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Allylic and Allenic Halide Synthesis via NbCl₅- and NbBr₅-Mediated Alkoxide Rearrangements

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Abstract
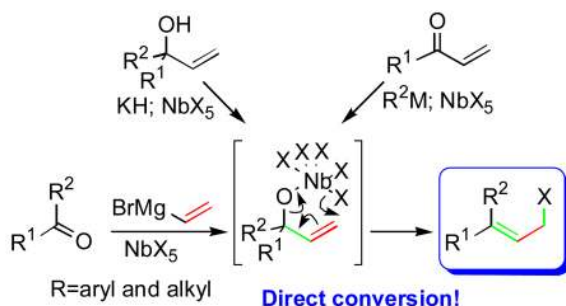
Addition of NbCl₅, or NbBr₅, to a series of magnesium, lithium, or potassium allylic or propargylic alkoxides directly provides allylic or allenic halides. Halogenation formally occurs through a metalla-halo-[3,3] rearrangement although concerted, ionic, and direct displacement mechanisms appear to operate 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 σ^*_{C-X} orbital and the adjacent π system[2] which facilitates 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[9] dependent with many reactions channeling through both S$_N$2 and S$_N$2' displacement manifolds.[10]

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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]

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=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]

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 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 and the corresponding alkoxide **11a**[26] treated with one of a variety of a 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] which may well be promoted by adventitious acid produced by partial hydrolysis.[34] The non-protic solvents CH$_3$CN, DMF, PhCH$_3$ and CCl$_4$ were significantly inferior to THF whereas Et$_2$O 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 minutes. 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 naïve hope of performing an in situ deprotonation-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 **13a** secured the unequivocal assignment of the olefin stereochemistry.[42]

The *trans*-stereochemistry of the allylic chloride **2a** formally arises 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. Isomerization 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 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 operate at least competitively and possibly predominate in some cases.

Chlorinating the cyclic allylic alcohol **4e** and the acyclic alcohols **4f–4h** with different propensities toward ionization confirm the presence of several competing chlorination mechanisms (Table 1, entries 4–7). Myrtenol (**4e**) exhibits a three-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 two equivalents[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 equivalents 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).

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 four volumes of dioxane and solid $NbCl_5$ were added. After 10 min the crude chloride[52] 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, 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.

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 and 1,1,2-trisubstituted allenes, respectively (Table 3, entries 1–4 and entry 5). The bromination is equally applicable to alcohols with adjacent aromatic or aliphatic substituents (Table 3, compare entry 1 with entries 2–5). 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.[59]

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 minutes solid $NbCl_5$ (1.2 equiv) was added as a dry powder. After 10 min[60] 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, 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 volumes 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, 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 (2M), 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 which was purified by radical chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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 one equivalent of $NbCl_5$, in the absence of base, affords only trace amounts of the chloride: (a)Yadav JS, Bhunia DC, Krishna KV, Srihari P. Tetrahedron Lett 2007;48:8306. (b)Coe EM, Jones CJ. Polyhedron 1992;11:3123. Related chlorination of benzylic alcohols with WCl_6 only requires 0.3 equivalents: Firouzabadi H, Shiriny F. Tetrahedron 1996;52:14929.

47. Malhotra KC, Banerjee UK, Chaudhry SC. J. Indian Chem. Soc 1980;58:868.

48. Bernady KF, Poletto JF, Nocera J, Mirando P, Schaub RE, Weiss MJ. 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.

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.

58. For recent uses of bromoallenes see: (a)Zhang W, Xu H, Xu H, Tang W. J. Am. Chem. Soc 2009;131:3832. [PubMed: 19245198] (b)Tang Y, Shen L, Dellaria BJ, Hsung RP. Tetrahedron Lett 2008;49:6404. (c)Xia YZ, Dudnik AS, Gevorgyan V, Li YH. J. Am. Chem. Soc 2008;130:6940. [PubMed: 18461941] (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 AR. Chem. Eur. J 2007;13:1273. (f) Tang CJ, Wu YK. Tetrahedron 2007;63:4887. (g)Shen LC, Hsung RP, Zhang YS, Antoline JE, Zhang XJ. Org. Lett 2005;7:3081. [PubMed: 15987210] (h)Ma S, Xie H. Tetrahedron 2005;61:251. (i)Trost BM, Stiles DT. Org. Lett 2005;7:2117. [PubMed: 15901148] (j)Xu B, Hammond GB. Angew. Chem., Int. Ed 2005;44:7404. (k)Hamaguchi H, Kosaka S, Ohno H, Tanaka T. Angew. Chem., Int. Ed 2005;44:1513.

