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Graphical Abstract

Development of a general copper-catalyzed vinylic Finkelstein reaction – application to the synthesis of the C1-C9 fragment of laingolide B

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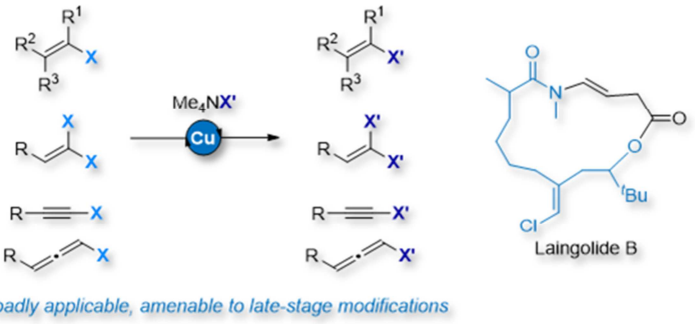

broadly applicable, amenable to late-stage modifications

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Development of a general copper-catalyzed vinylic Finkelstein reaction – application to the synthesis of the C1-C9 fragment of laingolide B

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ABSTRACT

An efficient and broadly applicable procedure for the copper-catalyzed vinylic Finkelstein reaction is reported. Using a simple, readily available and cheap catalytic system, a broad range of alkenyl iodides and bromides can be smoothly converted to their lower homologues with high yields and full retention of the double bond geometry. Key features of this vinylic Finkelstein reaction are its broad applicability, enabling the conversion of readily available alkenyl iodides to their less available brominated and chlorinated counterparts, and the mild reaction conditions compatible with a range of highly functionalized substrates. The potential of this vinylic halogen exchange reaction in total synthesis and medicinal chemistry was demonstrated by its successful use for the synthesis of the C1-C9 fragment of laingolide B and for the late-stage modification of drug-like molecules. The extension of this halogen exchange to the acetylenic and allenic Finkelstein reactions is also reported.

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1. Introduction

Alkenyl chlorides and bromides are important structural elements found in various molecules from the pharmaceutical and agrochemical industries. They are embedded in key drugs such as the sedative agent Placidy® **1**,[1] Clomiphene **2**, a drug used to stimulate ovulation and listed in the World Health Organization's list of essential medicines, the herbicide Centurion® **3**, the antiviral agent Usevir®/Brovavir® **4**,[2] the sedative propallylonal **5** and the anticancer agent Cytemba® **6** (Figure 1).

In addition to their importance in medicinal and agrochemical chemistry, chlorinated and brominated alkenes are also commonly found in a variety of simple to complex natural products. They are at the core structure of more than 700 natural products including terpenes, polypropionates, peptides or macrolides derivatives with a range of remarkable bioactivities. Representative examples of naturally occurring alkenyl chlorides include the DNA methyltransferase inhibitor halomon **7**,[3] the polyhalogenated monoterpene violacene **8**,[4] the fatty amides malyngamide Q **9**[5] and grenadamide C **10**,[6] the heterocyclic monoterpene costatone **11**,[7] the macrolide laingolide B **12**[8] and, which is certainly the most famous example, the highly potent cytotoxic spongistatin **13** (Figure 2).[9] Natural products containing a brominated alkene are equally important and include the unsaturated and brominated fatty acid xestospongic acid **14**,[10] the antifouling agent omaezallene **15**,[11] the spirobicycloundecane

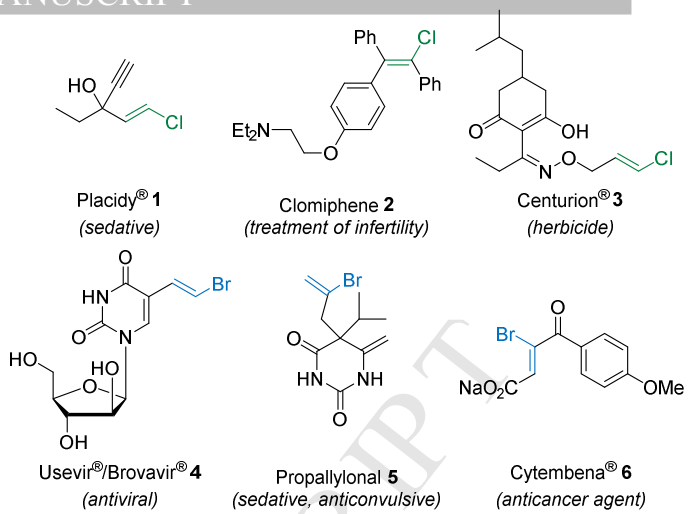


Figure 1. Alkenyl chloride/bromide-containing molecules from the pharmaceutical and agrochemical industries.

sesquiterpene kylinone **16**,[12] the antifungal and anticancer agent clathrynamide A **17**,[13] the acetylenic dibromochloro tetrahydropyran dactylyne **18**,[14] the cytotoxic rearranged sesterterpenoid neomangicol B **19**[15] and the cytotoxic marine macrolide dolastatin 19 **20**[16] (Figure 2).

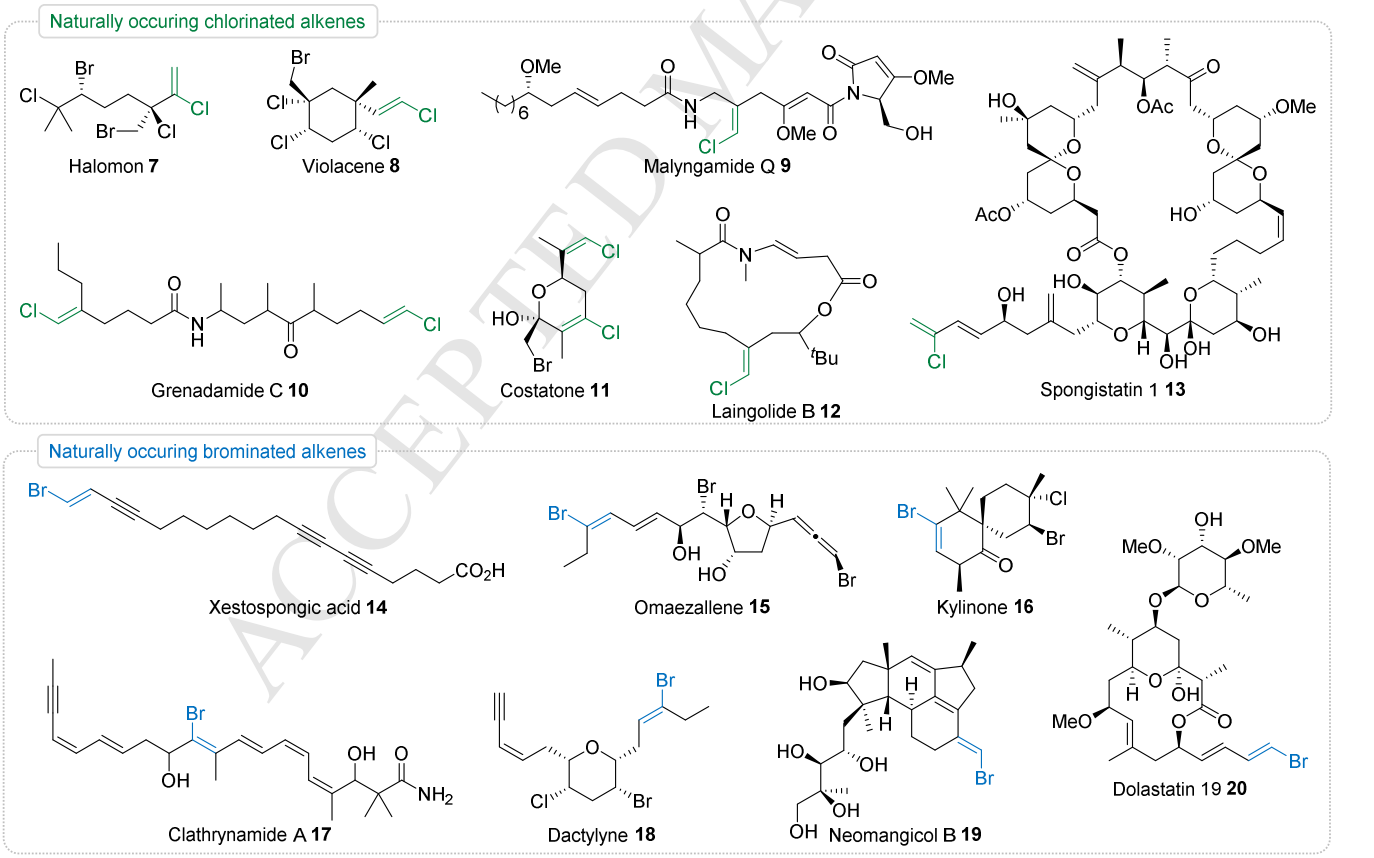
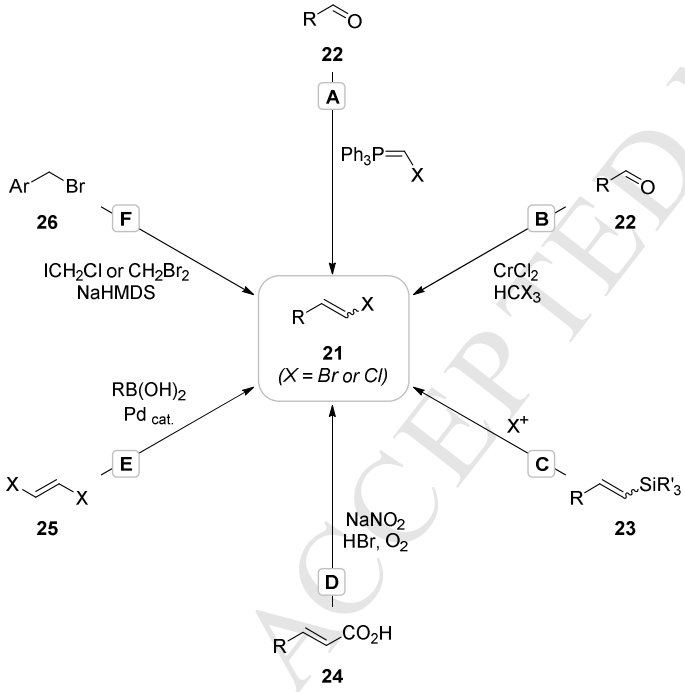


Figure 2. Representative examples of natural products containing a chlorinated or brominated alkene.

Besides their key role in natural and/or biologically relevant molecules, alkenyl halides are also of course major building blocks in chemical synthesis, notably as partners in cross-coupling reactions for the stereoselective synthesis of alkenes, mainly using palladium[17] and copper[18] catalysis.

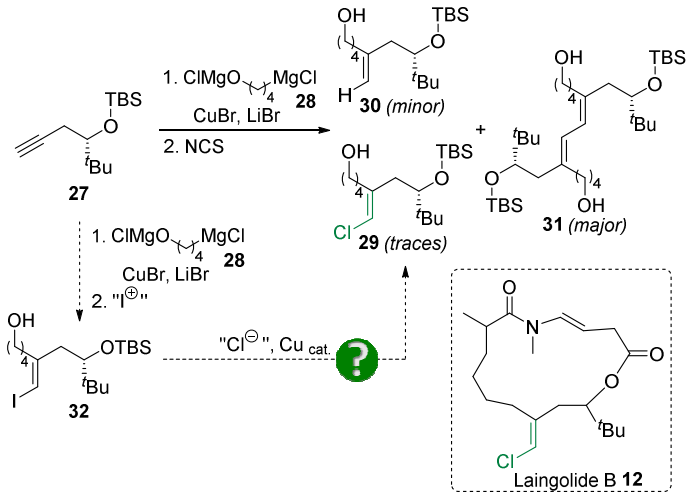
Based on these considerations, the availability of chlorinated and brominated alkenes, as single double bond isomers, is therefore of utmost importance. Despite their apparent simplicity, their synthesis is however far from trivial, with most methods suffering from low yields, limited substrate tolerance or lack of stereoselectivity. Indeed, classical processes for their synthesis,[19] mostly based on elimination from 1,2-dihalides, addition of hydrochloric/hydrobromic acid to alkynes, reduction of alkynyl halides or trapping of alkenyl metal reagents are poorly efficient and lack generality for the synthesis of chlorinated and brominated alkenes. The most efficient reactions available to date to prepare these useful building blocks **21** include the Stork-Zhao-type[20] (Scheme 1, route A) and Takai[21] (Scheme 1, route B) olefinations of aldehydes, which are however limited to the synthesis of alkenyl bromides, not fully stereoselective and often low-yielding. An alternative procedure, which might represent the most efficient and general entry to alkenyl bromides and chlorides **21** relies on the halodesilylation of vinylsilanes **23** (Scheme 1, route C), a high-yielding and highly stereospecific reaction which however requires the preparation of the starting silanes.[22] Another route to brominated alkenes involves the Hunsdiecker-type halodecarboxylation of acrylic acids **24**, which is however mostly restricted to the preparation of *E*-bromoalkenes (Scheme 1, route D).[23] The site selective cross-coupling of dihaloalkenes **25** (Scheme 1, route E)[24] and Charette's synthesis of *E*-β-aryl vinyl bromides and chlorides from benzyl bromides and dihalomethane derivatives[25] (Scheme 1, route F) are also worth mentioning, even if they are also restricted to the preparation of alkenyl bromide and chlorides with certain substitution patterns.



