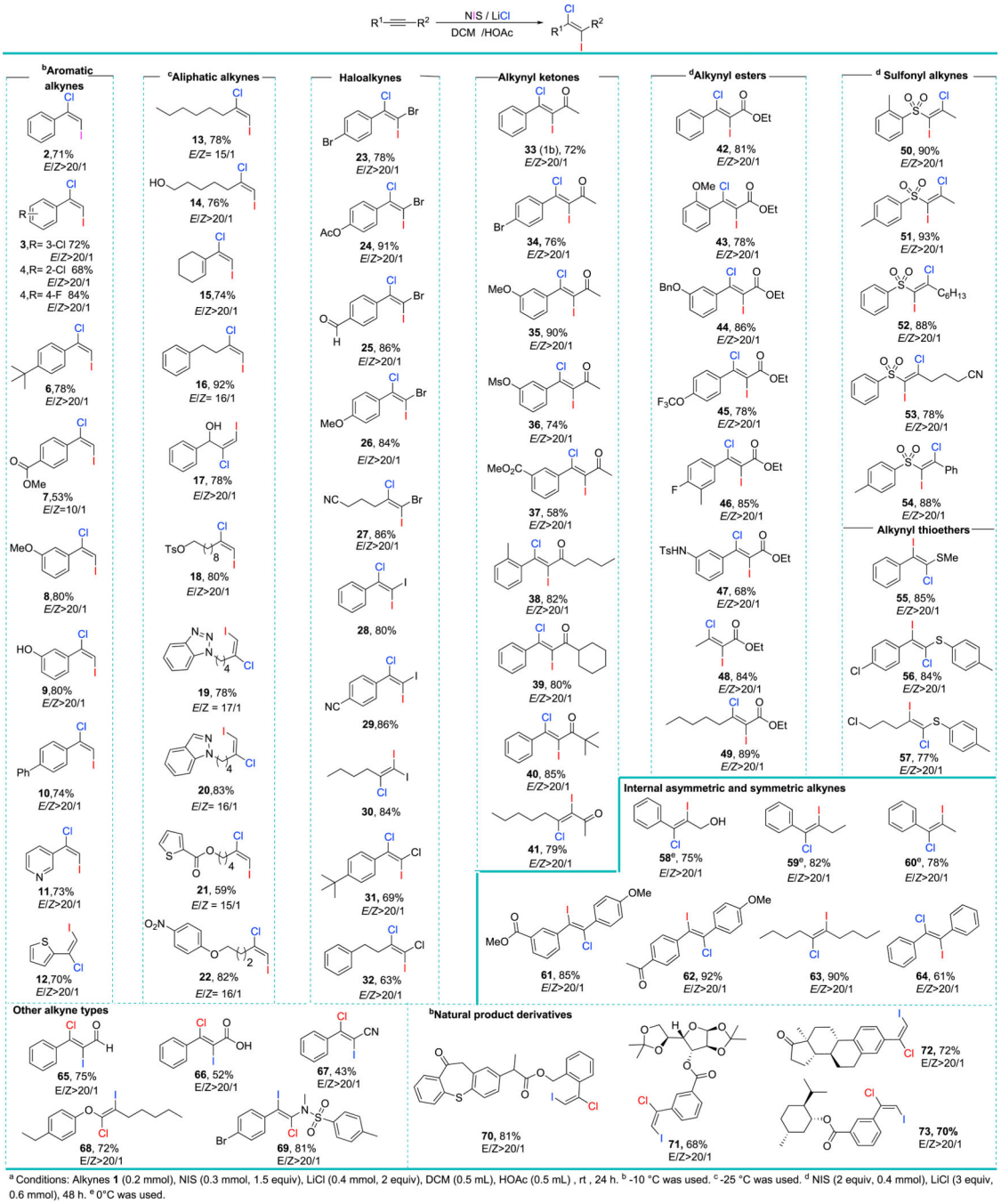
Haloalkenes are not only commonly found in biologically active natural products but also have been used extensively in cross-coupling reactions. More specifically, 1,2-dihaloalkenes are especially important synthons because of the presence of two synthetic handles that open a broad avenue to expeditiously generate multisubstituted alkenes. Dihalogenation of alkynes is a straightforward way to prepare 1,2-dihaloalkenes. However, existing alkyne dihalogenation methods either rely on the use of toxic reagents, such as IBr and ICl, lack regio-and stereoselectivity or have limited substrate scope. Thus, the development of a widely applicable and yet efficient alkyne dihalogenation method is still highly desired. Here, we have addressed the aforementioned issues based on an *in-situ*-generated dihalogenation of reagents, such as ICl and Ibr, by using the readily available N-halosuccinimide (NXS) and alkali metal halides as halogen sources. Our method offers an unprecedented substrate scope, the regio- and stereoselectivity for the synthesis of 1,2-dihaloalkenes. Our simple and mild conditions might find wild applications in the preparation of high-value building blocks for medicines and materials.

