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Direct Conversion of Aldehydes and Ketones to Allylic Halides by a NbX$_5$-[3,3] Rearrangement

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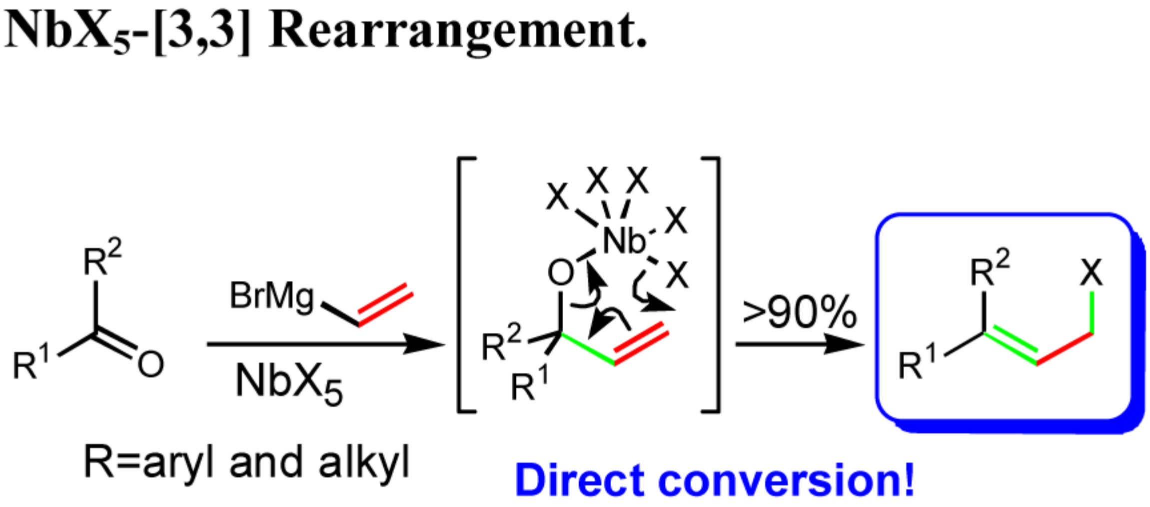
Abstract



Sequential addition of vinylmagnesium bromide and NbCl$_5$, or NbBr$_5$, to a series of aldehydes and ketones directly provides homologated, allylic halides. Transposition of the intermediate vinyl alkoxide is envisaged through a metalla-halo-[3,3] rearrangement with concomitant delivery of the halogen to the terminal carbon. The [3,3] rearrangement is equally effective for the conversion of a propargyllic alcohol to the corresponding allenyl bromide.

Keywords

Niobium pentachloride; niobium pentabromide; alkyl halides; halogenation; rearrangements

Allylic halides occupy a privaleged position as electrophiles.[1] Activation of the carbon-halogen bond by adjacent π electrons dramatically facilitates nucleophilic displacement,[2] allowing otherwise difficult bond constructions with a diverse range of carbon, heteroatom, and organometallic nucleophiles.[3] Allylic halides prepared as intermediates during total syntheses are typically prepared by halogenation of allylic alcohols. These in turn are often obtained by olefination-reduction sequences[4] because the direct "halo-olefination" of carbonyls with Wittig-type procedures is circumvented by elimination in the reagent.

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A conceptually direct method for converting aldehydes and ketones to allylic halides is through a sequenced vinyl addition-metalla-halo-[3,3]-rearrangement (Scheme 1).[5] Addition of vinylmagnesium bromide to an aldehyde or ketone generates the bromomagnesium alkoxide **2**,[6] potentially allowing transmetallation to a more oxophilic metal capable of weakening the carbon-oxygen bond for a metalla-halo-[3,3]-rearrangement.[7] Particularly Lewis acidic halometal alkoxides **3** may cause competitive ionization and halogenation leading to a mixture of allylic halide regioisomers[8] whereas metals bearing more nucleophilic halides would favor the rearranged allylic halide **4**.

$TiCl_4$ effectively promotes this sequence with aromatic aldehydes and with magnesium alkoxides derived from deprotonation of allylic alchohols.[7] Results presented below show that $NbCl_5$ and $NbBr_5$ expand the scope of this vinyl addition-metalla-halo-[3,3]-rearrangement to include aromatic *and* aliphatic aldehydes and aromatic and aliphatic ketones. In addition, the [3,3] rearrangement is equally effective for the conversion of a propargylic alcohol to the corresponding bromoallene implying a concerted rearrangement in distinction to the related reactions with $TiCl_4$.