59. Gibson VC, Kee TP, Shaw A. Polyhedron 1988;7:2217.

60. 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.
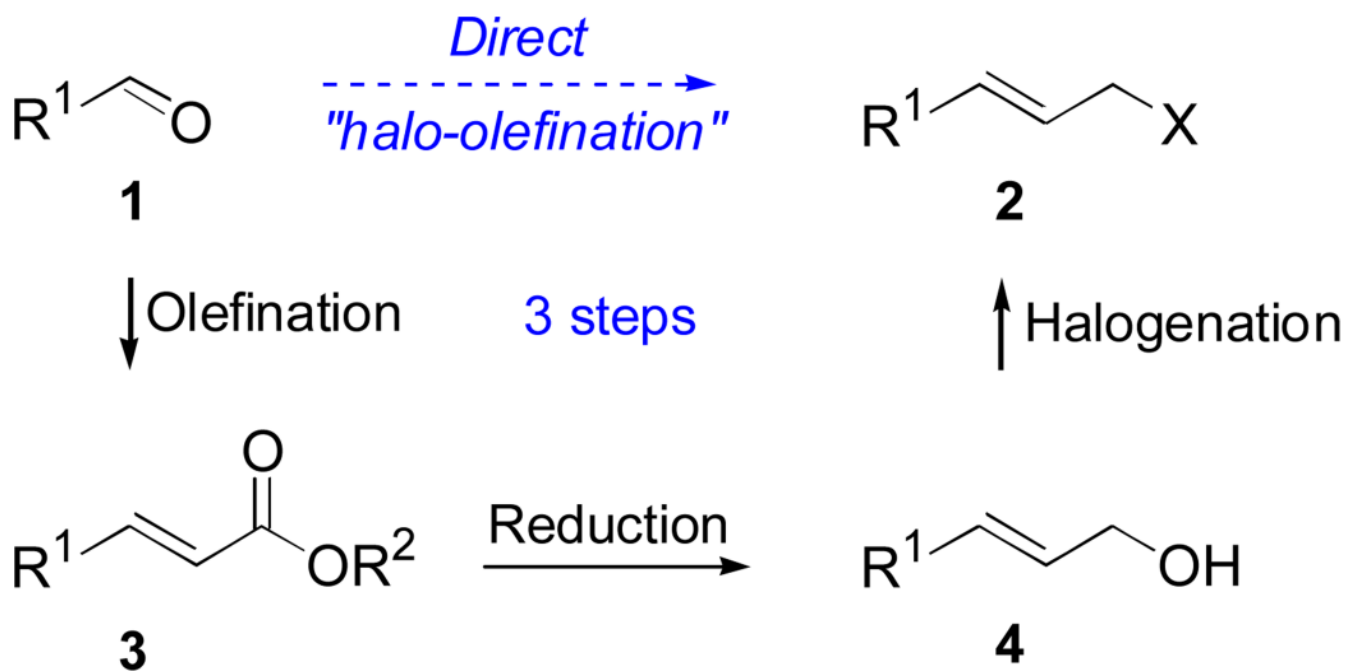
Scheme 1.
Typical Allylic Halide Synthesis
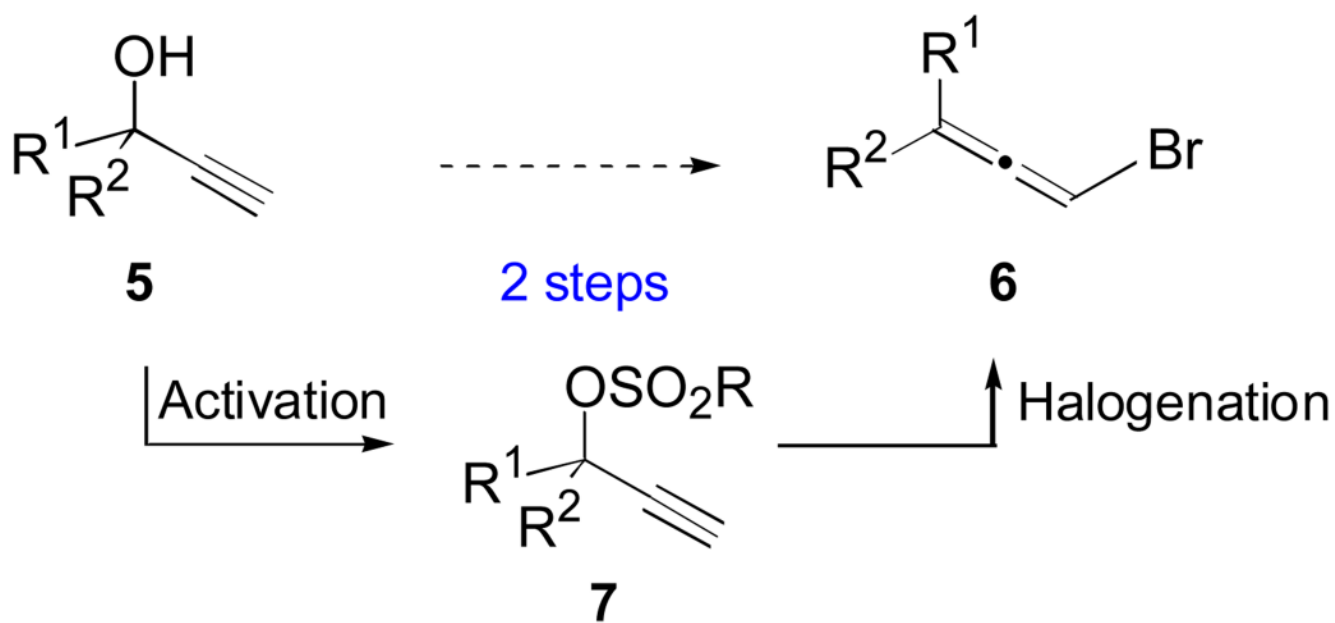
Scheme 2.
Typical Allenic Halide Synthesis