HIGHLIGHTS

Catalyst-free dihalogenation of diverse alkynes

Easy-handling halide sources—alkali metal halides

In-situ generation of ICl, IBr, BrCl, I_2, and Br_2



[a] Conditions: Alkynes **1** (0.2 mmol), NIS (0.3 mmol, 1.5 equiv), LiCl (0.4 mmol, 2 equiv), DCM (0.5 mL), HOAc (0.5 mL) , rt , 24 h. [b] -10 °C was used. [c] -25 °C was used. [d] NIS (2 equiv, 0.4 mmol), LiCl (3 equiv, 0.6 mmol), 48 h. [e] 0°C was used.

Figure 1.
The Scope of the Iodochlorination of Alkynes[a]

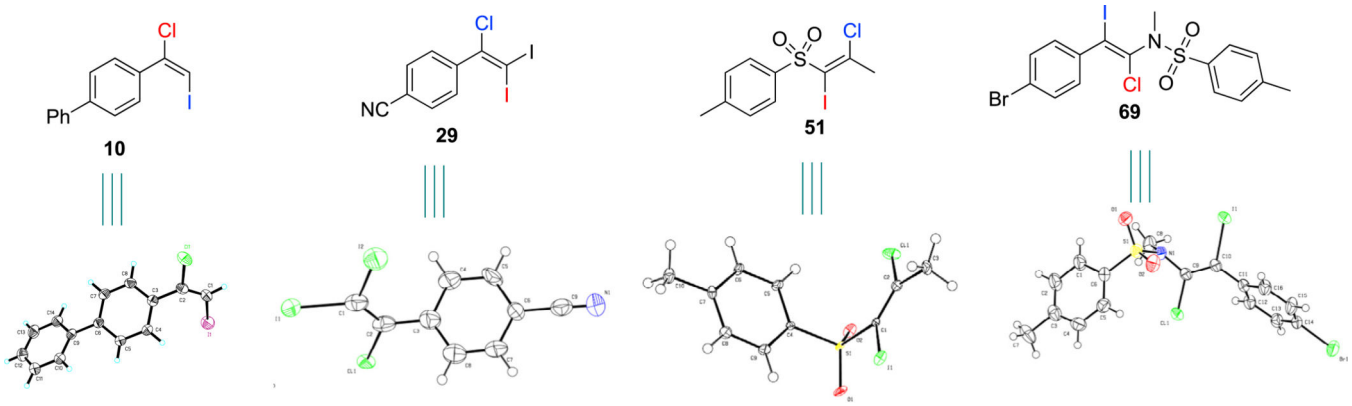
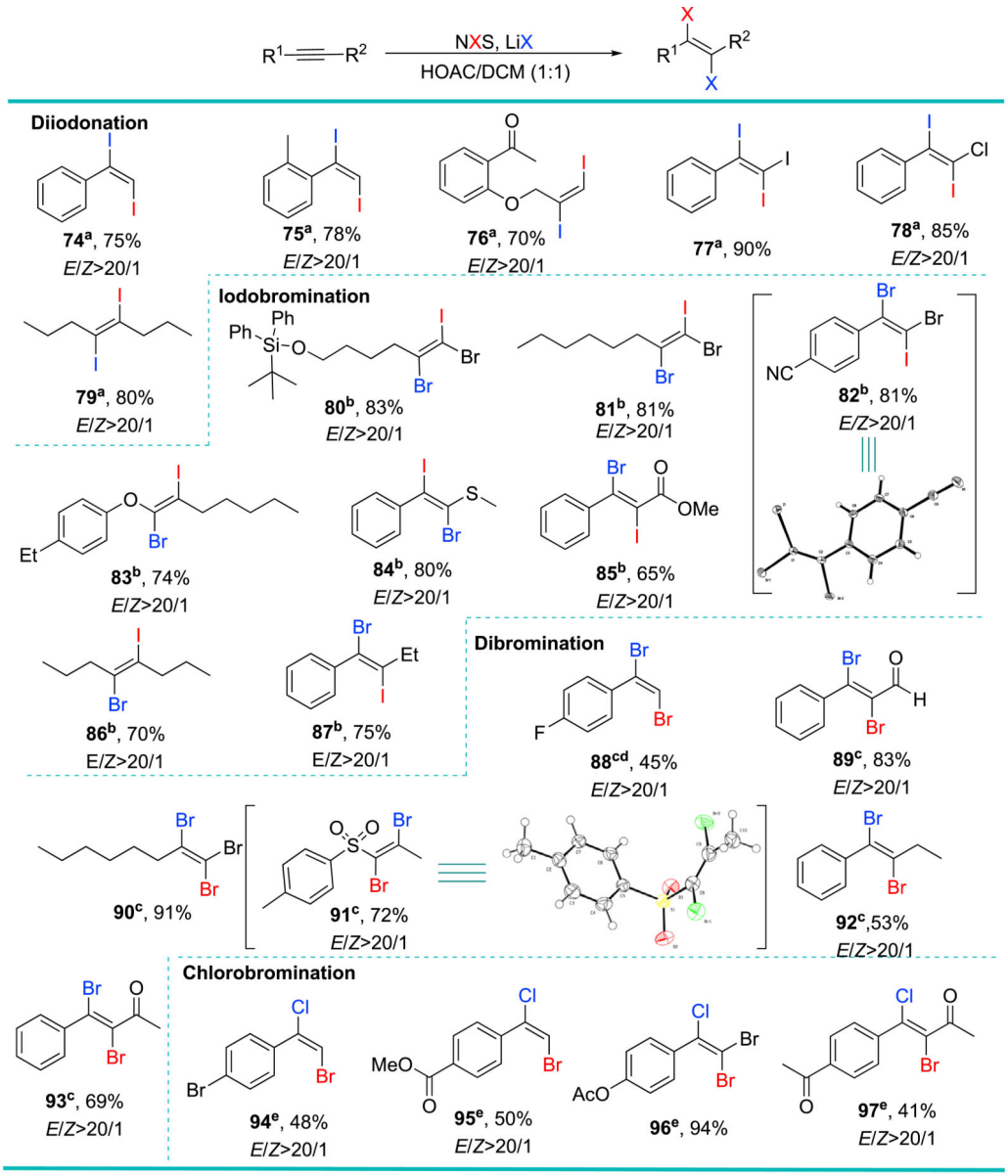