Exploring the viability of a sequenced vinyl addition-metalo-halo-[3,3]-rearrangement initially focused on identifying an optimal metal and solvent combination. Using the potassium alkoxide **6** as a prototype, a diverse range of metal chlorides were evaluated for their effectiveness in providing the allylic chloride **4a** (Scheme 2). Screening several oxophilic metals[9] identified dry[10] niobium pentachloride[11] in 1,4-dioxane as the optimal combination. After only 10 minutes at room temperature the alcohol **5** was completely converted to the allylic chloride **4a** in essentially quantitative yield. ^{1}H and ^{13}C NMR analysis of the crude product indicated the material to be pure.[12]

The use of niobium pentachloride is particularly intriguing because this strong Lewis acid[13] is employed under *basic* conditions. These conditions contrast with many related reactions[14] in which transition metal halides exhibit reactivity similar to that of HCl which might be liberated by contact of the reagent with moisture.[15] Mechanistically attack of the alkoxide **6** on $NbCl_5$ might trigger rearrangement from the niobiate **3a** having an expanded coordination sphere (Scheme 2).[16] Sequential ionization and chlorination of **3a** is a mechanistic possibility, although the absence of regio- and stereoisomers suggests this to be a minor reaction manifold. Synthetically the $NbCl_5$ rearrangement offers the advantage over related phosphonium-based reagents in facile isolation of (*E*)-allylic chlorides simply by an aqueous extraction to remove inorganic species.

Optimizing the metalo-halo-[3,3]-rearrangement with the allylic alcohol **5** provided a platform for directly converting aldehyde **1a** to the allylic chloride **4a** (Scheme 3). Partial ring opening of THF[17] by $NbCl_5$ led to a procedure in which vinylmagnesium bromide[18] was added to a 10 °C, THF solution of aldehyde **1a** followed by dilution with four volumes of 1,4-dioxane and addition of solid $NbCl_5$ (1.2 equiv). After 30 minutes the solution was washed with aqueous HCl and concentrated to provide the crude chloride[19] **4a** (99%).[20]

The naphthyl-substituted allylic chloride **4a** is challenging to purify. Silica-based purification methods resulted in significant mass loss suggesting partial alkylation of the solid-phase.[12] Consequently the crude chloride **4a** was redissolved in THF and reacted with sodium phenylsulfenylate (Scheme 3). The procedure efficiently provided the sulfide **7a** ratifying the efficiency of the niobium rearrangement in generating essentially pure allylic chloride **4a**.

Performing the vinyl addition-niobium rearrangement-sulfenylate displacement with a series of aldehydes efficiently provides the corresponding sulfides (Table 1). Aromatic aldehydes and ketones smoothly rearrange in the presence of $NbCl_5$ (Table 1, entries 1-5). The nitrile-containing aromatic aldehyde **1e** was less reactive toward $NbCl_5$ but was effectively halogenated with $NbBr_5$ (Table 1, entry 5). Aliphatic aldehydes are converted to the corresponding allylic chlorides with $NbCl_5$ but greater efficiency is obtained with $NbBr_5$ (Table 1, entries 6-7). The aliphatic ketone cyclohexanone reacted sluggishly even with $NbBr_5$ (Table 1, entry 8). In each case analysis of the intermediate allylic halide shows complete rearrangement prior to the sulfenylate displacement.

The metalo-halo-[3,3]-rearrangement is best suited to hydrocarbons. A conjugated aldehyde (Table 1, entry 4) and a nitrile (Table 1, entry 5) are readily tolerated whereas an acetal is not.[21] Effort to further probe the functional group tolerance is in progress.

The metalla-halo-[3,3]-rearrangement is not limited to the addition of vinylmagnesium halide to aldehydes and ketones. The strategy was extended to halogenation of the propargylic alcohol **8a** with the expectation that a concerted rearrangement would favor a haloallene (Scheme 4). Deprotonating **8a** and adding $NbCl_5$ afforded only a trace of the corresponding chloro allene at room temperature with full conversion requiring heating the reaction mixture to reflux. Under these thermal conditions considerable decomposition occurred whereas substituting $NbBr_5$ triggerred a smooth rearrangement at room temperature. After 2 h the bromoallene **10a** was obtained in 78% yield.

