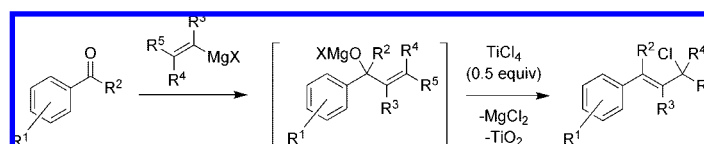# One-Pot Formation of Allylic Chlorides from Carbonyl Derivatives

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ABSTRACT

An efficient, one-pot method for the conversion of carbonyl electrophiles to allylic chlorides has been developed, by activating magnesium alkoxides in situ using $TiCl_4$.

The general use of carbocations as synthetic intermediates is limited by the strongly acidic conditions required for their generation.[1] Indeed, despite the relative stability of benzylic, allylic, and propargylic carbocations,[2] harsh conditions are often required for their formation. During our recent studies on the reactions of allylic alcohols, we wished to initiate the formation of allylic cations under mild, nonacidic reaction conditions. Since our desired allylic alcohol precursors could readily be prepared from addition of a vinylic organometallic reagent to a readily available benzaldehyde derivative **1**, we wondered whether it would be possible to affect direct β-heterolytic cleavage of the C—O bond in situ, formally eliminating a metal oxide as the leaving group (Scheme 1). The fate of the subsequent carbocation **3** could be envisaged to follow several pathways: (A) anion capture; (B) annulation (to give an indene); (C) addition of an added nucleophile.

Recently, elegant work by Kabalka and co-workers has demonstrated the ability of lithium alkoxides to undergo C—O bond cleavage upon treatment with several Lewis acids (most successfully BCl_3 and $FeCl_3$), with the subsequent

Scheme 1. C—O Bond Activation via Alkoxides
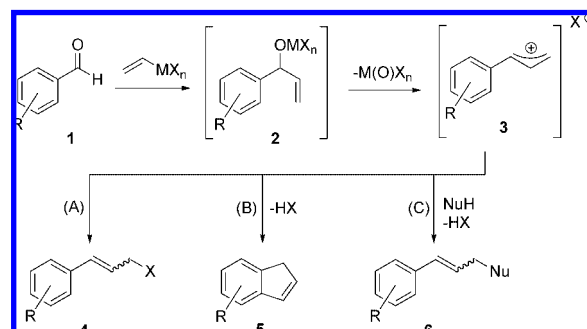
cations captured by allyl silanes.[3] Related work by Murai and co-workers has documented C—S bond cleavage.[4] For our cascade sequence however, we wished to focus on the use of commercially available vinyl magnesium halides as nucleophiles and hence the C—O cleavage of magnesium alkoxides, a situation which was largely undocumented. In one study regarding the synthesis of indene derivatives, Tolbert had demonstrated that isolated, heavily substituted magnesium alkoxides (generated upon addition of phenyl-

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(4) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780.

magnesium bromide to α,β-unsaturated ketones) undergo β-heterolytic cleavage when pyrolized at 160 °C under vacuum, to give indenes in moderate yield.[5] Several problems exist with this strategy as a synthetic method, however, including to the need to isolate the moisture- and air-sensitive crystalline magnesium alkoxides prior to reaction, the high temperatures required, and the need for significant substitution to avoid side reactions such as elimination and hydride abstraction. We reasoned that an alternative metal alkoxide may mediate the correct reactivity profile to allow mild, low-temperature β-heterolytic cleavage to form allylic cations directly from benzaldehydes. With this in mind, we selected commercially inexpensive titanium tetrachloride as a reaction partner, in light of its strong dehydrating capabilities[6] and precent for initating C−O bond cleavage, for example in Reetz's pinoeering work on the geminal dimethylation of ketones.[7] To our delight, exposure of the magnesium alkoxide **10** to titanium tetrachloride at low temperature, followed by warming to room temperature, resulted in the formation of (E)-allylic chloride **11** (see Scheme 2). The

