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Allylic and Allenic Halide Synthesis via $NbCl_5$- and $NbBr_5$-Mediated Alkoxide Rearrangements

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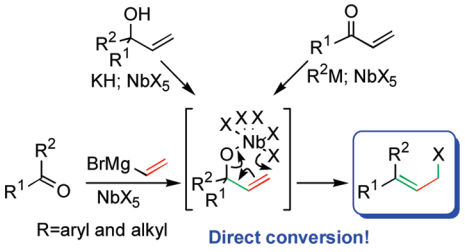


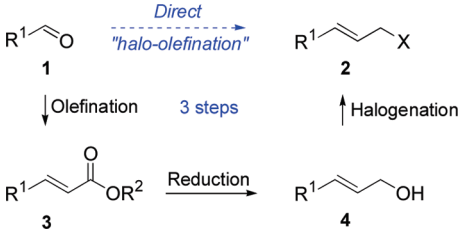
Addition of $NbCl_5$ or $NbBr_5$ to a series of magnesium, lithium, or potassium allylic or propargylic alkoxides directly provides allylic or allenic halides. Halogenation formally occurs through a metalla-halo-[3,3] rearrangement, although concerted, ionic, and direct displacement mechanisms appear to operate competitively. Transposition of the olefin is equally effective for allylic alkoxides prepared by nucleophilic addition, deprotonation, or reduction. Experimentally, the niobium pentahalide halogenations are rapid, afford essentially pure (*E*)-allylic or -allenic halides after extraction, and are applicable to a range of aliphatic and aromatic alcohols, aldehydes, and ketones.

Introduction

Allylic halides are powerful, versatile electrophiles.[1] The excellent electrophilicity stems from stereoelectronic interactions between the $\sigma^*_{C\text{-}X}$ orbital and the adjacent π system[2] that facilitate a range of efficient and predictable displacements.[3] Numerous natural product syntheses have harnessed the excellent electrophilicity of allylic halides to overcome difficult displacements and challenging cyclizations.[4]

Allylic halide intermediates in total synthesis campaigns are frequently synthesized from aldehydes through olefination−reduction−halogenation sequences (Scheme 1, **1** → **3** → **4** → **2**).[5] The three-step sequence is necessitated in part because the requisite Wittig reagents suffer facile halide ejection,[6] preventing a direct "halo-olefination" and partly because of the predictable conversion of primary allylic alcohols **4** to allylic halides **2** without rearrangement.[7] In contrast, regioselective halogenation of secondary allylic alcohols is reagent-[8] and structure-dependent[9] with many reactions channeling through both S_N2 and S_N2' displacement manifolds.[10]

SCHEME 1. Typical Allylic Halide Synthesis



Direct halogenation of propargylic alcohols similarly affords mixtures of regioisomeric halides.[10,11] Consequently a two-step sequence of alcohol activation, usually sulfonylation, followed by S_N2' halide displacement is typically employed to convert propargylic alcohols **5** to terminal allenic halides **6** (Scheme 2, **5** → **7** → **6**).[12] Subsequent transition-metal-catalyzed coupling allows a diverse range of bond constructions on these valuable synthetic partners.[13]

(1) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.
(2) *Stereoelectronic Effects*; Kirby, A. J. Oxford University Press: Bath, U.K., 1998; Chapter 5.
(3) (a) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124. (b) Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5560.
(4) For recent applications in synthesis, see: (a) Smith, A. B., III; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872. (b) Kashin, D.; Meyer, A.; Wittenberg, R.; Schöning, K.-U.; Kamlage, S.; Kirschning, A. *Synthesis* **2007**, 304. (c) Boukouvalas, J.; Robichaud, J.; Maltais, F. *Synlett* **2006**, 2480. (d) Mandal, A. K.; Schneekloth, J. S., Jr.; Kuramochi, K.; Crews, C. M. *Org. Lett.* **2006**, *8*, 427. (e) Zhang, T.; Liu, Z.; Li, Y. *Synthesis* **2001**, 393. (f) Tada, M.; Nishiiri, S.; Zhixiang, Y.; Imai, Y.; Tajima, S.; Okazaki, N.; Kitano, Y.; Chiba, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2657.