Direct transformation of aldehydes and ketones to the corresponding allylic halides is readily achieved through a vinyl addition metalo-halo-[3,3]-rearrangement strategy. Sequential addition of vinylmagnesium bromide and $NbCl_5$ or $NbBr_5$ to aromatic and aliphatic aldehydes and ketones provides essentially pure allylic chlorides for use in subsequent displacement reactions. The [3,3] rearrangement is equally effective in the case of a propargyllic alcohol, which provides the corresponding allenyl bromide. Synthetically, the addition-niobium halide rearrangement provides an efficient and direct conversion of aldehydes and ketones to allylic halides in one synthetic operation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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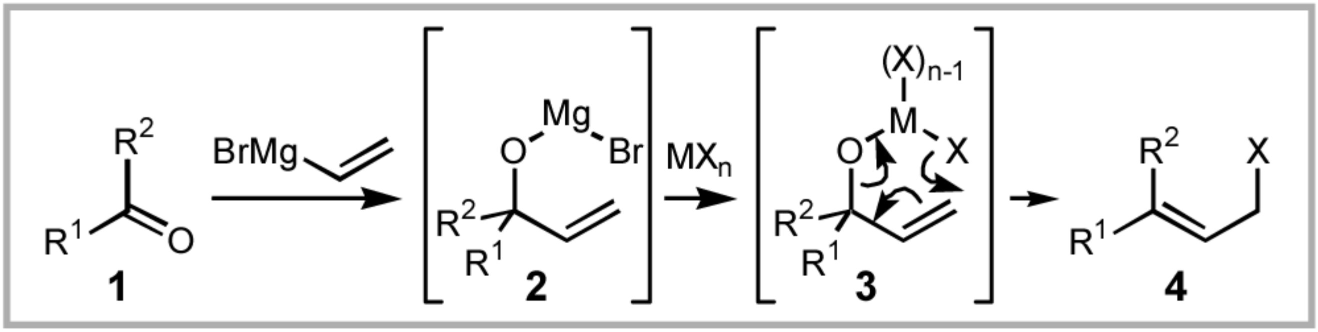
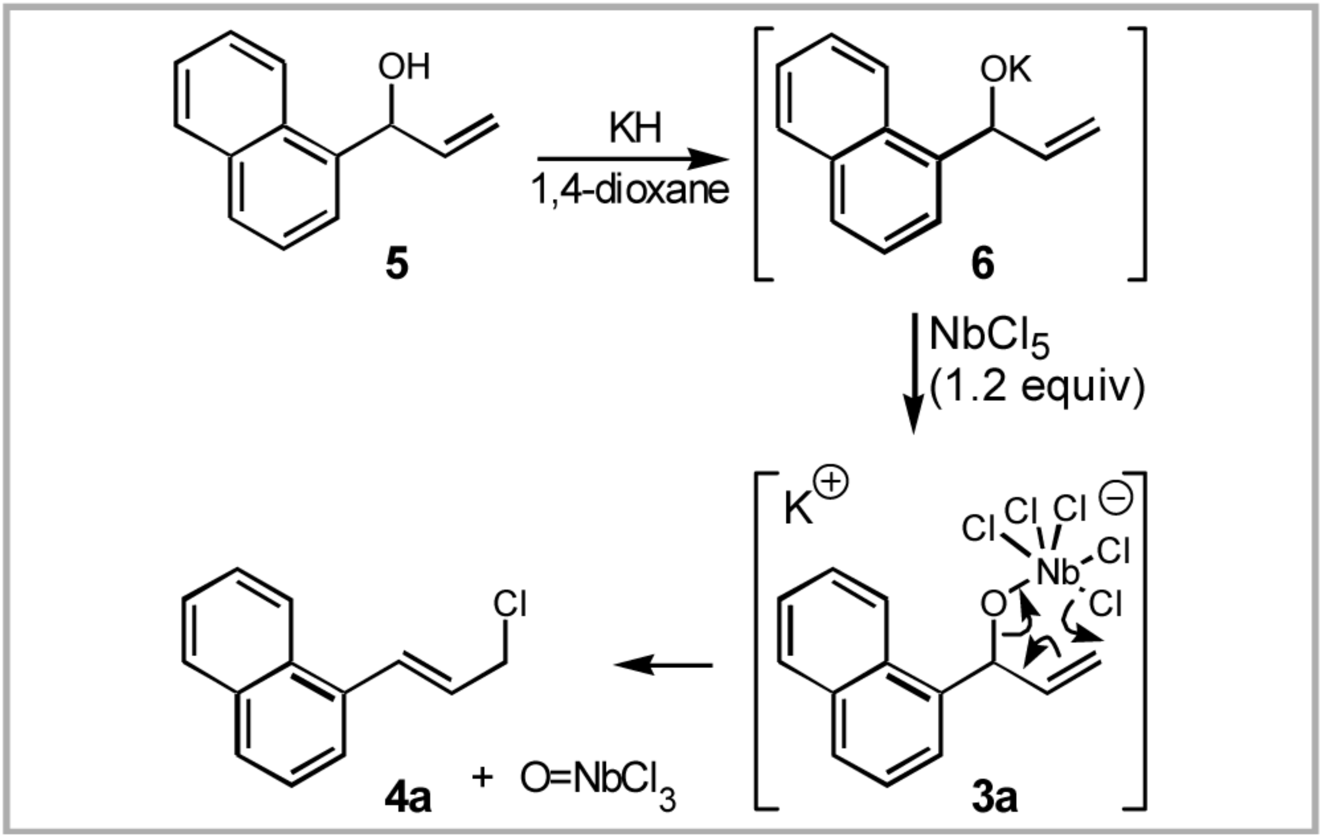
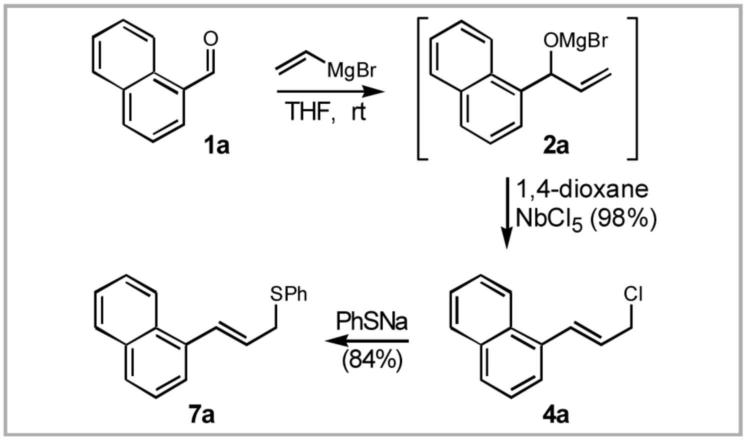