Scheme 2. One-Pot Formation of (E)-Allylic Chloride C−O Bond Activation via Alkoxides
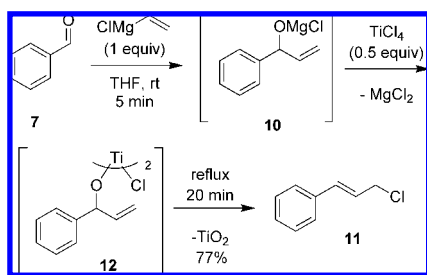
allylic chloride products are important substrates in a variety of reactions including metal-catalyzed allylation reactions.[8] For example, they have been recently been reported as substrates in nickel-catalyzed Negishi reactions[9] and in stereospecific zirconium-mediated S$_N$2′ substutions.[10] We therefore decided to examine the scope of this reaction further.

From the outset, the ideal order of addition of the reagents was unclear. Addition of titanium tetrachloride to benzaldehyde **1** should increase the electrophilicity of the carbonyl carbon following Lewis acid coordination. This should facilitate the low-temperature nucleophilic addition of vinylmagnesium chloride to give the corresponding titanium alkoxide (see **2**, MX$_n$ = ClTiX$_n$), which should eliminate to form the desired allylic chloride **4**. One complication of this approach, however, could be the propensity of the Grignard reagent to attack the electrophilic titanium center, leading to titanium ate complexes,[11] and mediating homocoupling of the Grignard reagent.[12] Alternatively, addition of vinyl-magnesium chloride to benzaldehyde **1** should give the corresponding magnesium alkoxide, which can undergo metathesis upon addition of titanium tetrachloride to give the titanium alkoxide. Subsequent elimination should form allylic chloride **4**. To find the optimum conditions, both experimental methods were investigated in parallel.

Addition of titanium tetrachloride (1−2 equiv) to benzaldehyde (**7**) at −78 °C, followed by addition of vinyl magnesium chloride (1−2 equiv) and warming to room temperature, gave moderate yields of the product **11**. In almost all cases however, residual benzaldehyde (**7**) was observed. We attributed this to the attack of the Grignard reagent onto the titanium center, initiating subsequent side reactions such as homocoupling[12] and reducing the equivalents of the active vinyl nucleophile. To overcome this hurdle, a two-step, one-pot procedure was developed whereby the Grignard reagent was added slowly to benzaldehyde (**7**) at ambient temperature. The mixture was then cooled to −78 °C for the addition of titanium tetrachloride. The low temperature was simply to control the exotherm of the addition. Warming to ambient temperature and then stirring overnight resulted in efficient production of (E)-allylic chloride **11**. Alternatively, by heating to reflux, the reaction was complete within 20 min. Under optimized conditions, the stoichiometry of titanium tetrachloride was lowered to 0.5, and the product was isolated in 77% yield (Scheme 2).[13]

Using the developed conditions, the scope of the reaction was surveyed varying the substitution pattern on the aromatic ring (Table 1). The reaction readily tolerated heavier substitution (entries 1 and 2), the use of electron-rich

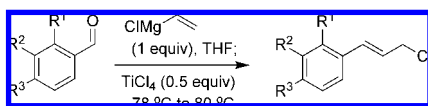(5) Tolbert, L. M. *J. Org. Chem.* **1979**, *44*, 4584–4588.

