

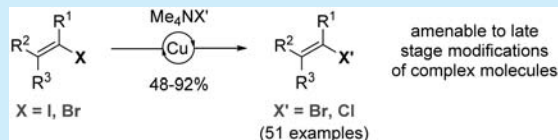
A General Copper-Catalyzed Vinylic Halogen Exchange Reaction

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S Supporting Information

ABSTRACT: An efficient and general system for the halogen exchange reaction in alkenyl halides has been developed. Upon reaction with catalytic amounts of copper iodide and *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine in the presence of tetramethylammonium chloride or bromide, a wide range of easily accessible alkenyl iodides can be smoothly transformed to their far less available chlorinated and brominated derivatives in excellent yields and with full retention of the double bond geometry. This reaction also enables the chlorination of bromoalkenes and could be extended to the use of *gem*-dibromoalkenes.



As a direct consequence of the development of metal-catalyzed cross-coupling reactions, organic halides are now among the most commonly used building blocks in chemical synthesis. They are indeed utilized in an impressive and ever growing number of reactions, notably for the formation of carbon–carbon and carbon–heteroatom bonds using palladium¹ and copper² catalysis. The efficiency of these reactions therefore strongly relies on the availability of the starting halides, and while most aryl halides are either commercially available or readily prepared regardless of the nature of the halogen atom, the situation is more complex in the vinyl series.³ Indeed, if alkenyl iodides are in most cases available through an array of efficient and selective methods such as iodolysis of vinylmetal species,⁴ Takai⁵ or Stork-Zhao⁶ olefinations, hydroiodination of alkynes,⁷ iododesilylation⁸/destannylation,⁹ or Hunsdiecker-type reactions,¹⁰ the synthesis of their brominated and chlorinated homologues is often much more challenging, mainly due to problems associated with low-yielding procedures, serious side reactions, poor stereoselectivity, or limitations to the synthesis of aryl-substituted derivatives.¹⁰

In addition to being versatile intermediates and building blocks for chemical synthesis, alkenyl bromides and chlorides are also commonly found in natural products. Representative examples include the cytotoxic and antibacterial neomangicols A **1** and B **2**,¹¹ laingolide B **3**,¹² or the costatols **4** and **5** (Figure 1).¹³ They are also at the core structure of various biologically active molecules from the pharmaceutical and agrochemical industries, the most representative examples being the well-known bromovinyl-uracil antiviral agent Usevir/Brovavir **6**,¹⁴ the sedative Placidyl **7**,¹⁵ or the herbicide Centurion **8**.

Due to their omnipresence in various areas of sciences, there is therefore a strong need for general and efficient methods enabling the selective synthesis of polysubstituted alkenyl halides, especially in the chlorinated and brominated series. Capitalizing on the greater availability of alkenyl iodides compared to their lower homologues, an interesting entry to these building blocks would rely on a halogen–halogen exchange. Provided that a complete conversion could be

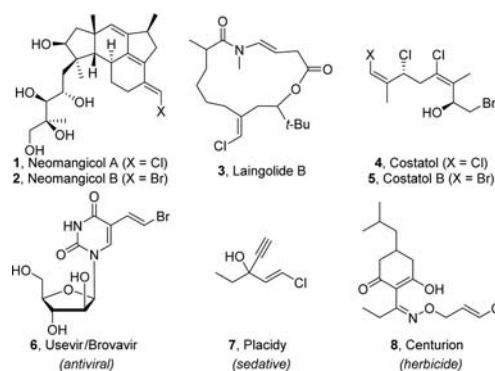


Figure 1. Alkenyl bromide-/chloride-containing natural and/or biologically active molecules.