Scheme 1. Most efficient methods for the preparation of alkenyl bromides and chlorides.

There is therefore a clear lack of general methods enabling the easy and reliable assembly of highly substituted brominated and chlorinated alkenes in a highly stereoselective manner. We actually faced this problem during a program aimed at the total synthesis of laingolide B **12**, a macrolide isolated in 2010 by the Luesch group from the marine cyanobacteria *Lyngbya bouillonii* from Guam.[8] Characteristic features of this natural product, whose relative and absolute configuration is still unknown, include a 15 membered-ring macrocyclic lactone, an endocyclic unconjugated enamide and an exocyclic chlorinated alkene.[26] While structurally-related macrolides such as palmyrolide A[27] or sanctolide A[27g,28] have already been successfully synthesized, there is no total synthesis of laingolide B reported to date,[29] most certainly because of its challenging skeleton and its poor stability. Motivated by the intriguing structure of this target, and in continuation of our program aimed at the synthesis of potent natural products,[30] we therefore decided to embark in the study of its total synthesis.

While the formation of the highly sensitive, unconjugated enamide in laingolide B **12** had been expected to be a challenging step, we did not anticipate the regio- and stereo- selective installation of the disubstituted chloroalkene in **12** to be problematic. After evaluating different strategies for this key step, we finally decided that it would be best performed by a carbocupration of terminal alkyne **27** with the organocopper reagent derived from Grignard **28**[31] followed by electrophilic chlorination of the intermediate vinylcopper species (Scheme 2).[32] If the carbocupration proceeded smoothly, the chlorination was found to be especially problematic since in all trials (>30): only traces of the desired vinyl chloride **29** could be observed, along with minor amounts of alkene **30**, the major product invariably being the diene **31** resulting from the oxidative dimerization of the intermediate vinylcopper promoted by *N*-chlorosuccinimide which acted as an oxidizing agent rather than as an electrophilic chlorination reagent in this case. Envisioning that this problem could be easily solved by using a more efficient electrophilic iodination (yielding to **32**) instead of the problematic chlorination, we then quickly realized that no general synthetic tool was available for the transformation of an alkenyl iodide to its chlorinated counterpart. Motivated by the potential of this vinylic halogen-halogen exchange and in continuation of our studies of copper-mediated reactions,[33,34] we recently reported a general copper-based catalytic system for the Finkelstein reaction in alkenyl halides.[35] We now report in this manuscript a full account on the development of this reaction as well as its use for the synthesis of the C1-C9 fragment of laingolide B.



Scheme 2. Preliminary studies on the total synthesis of laingolide B: the vinylic copper-mediated halogen exchange reaction as an efficient synthetic tool for the preparation of vinyl chlorides from readily available vinyl iodides?

2. Results and discussion

Alkenyl iodides being indeed readily available, in a stereocontrolled manner, by an array of efficient methods including iodolysis of vinylmetal species, Takai[21] or Stork-Zhao[20] olefinations, hydroiodination of alkynes,[36] iododesilylation[37]/destannylation,[38] Charette's procedure[25] or Hunsdiecker-type reactions,[39] a general process for their transformation into the corresponding bromides and chlorides could therefore be of great synthetic usefulness. This transformation would be thermodynamically driven, the carbon-iodide bond ($D°_{298}$(C-I) = 253 kJ.mol^{-1}), being less stable than the carbon-bromide ($D°_{298}$(C-Br) = 318 kJ.mol^{-1}) and carbon-chloride ($D°_{298}$(C-Cl) = 395 kJ.mol^{-1}) bonds.[40] While various catalysts have been reported for the extension of the halogen-halogen exchange reactions, originally known as "Finkelstein" or "halex" reactions, to the aromatic series,[41,42] their use with halogenated alkenes has been only scarcely studied, despite an obvious synthetic potential provided that the reaction would be highly stereospecific.[42c,43]

2.1. Optimization of the copper-catalyzed iodide to chloride exchange in alkenyl iodides.

Our first studies on the copper-catalyzed vinylic Finkelstein reaction focused on the iodide to chloride exchange starting from alkenyl iodides. In order for the transformation to be thermodynamically driven and to avoid shifting the equilibrium by selective precipitation of one halide, as in the original Finkelstein reaction,[44] all halides need to be fully soluble in the reaction mixture. The choice of both the solvent and the halide source therefore appears to be of crucial importance for the halogen exchange to proceed smoothly and a combination of tetramethylammonium chloride[42e] and ethanol was thus selected. Both tetramethylammonium chloride and iodide are indeed soluble in alcohols and do not decompose upon heating, ethanol being selected as the solvent mainly on the basis of its low boiling point, many chlorinated alkenes being also volatile.

These parameters being set, the optimization of the copper-catalyzed chlorination was performed using (*E*)-β-iodostyrene **33a** as a model substrate. The efficiency of a series of representative ligands commonly used in copper-catalyzed cross-coupling reaction was examined in combination with copper(I) iodide as the source of copper(I) in ethanol at 110 °C for two days. Results from those studies, collected in Figure 3, reveal a dramatic effect of the ligand used for the halogen/halogen exchange reaction. While O,O-bidentate and N,O- bidentate ligands such as ethylene glycol, isobutyrylcyclohexanone and proline were found to be poor ligands for this transformation, the use of N,N-bidendate ligands was found to be far superior. Indeed, 1,10-phenanthroline, 2,2'-bipyridine, bis-imines and 1,2-diamines successfully promoted the reaction with more or less efficiency, except in the case of *N,N'*-dimesitylethane-1,2-diimine and *N,N,N',N'*-tetramethylethylenediamine. Secondary diamines[45] were found to be the most efficient ligands and enabled a full conversion which is especially critical for halogen-halogen exchange reactions, the starting materials being in general hardly separable from the products. Based on these results, *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine was selected as the ligand for the copper-catalyzed vinylic Finkelstein reaction, (*E*)-β-iodostyrene **33a** being smoothly transformed to (*E*)-β-chlorostyrene **34a** in 76% NMR yield (82% isolated yield,[46] Scheme 3), full conversion and, importantly, full retention of the double bond geometry.[47]Performing the reaction at 80 °C resulted in a slightly lower NMR yield of 72% and other solvents such as butanol or DMSO were found to be equally efficient.

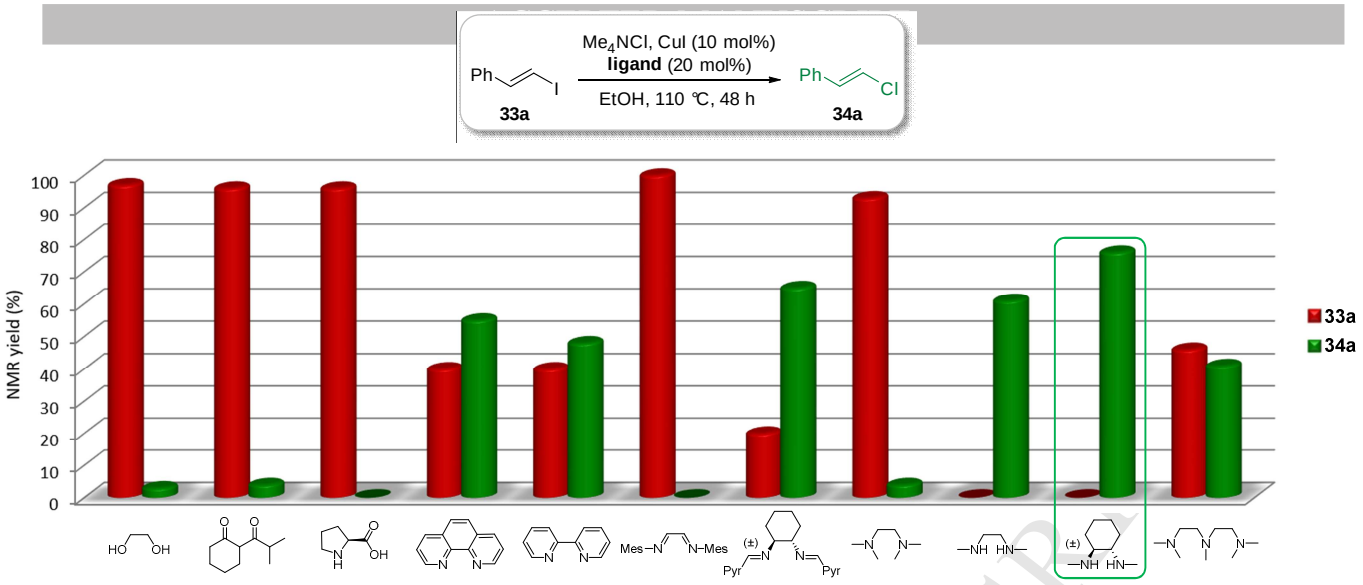
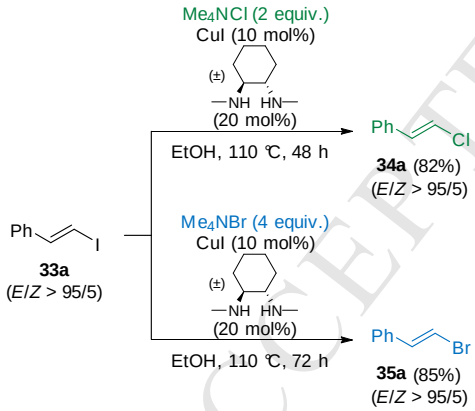


Figure 3. Compared efficiency of ligands for the copper-catalyzed iodide to chloride exchange in alkenyl iodides. Standard conditions: **33a** (1.0 mmol), tetramethylammonium chloride (2.0 mmol), copper(I) iodide (0.1 mmol), ligand (0.2 mmol), EtOH (2 mL), 110 °C, 48 h. NMR yields determined using 1.0 mmol of DMF as internal standard.

As expected, the iodide to bromide exchange was found to be more difficult due to the lower difference in bond energies and an incomplete conversion was observed when replacing tetramethylammonium chloride by tetramethylammonium bromide under the exact same conditions. This problem could however be easily overcome by increasing the amount of the bromide and increasing the reaction time. Indeed, the use of four equivalents of the ammonium bromide for 72 h allowed for a full conversion of **33a** to its brominated analogue **35a** which could be isolated in 85% yield as a single diastereoisomer (Scheme 3).[47]



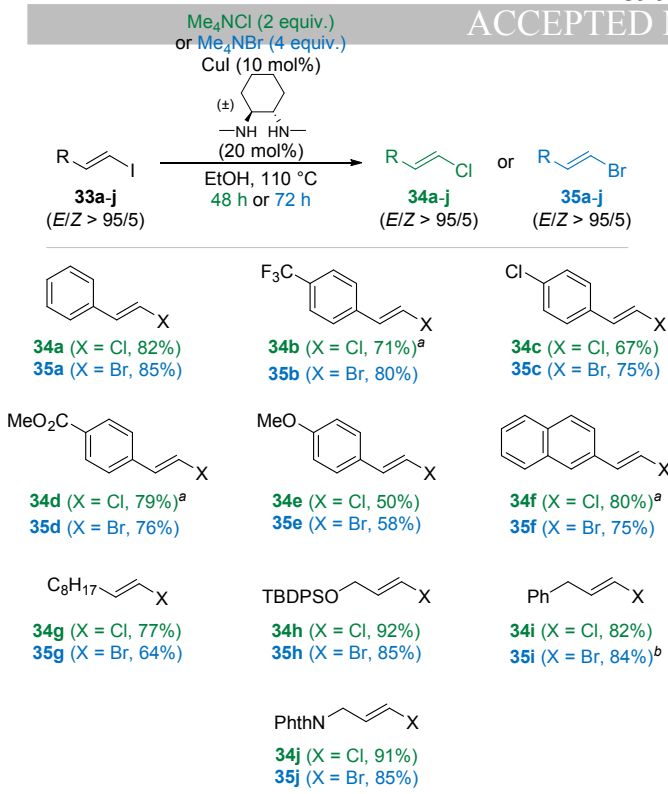
Scheme 3. Optimized conditions for the copper-catalyzed iodide to chloride/bromide exchange from (*E*)-β-iodostyrene.

Having in hand a set of optimized conditions for the copper-catalyzed conversion of alkenyl iodides to their chlorinated and brominated counterparts, we then moved to study of the scope and limitations of these halogen exchange reactions, starting with the examination of the reactivity of β-monosubstituted *E*-alkenyl iodides. Results from these studies are described in the following paragraphs.