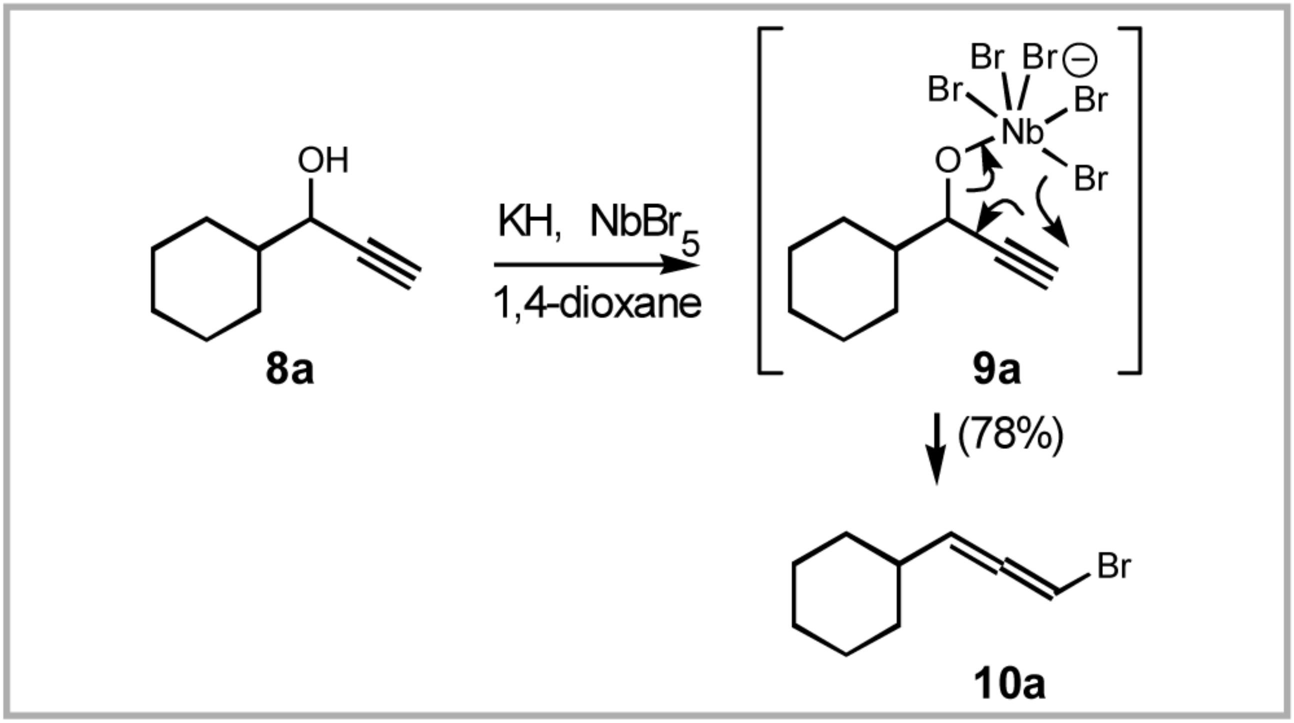
Scheme 1.
Vinyl Addition-Metalla-Halo-[3,3]-Rearrangement.