obtained, which should be possible due to the greater stability of the C–Cl ($D_{298}^{\circ}(\text{C–Cl}) = 395 \text{ kJ mol}^{-1}$) and C–Br ($D_{298}^{\circ}(\text{C–Br}) = 318 \text{ kJ mol}^{-1}$) bonds compared to the C–I bond ($D_{298}^{\circ}(\text{C–I}) = 253 \text{ kJ mol}^{-1}$),¹⁶ and that the configuration of the double bond is fully retained during the process, this vinylic halogen exchange could provide a straightforward and modular route to brominated and chlorinated alkenes from their readily available iodinated counterparts. While this halogen exchange process, commonly named the Finkelstein reaction, has been extensively studied in the aromatic series, for which a number of efficient catalytic systems have been reported,^{17,18} its use with alkenyl halides has been, for some unknown reasons, rather underestimated, despite the huge potential and synthetic utility of such a transformation.^{18c,19}

Motivated by the potential of this copper-catalyzed vinylic halogen–halogen exchange, we therefore decided to study the feasibility of such a reaction and we report in this manuscript a general system for the conversion of alkenyl iodides and bromides to their lighter homologues with high efficiency.

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Table 1. Optimization of the Copper-Catalyzed Iodine/Chlorine Exchange in Alkenyl Iodides

$\text{Ph}-\text{CH}=\text{CH}-\text{I} \xrightarrow[\text{EtOH, 110 } ^\circ\text{C, 48 h}]{\text{Me}_4\text{NCl, CuI (10 mol \%), ligand (20 mol \%)}} \text{Ph}-\text{CH}=\text{CH}-\text{Cl}$			
entry	ligand	9a (%) ^a	10a (%) ^a
1	ethylene glycol	97	3
2	2-isobutyl-1-cyclohexanone	96	4
3	proline	96	0
4	1,10-phenanthroline	40	55
5	2,2'-bipyridine	40	48
6	<i>N,N'</i> -dimesitylthane-1,2-diimine	100	0
7	TMEDA	93	4
8	<i>N,N'</i> -dimethylethylenediamine	0	61
9	<i>trans-N,N'</i> -dimethylcyclohexane-1,2-diamine	0	76
10	<i>N,N,N',N',N''</i> -pentamethyldiethylenetriamine	46	41

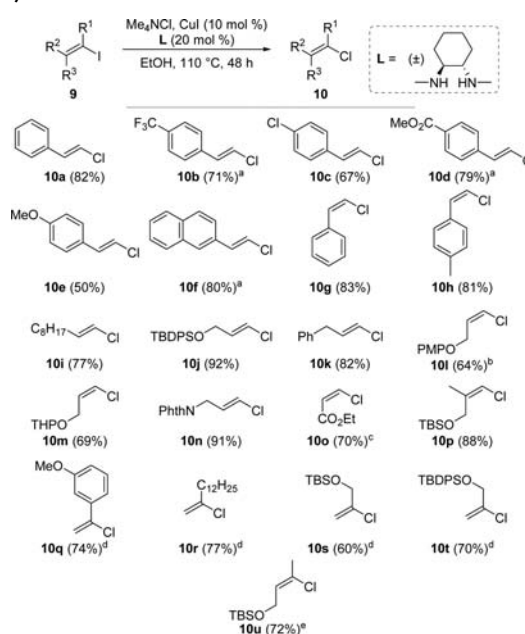
^aNMR yields determined using 1.0 equiv of DMF as an internal standard.

Our first studies focused on the iodide–chloride exchange starting from alkenyl iodides. The choice of the halogenating reagent and solvent for this transformation, which is thermodynamically driven, is crucial since both the starting and final halide salts have to be soluble in order for the equilibrium to be shifted toward the formation of the more stable alkenyl chloride. Tetramethylammonium chloride was therefore chosen as the source of chloride,^{18c} and ethanol was selected as the solvent to avoid problems associated with the low boiling points of some chloroalkenes.