2.2. Copper-catalyzed iodide to chloride/bromide exchange in β-monosubstituted E*-alkenyl iodides.*

A series of β-monosubstituted *E*-alkenyl iodides possessing representative substituents **33a-j** was submitted to the copper-catalyzed halogen exchange reaction under our optimized conditions. Results from these studies, summarized in Scheme 4, clearly demonstrate the generality of our process. The corresponding chlorinated **34a-j** and brominated **35a-j** alkenes being isolated in fair to excellent yields and with full retention of the double bond geometry in all cases.[47] The reaction was found to be compatible with a range of aromatic substituents, including electron-donating and electron-withdrawing ones, but was however sometimes more sluggish with monosubstituted *E*-alkenyl iodides possessing electron-poor aryl groups such as **33b** and **33d**. In these cases, switching to DMSO as the solvent for 24 hours enabled clean reactions. Substitution with various alkyl groups was also well tolerated and the reaction was found to be compatible with the presence of functional groups such as silyl ethers (**33h**) or a phthalimide (**33j**).

The copper-catalyzed bromination was found to be more challenging than the chlorination, a problem that could be solved, as already mentioned, by using 4 equivalents of tetramethylammonium bromide while 2 equivalents of the ammonium chloride were sufficient for the iodide to chloride exchange together with an increase of the reaction time from 48h to 72 h. In one case however, we were unable to drive the reaction to completion and (*E*)-(3-bromoallyl)benzene **35i** was isolated as a mixture containing 7% of the starting iodide, forcing the reaction conditions resulting in much lower yields. Except in this particular case, results collected in Scheme 4 highlight the generality and the efficiency of the copper-catalyzed iodide to chloride/bromide exchange starting from monosubstituted *E*-alkenyl iodides, the crude reaction mixtures being especially clean and the isolation of β-monosubstituted *E*-alkenyl chlorides **34a-j** and bromides **35a-j** as single stereoisomers[47] being therefore an easy task.



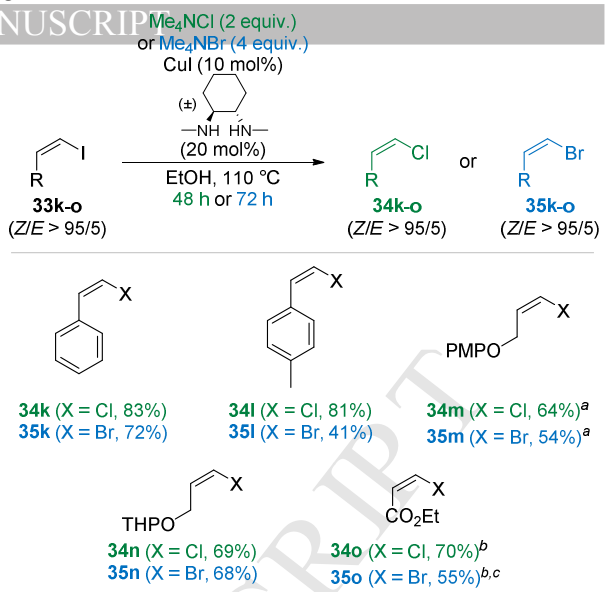
[a] *in DMSO for 24 h;* [b] *contaminated with 7% of the starting iodide.*

Scheme 4. Copper-catalyzed iodide to chloride/bromide exchange in β-monosubstituted *E*-alkenyl iodides.

2.3. Copper-catalyzed iodide to chloride/bromide exchange in β-monosubstituted Z-alkenyl iodides.

After examining the iodide to chloride/bromide exchange from a series of β-monosubstituted *E*-alkenyl iodides, we then moved to study of the scope and limitations of our copper-catalyzed halogen exchange reaction with challenging β-monosubstituted *Z*-alkenyl iodides, hoping that isomerization to the more stable *E* isomers would not become an issue. With this goal in mind, *Z*-iodoalkenes **33k-o** were reacted under our standard conditions for their chlorination and bromination. To our delight, the reaction was again found to be totally stereospecific, the chlorinated **34k-o** and brominated **35k-o** alkenes being formed as single *Z* isomers[47] (Scheme 5).

As in the previous case, the reaction was found to be general and broadly applicable, the chlorination and bromination proceeding smoothly in most cases. Some vinylic Finkelstein reactions were however found to be somewhat less efficient and required slight modifications of the reaction conditions. While the reactions involving aryl-substituted *Z*-alkenyl iodides **33k** and **33l** were found to proceed smoothly, except in the case of the bromination of **33l** which was, for some unknown reason, less efficient, the presence of an alkyl chain was found to be more substrate-dependent. As an example, the presence of a PMP ether close to the reacting center in **33m** was found to slow down the reaction and its chlorination to **34m** and its bromination to **35m** required an increase of the catalyst and performing the reaction in DMSO, respectively. In sharp contrast, replacing this PMP ether by a more coordinating THP group, such as in **33n**, restored a normal reactivity. The bromination was in general found to be more sluggish than the chlorination, which was however not problematic in most cases, except for the copper-catalyzed bromination of ethyl (*Z*)-3-iodoacrylate **33o**, the corresponding brominated acrylate **35o** being isolated together with 13% of unreacted starting iodide.

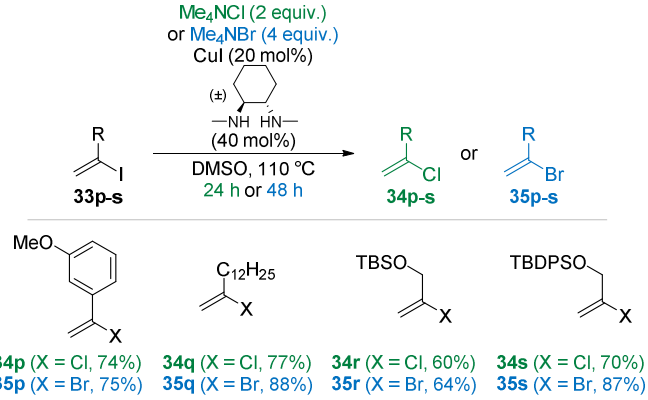


[a] *in DMSO using 20 mol% CuI and 40 mol% trans-N,N'-dimethylcyclohexane-1,2-diamine;* [b] *NMR yield using DMF as internal standard;* [c] *contaminated with 13% of the starting iodide.*

Scheme 5. Copper-catalyzed iodide to chloride/bromide exchange in β-monosubstituted *Z*-alkenyl iodides.

2.4. Copper-catalyzed iodide to chloride/bromide exchange in α-monosubstituted alkenyl iodides.

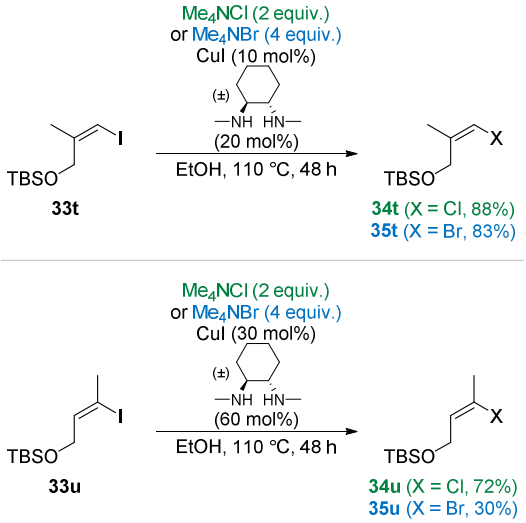
While the presence of a *cis* substituent in the β position was only found to have a slight influence on the copper-catalyzed vinylic Finkelstein reaction, moving this substituent closer to the iodide clearly had a marked effect on the halogen exchange. Upon reaction of a series of α-monosubstituted alkenyl iodides under our standard conditions, incomplete conversions were observed, resulting in the formation of mixtures of alkenyl halides. As shown in Scheme 6, full conversions could however be reached by doubling both the amount of copper(I) iodide and *trans-N,N'*-dimethylcyclohexane-1,2-diamine and using DMSO as the solvent for 24 h (chlorination) or 48 h (bromination). Under these modified conditions, various α-monosubstituted alkenyl iodides **33p-s** could be readily transformed to the corresponding chlorinated **34p-s** and brominated **35p-s** congeners in good to excellent yields, which should definitely be useful since brominated and chlorinated alkenes with such substitution patterns are quite challenging to prepare otherwise. Aryl and alkyl chains, functionalized or not, were well tolerated and silyl ethers were found to be compatible with the reaction conditions.



Scheme 6. Copper-catalyzed iodide to chloride/bromide exchange in α-monosubstituted alkenyl iodides.

2.5. Copper-catalyzed iodide to chloride/bromide exchange in disubtituted alkenyl iodides.

After the systematic study of the behavior of monosubstituted alkenyl iodides under our reaction conditions, we briefly examined the possibility of halogen exchange reactions starting from disubstituted iodoalkenes. β,β-Disubstituted alkenyl iodides **33t** was readily chlorinated and brominated using our optimized conditions to afford the corresponding alkenyl chloride **34t** and bromide **35t** in good yields (Scheme 7). Moving to *E*-α,β-disubstituted iodoalkene **33u** was, as anticipated, more problematic due to the increased steric hindrance around the C-I bond to be activated. Indeed, reaching full conversion with this challenging substrate required a substantial increase of the catalyst loading, 30 mol% of copper(I) iodide and 60 mol% of the ligand being needed in this case, which enabled its clean chlorination to **34u** and a moderately efficient bromination to **35u**.

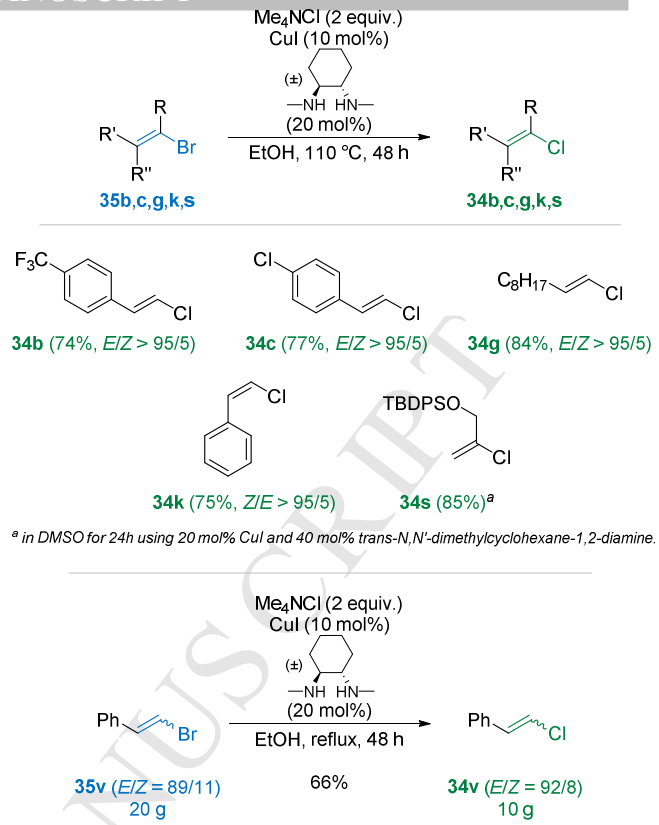


Scheme 7. Copper-catalyzed iodide to chloride/bromide exchange in disubstituted alkenyl iodides.

2.6. Copper-catalyzed bromide to chloride exchange in alkenyl bromides.

Having demonstrated the generality and broad substrate scope of the copper-catalyzed vinylic Finkelstein reaction from alkenyl iodides, we next moved to the more challenging chlorination of bromoalkenes. A set of brominated alkenes with representative substitution patterns **35b**,**c**,**g**,**k**,**s** was subjected to the conditions developed for the iodide to chloride exchange in alkenyl iodide. Results from these studies, shown in Scheme 8, clearly show that the exact same conditions could be successfully used to cleanly substitute the bromide atom from the starting brominated alkenes by a chloride with high efficiency and, as in all previous cases, with full retention of the double bond geometry.[47] The resulting chloroalkenes **34b**,**c**,**g**,**k**,**s** were obtained with yields that were found to be similar to the ones obtained starting from the corresponding iodoalkenes, therefore expanding the scope of the vinylic Finkelstein reaction to the use of brominated alkenes.

To further highlight the synthetic potential and the robustness of this last halogen exchange, its use on a multigram scale was demonstrated. 20 g of β-bromostyrene **35v**, commercially available as a 89/11 mixture of *E* and *Z* isomers, were therefore treated with two equivalents of tetramethylammonium chloride in the presence with 10 mol% of copper(I) iodide and 20 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine in refluxing ethanol for 2 d which produced the expected β-chlorostyrene **34v** which could be isolated by simple filtration in 66% yield and as a 92/8 mixture of *E* and *Z* isomers.[47]

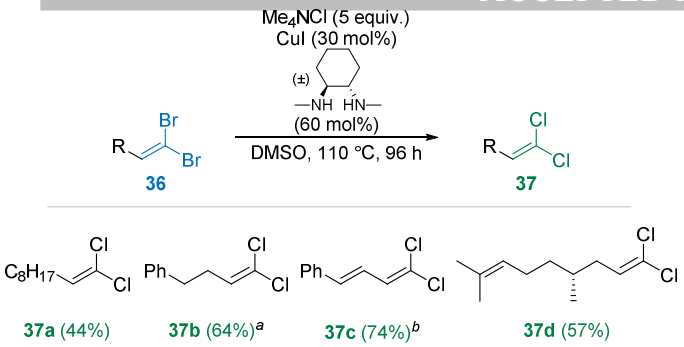


Scheme 8. Copper-catalyzed bromide to chloride exchange in alkenyl bromides.