Scheme 3.
Vinyl Addition-Metalla-Halo-[3,3]-Rearrangement
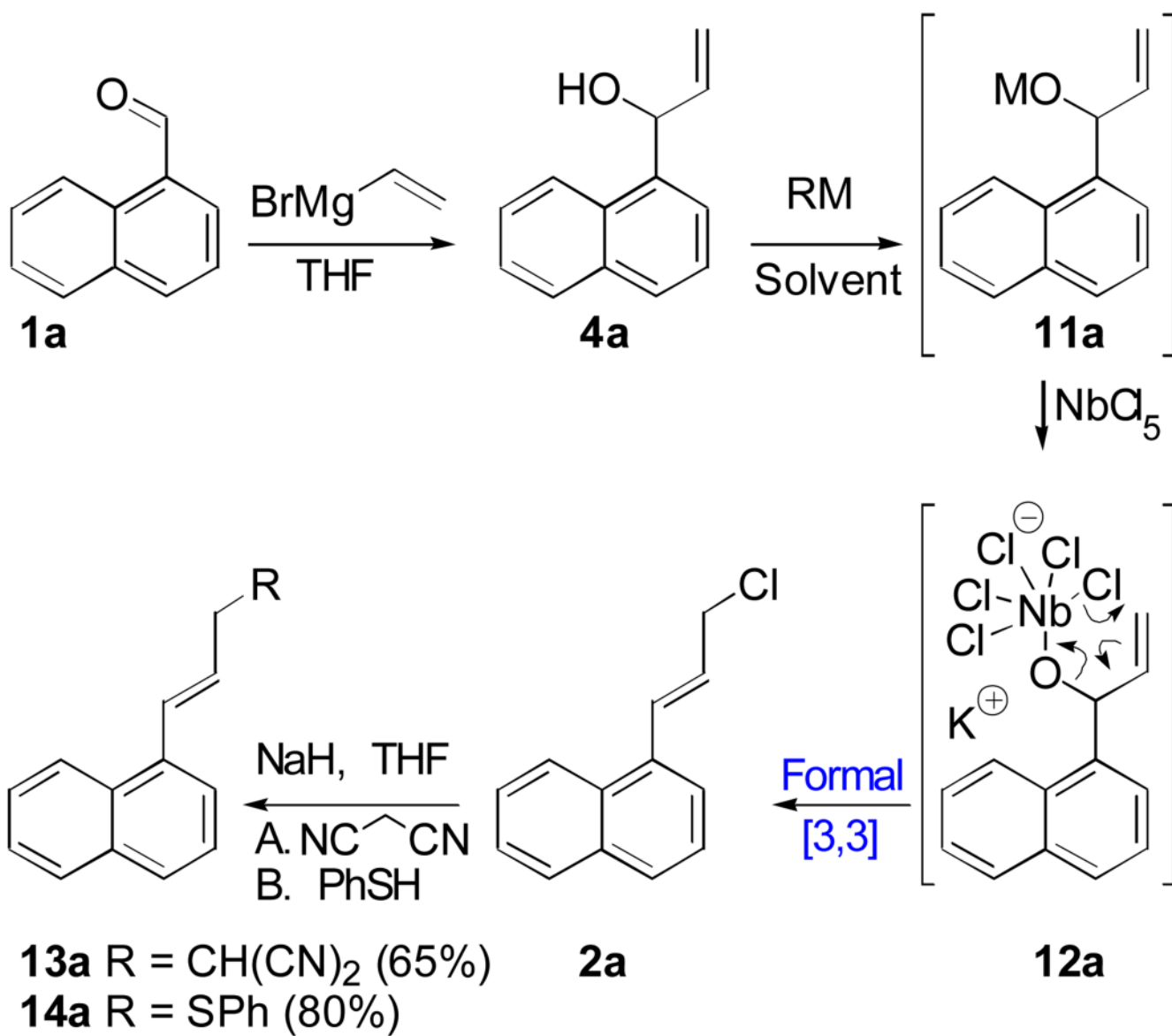
Scheme 4.