Figure 2. ORTEP Drawings of Obtained Products



[a] Alkyne **1** (0.2 mmol), NIS (0.3 mmol, 1.5 equiv), LiI (0.4 mmol, 2 equiv), HOAc (0.5 mL), DCM (0.5 mL), 0 °C - rt, 24h. [b] Alkyne **1** (0.2 mmol), NIS (0.3 mmol, 1.5 equiv), LiBr (0.4 mmol, 2 equiv), HOAc (0.5 mL), DCM (0.5 mL), 0 °C, 24 h. [c] Alkyne **1** (0.2 mmol), NBS (0.24 mmol, 1.2 equiv), LiBr (0.24 mmol, 1.2 equiv), HOAc (0.5 mL), DCM (0.5 mL), 0 °C, 24 h. [d] -30°C was used. [e] Alkyne **1** (0.2 mmol), NBS (0.24 mmol, 1.2 equiv), LiCl (0.24 mmol, 1.2 equiv), HOAc (0.4 mL), DCM (0.6 mL), -40 °C, 24h.

Figure 3. Scope of the Dihalogenation of Alkynes

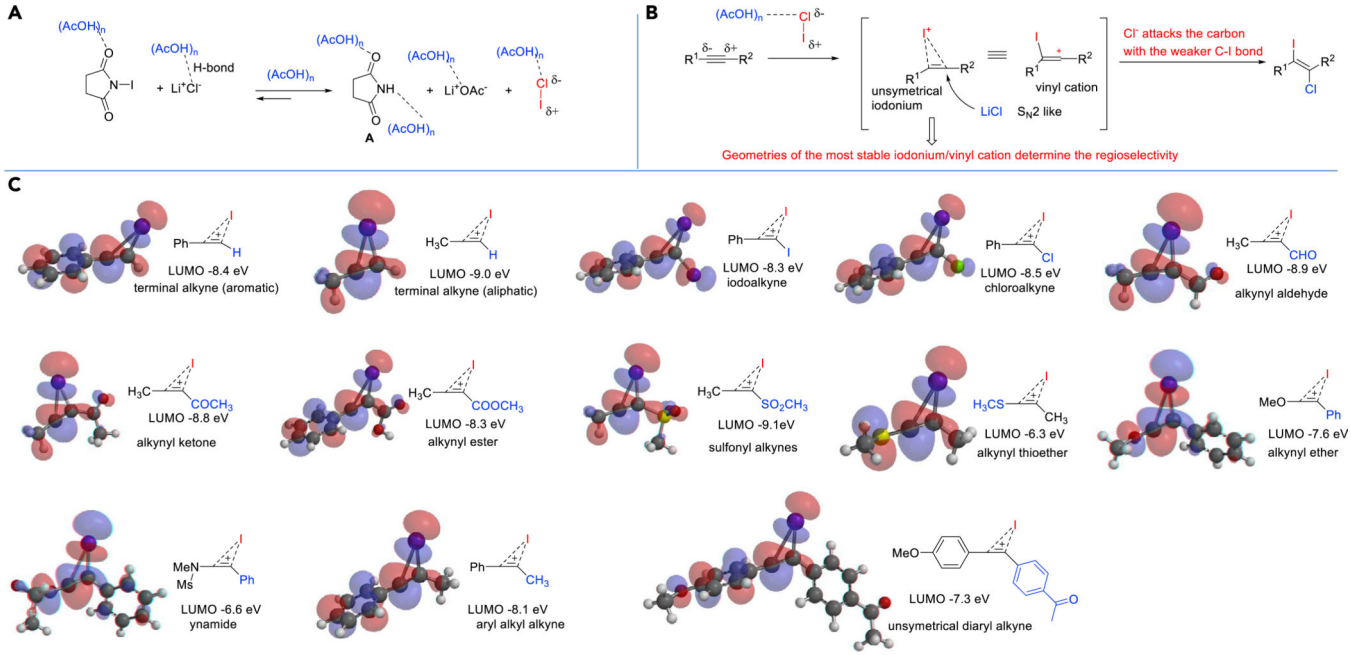


Figure 4. Proposed Mechanism and Geometries of Unsymmetrical Iodoniums

LUMOs were calculated at ωB97X-D/6–311++G** level of theory.