2.7. Extension to the copper-catalyzed halogen exchange in gem-dibromoalkenes, bromoalkynes and bromoallenes.

Given the efficiency of the vinylic halex reaction from alkenyl halides, we wondered if it could be extended to other substrates such as *gem*-dibromoalkenes, bromoalkynes and halogenated allenes which could be converted to their far less available lower homologues. While *gem*-dibromoalkenes are readily prepared using the Ramirez olefination[48] or the Lautens' modification,[49] the corresponding dichlorinated alkenes are much more complicated to prepare and their syntheses are too often low yielding.[50] The transformation of *gem*-dibromoalkenes to their dichlorinated analogues, useful building blocks in organic synthesis,[50] could therefore represent a valuable synthetic tool.

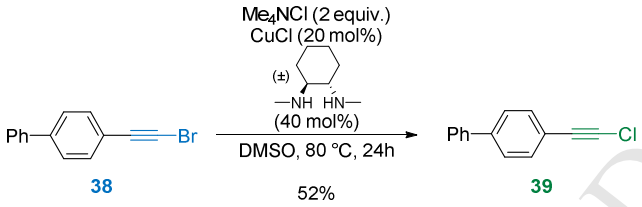
Preliminary studies on the dichlorination of monosubstituted *gem*-dibromoalkenes revealed that while the substitution of the less hindered bromide proceeded smoothly, the second substitution turned out to be more problematic, which is actually in line with the lower reactivity observed starting from α-substituted alkenyl bromides and *E*-α,β-disubsituted iodoalkenes. As in the latter case, full conversions could be obtained, at least in most cases, by using 30 mol% of copper(I) iodide and 60 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. In addition, running the reaction in DMSO for 4 days was strictly required for the reactions to go to completion: using these modified conditions, various *gem*-dibromoalkenes **36** could be transformed to the corresponding *gem*-dichloroalkenes **37** in fair to good yields (Scheme 9). It should be mentioned that the dichlorination of **36b** did not go to completion, the corresponding dichloroalkene **37b** being contaminated with 10% of a product resulting from a single halogen exchange while the reaction of styryl-substituted *gem*-dibromoalkene **36c** could be achieved using a lower amount of the catalytic system.



[a] contaminated with 10% of the monochlorinated product; [b] for 48 h using 20 mol% CuI and 40 mol% trans-N,N'-dimethylcyclohexane-1,2-diamine.

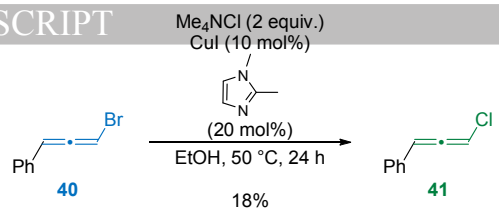
Scheme 9. Copper-catalyzed bromide to chloride exchange in *gem*-dibromoalkenes.

The extension of the halogen exchange reaction was next pursued by examining the possibility of an acetylenic Finkelstein reaction starting from bromoalkyne **38** (Scheme 10), a reaction that would, as in the previous case, enable the conversion of readily available starting materials such as **38** to their chlorinated analogues such as **39** which are more complicated to prepare.[51] The reaction was surprisingly difficult and required the use of two equivalents of tetramethylammonium chloride and 20 mol% of copper(I) chloride to reach full conversion, yielding to chloroalkyne **39** in a rather disappointing yield of 52%.



Scheme 10. Copper-catalyzed bromide to chloride exchange starting from a bromoalkyne.

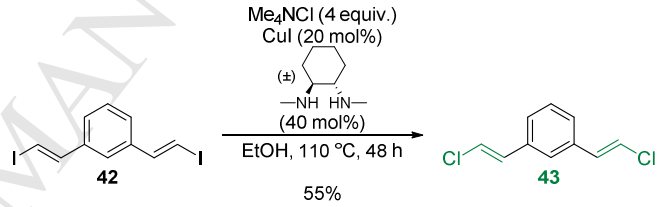
We finally moved to the last substrates of this study, halogenated allenes. Bromlinated allenes being found in a variety of natural products[52] and their iodinated analogues being readily prepared by a variety of efficient methods,[53] we anticipated that the transformation of the latter to the former could also be of synthetic usefulness. We therefore decided to test the possibility of performing an allenic version of the Finkelstein reaction. In this case, the main problem we faced was due to the poor stability of iodinated and brominated allenes which were found to undergo decomposition under the conditions we developed for the vinylic Finkelstein reaction. After an extensive screening of all reaction parameters, including copper sources, ligands, solvents, and temperature, the best result we could obtain so far is shown in Scheme 11. Upon reaction with tetramethylammonium chloride in the presence of 10 mol% of copper(I) iodide and 20 mol% of 1,2-dimethylimidazole in ethanol at 50 °C for a day, bromoallene **40** could be converted to its chlorinated analogue **41** in 18% yield only despite a full conversion of the starting material whose degradation seem to be faster than its chlorination.



Scheme 11. Copper-catalyzed bromide to chloride exchange starting from a bromoallene.

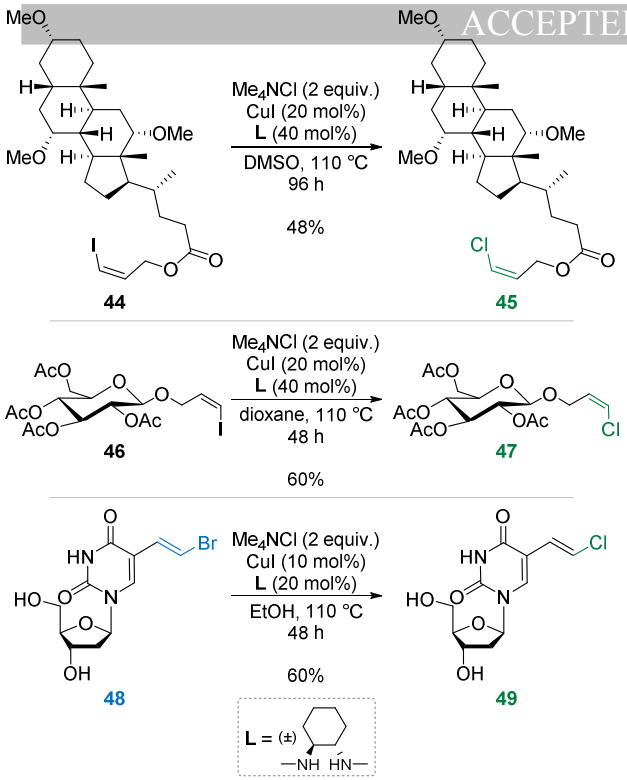
2.8. Copper-catalyzed vinylic halogen exchange reaction with complex and/or sensitive substrates.

Having demonstrated the robustness of the copper-catalyzed vinylic Finkelstein reaction, clearly delineating its scope and limitations, and attempting to expend it to the acetylenic and allenic series, we next decided to test our procedures in real-life situation to make sure they would be fully compatible with the presence of various functional groups and, therefore, of potential use with complex substrates. With this goal in mind, we therefore first examined the possibility of performing a double halogen exchange from bis-iodoalkene **42** under the conditions optimized for the iodide to chloride exchange. To our delight, the reaction was found to be quite efficient and gave the corresponding bis-chloroalkene **43** in 55% yield (Scheme 12).



Scheme 12. Copper-catalyzed double vinylic halogen exchange.

More complex and sensitive iodinated alkenes such as cholic acid **44** and peracetylglucose **46** derivatives were next subjected to the copper-catalyzed vinylic Finkelstein reaction (Scheme 13). To our great satisfaction, they were found to be smoothly transformed to the corresponding chlorinated derivatives **45** and **47** provided that 20 mol% of copper(I) iodide in combination with 40 mol% of the ligand were used in DMSO and dioxane, respectively. This clearly highlights the compatibility of our procedure with complex substrates and its potential usefulness for late-stage modification of complex molecules. Moreover, this copper-catalyzed vinylic halex reaction could potentially represent a useful tool in medicinal chemistry, various bioactive molecules possessing an halogenated alkene moiety, as demonstrated with the transformation of deoxy-brovarin **48**, without protection of the alcohols and the pyrimidinedione that could potentially interfere in the reaction, to its chlorinated analogue **49** in 60% yield.



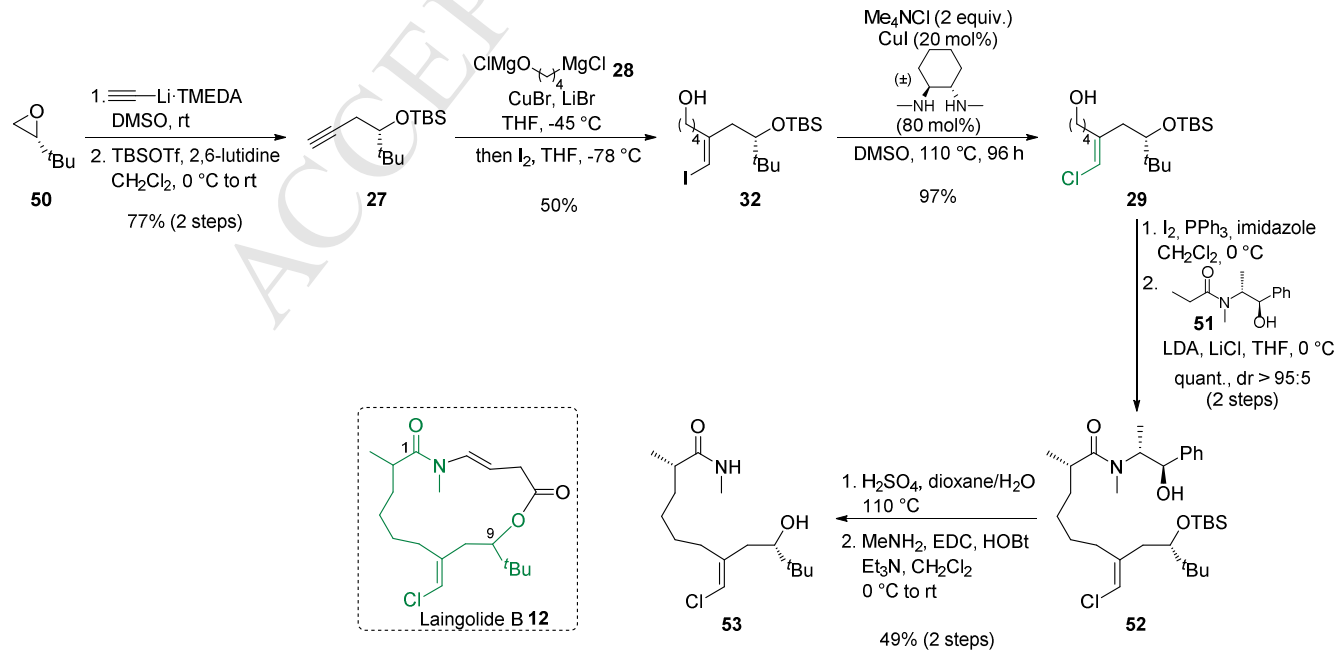
Scheme 13. The copper-catalyzed vinylic Finkelstein reaction in action with complex substrates.

As already mentioned in the introduction of this manuscript, these studies were actually initiated by problems we met *en route* to laingolide B, a naturally occurring alkenyl chloride for which the installation of this skeletal element ended up being quite troublesome. We could therefore hardly finish our studies without checking if the copper-catalyzed vinylic reaction we had developed could bring a solution to this problem, which will be briefly described in the last paragraphs of this manuscript.

2.9. Use of the copper-catalyzed vinylic halogen exchange reaction as a key step for the synthesis of an advanced precursor en route to laingolide B.

As discussed earlier, the first strategy we envisioned for the introduction of the disubstituted chloroalkene of laingolide B **12** was based on a carbocupration/electrophilic chlorination sequence, which was not anticipated to be problematic. All chlorination reagents and experimental procedures evaluated resulted in a total failure, the oxidative dimerization of the intermediate vinylcopper being the main reaction observed. To avoid this problem, a carbocupration/electrophilic iodination sequence was therefore envisioned and this sequence would then have to be followed by a challenging iodide to chloride exchange.

Based on this revised synthetic route to laingolide B, the synthesis was therefore initiated and started from previously reported enantiopure (*R*)-2-(*tert*-butyl)oxirane **50**[54] (Scheme 14). As a note, the relative and absolute configuration of laingolide B being still unknown, the configuration of the starting epoxide was chosen arbitrarily. Ring opening of this epoxide with lithium acetylide/TMEDA complex followed by direct protection of the resulting alcohol as a TBS ether gave terminal alkyne **27**, the substrate for the carbocupration step, in 77% yield. The carbocupration of **27** with the organocopper reagent derived from Grignard **28** followed by electrophilic iodination went rather smoothly and gave the desired alkenyl iodide **32** in 50% yield. This set the stage for the crucial vinylic Finkelstein reaction which gratifyingly proceeded extremely well since **32** could be readily and efficiently transformed to its chlorinated derivative **29** in a remarkable 97% yield, without isomerization of the double bond. It ought however to be mentioned that the use of 20 mol% of copper(I) iodide and 40 mol% of the ligand gave a slightly inferior result in this case, which might be attributed to the chelation of the unprotected alcohol to the copper center, a chelation that can be avoided by using an excess of the ligand compared to copper. The rest of the synthesis of the southern fragment **53** of laingolide B, for which the configuration of the second stereocenter was also arbitrarily chosen, was quite straightforward and relied on standard and well-established procedures. Iodination of the alcohol in **29** followed by a fully diastereoselective Myers alkylation with



Scheme 14. The copper-catalyzed vinylic halex reaction as a key step for the synthesis of an advanced precursor of laingolide B.