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(13) Standard procedure for the one-pot conversion of benzaldehyde derivatives to (E)-allylic chlorides. (E)-(3-Chloroprop-1-enyl)benzene (**11**). Vinylmagnesium chloride (1.2 mL, 1.6 M in THF, 1.90 mmol) was added slowly to benzaldehyde (0.2 mL, 1.88 mmol) in dry THF (5 mL) at ambient temperature. The mixture was stirred and monitored by TLC. After full consumption of benzaldehyde, the mixture was cooled to −78 °C, and TiCl$_4$ (0.1 mL, 0.95 mmol) was added. The reaction was allowed to rise to ambient temperature, before warming to 80 °C. The reaction was stirred for 20 min at 80 °C and then quenched with water (10 mL). EtOAc (10 mL) was added and the resulting phases separated. The organic layer was washed with water and the aqueous layer extracted EtOAc (3 × 10 mL). The combined organic phase was dried over anhydrous MgSO$_4$, and the solvent was evaporated under reduced pressure. Flash column chromatography (SiO$_2$, EtOAc: Hexane, 1:4) afforded allylic chloride **11** (218 mg, 77%) as a yellow oil: R_f = 0.4 (SiO$_2$, EtOAc:Hexane, 1:4); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38−7.41 (m, 2H), 7.31−7.35 (m, 2H), 7.26−7.29 (m, 1H), 6.66 (d, J = 15.6 Hz, 1H), 6.32 (dt, J = 15.6, 7.2 Hz, 1H), 4.25 (dd, J = 7.2, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.5, 134.2, 128.6, 128.3, 126.7, 124.9, 45.4. (See Supporting Information for full experimental and characterization data.)

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Table 1. Synthetic Scope of the Methodology

entry	R^1	R^2	R^3	substrate	product	yield (%)
1	Me	H	H	13	21	67
2	Me	H	Me	14	22	73
3	OMe	H	H	15	23	95[a]
4	H	OMe	H	16	24	59
5	H	H	CN	17	25	78[b]
6	H	H	CO_2Me	18	26	76
7	NO_2	H	H	19	27	0
8	H	H	NMe_2	20	28	0

[a] Product isolated crude (ca. 95% pure) as unstable to SiO_2 chromatography. [b] Reaction performed in two steps. Yield refers to second step.

Table 2. Further Synthetic Scope of the Methodology

entry	alkoxide	product	yield (%)[a]
1	29	36	78
2	30	37	81[b]
3	31	38	95[b]
4	32	39	80
5	33	40	80
6	34	41	60[c]
7	35	42	50[c]

[a] Reagents and conditions: $TiCl_4$ (0.5 equiv), THF, −78 to 80 °C. [b] Product isolated crude (>95% pure) as elimination occurred upon purification. [c] Reaction time, 36 h.

aromatics (entries 3 and 4), and the use of electron-poor aromatics (entries 5 and 6), with the products isolated in moderate to excellent yield. Nitro-aromatic substrates (entry 7) proved problematic, presumably due to the known reactivity of nitro groups with vinyl magnesium chloride,[14] whereas amino substrates (entry 8) also gave extensive decomposition due to the known oxidative reactions of aniline derivatives with $TiCl_4$.[15]

To extend this methodology further, we investigated the use of more heavily substituted Grignard reagents as nucleophiles as well as the use of both aromatic aldehydes and ketones, and aliphatic aldehydes as substrates. Unfortunately, using only 1 equiv of more heavily substituted Grignard reagents, such as commercially available 1-methyl-1-propenylmagnesium bromide, we consistently saw competing reduction of our carbonyl substrate.[16] The use of additives such as HMPA[17] failed to combat this shortcoming. Increasing the number of equivalents of the Grignard reagent resulted in the minimization of this reduction side-reaction but was not compatible for our one-pot system. For this reason, we synthesized a variety of allylic alcohols from the corresponding bulky Grignard reagents and aldehydes or ketones (see Supporting Information) and then used these in our developed reaction, regenerating the magnesium alkoxides via deprotonation using *iso*-propyl magnesium chloride (Table 2).