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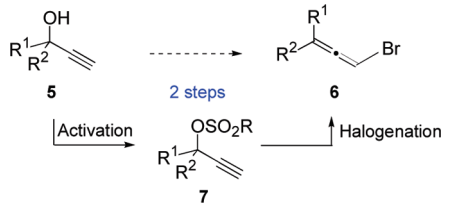
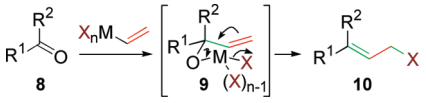
SCHEME 2. Typical Allenic Halide Synthesis



The inherent utility of allylic and allenic halides[14] stimulated a direct[15] synthesis from carbonyl and alcoholic precursors. Conceptually the transformation centers on a metalla-halo-[3,3] rearrangement[16] predicated on metal oxide eliminations[17] and the privileged nature of six-membered transition structures (Scheme 3).[18] Addition of a vinyl metal bearing an appropriate halide was envisaged to access the allylic alkoxide **9** and trigger a concerted rearrangement to the corresponding allylic halide **10**. As sporadically happens in chemical research,[19] the same concept was being simultaneously pursued with allylic chlorotitanium alkoxides (**9**, $MX_n = TiCl_3$).[20] Mechanistic experiments with these titanium alkoxides implicated a stepwise ionization−halogenation sequence rather than a concerted rearrangement, although in principle tuning the metal oxophilicity and halogen nucleophilicity should favor a concerted halogen transfer.[21]

SCHEME 3. Vinyl Addition−Metalla-halo-[3,3] Rearrangement



Publication of the pioneering titanium-based allylic chloride synthesis[20] was closely followed by communication[22] of a complementary niobium pentahalide procedure. Although preliminary, the use of niobium broadened the substrate scope and offered the promise of a general approach to both allylic and allenic halides through a concerted rearrangement. Complete details of these niobium pentachloride and pentabromide rearrangements are provided with an emphasis on mechanistic insight; extended substrate scope to include allylic alcohols, aldehydes, enals, ketones, and enones; cascade reduction−halogenation and addition−halogenation strategies; and the synthesis of allenic bromides.

Results and Discussion

The metalla-halo-[3,3] rearrangement strategy requires a metal halide capable of simultaneously activating the allylic alcohol, delivering a halogen in an S_N2' displacement, and forming a stable metal oxide. Addition of vinylmagnesium bromide to 1-naphthaldehyde (**1a**),[23] as with aldehydes in general,[24] forms an allylic magnesium alkoxide but does not

(5) For recent examples, see: (a) White, J. D.; Lincoln, C. M.; Yang, J.; Martin, W. H. C.; Chan, D. B. *J. Org. Chem.* **2008**, *73*, 4139. (b) Arteaga, J. F.; Domingo, V.; Quílez del Moral, J. F.; Barrero, A. F. *Org. Lett.* **2008**, *10*, 1723. (c) Janssen, D.; Kalesse, M. *Synlett* **2007**, 2667. (d) Chow, S. Y.; Williams, H. J.; Pennington, J. D.; Nanda, S.; Reibenspies, J. H.; Scott, A. I. *Tetrahedron* **2007**, *63*, 6204. (e) Wang, Y.; Ma, J.; Cheon, H.-S.; Kishi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 1333. (f) Ma, J.; Cheon, H.-S.; Kishi, Y. *Org. Lett.* **2007**, *9*, 319. (g) Noguchi, N.; Nakada, M. *Org. Lett.* **2006**, *8*, 2039. (h) Yoshimura, T.; Yakushiji, F.; Kondo, S.; Wu, X.; Shindo, M.; Shishido, K. *Org. Lett.* **2006**, *8*, 475. (i) Chow, S. Y.; Williams, H. J.; Huang, Q.; Nanda, S.; Scott, A. I. *J. Org. Chem.* **2005**, *70*, 9997. (j) Brittain, D. E. A.; Griffiths-Jones, C. M.; Linder, M. R.; Smith, M. D.; McCusker, C.; Barlow, J. S.; Akiyama, R.; Yasuda, K.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 2732. (k) Zhou, X.-T.; Carter, R. G. *Chem. Commun.* **2004**, 2138. (l) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1927. (m) Christoph, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189. (n) Chun, J.; Li, G.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2002**, *67*, 2600. (o) Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem.* **2001**, 1873. (p) Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681. (q) Schinzer, D.; Muller, N.; Fischer, A. K.; Priess, J. W. *Synlett* **2000**, 1265. (r) Ramaseshan, M.; Robitaille, M.; Ellingboe, J. W.; Dory, Y. L.; Deslongchamps, P. *Tetrahedron Lett.* **2000**, *41*, 4737.

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(11) Baker, C. S.; Landor, P. D.; Landor, S. R.; Patel, A. N. *J. Chem. Soc.* **1965**, 4348.

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(16) For related metallotropic rearrangements with allylic alcohols, see: (a) Fox, R. J.; Lalic, G.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 14144. (b) Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813. (c) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842. (d) Belgacem, J.; Kress, J.; Osborn, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 1501. (e) Matsubara, S.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 3741. For a summary of sigmatropic rearrangements of propargyl-type π-systems to allenic derivatives, see: Banert, K. *Liebigs Ann/Recuil* **1997**, 2005 and references therein.

(17) (a) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 3668. (b) Fleming, F. F.; Shook, B. C. *Tetrahedron Lett.* **2000**, *41*, 8847 and references therein.

(18) Yang, J. In *Six-Membered Transition Structures in Organic Synthesis*; Wiley: Hoboken, NJ, 2008.