With these parameters set, a screening of the efficiency of various representative ligands commonly used in copper catalysis was performed using copper iodide as the source of copper(I) and β -iodo-styrene **9a** as a model substrate. Results from these studies are shown in Table 1 and demonstrate a dramatic effect of the ligand used for this halogen–halogen exchange reaction. Indeed, while bidentate *O,O*- and *N,O*- ligands such as ethylene glycol, 2-isobutylcyclohexanone, and L-proline were found to be totally ineffective to promote the chlorination of **9a**, bidentate *N,N*-ligands were found to be much more efficient in most cases. Among these ligands, which include a set of representative phenanthroline, bipyridine, bis-imine, and diamine derivatives, only secondary 1,2-diamines such as *N,N'*-dimethylethylenediamine and *trans-N,N'*-dimethylcyclohexane-1,2-diamine enabled a full conversion. The latter was more effective, allowing the smooth transformation of alkenyl iodide **9a** to the corresponding chloride **10a** in 76% NMR yield and with full conservation of the double bond geometry since no traces of the *Z*-isomer could be detected in the crude reaction mixture. Of note, decreasing the reaction temperature to 80 °C resulted in a slightly lower yield of 72% and other solvents such as butanol and DMSO, which avoids performing the reaction above the boiling point of the solvent, were also found to be suitable solvents.

This optimized catalytic system was next applied to the chlorination of a set of iodoalkenes **9** possessing representative substitution patterns and electronic properties. As evidenced by results shown in Scheme 1, the copper catalyzed halogen exchange was found to be general and allowed us to unite a rather large collection of alkenyl chlorides **10** that could efficiently be obtained in fair to good yields from their readily available iodinated derivatives **9**. Importantly, complete conversions could be obtained in all cases, a key point for this iodine/chlorine exchange to be of synthetic value since the separation of **9** from

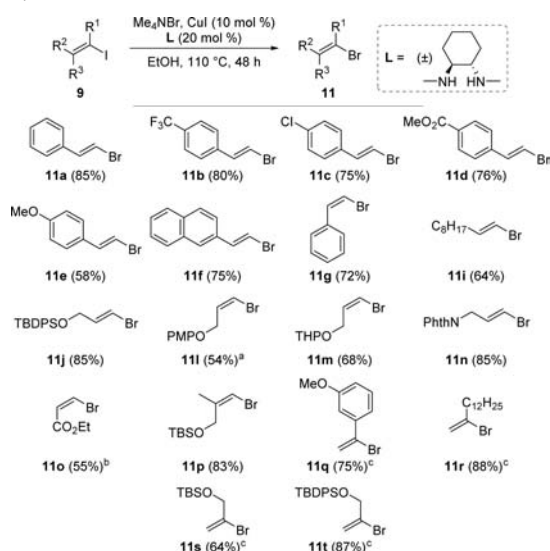
Scheme 1. Copper-Catalyzed Iodide to Chloride Exchange in Alkenyl Iodides



^aIn DMSO for 24 h. ^bIn DMSO using 20 mol % CuI and 40 mol % L. ^cNMR yield using DMF as internal standard. ^dIn DMSO for 24 h using 20 mol % CuI and 40 mol % L. ^eUsing 30 mol % CuI and 60 mol % L.

10 is almost impossible. A range of β -iodo-styrene derivatives could be smoothly transformed to their chlorinated analogues **10a–h** in good yields, regardless of their electronic properties, electron-poor **9b–d** and electron-rich **9e,h** iodo-styrenes reacting with similar efficiencies, the reaction being best performed in DMSO in some cases. The configuration of the double bond was found to have little influence on the outcome of the copper-catalyzed chlorination since *E*- and *Z*-chlorinated styrenes **9a–f** and **9g,h** were found to react equally well and no isomerization could be detected in all cases. In addition, the absence of a base in the reaction mixture enabled a clean conversion of *Z*- β -iodo-styrenes **9g,h** without competitive elimination to the corresponding terminal alkyne. More challenging β -alkyl-substituted alkenyl iodides **9i–n** were also found to smoothly undergo the iodide to chloride exchange, and the configuration of the alkene was also completely retained. Even the sensitive and readily isomerized *Z*- β -iodo-acrylate **9o**, a compound for which it should be noted that no reaction occurred in the absence of the copper catalyst, could be smoothly chlorinated to **10o** in 70% yield without isomerization. The presence of an additional substituent such as in **10p** did not slow down the reaction, since a clean chlorination could still be performed. Moving to the chlorination of α -substituted iodoalkenes such as **9q–t** required a slight modification of the reaction conditions which was found to be best performed, in this case, using a shorter reaction time (24 h vs 48 h) and a higher catalyst loading in DMSO, conditions that allowed for a full conversion without noticeable degradation of both the starting materials and products. Using these modified conditions, the corresponding α -substituted chloroalkenes **10q–t** could be obtained in synthetically useful yields (60–77%). Finally, the presence of two substituents close to the C–I bond was found to slow down the reaction and required the halogen exchange reaction to be performed for 48 h with a higher amount of both