Scheme 2.
Metalla-Halo-[3,3]-Rearrangement.



Scheme 3.
Direct Vinyl-Addition $NbCl_5$ Halogenation.

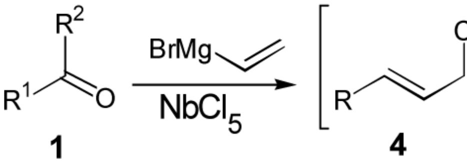


Scheme 4.

NbBr$_5$-Rearrangement to an Allenyl Bromide.

Table 1

Sequential Addition-Chlorination-Sulfenylation.



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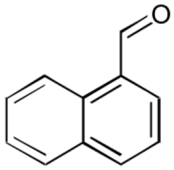
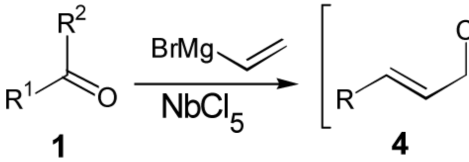
1	 **1a**	



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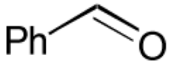
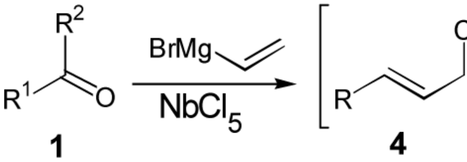
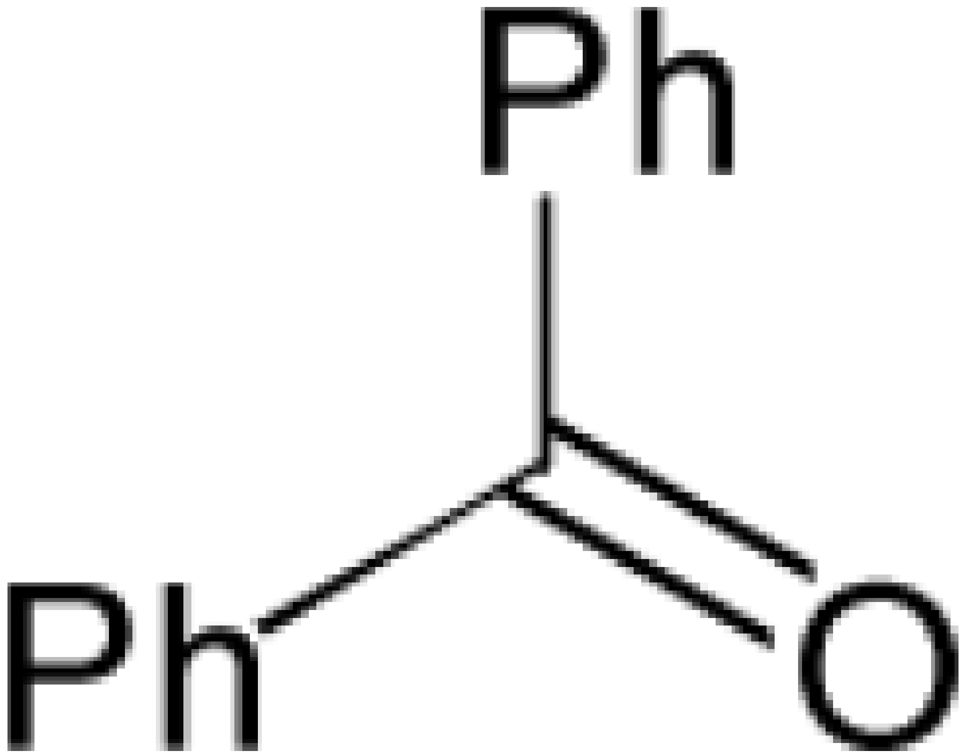
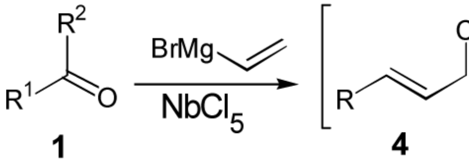
2	 **1b**