(1*R*,2*S*)-*N*-propionylephedrine **51**,[55] hydrolysis of the amide upon treatment with sulfuric acid and subsequent coupling of the resulting acid with methylamine gave the targeted advanced precursor **53** containing the fully elaborated C1-C9 fragment of laingolide B, further demonstrating the synthetic usefulness of our copper-catalyzed vinylic Finkelstein reaction.

3. Conclusions and outlook

In conclusion, we have reported an efficient and broadly applicable procedure for the copper-catalyzed vinylic Finkelstein reaction. Using a simple, readily available and cheap catalytic system, a broad range of alkenyl iodides could be smoothly converted to the corresponding brominated and chlorinated alkenes with high yields and full retention of the double bond geometry upon reaction with tetramethylammonium bromide and chloride. The reaction could be successfully extended to the chlorination of alkenyl bromides and to the dichlorination of *gem*-dibromoalkenes. The extension of this halogen exchange to the acetylenic and allenic Finkelstein reactions was also studied but found to be less efficient.

Key features of this vinylic Finkelstein reaction are its broad applicability, enabling the conversion of readily available alkenyl iodides to their less available lower homologues, and the mild reaction conditions compatible with a range of highly functionalized substrates. The synthesis of the southern fragment of laingolide B clearly highlights the synthetic usefulness of this reaction which should find various applications in synthesis and medicinal chemistry, where our copper-catalyzed vinylic halogen exchange reaction can be used for the late-stage modification of complex molecules and drugs. Further extension of this reaction to the fluorination of alkenyl iodides are underway and will be reported in due course.

4. Experimental section

4.1. General methods and materials

All reactions were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. All solvents were reagent grade. Tetrahydrofuran was freshly distilled from sodium/benzophenone under argon, dichloromethane was distilled from calcium hydride under argon. Dimethylsulfoxide and dioxane were bought over molecular sieves in AcroSeal® bottles from Acros Organics and used as supplied. Copper(I) iodide (99.999% purity) was purchased from Aldrich and used as supplied. The starting iodoalkenes were synthesized according to previously reported procedures; whenever they hadn't been reported before, their preparation has been described in our preliminary communication.[35] All other reagents were used as supplied. Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kieselgel $60F_{254}$ plates. Flash chromatography and filtrations were performed with silica gel 60 (particle size 40-63 µm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Proton NMR spectra were recorded using an internal deuterium lock at ambient temperature on Brucker 300 and 400 MHz spectrometers. Internal reference of δ_H 7.26 was used for $CDCl_3$. Internal reference of δ_H 2.50 was used for $(CD_3)_2SO$. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, app.= apparent), coupling constants (*J*/Hz) and integration. Resonances that are either partially or fully obscured are denoted obscured (obs.). Carbon-13 NMR spectra were recorded at 75 or 100 MHz using $CDCl_3$ (δ_C 77.16) or $(CD_3)_2SO$ (δ_C 39.52) as internal reference. Fluorine-19 NMR spectra were recorded at 377 MHz using C_6F_6 (δ_F -164.92) as external reference. Optical rotations were recorded on an Atago AP-100 automatic polarimeter at 589 nm and reported as follows: $[\alpha]_D^{25}$, concentration (*c* in g/100 mL), and solvent. Melting points were recorded on a Stuart Scientific Analogue SMP11. Infrared spectra were recorded on a Brucker Alpha Spectrometer (ATR). High-resolution mass-spectra were obtained on a Waters QTof API US, a Thermo Finnigan MAT 95XP spectrometer or on a Waters XevoQTof spectrometer.

4.2. Synthetic procedures and characterization data

4.2.1. General procedure for the copper-catalyzed iodide/bromide to chloride/bromide exchange in alkenyl iodides/bromides. An oven dried 15 mL resealable pressure tube was charged with copper(I) iodide (19 mg, 0.1 mmol, 10 mol% unless specified otherwise), tetramethylammonium chloride (219 mg, 2.0 mmol) or tetramethylammonium bromide (616 mg, 4.0 mmol) and the iodoalkene or bromoalkene (1.0 mmol). The tube was fitted with a rubber septum, evacuated under vacuum, backfilled with argon and *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine (31 µL, 0.2 mmol, 20 mol% unless specified otherwise) and ethanol (or DMSO or dioxane when specified) (2 mL) were next added. The tube was closed with a Teflon-coated screw cap and the resulting suspension was stirred and heated at 110 °C in a preheated oil bath for 48 h (unless specified otherwise). When the reaction was run in ethanol or dioxane, the crude reaction mixture was cooled to rt, diluted with ethyl acetate, filtered on a plug of silica gel and concentrated. When the reaction was run in DMSO, the crude reaction mixture was cooled to rt, diluted with water (15 mL), extracted thrice with diethyl ether and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography over silica gel to afford the desired chlororinated or brominated alkene.

4.2.1.1. (E)-(2-Chlorovinyl)benzene ***34a***.[25] Yield: 82% (113 mg, 0.82 mmol). Solvent system for flash chromatography: pentane.

4.2.1.2. (E)-(2-Bromovinyl)benzene ***35a***.[25] Yield: 85% (154 mg, 0.85 mmol). Solvent system for flash chromatography: pentane.

4.2.1.3. (E)-1-(2-Chlorovinyl)-4-(trifluoromethyl)benzene ***34b***.

- From the corresponding iodoalkene: reaction performed in DMSO for 24 h. Yield: 71% (148 mg, 0.71 mmol).
- From the corresponding bromoalkene: yield (reaction performed on a 0.2 mmol scale): 74% (31 mg, 0.14 mmol).

Solvent system for flash chromatography: pentane; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 13.5 Hz, 1H), 6.75 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 132.2, 130.1 (q, *J* = 32.3 Hz), 126.4, 125.9 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 270.4 Hz), 121.6; ^{19}F NMR (377 MHz, $CDCl_3$): δ -65.8 (s); IR (ATR): ν_{max} 3074, 1614, 1412, 1324, 1165, 1123, 1109, 1067, 1017, 931, 845, 823, 795, 755, 728 cm^{-1}; EIHRMS *m/z* calcd for $C_9H_6{}^{35}ClF_3$ $[M]^+$ 206.0105, found 206.0106.

4.2.1.4. (E)-1-(2-Bromovinyl)-4-(trifluoromethyl)benzene ***35b***.[56] Reaction performed in DMSO for 24 h. Yield: 80% (200 mg, 0.80 mmol). Solvent system for flash chromatography: pentane.

4.2.1.5. (E)-1-(2-Chlorovinyl)-4-chlorobenzene ***34c***.

- From the corresponding iodoalkene: yield: 67% (116 mg, 0.67 mmol). Solvent system for flash chromatography: cyclohexane/EtOAc: 98/2; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 7.5 Hz, 4H), 7.50-7.38 (m, 6H), 6.27 (dt, J = 12.9 and 1.8 Hz, 1H), 6.03 (dt, J = 13.2 and 4.8 Hz, 1H), 4.20 (dd, J = 4.8 and 1.5 Hz, 2H), 1.1 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.3, 132.3, 129.9, 127.9, 119.0, 62.7, 26.9, 19.3; IR (ATR): ν_{max} 2930, 2857, 1471, 1376, 1111, 1067, 1007, 962, 926, 822, 767, 738, 700, 614 cm^{-1}; EIHRMS *m/z* calcd for $C_{19}H_{23}{}^{35}ClOSi$ $[M]^+$ 330.1201, found 330.1205.

mmol).
- From the corresponding bromoalkene: yield (reaction performed on a 0.2 mmol scale): 77% (27 mg, 0.15 mmol).
Solvent system for flash chromatography: pentane; White solid; Mp: 33 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 13.8 Hz, 1H), 6.62 (d, J = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0, 133.2, 132.2, 129.1, 127.4, 119.5; IR (ATR): ν_{max} 1488, 1403, 1090, 1012, 944, 927, 832, 818 cm^{-1}; EIHRMS *m/z* calcd for $C_8H_6{}^{35}Cl_2$ $[M]^+$ 171.9841, found 171.9851.

4.2.1.6. (E)-1-(2-Bromovinyl)-4-chlorobenzene ***35c***.[56] Yield: 75% (163 mg, 0.75 mmol). Solvent system for flash chromatography: pentane.

4.2.1.7. (E)-Methyl-4-(2-chlorovinyl)benzoate ***34d***.[57] Reaction performed in DMSO for 24 h. Yield: 79% (155 mg, 0.79 mmol). Solvent system for flash chromatography: petroleum ether/EtOAc: 98/2.

4.2.1.8. (E)-Methyl-4-(2-bromovinyl)benzoate ***35d***.[58] Yield (reaction performed on a 0.5 mmol scale): 76% (92 mg, 0.38 mmol). Solvent system for flash chromatography: petroleum ether/EtOAc: 98/2.

4.2.1.9. (E)-(2-Chlorovinyl)-4-methoxybenzene ***34e***.[24b] Yield: 50% (84 mg, 0.50 mmol). Solvent system for flash chromatography: cyclohexane/EtOAc: 95/5.

4.2.1.10. (E)-(2-Bromovinyl)-4-methoxybenzene ***35e***.[25] Yield: 58% (122 mg, 0.58 mmol). Solvent system for flash chromatography: cyclohexane/EtOAc: 95/5.

4.2.1.11. (E)-2-(2-Chlorovinyl)naphthalene ***34f***.[57] Reaction performed in DMSO for 24 h. Yield: 80% (151 mg, 0.80 mmol). Solvent system for flash chromatography: pentane.

4.2.1.12. (E)-2-(2-Chlorovinyl)naphthalene ***35f***.[59] Yield (reaction performed on a 0.5 mmol scale): 75% (87 mg, 0.38 mmol). Solvent system for flash chromatography: pentane.

4.2.1.13. (E)-1-Chlorodec-1-ene ***34g***.
- From the corresponding iodoalkene: yield: 77% (134 mg, 0.77 mmol).
- From the corresponding bromoalkene (reaction performed on a 0.2 mmol scale): yield: 84% (29 mg, 0.16 mmol).
Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96-5.84 (m, 2H), 2.04 (app. qd, J = 7.2 and 1.2 Hz, 2H), 1.41-1.20 (m, 12H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 116.7, 32.0, 31.0, 29.5, 29.4, 29.1, 29.0, 22.8, 14.2; IR (ATR): ν_{max} 2956, 2925, 2855, 1457, 1377, 931, 805, 721 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{19}{}^{35}Cl$ $[M]^+$ 174.1170, found 174.1178.

4.2.1.14. (E)-1-Bromodec-1-ene ***35g***. Yield: 64% (140 mg, 0.64 mmol). Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 (dt, J = 13.5 and 7.2 Hz, 1H), 6.00 (dt, J = 13.5 and 1.2 Hz, 1H), 2.03 (app. qd, J = 7.2 and 0.9 Hz, 2H), 1.44-1.37 (m, 2H), 1.32-1.21 (m, 10H), 0.88 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 104.1, 33.1, 32.0, 29.5, 29.4, 29.1, 28.8, 22.8, 14.2; IR (ATR): ν_{max} 2955, 2925, 2854, 1620, 1377, 1216, 933, 735, 705 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{19}{}^{79}Br$ $[M]^+$ 218.0665, found 218.0667.

4.2.1.15. (E)-1-tert-Butyldiphenylsilyloxy-3-chloroprop-2-ene ***34h***. Yield (reaction performed on a 0.5 mmol scale): 92% (151 mg, 0.46 mmol). Solvent system for flash chromatography: cyclohexane/ethyl acetate: 98/2.

4.2.1.16. (E)-3-Bromo-1-tert-butyldiphenylsilyloxy-prop-2-ene ***35h***.[60] Yield (reaction performed on a 0.2 mmol scale): 85% (64 mg, 0.17 mmol). Solvent system for flash chromatography: cyclohexane/ethyl acetate: 98/2.

4.2.1.17. (E)-(3-Chloroallyl)benzene ***34i***. Yield: 82% (125 mg, 0.82 mmol). Solvent system for flash chromatography: pentane; Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.12 (m, 5H), 6.15-5.95 (m, 2H), 3.39 (d, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 132.7, 128.8, 128.6, 126.7, 118.5, 37.2; IR (ATR): ν_{max} 3028, 1702, 1632, 1495, 1453, 1431, 1286, 1241, 1124, 943, 779, 747, 697 cm^{-1}; EIHRMS *m/z* calcd for $C_9H_9{}^{35}Cl$ $[M]^+$ 152.0387, found 152.0391.