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(20) Fuchter, M. J.; Levy, J.-N. *Org. Lett.* **2008**, *10*, 4919.

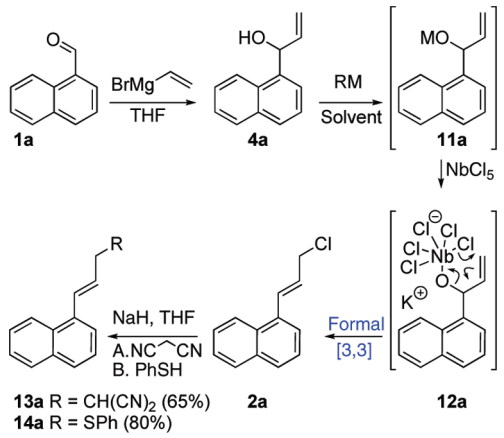
(21) For a related transformation of alcohols to iodides with $ZrCl_4$ and NaI, see: Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2004**, *45*, 7451.

(22) Fleming, F. F.; Ravikumar, P. C.; Yao, L. *Synlett* **2009**, 1077.

(23) Bouziane, A.; Carboni, B.; Bruneau, C.; Carreaux, F.; Renaud, J.-L. *Tetrahedron* **2008**, *64*, 11745. Refluxing the bromomagnesium alkoxide intermediate does not afford any allylic bromide.

(24) A search using SciFinder Scholar identified over 4,000 reactions in which vinylmagnesium bromide affords an allylic alcohol (04/27/09).

SCHEME 4. Optimizing the Metalla-halo-[3,3] Rearrangement



trigger an allylic rearrangement (Scheme 4, **1a** → **4a**).[25] Assuming that magnesium was insufficiently Lewis acidic, the allylic alcohol **4a** was deprotonated with an organometallic base,[26] and the corresponding alkoxide **11a** was treated with one of a variety of metal salts (Scheme 4). Screening numerous metal halides quickly identified the Lewis acidic, oxophilic, high-valent transition metals[27] $TiCl_4$, $ZrCl_4$, $NbCl_4$, and $NbCl_5$ as being competent reagents.[28] Sequential addition of KH and either $TiCl_4$, $ZrCl_4$, $NbCl_4$, or $NbCl_5$ to a THF solution of **4a** afforded varying proportions of the allylic chloride **2a**, unreacted allylic alcohol **4a**, and 1,4-dichlorobutane arising from the chlorination of THF (Scheme 4, **4a** → **2a**).

Niobium pentachloride was selected for further optimization because of a greater tolerance to ethereal solvents,[29] the precedent for chlorinating aliphatic alcohols under forcing conditions,[30] and the convenience of using commercial, anhydrous, powdered $NbCl_5$.[31] Employing the strong Lewis acid[32] $NbCl_5$ under basic conditions is unusual and contrasts with related reactions of high-valent metal halides[33] that may well be promoted by adventitious acid produced by partial hydrolysis.[34] The nonprotic solvents CH_3CN, DMF, $PhCH_3$, and CCl_4 were significantly inferior to THF, whereas Et_2O and *t*-BuOMe afforded comparable results. Reasoning that a bidentate ethereal solvent might be more effective led to the use of 1,4-dioxane, which allowed essentially complete conversion to spectroscopically pure **2a** in 10 min. Aqueous extraction readily removes the spent niobium salt, providing pure chloride **2a** upon concentration, a significant advantage over related phosphonium-based reagents.[35]

Deprotonating the naphthyl alcohol **4a** with KH in dioxane followed by addition of niobium pentachloride affords the (*E*)-allylic chloride **2a** in 98% yield. Bulb-to-bulb distillation does not change the spectral purity but decreases the yield to 70% as a result of polymerization in the still pot.[36] Rapidly eluting the crude allylic chloride **2a** through a short pad of silica or alumina *decreases* the purity with a concomitant 30−40% mass loss, presumably through irreversible adsorption on silica gel.[37]

An efficient displacement of the allylic chloride was pursued as an additional proof of reaction efficiency. Initially the anion of malononitrile was selected with the naive hope of performing an in situ chlorination−displacement sequence.[38] No displacement occurs in dioxane,[39] whereas THF provided the substituted malononitrile **13a** in 65% yield accompanied by 24% of the product of double malononitrile displacement (Scheme 4). Although the overall yield was high, attention was shifted to phenyl sufenylate as a potent nucleophile[40] capable of only a single displacement. Not only is the overall chlorination−sulfenylation very efficient (Scheme 4, **2a** → **14a**), but X-ray crystallography[41] of the resulting sulfide **14a** secured the unequivocal assignment of the olefin stereochemistry.[42]