entry	**aldehyde**	
3	 **1c**	



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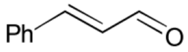
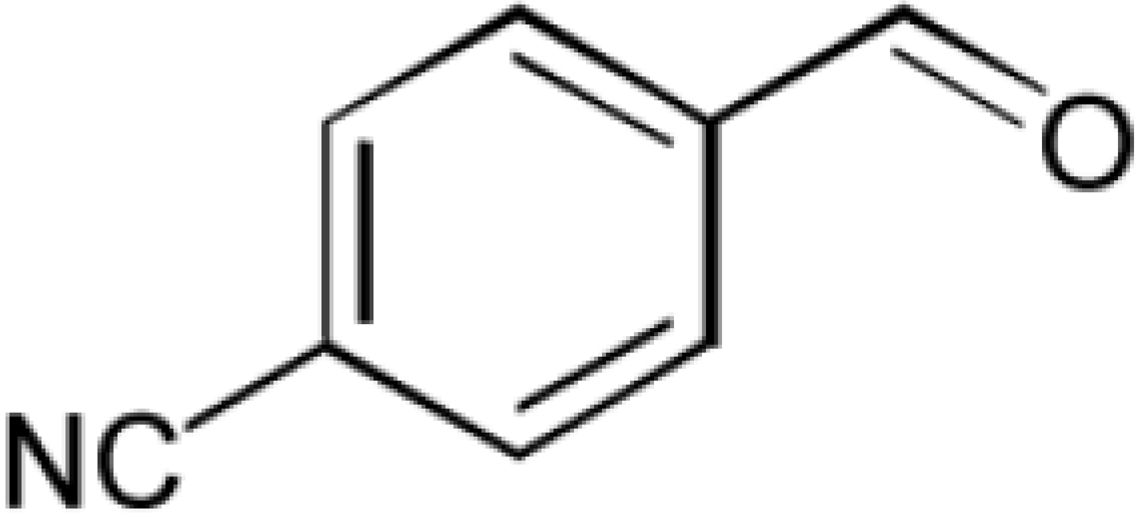
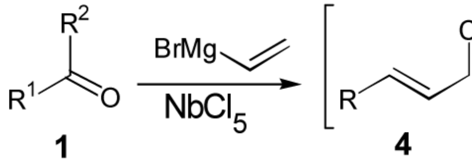
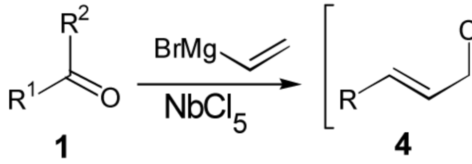
4	 **1d**
5	 **1e**