In general, substitution patterns were well tolerated. Substrates bearing tertiary alkoxide centers (entries 1 and 2) readily underwent the reaction, and impressively, substrate 30 (entry 2) resulted in formation of a tetrasubstituted double bond, which are known to be challenging synthetic targets.[18] Monosubstitution of the terminal alkene position posed no problem (entry 3), and the product 38 was isolated in excellent yield. However, in general, for the more heavily

substituted products, elimination of HCl to give an olefin was an issue and precluded further purification of 38 (see Supporting Information). Disubstitution of the terminal alkene resulted in unavoidable elimination (entries 4 and 5), although the corresponding dienes were isolated in good yield (with product 40 isolated as a mixture of regioisomers). To our delight, aliphatic systems also proved applicable to the rearrangement (entries 6 and 7), albeit with longer reaction times, and the products were isolated in moderate yield.

Although the development of this methodology demonstrated the ability of $TiCl_4$ to mediate the C−O bond cleavage of magnesium alkoxides, it was still unclear whether heterolytic C−O bond cleavage to give a free allylic cation 43 was occurring, with subsequent capture of the most stable conformer of this species,[5] to produce an (E)-allylic chloride selectively or whether the reaction was proceeding through a closed, six-membered transition state 44, either somewhat concerted[19] or S_{Ni}' (Scheme 3). We therefore initiated a number of experiments to determine the mechanistic pathway.

Kabalka and others have detailed the ability of allyl trimethylsilane to capture cationic intermediates;[3] however, its presence under our reaction protocol resulted in no such capture, and the expected allylic chloride was the only reaction product. Interestingly, we were also unable to scavenge and free chloride anions from solution using a variety of silver salts. Conversely with analogous substrates but using either lithium alkoxides or $FeCl_3$ or BCl_3 instead of $TiCl_4$ resulted in the formation of the same products albeit with a lower degree of reactivity. These conditions have been

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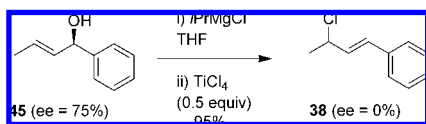
Scheme 3. Potential Reaction Mechanisms
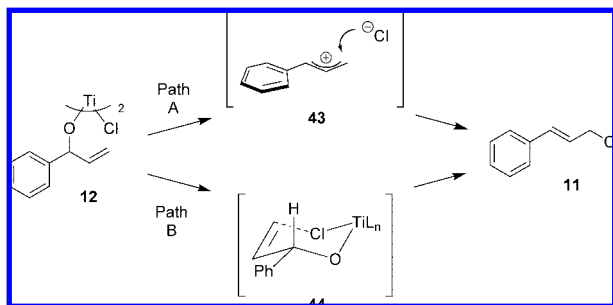
previously demonstrated by Kabalka and co-workers,[3] to react via a cationic pathway.

As a more conclusive probe, we prepared a chiral alkoxide derived from alcohol **45**[20] and measured the degree of chirality transfer upon reaction (Scheme 4). No transfer of

Scheme 4. Mechanistic Studies

chiral information (75% ee to 0% ee) was observed upon reaction, as judged by chiral HPLC. This suggests that heterolytic C—O bond cleavage to give a free allylic cation

43 (Scheme 3, path A) is occurring in our developed reaction. However, it is germane to state that since the chromatogram from the HPLC indicated the presence of contaminants (i.e., diene) arising from HCl elimination we cannot rule out the possibility that product **38** racemizes on the HPLC column. Unfortunately, attempts at alternative chiral analyses, such as the use of chiral shift reagents, or chiral GC failed to resolve the enantiomers of **38**. Flash chromatography resulted in both elimination and decomposition, and the average crude optical rotation of the product was 4 degrees.

In conclusion, we have developed a novel method of converting either allylic alcohols or benzaldehyde derivatives into (E)-allylic chlorides via $TiCl_4$-mediated C—O bond activation of magnesium alkoxides. Initial mechanistic studies have indicated that, as in the related systems of Kabalka and co-workers,[3] this reaction appears to proceed via cationic intermediates and thus contributes to the notion that Lewis acids can be used to generate cations from alkoxides under mild, nonacidic conditions.

Supporting Information Available: Experimental procedures and tabulated spectral data and scanned images of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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