The *trans* stereochemistry of the allylic chloride **2a** is formally installed from a metalla-halo-[3,3] rearrangement, although concerted, ionic, and direct displacement mechanisms appear to operate competitively depending on the structure of the allylic alcohol (Table 1). Geraniol (**4b**), linalool (**4c**), and nerol (**4d**) generate mixtures of allylic chlorides accompanied by terpenyl chloride (**2e**). Principal conversion of geraniol (**4b**) to geranyl chloride (**2c**, Table 1, entry 1) likely occurs through a direct displacement,[30] whereas formation of terpenyl chloride (**2e**) requires a change in olefin stereochemistry. Conversion of geraniol (**4b**) to linaloyl chloride (**2b**) is precedented[43] and would facilitate an ionic or $NbCl_5$-promoted cyclization to terpenyl chloride (**2e**).[44]

A signature of a concerted metalla-halo-[3,3] chlorination, dictated by the cyclic transition structure, is preferential

(25) A control experiment in which non-1-en-3-ol was treated with vinylmagnesium bromide led only to recovered alcohol, establishing that the bromomagnesium alkoxide does not participate in a bromo-[3,3] rearrangment.

(26) KH was consistently superior over MeMgCl, BuLi, and NaH.

(27) For the strong M-O bond energy in the series Ti-O, Zr-O, Nb-O, see: (a) Loock, H.-P.; Simard, B.; Wallin, S.; Linton, C. *J. Chem. Phys.* **1998**, *109*, 8980. (b) Conner, J. A. *Top. Curr. Chem.* **1977**, *71*, 71.

(28) Smitha, G.; Chandrasekhar, S.; Reddy, C. S. *Synthesis* **2008**, 829.

(29) Ether is slowly cleaved with $NbCl_5$: Cowley, A.; Fairbrother, F.; Scott, N. *J. Chem. Soc.* **1958**, 3133.

(30) Coe, E. M.; Jones, C. J. *Polyhedron* **1992**, *11*, 3123.

(31) Dry niobium pentachloride powder was weighed in a glovebox and transferred directly to the reaction flask under a blanket of dry nitrogen.

(32) $NbCl_5$ is a strong Lewis acid, and $NbBr_5$ is expected to be of similar, though unknown, acidity: Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem.—Eur. J.* **2000**, *6*, 3491.

(33) Smitha, G.; Chandrasekhar, S.; Reddy, C. S. *Synthesis* **2008**, 829.

(34) Control experiments with dry HCl show that the formation of allylic chlorides is accompanied by more byproducts than in S_N2' displacements: Kishali, N.; Polat, M. F.; Altundas, R.; Kara, Y. *Helv. Chim. Acta* **2008**, *91*, 67.

(35) See ref 10.

(36) The instability of allylic halides has been noted previously: (a) Levina, R. Y.; Kaikaris, P. A.; Simolin, A. V.; Treshchova, E. G. *Zh. Obshch. Khim.* **1958**, *28*, 2309. (b) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1947**, *30*, 1876. (c) Campbell, K. N.; Eby, L. T. *J. Am. Chem. Soc.* **1940**, *62*, 1798.

(37) Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673.

(38) The niobium-based chlorination tolerates excess KH.

(39) Presumably because of the low solvent polarity, which has a dielectric constant of 2.209 at 25 °C: *CRC Handbook of Chemistry and Physics*; Weast, R. C., Ed.; CRC Press: Boca Raton, 1983−1984; E-51.

(40) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.

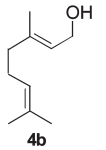
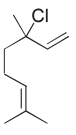
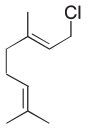
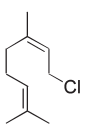
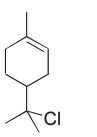
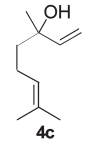
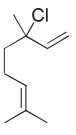
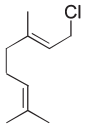
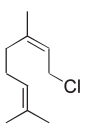
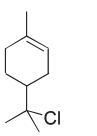
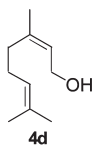
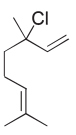
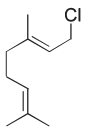
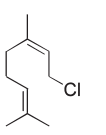
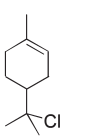
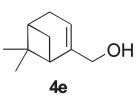
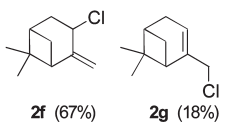
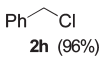
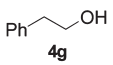
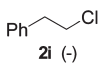
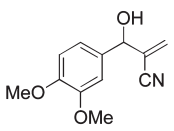
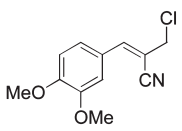
(41) The authors have deposited the crystallographic data with the Cambridge Crystallographic Data Center (CCDC no. 712587). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(42) The ^{1}H NMR coupling constants of the allylic chloride, nitrile, and sulfide were all 15, which falls in the range for a *trans*-alkene but is only slightly greater than the normal range for *cis*-alkenes: Gunther, H. In *NMR Spectroscopy. Basic Principles, Concepts, and Applications in Chemistry*, 2nd ed.; Wiley: Chichester, 1998; p 45.