4.2.1.18. (E)-(3-Bromoallyl)benzene ***35i***.[61] Yield: 84% (167 mg, 0.84 mmol). Contaminated with 7% of the starting iodoalkene. Solvent system for flash chromatography: pentane.

4.2.1.19. (E)-3-Chloro-1-phthalimido-prop-2-ene ***34j***. Yield (reaction performed on a 0.5 mmol scale): 91% (101 mg, 0.45 mmol). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 80/20; White solid; Mp: 102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (dd, J = 5.4 and 3.0 Hz, 2H), 7.72 (dd, J = 5.7 and 3.0 Hz, 2H), 6.35 (d, J = 13.5 Hz, 1H), 6.00 (dt, J = 13.2 and 7.2 Hz, 1H), 4.26 (dd, J = 6.3 and 0.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 134.3, 132.1, 126.9, 123.6, 123.5, 37.4; IR (ATR): ν_{max} 3078, 1703, 1429, 1393, 1345, 1120, 1044, 941, 798, 717, 614 cm^{-1}; ESIHRMS *m/z* calcd for $C_{11}H_9{}^{35}ClNO_2$ $[M+H]^+$ 222.0316, found 222.0318.

4.2.1.20. (E)-3-Bromo-1-phthalimido-prop-2-ene ***35j***. Yield (reaction performed on a 0.5 mmol scale): 85% (113 mg, 0.42 mmol). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 80/20; White solid; Mp: 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (dd, J = 5.4 and 3.0 Hz, 2H), 7.71 (dd, J = 5.4 and 3.0 Hz, 2H), 6.45 (dt, J = 13.5 and 0.9 Hz, 1H), 6.27 (app. dt, J = 13.8 and 6.6 Hz, 1H), 4.24 (dd, J = 6.6 and 0.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 134.3, 132.1, 130.9, 123.6, 111.0, 39.1; IR (ATR): ν_{max} 2926, 1705, 1466, 1430, 1392, 1344, 1307, 1222, 1039, 941, 928, 712 cm^{-1}; ESIHRMS *m/z* calcd for $C_{11}H_9{}^{79}BrNO_2$ $[M+H]^+$ 265.9811, found 265.9806.

4.2.1.21. (Z)-(2-Chlorovinyl)benzene ***34k***.
- From the corresponding iodoalkene: yield: 83% (115 mg, 0.83 mmol).
- From the corresponding bromoalkene (reaction performed on a 0.2 mmol scale): yield: 75% (21 mg, 0.15 mmol).
Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 7.2 Hz, 2H), 7.41-7.29 (m, 3H), 6.64 (d, J = 8.1 Hz, 1H), 6.27 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 129.4, 129.3, 128.4, 128.3, 117.7; IR (ATR): ν_{max} 3025, 1617, 1491, 1445, 1346, 926, 846, 772, 722, 689, 658 cm^{-1}; EIHRMS *m/z* calcd for $C_8H_7{}^{35}Cl$ $[M]^+$ 138.0231, found 138.0239.

4.2.1.22. (Z)-(2-Bromovinyl)benzene ***35k***.[62] Yield: 72% (131 mg, 0.72 mmol). Solvent system for flash chromatography: pentane.

4.2.1.23. (Z)-(2-Chlorovinyl)-4-methylbenzene ***34l***. Yield: 81% (115 mg, 0.81 mmol). Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.21 (d, *J* = 8.1 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 131.5, 129.3, 129.3, 129.1, 116.8, 21.5; IR (ATR): ν_{max} 2922, 1615, 1509, 1448, 1344, 1173, 1120, 856, 821, 786, 730, 694, 621 cm^{-1}; EIHRMS *m/z* calcd for $C_9H_9{}^{35}Cl$ $[M]^+$ 152.0387, found 152.0393.

4.2.1.24. (Z)-(2-Bromovinyl)-4-methylbenzene ***35l***.[63] Reaction performed for 72 h. Yield: 41% (80 mg, 0.41 mmol). Solvent system for flash chromatography: pentane.

4.2.1.25. (Z)-3-Chloro-1-(4-methoxy)phenyloxy-prop-2-ene ***34m***. Reaction performed in DMSO using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 64% (64 mg, 0.32 mmol). Solvent system for flash chromatography: pentane/Et_2O: 98/2; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 4H), 6.23 (dt, *J* = 7.2 and 1.8 Hz, 1H), 6.05 (dt, *J* = 7.2 and 1.5 Hz, 1H), 4.72 (dd, *J* = 5.7 and 1.8 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 152.4, 128.4, 120.7, 115.8, 114.8, 64.4, 55.7; IR (ATR): ν_{max} 2833, 1506, 1462, 1227, 1181, 1107, 1039, 823, 751, 700 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{11}{}^{35}ClO_2$ $[M]^+$ 198.0442, found 198.0452.

4.2.1.26. (Z)-3-Bromo-1-(4-methoxy)phenyloxy-prop-2-ene ***35m***. Reaction performed in DMSO using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 54% (66 mg, 0.27 mmol). Solvent system for flash chromatography: pentane/Et_2O: 98/2; Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (s, 4H), 6.47-6.33 (m, 2H), 4.66 (dd, *J* = 5.1 and 1.1 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 152.4, 131.6, 115.8, 114.8, 109.7, 67.0, 55.9; IR (ATR): ν_{max} 2832, 1505, 1461, 1290, 1227, 1180, 1038, 823, 753, 676 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{11}{}^{79}BrO_2$ $[M]^+$ 241.9937, found 241.9947.

4.2.1.27. (Z)-3-Chloro-1-(2-tetrahydro-2H-pyranyloxy)-prop-2-ene ***34n***. Yield: 69% (122 mg, 0.69 mmol). Solvent system for flash chromatography: pentane/Et_2O: 80/20; Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.15 (dt, *J* = 7.2 and 1.8 Hz, 1H), 5.98 (app. dd, *J* = 12.9 and 6.3 Hz, 1H), 4.65 (t, *J* = 3.6 Hz, 1H), 4.41 (A of ABXY syst., *J* = 13.3, 5.6 and 1.7 Hz, 1H), 4.26 (B of ABXY syst., *J* = 13.3, 6.4 and 1.6 Hz, 1H), 3.88 (m, 1H), 3.53 (m, 1H), 1.88-1.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.0, 120.1, 98.7, 62.9, 62.5, 30.7, 25.5, 19.6; IR (ATR): ν_{max} 2942, 1634, 1454, 1351, 1201, 1156, 1120, 1070, 1029, 964, 906, 870, 815, 733, 683 cm^{-1}; ESIHRMS *m/z* calcd for $C_8H_{13}{}^{35}ClO_2$ $[M]^+$ 176.0599, found 176.0609.

4.2.1.28. (Z)-3-Bromo-1-(2-tetrahydro-2H-pyranyloxy)-prop-2-ene ***35n***. Yield: 68% (151 mg, 0.68 mmol). Solvent system for flash chromatography: pentane/Et_2O: 80/20; Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (m, 2H), 4.65 (t, *J* = 3.9 Hz, 1H), 4.36 (A of ABXY syst., *J* = 6.7, 4.9 and 1.3 Hz, 1H), 4.21 (B of ABXY syst., *J* = 7.3, 5.7 and 1.2 Hz, 1H), 3.88 (m, 1H), 3.53 (m, 1H), 1.91-1.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.0, 120.1, 98.7, 62.9, 62.5, 30.7, 25.5, 19.6; IR (ATR): ν_{max} 2942, 1634, 1454, 1351, 1201, 1156, 1120, 1070, 1029, 964, 906, 870, 815, 733, 683 cm^{-1}; EIHRMS *m/z* calcd for $C_8H_{13}{}^{79}BrO_2$ $[M]^+$ 220.0093, found 220.0096.

4.2.1.29. (Z)-Ethyl-4-chlorobut-3-enoate ***34o***.[64] This compound is extremely volatile. NMR yield using DMF as an internal standard: 70%.

4.2.1.30. (Z)-Ethyl-4-bromobut-3-enoate ***35o***.[64] This compound is extremely volatile. NMR yield using DMF as an internal standard: 55%. Contaminated with 13% of the starting iodoalkene.

4.2.1.31. 1-(1-Chlorovinyl)-3-methoxybenzene ***34p***. Reaction performed in DMSO for 24 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 74% (63 mg, 0.37 mmol). Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.15 (m, 3 H), 6.92-6.87 (m, 1H), 5.76 (d, *J* = 1.5 Hz, 1H), 5.52 (d, *J* = 1.8 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 139.9, 138.5, 129.5, 119.0, 114.8, 113.1, 112.4, 55.5; IR (ATR): ν_{max} 2940, 1692, 1598, 1580, 1484, 1464, 1431, 1320, 1288, 1261, 1197, 1167, 1042, 908, 880, 781, 732, 666 cm^{-1}; EIHRMS *m/z* calcd for $C_9H_9{}^{35}ClO$ $[M]^+$ 168.0336, found 168.0337.

4.2.1.32. 1-(1-Chlorovinyl)-3-methoxybenzene ***35p***.[65] Reaction performed in DMSO for 48 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale):)75% (80 mg, 0.38 mmol). Solvent system for flash chromatography: pentane.

4.2.1.33. 2-Chlorotetradec-1-ene ***34q***. Reaction performed in DMSO for 24 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 77% (89 mg, 0.39 mmol). Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.13 (d, *J* = 0.9 Hz, 1H), 5.10 (d, *J* = 1.2 Hz, 1H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.61-1.52 (m, 2H), 1.33-1.21 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 111.8, 39.3, 32.1, 29.8 (2C), 29.7, 29.5 (2C), 28.7, 27.3, 22.9, 14.3; IR (ATR): ν_{max} 2923, 2853, 1634, 1465, 1173, 908, 876, 735, 640, 617 cm^{-1}; EIHRMS *m/z* calcd for $C_{14}H_{27}{}^{35}Cl$ $[M]^+$ 230.1796, found 230.1798.

4.2.1.34. 2-Bromotetradec-1-ene ***35q***.[66] Reaction performed in DMSO for 48 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 88% (122 mg, 0.44 mmol). Solvent system for flash chromatography: pentane.

4.2.1.35. 1-tert-Butyldimethylsilyloxy-2-chloro-prop-2-ene ***34r***. Reaction performed in DMSO for 24 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 60% (61 mg, 0.30 mmol). Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50 (d, *J* = 1.5 Hz, 1H), 5.28 (d, *J* = 1.2 Hz, 1H), 4.15 (t, *J* = 1.5 Hz, 2H), 0.92 (s, 9H), 0.1 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 110.6, 65.9, 25.9, 18.5, -5.2; IR (ATR): ν_{max} 2929, 2857, 1645, 1462, 1256, 1093, 884, 837, 777, 698 cm^{-1}; EIHRMS *m/z* calcd for $C_9H_{19}{}^{35}ClOSi$ $[M]^+$ 206.0888, found 206.0890.

4.2.1.36. 2-Bromo-1-tert-butyldimethylsilyloxy-prop-2-ene ***35r***.[67] Reaction performed in DMSO for 48 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 64% (80 mg, 0.32 mmol). Solvent system for flash chromatography: pentane/Et_2O: 98/2.

4.2.1.37. 1-tert-Butyldiphenylsilyloxy-2-chloro-prop-2-ene ***34s***.

From the corresponding iodoalkene: reaction performed in DMSO for 24 h using 20 mol% of copper(I) iodide and 40 mol%

of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 70% (115 mg, 0.35 mmol).
- From the corresponding bromoalkene: reaction performed in DMSO for 24 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.2 mmol scale): 85% (56 mg, 0.17 mmol).
Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.64 (m, 4H), 7.49-7.36 (m, 6H), 5.66 (d, J = 1.5 Hz, 1H), 5.34 (d, J = 1.5 Hz, 1H), 4.18 (t, J = 1.5 Hz, 2H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 135.6, 133.1, 130.1, 128.0, 110.9, 66.3, 26.9, 19.4; IR (ATR): ν_{max} 2931, 2857, 1647, 1472, 1427, 1111, 1089, 885, 824, 738, 700, 613 cm^{-1}; EIHRMS *m/z* calcd for $C_{19}H_{23}{}^{35}ClOSi$ $[M]^+$ 330.1201, found 330.1211.

4.2.1.38. 2-Bromo-1-tert-butyldiphenylsilyloxy-prop-2-ene ***35s***.[68] Reaction performed in DMSO for 24 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 87% (122 mg, 0.44 mmol). Solvent system for flash chromatography: pentane.

4.2.1.39. (Z)-1-tert-Butyldimethylsilyloxy-3-chloro-2-methyl-prop-2-ene ***34t***. Yield: 88% (196 mg, 0.88 mmol). Solvent system for flash chromatography: pentane/Et_2O: 98/2; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (s, 1H), 4.33 (s, 2H), 1.79 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 111.3, 61.7, 26.0 (2C), 18.5, -5.2; IR (ATR): ν_{max} 2955, 1471, 1252, 1088, 836, 775, 667 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{21}{}^{35}ClOSi$ $[M]^+$ 220.1045, found 220.1048.