Scheme 2. Copper-Catalyzed Iodide to Bromide Exchange in Alkenyl Iodides



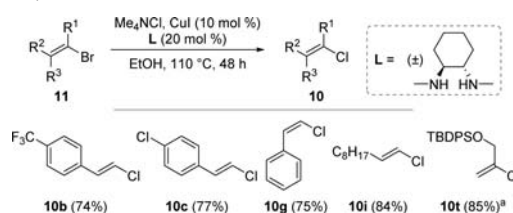
^aIn DMSO for 48 h. ^bNMR yield using DMF as internal standard, contaminated with 13% of the starting iodide. ^cIn DMSO using 20 mol % CuI and 40 mol % L.

copper iodide and the ligand, affording the corresponding alkenyl chloride **10u** in 72% yield. It ought to be mentioned that the reaction, which is performed under neutral conditions, was found to be compatible with a range of functional groups including benzyl groups, esters, phthalimide, acetals, or silyl ethers, and even a labile allylic PMP ether such as that in **10l** was well tolerated under the reaction conditions; no competitive nucleophilic substitution by the halides present in the reaction mixture could be observed.

Given the efficiency of the copper-catalyzed iodide to chloride exchange in alkenyl iodides, we next decided to investigate its extension to the less favorable synthesis of bromoalkenes, building blocks of great interest and whose synthesis can also be problematic in some cases. As expected, the lower difference in carbon–halogen bond energies for the copper-catalyzed iodide to bromide exchange in alkenyl iodides compared to the iodide to chloride exchange resulted in a more sluggish reaction and in incomplete conversion when the exact same conditions were applied to the bromination of **9a** using tetramethylammonium bromide instead of tetramethylammonium chloride. Doubling the amount of tetramethylammonium bromide however allowed the reaction to completely shift to the exclusive formation of the corresponding brominated derivative **11a** which could be gratefully obtained in 85% yield. A scope and limitations study using similar substrates as those used in the previous one demonstrated both the generality and broad substrate scope of this second halogen/halogen exchange which could be applied to the preparation of a wide range of polysubstituted bromoalkenes **11** from their iodinated counterparts **9** (Scheme 2).

Having suitable conditions in hands for the conversion of alkenyl iodides to their chlorinated and brominated counterparts, we next briefly evaluated a last halogen–halogen exchange in the vinylic series: the copper-catalyzed chlorination of alkenyl bromides. Results from these studies are collected in Scheme 3 and show that the same catalytic system optimized for the chlorination of alkenyl iodides can also be efficiently used for the synthesis of chlorinated alkenes **10** from the corresponding

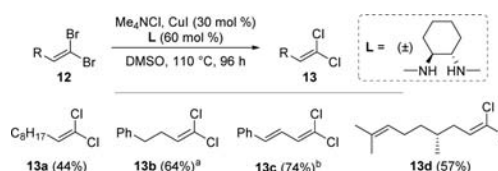
Scheme 3. Copper-Catalyzed Bromide to Chloride Exchange in Alkenyl Bromides



^aIn DMSO for 24 h using 20 mol % CuI and 40 mol % L.

brominated olefins **11** using 2 equiv of tetramethylammonium chloride. As in previous cases, the reaction was found to be rather general, regardless of the substitution pattern, the configuration, or the electronic properties of the starting materials, and the chloroalkenes **10** could be readily obtained as single isomers by simple concentration of the crude mixtures followed by filtration over a plug of silica gel. The yields obtained, in the 74–85% range, highlight the synthetic potential of this copper-catalyzed bromide to chloride exchange.