(43) Cori, O.; Chayet, L.; Perez, L. M.; Bunton, C. A.; Hachy, D. *J. Org. Chem.* **1986**, *51*, 1310.

(44) Extended reaction times change the product ratio, consistent with a $NbCl_5$-promoted cyclization, but considerable decomposition occurs, which could potentially cause selective removal of one or more of the allylic chlorides.

TABLE 1. Allylic Alcohol Chlorinations with $NbCl_5$

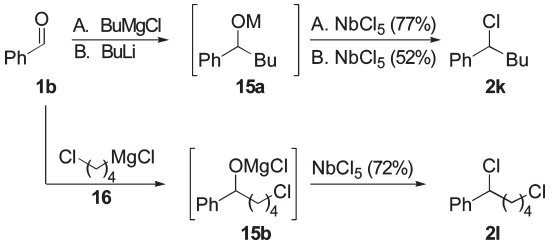
entry	alcohol	allylic chloride			
1	 **4b**	 **2b** (9%)	 **2c** (69%)	 **2d** (-)	 **2e** (10%)
2	 **4c**	 **2b** (4%)	 **2c** (62%)	 **2d** (-)	 **2e** (24%)
3	 **4d**	 **2b** (3%)	 **2c** (15%)	 **2d** (15%)	 **2e** (51%)
4	 **4e**		 **2f** (67%)	**2g** (18%)	
5	 **4f**		 **2h** (96%)		
6	 **4g**		 **2i** (-)		
7	 **4h**		 **2j** (96%)		

formation of an (*E*)-allylic chloride (Scheme 3). Linalool (**4c**) participates in the chlorination to afford some terpenyl chloride but mainly (*E*)-geranyl chloride (**2c**). The absence of (*Z*)-neryl chloride (**2d**) is consistent with a metalla-halo-[3,3] rearrangement, although the presence of multiple products from these terpenes strongly implies ionization as a significant pathway (Table 1, entry 2).[45] Nerol (**4d**) affords a mixture of all four allylic chlorides with terpenyl chloride (**2e**) predominating, presumably because the (*Z*)-olefin geometry facilitates cyclization (Table 1, entry 3). Although these chlorinations can formally be viewed as metalla-halo-[3,3] rearrangements, the formation of regioisomeric mixtures suggests that direct displacement and ionization mechanisms at least operate competitively and possibly predominate in some cases.

Chlorinating the cyclic allylic alcohol **4e** and the acyclic alcohols **4f**−**4h** with different propensities toward ionization confirms the presence of several competing chlorination mechanisms (Table 1, entries 4−7). Myrtenol (**4e**) exhibits a 3-fold preference for the rearranged chloride **2f** despite having a less stable exocyclic olefin compared to the endocyclic chloride **2g** (Table 1, entry 4). Benzyl alcohol (**4f**), in which a metalla-halo-[3,3] rearrangement is prevented, undergoes halogenation considerably slower and requires 2 equiv[46] of $NbCl_5$, implying displacement via a bis-niobium complex.[47] Activation of the alcohol by an adjacent π-system seems to be significant as the attempted chlorination of **4g** was not successful (Table 1, entry 6). In contrast, the hydroxyalkenenitrile **4h** bearing two adjacent π-systems affords exclusively the rearranged chloride **2j** (Table 1, entry 7). Although several mechanisms appear to compete in the $NbCl_5$ chlorination, the metalla-halo-[3,3] rearrangement seems to dominate when olefin migration leads to a more stable allylic chloride.

The ability to chlorinate benzyl alcohol stimulated a direct nucleophilic addition−chlorination with aldehydes (Scheme 5). Adding BuMgCl or BuLi to benzaldehyde affords metal alkoxides **15a** that are readily transformed into the secondary benzylic chloride **2k** upon exposure to 2.5 equiv of $NbCl_5$. An analogous addition of the chlorine-containing Grignard reagent **16**[48] efficiently provides the dichloride **2l**, indicating that $NbCl_5$ tolerates additional chlorination in the substrate (Scheme 5).

SCHEME 5. Organometallic Addition−Chlorination with $NbCl_5$



The sequential addition−chlorinations with benzaldehyde (Scheme 5) provided an excellent foundation for the direct halo-olefination of aldehydes and ketones (Table 2).[49] In the optimized procedure, vinylmagnesium bromide[50] was added to a THF solution[51] of the aldehyde, and then 4 volumes of dioxane and solid $NbCl_5$ were added. After 10 min the crude chloride[52]

(45) An analogous rearrangement with $NbBr_5$ affords mainly geranyl bromide (86%) accompanied by terpenyl bromide (12%) consistent with a more rapid cyclization of any linaloyl bromide.