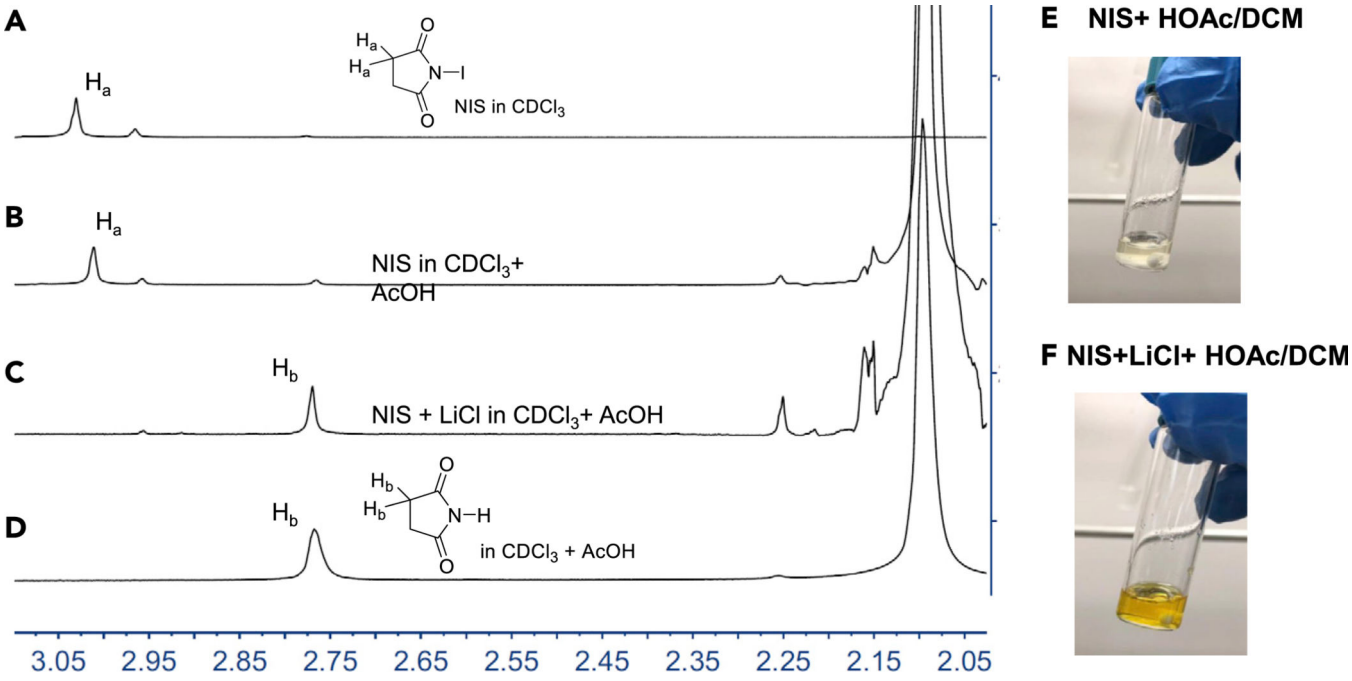
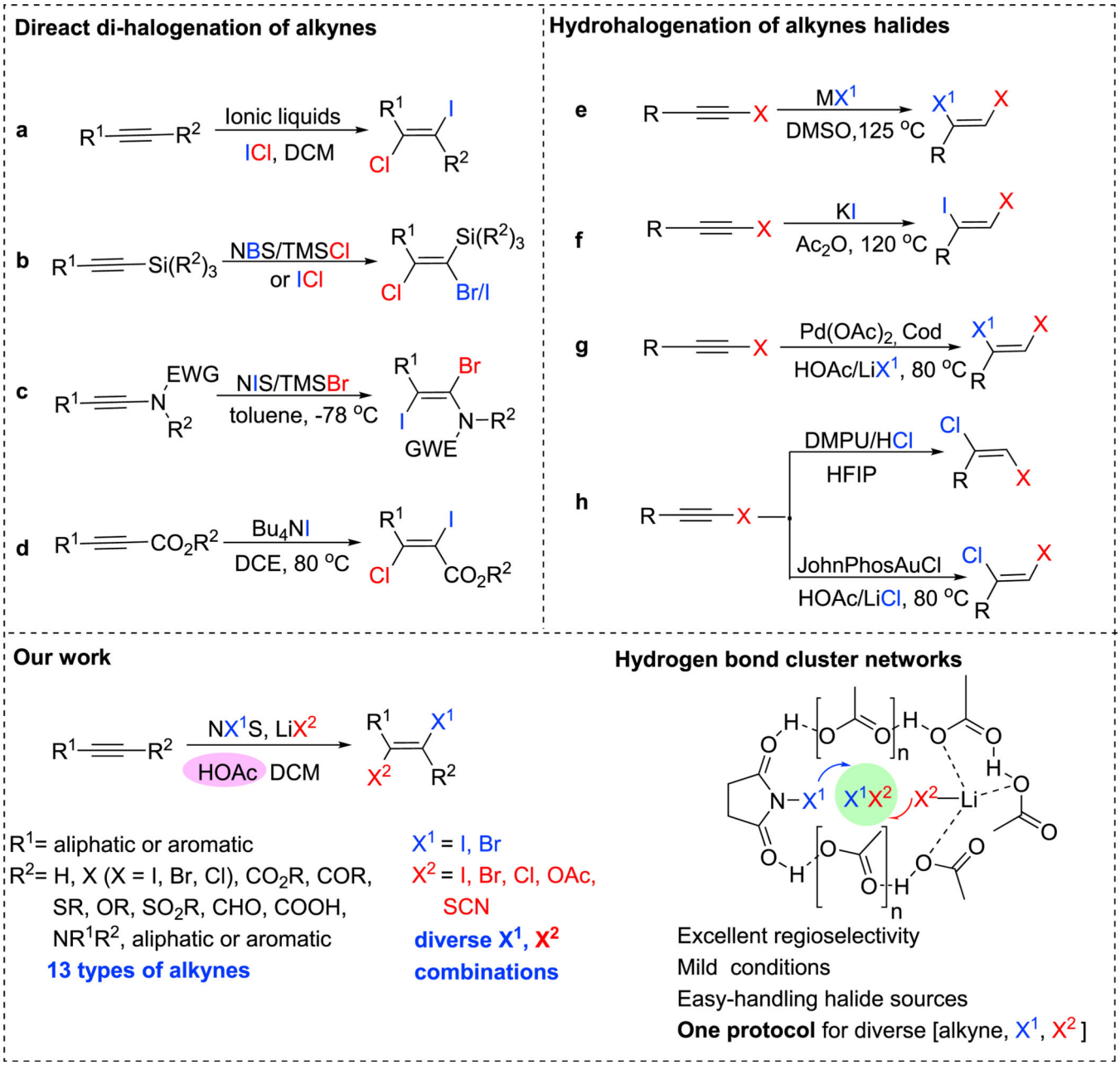