4.2.1.40. (Z)-3-Bromo-1-tert-butyldimethylsilyloxy-2-methyl-prop-2-ene ***35t***. Yield: 83% (209 mg, 0.83 mmol). Solvent system for flash chromatography: pentane/Et_2O: 98/2; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (t, J = 1.2 Hz, 1H), 4.30 (s, 2H), 1.82 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 99.9, 64.2, 26.0, 19.9, 18.4, -5.2; IR (ATR): ν_{max} 2954, 2929, 2856, 1471, 1252, 1090, 836, 776, 710, 667 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{21}{}^{79}BrOSi$ $[M]^+$ 264.0540, found 264.0544.

4.2.1.41. (Z)-1-tert-Butyldimethylsilyloxy-3-chloro-3-methyl-prop-2-ene ***34u***. Reaction performed in DMSO using 30 mol% of copper(I) iodide and 60 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 72% (80 mg, 0.36 mmol). Solvent system for flash chromatography: pentane/Et_2O: 98/2; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (t, J = 5.7 Hz, 1H), 4.30 (dd, J = 5.7 and 0.9 Hz, 2H), 2.10 (d, J = 0.9 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.2, 126.1, 60.8, 26.0, 25.9, 18.3, -5.2; IR (ATR): ν_{max} 2929, 1471, 1255, 1101, 1061, 836, 776, 666 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{21}{}^{35}ClOSi$ $[M]^+$ 220.1045, found 220.1047.

4.2.1.42. (Z)-3-Bromo-1-tert-butyldimethylsilyloxy-3-methyl-prop-2-ene ***35u***. Reaction performed in DMSO using 30 mol% of copper(I) iodide and 60 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 30% (40 mg, 0.15 mmol). Solvent system for flash chromatography: pentane/Et_2O: 98/2; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (tq, J = 5.4 Hz and 1.5 Hz, 1H), 4.26 (dq, J = 5.4 Hz and 1.5 Hz, 2H), 2.29 (q, J = 1.2 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.5, 121.8, 63.7, 28.8, 26.1, 18.5, -5.0; IR (ATR): ν_{max} 2930, 1472, 1254, 1100, 1059, 836, 776, 666 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{21}{}^{79}BrOSi$ $[M]^+$ 264.0540, found 264.0542.

4.2.1.43. (2-Chlorovinyl)benzene ***34v***. Reaction performed in refluxing ethanol from a 20 g (109 mmol) of β-bromostyrene (89/11 mixture of *E* and *Z* isomers). Yield: 66% (10 g, 72 mmol, 92/8 mixture of *E* **34a** and *Z* **34k** isomers). Purified by filtration over a plug of silica gel eluting with pentane.

4.2.1.44. 1,3-bis[(E)-2-Chlorovinyl]benzene ***43***. Reaction performed using 4 equiv. of tetramethylammonium chloride, 20 mol% of copper(I) iodide and 40 mol% of trans-*N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 55% (54 mg, 0.28 mmol). Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.27 (m, 1H), 7.24-7.15 (m, 3H), 6.81 (d, J = 13.8 Hz, 2H), 6.66 (d, J = 13.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 132.9, 129.4, 125.8, 124.1, 119.6; IR (ATR): ν_{max} 3073, 1613, 1484, 1272, 1231, 933, 908, 835, 766, 733, 687 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_8{}^{35}Cl_2$ $[M]^+$ 197.9998, found 198.0003.

4.2.1.45. (Z)-3-Chloroallyl (R)-4-[(3R,5S,7R,8R,9S,10S,12S, 13R,14S,17R)-3,7,12-trimethoxy-10, 13-dimethylhexadeca-hydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoate ***45***. Reaction performed in DMSO for 96 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.15 mmol scale): 48% (38 mg, 70 µmol). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 80/20; Colorless oil; $[\alpha]_D^{25}$ +34.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.21 (dt, J = 7.5 and 1.5 Hz, 1H), 5.93 (app. q, J = 7.2 Hz, 1H), 4.76 (dd, J = 6.0 and 1.5 Hz, 2H), 3.35 (br. s, 1H), 3.33 (s, 3H), 3.25 (s, 3H), 3.20 (s, 3H), 3.15-3.10 (m, 1H), 3.05-2.92 (m, 1H), 2.38 (m, 1H), 2.30-2.15 (m, 2H), 2.14-2.01 (m, 2H), 1.95-1.68 (m, 8H), 1.64-1.27 (m, 7H), 1.27-1.12 (m, 3H), 0.94-0.86 (m, 7H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 126.5, 121.8, 82.1, 80.9, 77.1, 59.7, 56.0, 55.8, 55.5, 46.3, 46.2, 42.7, 42.1, 39.7, 35.4, 35.2, 35.0, 34.6, 31.1, 31.0, 28.1, 27.9, 27.5, 26.9, 23.3, 23.0, 22.1, 17.5, 12.6; IR (ATR): ν_{max} 2934, 1739, 1372, 1159, 1101, 908, 732 cm^{-1}; ESIHRMS *m/z* calcd for $C_{30}H_{50}{}^{35}ClO_5$ $[M+H]^+$ 525.3341, found 525.3336.

4.2.1.46. O-α-(2-O,3-O,4-O,6-O-Tetraacetyl-glucopyrano-syl)-[(Z)-3-chloroprop-2-en-1-ol] ***47***. Reaction performed in dioxane for 48 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield (reaction performed on a 0.5 mmol scale): 60% (128 mg, 0.3 mmol). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30; White solid; Mp: 94 °C; $[\alpha]_D^{25}$ +8.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.17 (d, J = 7.2 Hz, 1H), 5.87 (app. q, J = 6.0 Hz, 1H), 5.17 (t, J = 9.6 Hz, 1H), 5.05 (t, J = 9.6 Hz, 1H), 4.95 (t, J = 8.1 Hz, 1H), 4.50 (d, J = 8.1 Hz, 1H), 4.40 (td, J = 5.4 and 1.2 Hz, 2H), 4.23 (dd, J = 12.3 and 4.8 Hz, 1H), 4.10 (dd, J = 12.3 and 2.1 Hz, 1H), 3.67 (dq, J = 9.9 and 2.4 Hz, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 170.3, 169.3 (2C), 127.6, 121.4, 99.9, 72.9, 72.0, 71.3, 68.4, 64.6, 61.9, 20.8 (2C), 20.6 (2C); IR (ATR): ν_{max} (cm^{-1}) 1747, 1364, 1219, 1163, 1036, 906, 758 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{24}{}^{35}ClO_{10}$ $[M+H]^+$ 423.1053, found 423.1048.

4.2.1.47. (E)-5-(2-Chlorovinyl)-2'-deoxyuridine ***49***.[69] Yield (reaction performed on a 0.5 mmol scale): 60% (87 mg, 0.30 mmol). Solvent system for flash chromatography: EtOAc.

4.2.2. General procedure for the copper-catalyzed bromide to chloride exchange in gem-dibromoalkenes. An oven dried 15 mL resealable pressure tube was charged with copper(I) iodide (28 mg, 0.15 mmol), tetramethylammonium chloride (274 mg, 2.5 mmol) and the *gem*-dibromoalkene (0.5 mmol). The tube was fitted with a rubber septum, evacuated under vacuum, backfilled

with argon and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (47 µL, 0.3 mmol) and DMSO (1 mL) were next added. The resealable pressure tube was closed with a Teflon-coated screw cap and the resulting suspension was stirred and heated at 110 °C in a preheated oil bath for 96 h. The resulting mixture was cooled, diluted with water (15 mL), extracted thrice with diethyl ether and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography over silica gel to afford the desired vinyl dichloride.

4.2.2.1. 1,1-Dichlorodec-1-ene ***37a.***[70] Yield: 44% (46 mg, 0.22 mmol). Solvent system for flash chromatography: pentane.

4.2.2.2. (4,4-Dichlorobut-3-en-1-yl)benzene ***37b***. Yield: 64% (64 mg, 0.32 mmol). Contaminated with 10% of the corresponding bromo-chloro-alkene. Solvent system for flash chromatography: pentane; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.27 (m, 2H), 7.25-7.16 (m, 3H), 5.88 (t, J = 7.2 Hz, 1H), 2.73 (t, J = 7.5 Hz, 2H), 2.50 (app. q, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 129.0, 128.7, 128.5, 126.4, 120.8, 34.4, 31.4; IR (ATR): ν_{max} 3028, 1691, 1496, 1454, 1084, 1030, 878, 746, 698 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_{10}{}^{35}Cl_2$ $[M]^+$ 200.0154, found 200.0153.

4.2.2.3. (E)-1-(4,4-Dichlorobuta-1,3-dienyl)benzene ***37c***. Reaction performed in DMSO for 48 h using 20 mol% of copper(I) iodide and 40 mol% of *trans-N,N'*-dimethylcyclohexane-1,2-diamine. Yield: 74% (74 mg, 0.37 mmol). Solvent system for flash chromatography: pentane; Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, J = 7.5 Hz, 2H), 7.39-7.27 (m, 3H), 6.89 (dd, J = 15.6 and 10.5 Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 6.58 (d, J = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 135.3, 129.3, 128.9, 128.6, 126.9, 122.9, 121.6; IR (ATR): ν_{max} 3037, 1701, 1494, 1453, 1158, 966, 903, 749, 696 cm^{-1}; EIHRMS *m/z* calcd for $C_{10}H_8{}^{35}Cl_2$ $[M]^+$ 197.9998, found 198.0000.

4.2.2.4. (R)-1,1-Dichloro-4,8-dimethylnona-1,7-diene ***37d***. Yield: 57% (64 mg, 0.28 mmol). Solvent system for flash chromatography: pentane; Pale yellow oil; $[\alpha]_D^{25}$ -3.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (t, J = 7.5 Hz, 1H), 5.08 (t, J = 6.6 Hz, 1H), 2.24-2.11 (m, 1H), 2.09-1.92 (m, 3H), 1.68 (s, 3H), 1.60 (br. s, 4H), 1.40-1.28 (m, 1H), 1.26-1.12 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.6, 129.0, 124.6, 120.3, 36.9, 36.8, 32.5, 25.9, 25.7, 19.6, 17.8; IR (ATR): ν_{max} 2963, 2914, 1619, 1453, 1378, 1118, 914, 853, 621 cm^{-1}; EIHRMS *m/z* calcd for $C_{11}H_{18}{}^{35}Cl_2$ $[M]^+$ 220.0780, found 220.0776.

4.2.3. Copper-catalyzed acetylenic bromide to chloride exchange: 4-(chloroethynyl)-1,1'-biphenyl 39.[71] An oven dried 15 mL resealable pressure tube was charged with copper(I) chloride (20 mg, 0.2 mmol), tetramethylammonium chloride (219 mg, 2.0 mmol) and 4-(bromoethynyl)-1,1'-biphenyl (257 mg, 1.0 mmol). The tube was fitted with a rubber septum, evacuated under vacuum, backfilled with argon and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (63 µL, 0.4 mmol) and DMSO (1 mL) were next added. The resealable pressure tube was closed with a Teflon-coated screw cap and the resulting suspension was stirred and heated at 80 °C in a preheated oil bath for 24 h. The resulting mixture was cooled, diluted with water (15 mL), extracted thrice with ethyl acetate and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography over silica gel (elution with petroleum ether) to afford the desired 4-(chloroethynyl)-1,1'-biphenyl **39** as a white solid (110 mg, 0.52 mmol, 52%).

4.2.4. Copper-catalyzed allenic bromide to chloride exchange: (3-chloropropa-1,2-dien-1-yl)benzene 41.[72] An oven dried 15 mL resealable pressure tube was charged with copper(I) iodide (10 mg, 0.05 mmol), tetramethylammonium chloride (110 mg, 1.0 mmol) and (3-bromopropa-1,2-dien-1-yl)benzene (97 mg, 0.5 mmol). The tube was fitted with a rubber septum, evacuated under vacuum, backfilled with argon and 1,2-dimethylimidazole (9 µL, 0.1 mmol) and ethanol (1 mL) were next added. The resealable pressure tube was closed with a Teflon-coated screw cap and the resulting suspension was stirred and heated at 50 °C in a preheated oil bath for 24 h. The resulting mixture was cooled, diluted with diethyl ether, filtered over a plug of silica gel and concentrated. The crude residue was finally purified by flash column chromatography over silica gel (elution with pentane) to afford the desired 4-(chloroethynyl)-1,1'-biphenyl **41** as a colorless oil (15 mg, 0.09 mmol, 18%).