Optimizing the Metalla-Halo-[3,3]-Rearrangement
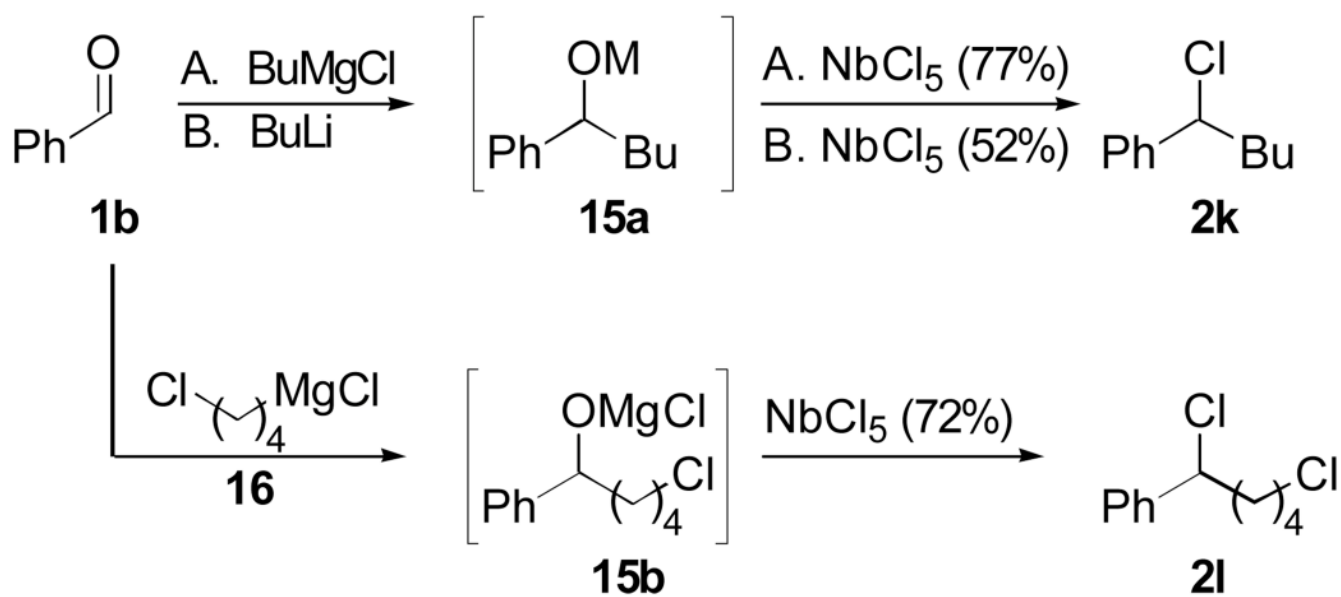
Scheme 5.
Organometallic Addition-Chlorination