(46) One equivalent of $NbCl_5$ cleanly affords equal ratios of benzyl alcohol and benzyl chloride, whereas less than 1 equiv of $NbCl_5$, in the absence of base, affords only trace amounts of the chloride : (a) Yadav, J. S.; Bhunia, D. C.; Krishna, K. V.; Srihari, P. *Tetrahedron Lett*. **2007**, *48*, 8306. (b) Coe, E. M.; Jones, C. J. *Polyhedron* **1992**, *11*, 3123. Related chlorination of benzylic alcohols with WCl_6 only requires 0.3 equiv: Firouzabadi, H.; Shiriny, F. *Tetrahedron* **1996**, *52*, 14929.

(47) Malhotra, K. C.; Banerjee, U. K.; Chaudhry, S. C. *J. Indian Chem. Soc*. **1980**, *58*, 868.

(48) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem*. **1980**, *45*, 4702.

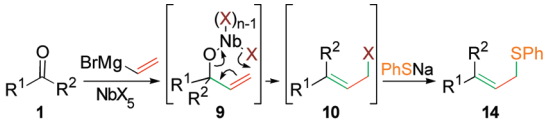
(49) Addition of the Grignard reagent prior to the addition of $NbCl_5$ or $NbBr_5$ is required to avoid transmetallation to an organoniobium species because these organoniobiums are weak nucleophiles that do not react with ketones: Kauffmann, T.; Antfang, E.; Ennen, B.; Klas, N. *Tetrahedron Lett*. **1982**, *23*, 2301.

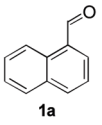
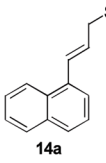
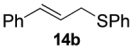
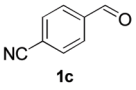
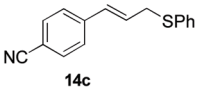
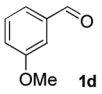
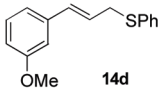
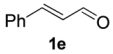
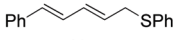
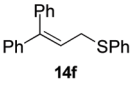
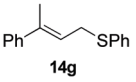
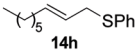
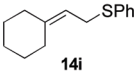
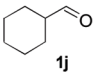
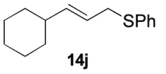
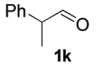
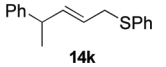
(50) Vinylmagnesium chloride in THF is significantly less efficient in contrast to the related procedure employing $TiCl_4$.[20]

(51) Optimization experiments revealed the necessity of THF in the Grignard addition as the use of dioxane caused incomplete addition.

(52) Close scrutiny of the intermediate chloride revealed the presence of less than 5% of a closely related material that was eventually identified as the corresponding (*E*)-allylic bromide. The naphthyl bromide could arise by in situ displacement of the chloride by the bromide present from the Grignard reagent or potentially through a mixed Mg-Nb species.

TABLE 2. Direct Halo-olefination−Sulfide Displacement of Aldehydes and Ketones



entry	aldehyde	sulfide	yield [a]
1	 1a	 14a	84 (84)
2	 1b	 14b	72 (79)
3	 1c	 14c	66 [b]
4	 1d	 14d	57 [b]
5	 1e	 14e	89
6	 8f	 14f	78
7	 8g	 14g	78 [b]
8	 1h	 14h	85 [b] (95)
9	 8i	 14i	44 [b]
10	 1j	 14j	84 [b] (66)
11	 1k	 14k	76 (98)

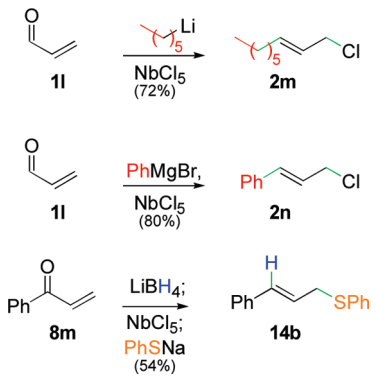
[a]Isolated yields of the sulfides. The yields in parentheses are for the corresponding halide that was isolated in cases where the material was stable to distillation or rapid purification on silica gel. [b]Prepared with $NbBr_5$.

was isolated and subjected to phenylsulfenylate displacement in THF to afford the corresponding sulfide. In each case, ^{1}H NMR analysis of the crude chloride and sulfide reaction mixture identified the (*E*)-alkene as the sole geometric isomer.