entry	aldehyde
6	 **1f**



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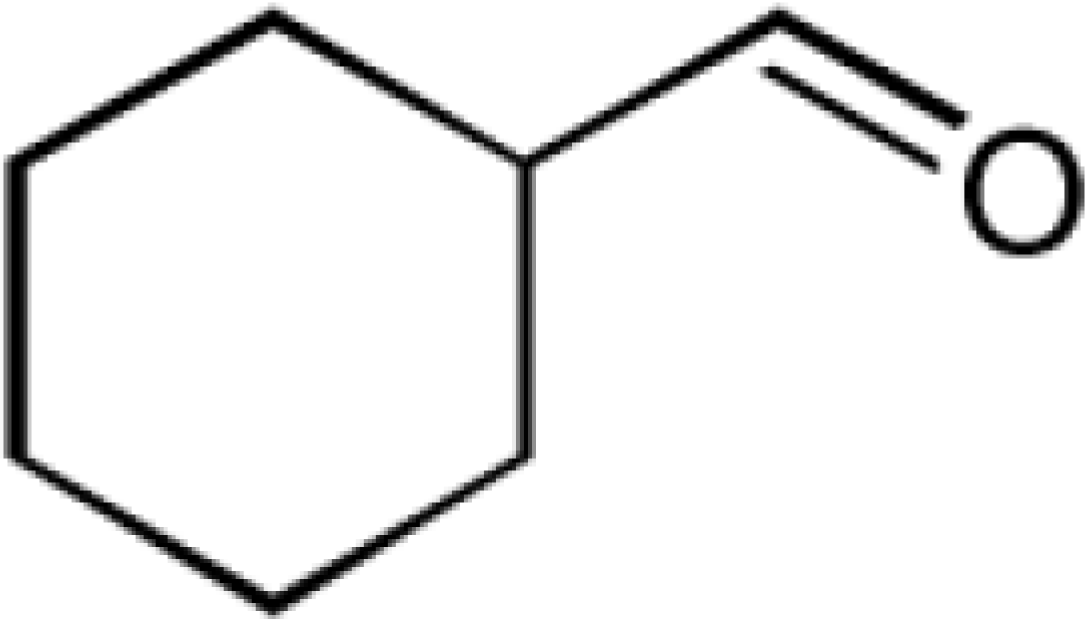
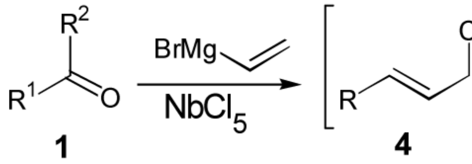
7	 **1g**



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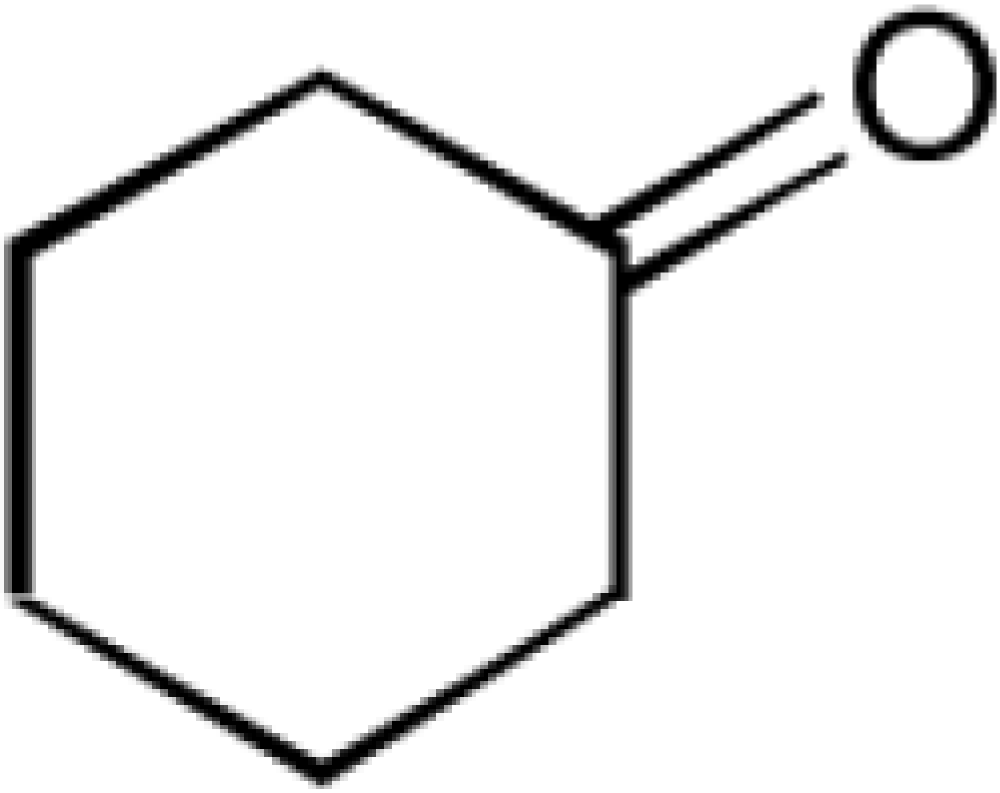
8	 **1h**

[a] Performed with $NbBr_5$ rather than $NbCl_5$.