with NbCl$_5$
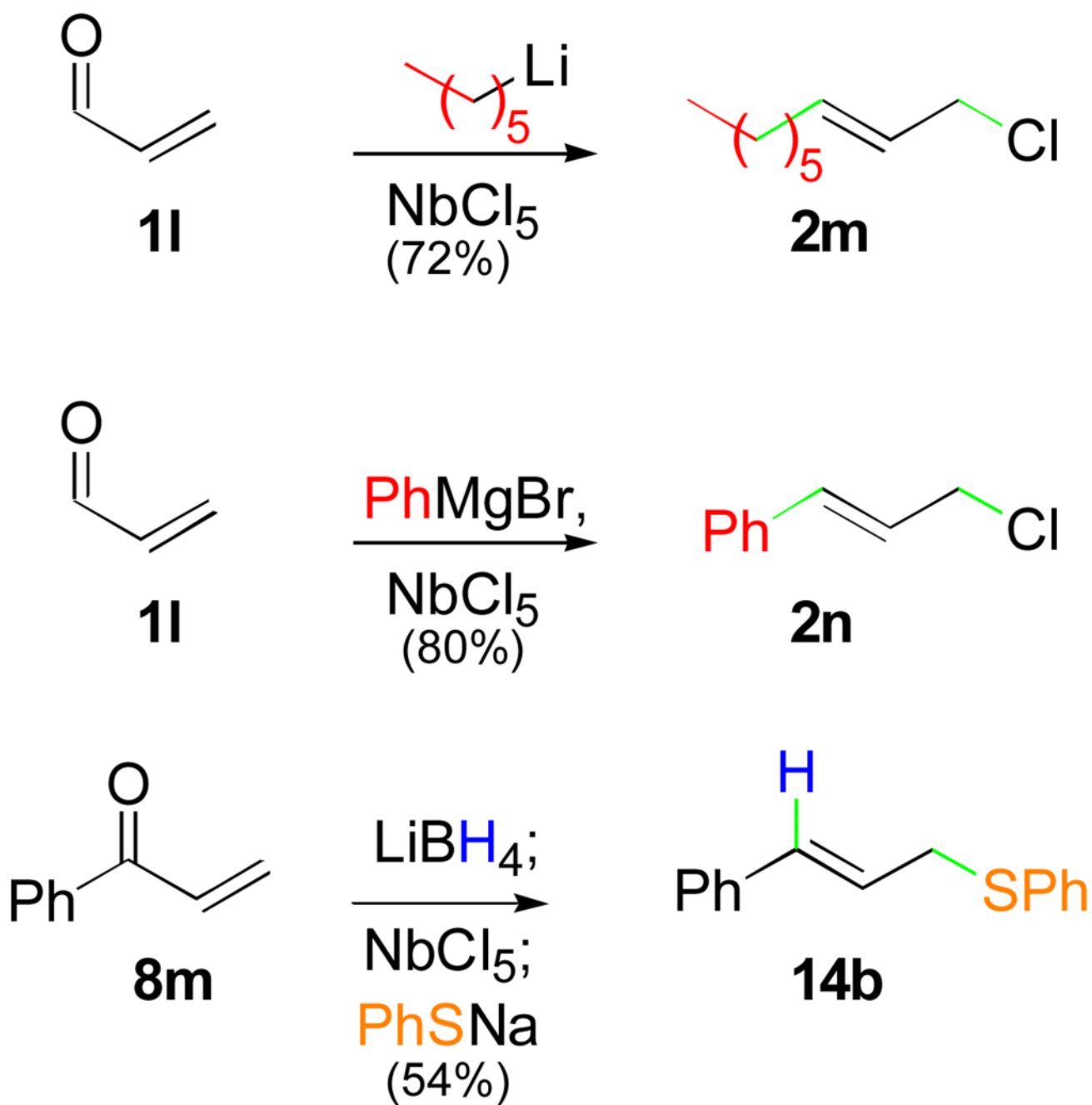
Scheme 6.
Organometallic-Addition- NbCl$_5$ Chlorination.