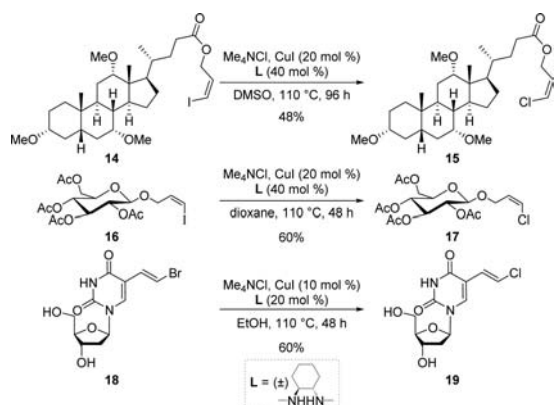
To further demonstrate the applicability of our procedure, we next decided to study the possibility of performing a double vinylic Finkelstein reaction from *gem*-dibromoalkenes **12**. Besides expanding the scope of our reaction, the feasibility of this reaction would allow conversion of these readily available dibromides to the corresponding dichlorides **13** whose synthesis is much more difficult and low-yielding²⁰ besides a synthetic usefulness that does not have to be demonstrated anymore.²⁰ Preliminary studies showed that if the first substitution of the less hindered bromide was quite simple, the second one was much more sluggish and the standard conditions used for the bromide to chloride exchange starting from bromoalkenes only gave inseparable mixtures of dibromo-, dichloro-, and bromo,chloro alkenes. A brief reoptimization revealed that the reaction could be driven to completion by increasing the amount of the catalytic system together with increasing the reaction time to 96 h: using these conditions, we were glad to note that various dibromoalkenes **12** could be converted to their dichlorinated derivatives **13** in fair to good yields (Scheme 4).

Scheme 4. Copper-Catalyzed Bromide to Chloride Exchange in *gem*-Dibromoalkenes

^aContaminated with 10% of the monochlorinated alkene. ^bFor 48 h using 20 mol % CuI and 40 mol % L.

Having demonstrated the generality of our copper-catalyzed vinylic halogen exchange reaction and its rather broad applicability, we next decided to try to push our procedures to their limits and to test them in more complex situations. With this goal in mind, their compatibility with more complex substrates was then evaluated starting first from cholic acid and peracetyl-glucose derivatives embedded with an appending alkenyl iodide **14** and **16** (Scheme 5). We were pleased to see that their chlorination proceeded well, the corresponding alkenyl chlorides **15** and **17** being obtained in moderate to good yields

Scheme 5. Copper-Catalyzed Vinylic Finkelstein Reaction with Complex/Sensitive Substrates



under our standard conditions, clearly demonstrating the potential of the copper-catalyzed vinylic Finkelstein reaction for the late-stage modification of complex substrates. Alkenyl halides being integral to the core structure of a wide range of biologically active molecules from the pharmaceutical and agrochemical industries, we envisioned that the vinylic halogen exchange reaction could be of potential interest for the modification of the nature of the halogen atom of the alkenyl halide moiety directly on the final drug or drug-like molecule rather than going back to the early steps of the synthetic route to perform this modification. To test this possibility, deoxy-brovavir **18** was directly engaged in the vinylic halogen exchange reaction under our optimized conditions, without protection of the alcohols and the pyrimidinone that could potentially interfere in the reaction. A clean reaction yielding the chlorinated analogue of deoxy-brovavir **19** occurred, further demonstrating the synthetic usefulness of our procedures.

In conclusion, we have developed an efficient and broadly applicable system for the vinylic Finkelstein reaction. Upon reaction with catalytic amounts of copper iodide and *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine in the presence of tetramethylammonium chloride or bromide, a wide range of easily accessible alkenyl iodides can be smoothly transformed to their far less available chlorinated and brominated derivatives in excellent yields and with full retention of the double bond geometry. This reaction also enables the chlorination of bromoalkenes and could be successfully extended to the halogen exchange reaction starting from *gem*-dibromoalkenes. The neutral reaction conditions of this vinylic Finkelstein reaction additionally enable the use of this procedure for the late-stage halogen exchange from complex and/or sensitive alkenyl halides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b00678](https://doi.org/10.1021/acs.orglett.6b00678).

Detailed experimental procedures and full characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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