Aromatic aldehydes (**1a**−**1d**), enals (**1e**), and ketones (**8f** and **8g**) are smoothly converted to the corresponding chlorides and sulfides (Table 2, entries 1−7). *p*-Cyanobenzaldehyde (**1c**) reacts sluggishly with $NbCl_5$, whereas $NbBr_5$ was more significantly reactive,[53] a trend apparent in the addition−halogenations with aliphatic aldehydes and ketones (Table 2, entries 8−11).[54] The substrates tolerate a nitrile group, a methoxy ether, and adjacent unsaturation in the aldehyde (Table 2, entries 3, 4, and 5, respectively). Despite $NbCl_5$ being able to cleave methyl ethers,[55] the methyl ether containing aldehyde **1d** is smoothly converted to the allylic chloride provided that the temperature is lowered to 0 °C.[56] Acetals are not well tolerated,[57] suggesting that the method is best suited to the synthesis of hydrocarbon scaffolds bearing limited heteroatom substituents.

The niobium-mediated halogenation of metal alkoxides is equally effective for the addition of organometallics to unsaturated carbonyl compounds (Scheme 6). Sequential addition of hexyllithium or PhMgCl and $NbCl_5$ to acrolein (**1l**) efficiently provides the allylic chloride **2m** and cinnamyl chloride (**2n**), respectively. Reducing ketone **8m** with $LiBH_4$ and adding $NbCl_5$ affords the corresponding chloride that was displaced with sulfenate in an overall reductive-sulfenylation with translocation of the double bond. Collectively these addition−chlorination and reduction−chlorination sequences imply significant scope for halogenating allylic alkoxide intermediates.

SCHEME 6. Organometallic Addition−$NbCl_5$ Chlorination



The proclivity of allylic alcohols to participate in the formal metalla-halo-[3,3] rearrangement stimulated expanding the substrate scope to include propargylic alcohols (Table 3). Sequential deprotonation and chlorination of the propargylic alcohol **5a** afforded only a trace of the allenyl chloride at room temperature, whereas coaxing the reaction through heating caused considerable decomposition. $NbBr_5$ proved to be a more efficient halogenating agent, triggering a smooth rearrangement at room temperature (Table 3, entry 1).

The $NbBr_5$ rearrangement is of reasonably broad scope and provides rapid access to synthetically versatile bromoallenes (Table 3).[58] Secondary and tertiary propargylic alcohols react with similar efficiency in affording 1,2-disubstituted

(53) The greater nucleophilicity of $NbBr_5$ is consistent with the related bromination of α-hydroxyacrylates where $TiBr_4$ acts through a direct displacement on the oxygen-bearing carbon: Shi, M.; Wang, C.-J. *Tetrahedron* **2002**, *58*, 9063.

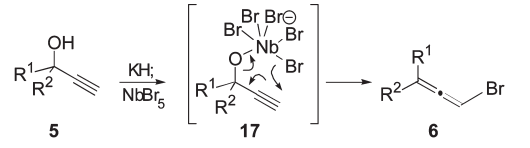
(54) ^{1}H NMR analysis of the crude allylic chloride or bromide indicated complete rearrangement to the allylic halide prior to the sulfenylate displacement.

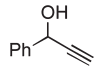
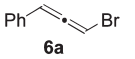
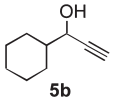
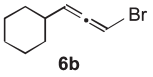
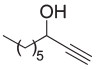
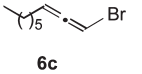
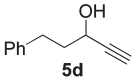
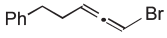
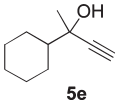
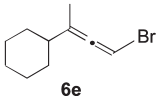
(55) Arai, S.; Sudo, Y.; Nishida, A. *Synlett* **2004**, 1104.

(56) Extended exposure of *m*-methoxybenzaldehyde (**1d**) to $NbCl_5$ reduces the yield of the reaction with ^{1}H NMR analysis being consistent with methyl-ether cleavage.

(57) Performing the addition−rearrangement−sulfenylate displacement with piperonal proceeded in 20% yield with the minor reaction components exhibiting spectral data consistent with acetal cleavage.

TABLE 3. Metala-halo-[3,3] Rearrangement of Propargylic Alcohols



entry	propargyllic alcohol	allenic bromide	yield (%)
1	 **5a**	 **6a**	53
2	 **5b**	 **6b**	78
3	 **5c**	 **6c**	62
4	 **5d**	 **6d**	65
5	 **5e**	 **6e**	57

and 1,1,2-trisubstituted allenes, respectively (Table 3, entries 1−4 and 5). The bromination is equally applicable to alcohols with adjacent aromatic or aliphatic substituents (Table 3, compare entry 1 with entries 2−5).[59] Formally, the allenyl bromide synthesis is envisaged through the hexacoordinate niobiate **17**,[47] although full or partial ionization may occur during the olefin transposition. Internal delivery of the halogen to the olefin terminus is likely promoted by concomitant formation trichloroniobium oxide.[60]

Conclusion

Allylic and allenic halides are readily generated by adding $NbCl_5$ or $NbBr_5$ to allylic or propargylic alkoxides. The halogenation formally occurs through a metalla-halo-[3,3] rearrangement, although ionization and direct displacement mechanisms appear to operate competitively. The intermediate allylic alkoxides can be prepared by deprotonation or, equally as effectively, through an organometallic addition or reduction allowing the direct conversion of an aldehyde or ketone to the corresponding allylic chloride. Particularly useful is the direct "halo-olefination" of aromatic and aliphatic aldehydes by sequential addition of vinylmagnesium bromide and $NbCl_5$ or $NbBr_5$. Secondary or tertiary propargylic alcohols react similarly with $NbBr_5$ to afford allenylic bromides. The halides are readily isolated in pure form through simple extraction and can be used in subsequent displacements without prior purification.