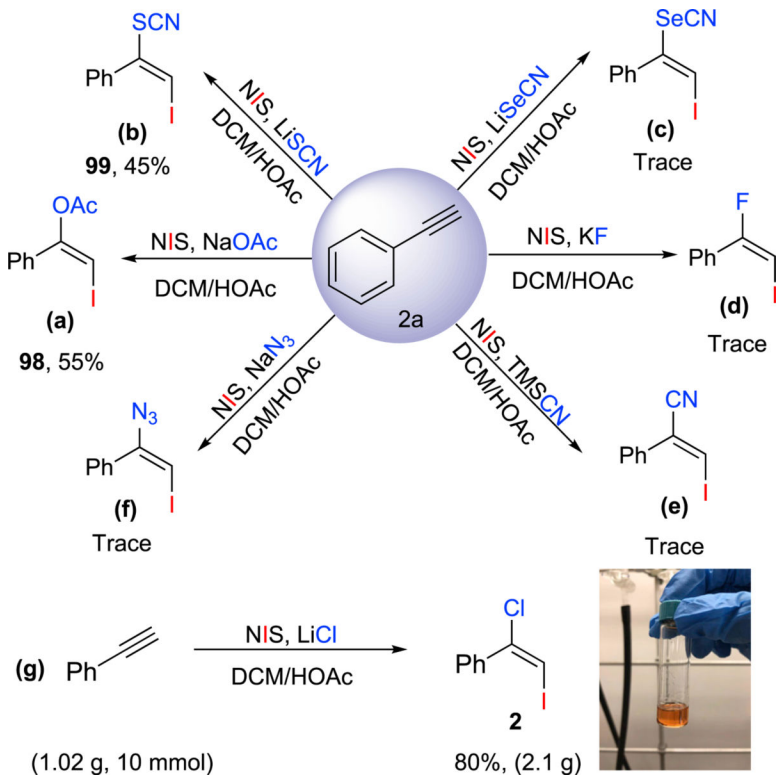