Table 1

Allylic Alcohol Chlorinations with NbCl$_5$
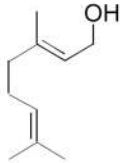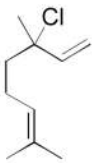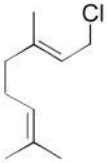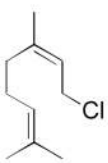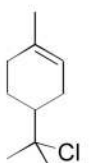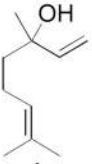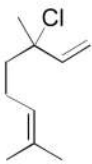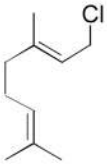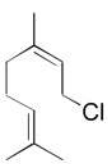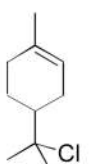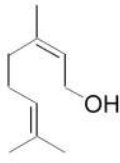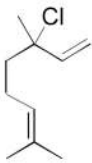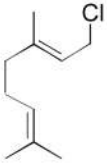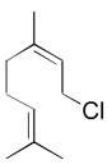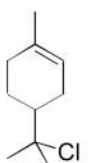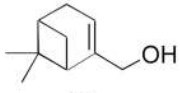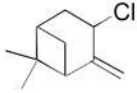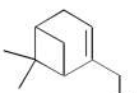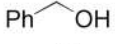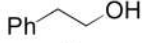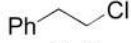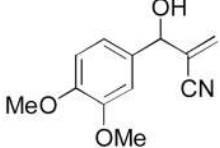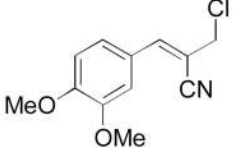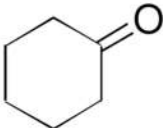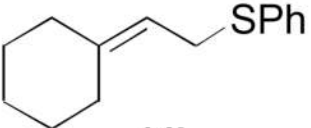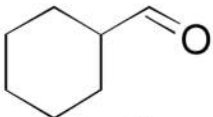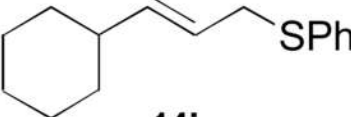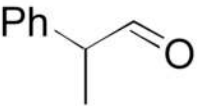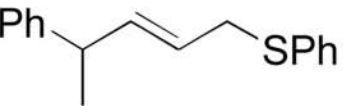
entry	alcohol				allylic chloride

Entry 1: **4b** → **2b** (9%) **2c** (69%) **2d** (-) **2e** (10%)

Entry 2: **4c** → **2b** (4%) **2c** (62%) **2d** (-) **2e** (24%)

Entry 3: **4d** → **2b** (3%) **2c** (15%) **2d** (15%) **2e** (51%)

Entry 4: **4e** → **2f** (67%) **2g** (18%)

Entry 5: Ph—OH **4f** → Ph—Cl **2h** (96%)

Entry 6: Ph—OH **4g** → Ph—Cl **2i** (-)

Entry 7: **4h** → **2j** (96%)

Table 2

Direct Halo-Olefination-Sulfide Displacement of Aldehydes and Ketones
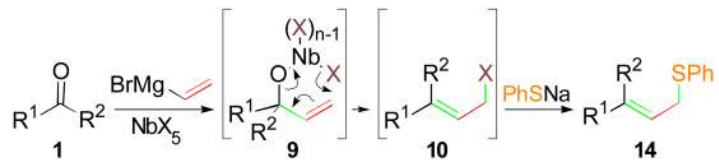
entry	aldehyde	sulfide	yield [a]
1	1a	14a	84 (84)
2	1b	14b	72 (79)
3	1c	14c	66[b]
4	1d	14d	57[b]
5	1e	14e	89
6	8f	14f	78
7	8g	14g	78[b]
8	1h	14h	85[b] (95)

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 which was isolated in cases where the material was stable to distillation or rapid purification on silica gel.

[b]Prepared with NbBr5.

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