Experimental Section

General Chlorination Procedure for Allylic Alcohols. Potassium hydride (30% dispersion in mineral oil, 1.2 equiv) was washed with hexane (3 mL), and then a dioxane solution of the allylic alcohol (1 equiv) was added dropwise. After 5 min solid $NbCl_5$ (1.2 equiv) was added as a dry powder. After 10 min[61] the reaction mixture was poured into 2 M HCl and then extracted with ethyl acetate.

General Procedure for the Direct Synthesis of Allylic Chlorides from Aldehydes. A THF solution of vinyl magnesium bromide (0.7 M solution) was added to a 10 °C THF solution (0.75−0.85 M) of the aldehyde. After 15 min, 1,4-dioxane (4 volumes relative to THF) and solid $NbCl_5$ (2.5 equiv) were added sequentially. After 10 min the reaction mixture was poured into 2 M HCl and extracted with ethyl acetate, and the combined organic extract was then washed with brine and dried (Na_2SO_4).

General Addition−Chlorination−Sulfide Displacement Procedure. A THF solution of vinyl magnesium bromide (0.7 M solution) was added to a 10 °C THF solution (0.75−0.85 M) of the aldehyde or ketone. After 15 min, 1,4-dioxane (4 vol relative to THF) and solid $NbCl_5$ (1.2 equiv) were added sequentially. After 10 min the reaction mixture was poured into 2 M HCl and extracted with ethyl acetate, and the combined organic extract was then washed with brine and dried (Na_2SO_4). A THF solution (0.2 M) of the crude, essentially pure, allylic chloride was added to a 10 °C THF suspension of sodium hydride (2.0−2.5 equiv) to which had been added thiophenol (2.0−2.5 equiv). The reaction mixture was allowed to warm to rt over 16 h, poured into an aqueous sodium hydroxide solution (2% by weight), and then extracted with ethyl acetate. The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to furnish an oily residue that was purified by radial chromatography to furnish the pure sulfide.

General Allenyl Bromide Rearrangement Procedure. A dioxane solution of the propargyllic alcohol (1 equiv) was added to a dioxane solution of potassium hydride (1.2 equiv). After 10 min, the solid niobium bromide (1.2 equiv) was added. After 2 h, the reaction mixture was poured into HCl (2 M), and the phases were separated. The aqueous phase was extracted with EtOAc, and then the combined organic phase was washed with brine, dried ($NaSO_4$), and concentrated to provide an oil that was purified by radical chromatography.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds, an ORTEP for **14a**, and complete experimental details following the general procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

(58) For recent uses of bromoallenes, see: (a) Zhang, W.; Xu, H.; Xu, H.; Tang, W. *J. Am. Chem. Soc.* **2009**, *131*, 3832. (b) Tang, Y.; Shen, L.; Dellaria, B. J.; Hsung, R. P. *Tetrahedron Lett.* **2008**, *49*, 6404. (c) Xia, Y. Z.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. H. *J. Am. Chem. Soc.* **2008**, *130*, 6940. (d) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Fujii, N.; Tanaka, T. *Chem.—Eur. J.* **2007**, *13*, 1692. (e) Vaz, B.; Dominguez, M.; Alvarez, R.; de Lera, A. R. *Chem.—Eur. J.* **2007**, *13*, 1273. (f) Tang, C. J.; Wu, Y. K. *Tetrahedron* **2007**, *63*, 4887. (g) Shen, L. C.; Hsung, R. P.; Zhang, Y. S.; Antoline, J. E.; Zhang, X. J. *Org. Lett.* **2005**, *7*, 3081. (h) Ma, S.; Xie, H. *Tetrahedron* **2005**, *61*, 251. (i) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (j) Xu, B.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7404. (k) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1513.

(59) For the regioselective conversion of α-aryl propargylic alcohols **5** (R^2 = Ar) to allenyl bromides see: Sakai, N.; Maruyama, T.; Konakahara, T. *Synlett* **2009**, 2105.

(60) Gibson, V. C.; Kee, T. P.; Shaw, A. *Polyhedron* **1988**, *7*, 2217.

(61) Thin layer chromatography allows convenient monitoring of sluggish reactions. Samples can be directly removed and applied to a TLC plate and are conveniently analyzed because most allylic alcohols are considerably more polar than the corresponding chloride.