Figure 5.

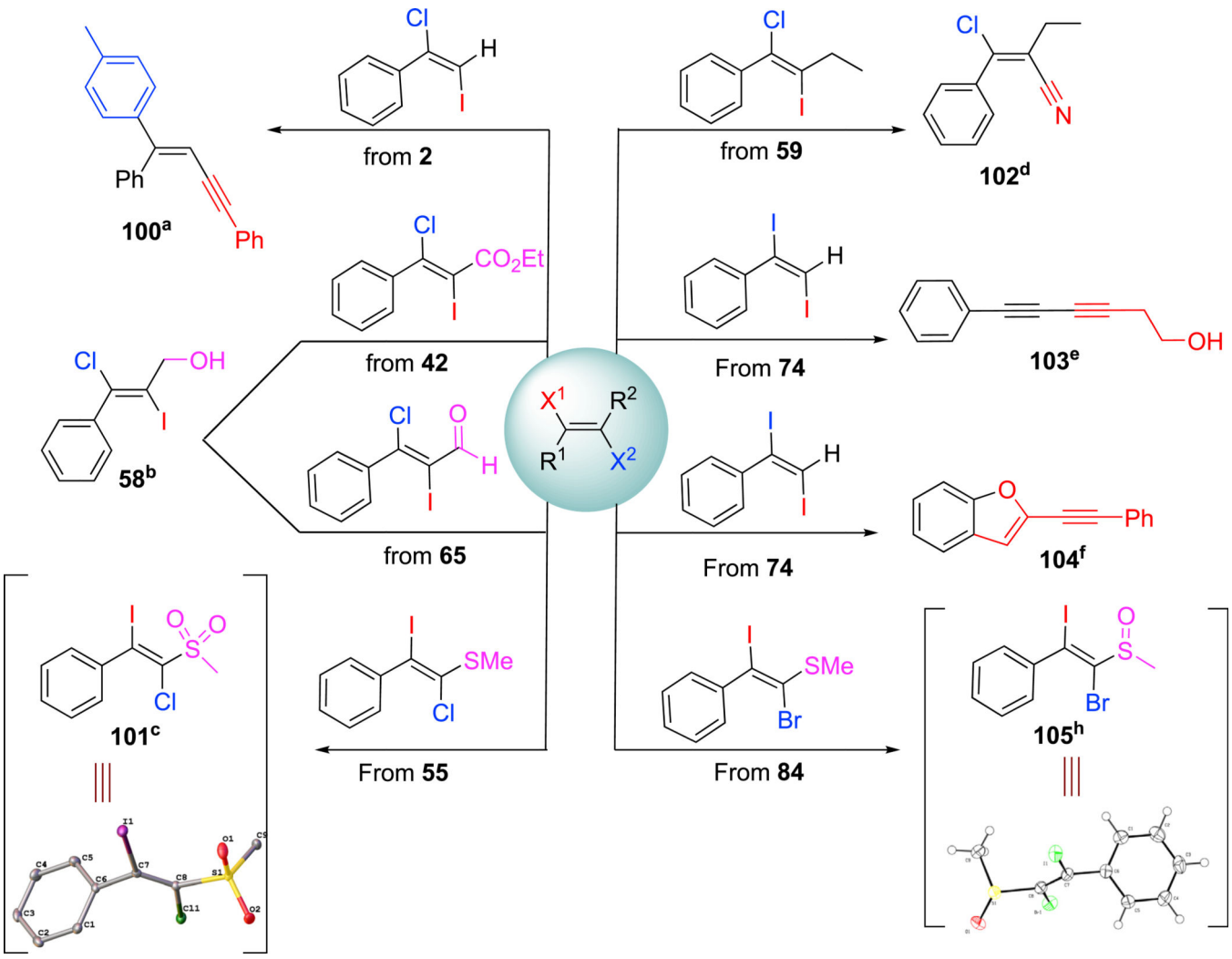
(A–F) ^{1}H NMR spectra of (A) NIS; (B) NIS and HOAc; (C) LiCl: NIS (1: 1) in HOAc after 1 h. (D) succinimide in $CDCl_3$ and HOAc. (E) NIS In HOAc-DCM (F) Nis, LiCl in HOAc-DCM.



Scheme 1. Strategies for the Synthesis of 1,2-Dihaloalkenes



Scheme 2. Iodo-Functionalization of Alkynes and Large-Scale Synthesis



Scheme 3. Synthetic Applications

Table 1.

Optimization of the Reaction Conditions

Entry	Electrophilic X^+	Nucleophilic Halogen	Solvent	Yields %[a] (1b:1c:1d)
1	ICl (1.2 equiv)	n/a	DCM	95 8:1:0)
2	n/a	Bu_4NI (3 equiv)	DCE (80 C)	Complex[b]
3	NIS	TMSCl	DCM	89 0:0:100)
4	NIS	PhCOCl	DCM	85 0:0:100)
5	NIS	AcCl	DCM	45 0:0:100)
6	NIS	LiCl	CH_3CN	Trace
7	NIS	LiCl	HFIP	Trace
8	NIS	LiCl	HOAc	71 90:10:0)
9[c]	NIS	LiCl	HOAc/DCM	80 98:2:0)
10[c]	DIH[d]	LiCl	HOAc/DCM	81 97:3:0)
11	ICl(1.5 equiv)	n/a	HOAc/DCM	93 88:12:0)
12	IOAc	LiCl(2 equiv)	HOAc/DCM	66 67:33:0)
13	IOAc	LiCl (4 equiv)	HOAc/DCM	40 61:39:0)
14[c]	NCS	I_2	Toluene	82 77:23:0)
15[d]	NCS	I_2,	HOAC/DCM	75 82:18:0)

Conditions: alkynes 1a (0.2 mmol), NIS (0.3 mmol, 1.5 equiv), Cl^- reagent (0.4 mmol, 2 equiv), solvent (1 mL), 24 h.

[e] 5 mol % of thiourea catalyst[34] was used.

[a] Yields were determinated by NMR.

[b] Both hydrochlorinated and dichlorinated products were detected.

[c] HOAc/DCM (0.5/0.5 mL).

[d] DIH: 1,3-diiodo-5,5-dimethylhydantion.