4.2.5. Synthesis of the C1-C9 fragment of laingolide B.

4.2.5.1. (S)-4-tert-Butyldimethylsilyloxy-5,5-dimethylhex-1-yne ***27***. To a solution of (*R*)-*tert*-butyloxirane **50**[54] (3.5 g, 35.0 mmol) in DMSO (35 mL) was added via cannula a suspension of lithium acetylide ethylenediamine complex (12.9 g, 140 mmol) in DMSO (15 mL). The slightly exothermic resulting mixture was directly cooled to 0 °C, then slowly warmed to rt and stirred overnight. The reaction mixture was poured into a mixture of water and ice and the aqueous layer was extracted thrice with diethyl ether. Combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated at 300 mbar without heating. The crude residue was directly dissolved in dichloromethane (35 mL) and 2,6-lutidine (8.2 mL, 70.0 mmol) was added. The resulting reaction mixture was cooled to 0 °C before adding dropwise trimethylsilyl trifluoromethanesulfonate (8.9 mL, 70.0 mmol). The reaction mixture was then stirred for 4 h at 0 °C then quenched with water and the aqueous layer was extracted thrice with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography (petroleum ether) yielding the desired alkyne **27** as a colorless oil (6.5 g, 27.0 mmol, 77%); $[\alpha]_D^{25}$ -12.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.48 (t, J = 5.1 Hz, 1H), 2.48 (app. dq , J = 17.4 and 2.7 Hz, 1H), 2.18 (app. dq, J = 17.4 and 2.7 Hz, 1H), 1.97 (t, J = 2.7 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 84.2, 79.6, 70.3, 36.6, 26.5 (2C), 23.9, 18.6, -3.3, -4.2; IR (ATR): ν_{max} 2956, 1253, 1366, 1093, 910, 836, 774, 736, 626 cm^{-1}; EIHRMS *m/z* calcd for $C_{14}H_{28}OSi$ $[M]^+$ 240.1904, found 240.1907.

4.2.5.2. (S,E)-7-(tert-Butyldimethylsilyloxy)-5-(iodomethylene)-8,8-dimethylnonan-1-ol ***32***. Copper(I) bromide (2.2 g, 15.0 mmol) and lithium bromide (2.6 g, 30.0 mmol) were charged in a 250 mL round bottom flask, washed with toluene and concentrated (this operation was repeated three times) and dried under high vacuum for 6 h. The flask was then evacuated under high vacuum, backfilled with argon and fitted with a rubber septum. Copper bromide and lithium bromide were dissolved in THF (30 mL) and cooled to -45 °C before adding dropwise a solution of 1-(3-propyloxymagnesiumchloride)magnesium chloride (0.47 M in THF, 64 mL, 30.0 mmol).[31] The resulting dark orange reaction mixture was stirred for 1 h at -45 °C before adding alkyne **27** (1.8 g, 7.5 mmol). The reaction mixture was slowly allowed to warm to rt, stirred for 24 h then cooled to -78 °C before adding a solution of iodine (2.9 g, 11.3 mmol) in THF (20 mL). The reaction mixture was then allowed to slowly warm to rt, stirred overnight and then quenched with an aqueous solution of saturated aqueous ammonium chloride/ aqueous ammonia (25%)

(1:1 solution). The aqueous layer was extracted thrice with diethyl ether (70 mL), the combined organic layers were washed with a 10% aqueous solution of sodium bisulfite (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography (petroleum ether/ ethyl acetate: 80/20) yielding the desired alkenyl iodide **32** as a colorless oil (1.6 g, 3.6 mmol, 50%); $[\alpha]_D^{25}$ +13.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.90 (s, 1H), 3.68 (app. q, *J* = 6.0 Hz, 2H), 3.40 (dd, *J* = 8.7 and 2.4 Hz, 1H), 2.46 (app. d, *J* = 14.1 Hz, 1H), 2.39-2.27 (m, 1H), 2.32-2.07 (m, 2H), 1.66-1.56 (m, 2H), 1.54-1.43 (m, 2H), 1.33-1.22 (m, 1H), 0.88 (s, 9H), 0.86 (s, 9H), -0.02 (s, 3H), -0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.3, 78.6, 78.1, 63.1, 41.3, 36.7, 36.4, 32.7, 26.8, 26.5, 23.8, 18.7, -2.6, -3.3; IR (ATR)**:** ν_{max} 2954, 1472, 1366, 1255, 1086, 935, 834, 809, 773 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{38}IO_2Si$ $[M+H]^+$ 441.1680, found 441.1684.

4.2.5.3. (S,E)-7-(tert-Butyldimethylsilyloxy)-5-(chloromethylene)-8,8-dimethylnonan-1-ol ***29****.* An oven dried 15 mL resealable pressure tube was charged with copper(I) iodide (38 mg, 0.2 mmol), tetramethylammonium chloride (220 mg, 2.0 mmol) and iodoalkene **32** (1.0 mmol). The tube was fitted with a rubber septum, evacuated under vacuum, backfilled with argon and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (126 µL, 0.8 mmol) and DMSO (2 mL) were next added. The resealable pressure tube was closed with a Teflon-coated screw cap and the resulting suspension was stirred and heated at 110 °C in a preheated oil bath for 96 h. The crude reaction mixture was cooled to rt, diluted with water (15 mL), extracted thrice with diethyl ether and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography (petroleum ether/ ethyl acetate: 80/20) yielding the desired alkenyl chloride **29** as a colorless oil (340 mg, 0.97 mmol, 97%); $[\alpha]_D^{25}$ +14.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.79 (s, 1H), 3.68 (app. q, *J* = 4.2 Hz, 2H), 3.36 (dd, *J* = 8.7 and 2.1 Hz, 1H), 2.45 (m, 1H), 2.35 (app. d, *J* = 13.8 Hz, 1H), 2.03-1.91 (m, 2H), 1.66-1.37 (m, 4H), 1.28-1.21 (m, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.00 (s, 3H), -0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.2, 114.6, 62.9, 38.5, 36.1, 32.5, 29.7, 26.6, 26.3, 23.4, 18.5, -3.2, -3.6; IR (ATR): ν_{max} 2954, 1256, 1086, 937, 835, 809, 773 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{38}{}^{35}ClO_2Si$ $[M+H]^+$ 349.2324, found 349.2321.

4.2.5.4. (2S,9S,E)-9-(tert-Butyldimethylsilyloxy)-7-(chloromethylene)-N-[(1R,2R)-1-hydroxy-1-phenyl-propan-2-yl]-N,2,10,10-tetramethylundecanamide ***52****.* To a solution of triphenylphosphine (462 mg, 1.8 mmol) and imidazole (146 mg, 2.1 mmol) in dichloromethane (6 mL) was added iodine (447 mg, 1.8 mmol) in one portion at 0 °C. The bright yellow reaction mixture was stirred at 0 °C for 10 min before adding dropwise a solution of **29** (440 mg, 1.3 mmol) in dichloromethane (0.5 mL). The reaction mixture was warmed to rt, stirred for 4 h in the dark and filtered over a plug of silica gel. The crude residue (496 mg, 1.1 mmol) was used in the next step without further purification.

A 25 mL round bottom flask was charged with lithium chloride (533 mg, 12.6 mmol), dried under vacuum with a heatgun for 15 min, cooled to rt and finally suspended in THF (4.5 mL). Diisopropylamine (590 µL, 4.2 mmol) was added and the resulting suspension was cooled to -78 °C before adding dropwise *n*-butyllithium (2.4M in hexane, 1.7 mL, 3.9 mmol). The light yellow suspension was warmed to 0 °C for 15 min then cooled to -78 °C before adding dropwise an ice-cooled solution of (1*R*,2*R*)-(-)-pseudoephedrine propionamide **51** (443 mg, 2.0 mmol) in THF (5.0 mL). The reaction mixture was stirred successively at -78 °C for 1 h, 0 °C for 15 min and rt for 5 min and cooled back to 0 °C. A solution of the intermediate iodide (437 mg, 1.0 mmol) in THF (1.3 mL) was then added dropwise and the resulting reaction mixture was stirred for 19 h at 0 °C, 1 h at rt, and quenched by addition of a saturated aqueous solution of ammonium chloride (30 mL) and diluted with water (20 mL). The aqueous layer was extracted five times with ethyl acetate (50 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography (petroleum ether/ethyl acetate: 60/40) yielding the desired alkylated product **52** as a pale yellow oil (554 mg, 1.0 mmol, quantitative yield); $[\alpha]_D^{25}$ -23.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($(CD_3)_2SO$, 400 MHz, 383 K): δ 7.37-7.27 (m, 4H), 7.26-7.20 (m, 1H), 5.94 (s, 1H), 5.00 (br. s, 1H), 4.59 (d, *J* = 6.0 Hz, 1H), 3.53 (dd, *J* = 8.0 and 3.2 Hz, 1H), 2.83 (s, 3H), 2.73-2.62 (m, 1H), 2.41 (app. dd, *J* = 14.4 and 1.2 Hz, 1H), 2.35-2.26 (m, 1H), 2.13-2.00 (m, 2H), 1.64-1.52 (m, 1H), 1.46-1.17 (m, 6H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 18H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz, 383 K): δ 175.4, 143.0, 140.1, 127.2, 126.3, 126.1, 113.0, 78.5, 76.8, 73.8, 37.7, 35.1, 34.4, 32.9, 29.3, 26.2, 26.1, 25.6, 25.5, 17.4, 16.8, -4.1, -4.6 (1C not observed); IR (ATR): ν_{max} 2955, 1620, 1256, 1085, 835, 756, 701 cm^{-1}; ESIHRMS *m/z* calcd for $C_{31}H_{55}{}^{35}ClNO_3Si$ $[M+H]^+$ 552.3634, found 552.3636.

4.2.5.5. (2S,9S,E)-9-(tert-Butyldimethylsilyloxy)-7-(chloromethylene)-2,10,10-trimethyl-undecanoic acid. A 4M solution of sulfuric acid in water (2.7 mL) was slowly added to a solution **52** (150 mg, 0.15 mmol) in dioxane (2.7 mL) at 0 °C. The resulting reaction mixture was heated to reflux for 6 h, cooled to rt, diluted with water (5 mL), carefully basified to pH 12 and washed five times with ethyl acetate (5 mL). The resulting aqueous layer was carefully acidified to pH 3, extracted three times with dichloromethane (5 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to give the desired (2*S*,9*S*,*E*)-9-(*tert*-butyldimethylsilyloxy)-7-(chloromethylene)-2,10,10-trimethyl-undecanoic acid (50 mg, 171 µmol, 63%) which was used in the next step without further purification; $[\alpha]_D^{25}$ +12.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.89 (s, 1H), 3.30 (dd, *J* = 10.5 and 1.5 Hz, 1H), 2.54-2.36 (m, 2H), 2.32 (app. d, *J* = 13.8 Hz, 1H), 2.13-2.00 (m, 1H), 1.94 (dd, *J* = 14.1 and 10.5 Hz, 1H), 1.77-1.61 (m, 1H), 1.55-1.30 (m, 5H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 182.9, 140.4, 114.5, 76.4, 39.4, 37.3, 34.8, 33.4, 29.8, 27.1, 27.0, 25.8, 17.0; IR (ATR): ν_{max} 2943, 1706, 1216, 750 cm^{-1}; ESIHRMS *m/z* calcd for $C_{15}H_{28}{}^{35}ClO_3$ $[M+H]^+$ 291.1721, found 291.1715.

4.2.5.6. (2S,9S,E)-7-(Chloromethylene)-9-hydroxy-N,2,10,10-tetramethylundecanamide ***53*** *(C1-C9 fragment of laingolide B).* To a solution of (2*S*,9*S*,*E*)-9-(*tert*-butyldimethylsilyloxy)-7-(chloromethylene)-2,10,10-trimethyl-undecanoic acid (53 mg, 182 µmol) in dichloromethane (10.3 mL) were added hydroxybenzotriazole (49 mg, 0.36 mmol), *N*-methylamine (2M in THF, 273 µL, 0.55 mmol) and triethylamine (238 µL, 1.7 mmol). The resulting reaction mixture was cooled to 0 °C before adding dropwise a solution of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (146 mg, 0.77 mmol) in dichloromethane (7.3 mL), warmed to rt, stirred overnight and quenched with a 0.1 M aqueous solution of hydrochloric acid. The organic layer was washed successively with a 0.1M aqueous solution of hydrochloric acid (15 mL), a saturated aqueous solution of sodium bicarbonate (15 mL), water (15 mL), brine (15 mL) and dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was finally purified by flash column chromatography (petroleum ether/ethyl acetate: 20/80) yielding the desired amide **53** as a pale yellow oil (42 mg, 138 µmol, 76%); $[\alpha]_D^{25}$ +18.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.87 (s, 1H), 5.59 (br. s, 1H), 3.27 (ddd, *J* = 10.5, 3.6

and 1.8 Hz, 1H), 2.78 (d, J = 4.8 Hz, 3H), 2.44-2.33 (m, 1H), 2.30 (dt, J = 14.1 and 1.8 Hz, 1H), 2.15-1.94 (m, 2H), 1.94-1.85 (m, 1H), 1.72-1.55 (m, 2H), 1.48-1.20 (m, 5H), 1.10 (d, J = 6.9 Hz, 3H), 0.9 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.5, 140.9, 114.5, 76.6, 41.9, 37.6, 35.1, 34.4, 30.2, 27.7, 27.4, 26.6, 26.1, 18.3; IR (ATR): ν_{max} 3312, 2935, 1650, 1555, 1411, 1069, 756 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{31}{}^{35}ClNO_2$ $[M+H]^+$ 304.2038, found 304.2039.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra.