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New Highly Nucleophilic and Practically Accessible Chlorocarbenoids for Carbonyl Olefination

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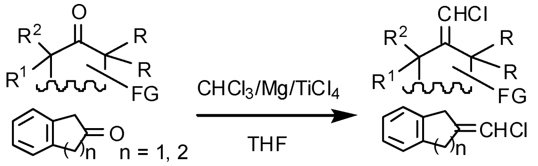
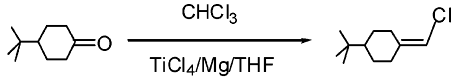


Direct oxidative addition of $CHCl_3$ to the Mg−$TiCl_4$ bimetallic species resulted in the generation of a highly nucleophilic and practically convenient chloromethylenetitanium complex, which efficiently effected condensation even with enolizable or inert carbonyl compounds, such as sterically congested ketones, to provide vinyl chloride compounds.

Formation of C=C bonds by means of metallocarbenes constitutes a particularly valuable synthetic strategy. The importance of vinyl halides as building blocks for construction of useful molecules such as alkylidene complexes,[1] carbonyl compounds,[2] acetylenes,[3a] and dienes[3b] makes their availability by such processes important. Despite the vast number of titanium−carbene-mediated carbonyl-olefinations,[4,5] remarkably few reactions of halocarbenoids are described except for the $CrCl_2$-[6a] and $Cp_2Ti[P(OEt)_3]_2$-promoted[6b] direct halomethylenation of aldehydes or ketones with haloforms. These latter processes do not generally extend to enolizable and sterically hindered ketones, and the use of large-excess of relatively expensive $CrCl_2$ and Cp_2TiCl_2 is unavoidable.[7] In searching for a new and practical strategy based upon the concept of the C−Cl bond activation promoted by highly active bimetallic species (Scheme 1), we turned our attention to the elaboration of chloroform initiated by simple metal-chlorine exchanges.

We wish to report protocols whereby direct oxidative addition of $CHCl_3$ to the Mg−$TiCl_4$ bimetallic species[5] resulted in the generation of a highly nucleophilic and practically convenient chloromethylenetitanium complex, which efficiently effected condensation even with enolizable or inert carbonyl compounds, such as sterically congested ketones, to provide vinyl chloride compounds.

Earlier work in our laboratories established the feasibility of the elaboration of CH_2Cl_2 into an unusual titanium methylene complex.[5] Believing a Mg−Ti inorganic Grignard reagent[5,8] might be more reactive than either titanium(II) complexes[9a] or Mg−Hg species,[9b] which had been used to activate *gem*-dihalides, we explored the oxidative addition of $CHCl_3$ to the Mg/$TiCl_4$ system. Expectedly, exposure of the simple cyclic ketone **1a** to $TiCl_4$/Mg in $CHCl_3$ and THF at ambient temperature did indeed produce the desired vinyl chloride **2a** but also led to dimerization and reduction products. Thus, adding a 1 M solution of **1a** in THF to a mixture of $TiCl_4$ (3 equiv) and Mg (8 equiv) in 5 mL of $CHCl_3$ at 10−15 °C followed by stirring at ambient temperature for 1 h gave a 66% yield of **2a** in addition to dimerization and reduction products.



1a **2a** (66%)

The relatively polar pinacol dimerization product was partially purified and characterized by infrared absorption at 3455 (OH). Characteristic NMR signals appear between δ 1.83−0.84 for the cyclohexyl and *tert*-butyl protons. Lowering the reaction temperature in an effort to stop the undesired dimerization and reduction also essentially halted the chloromethylenation reaction. Increasing the amount of $TiCl_4$/Mg and/or THF failed to improve the vinyl chloride formation. Replacing THF with other additives including ether, 1,4-dioxane, acetonitrile, NEt_3, pyridine, and TMEDA gave no reaction.

Extension of these observations to other ketones confirms their generality. A rigid tricyclic ketone, adamantanone **1b**, reacted efficiently with a 2:8 $TiCl_4$/Mg

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(6) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Takeda, T.; Endo, Y.; Reddy, A. C. S.; Sasaki, R.; Fujiwara, T. *Tetrahedron* **1999**, *55*, 2475.

(7) For some examples of traditional Wittig chloromethylenation, see: (a) Seyferth, D.; Grim, S. O.; Read, T. O. *J. Am. Chem. Soc.* **1960**, *82*, 1510. (b) Wittig, G.; Schlosser, M. *Angew. Chem.* **1960**, *72*, 324. (c) Seyferth, D.; Grim, S. O.; Read, T. O. *J. Am. Chem. Soc.* **1961**, *83*, 1617. (d) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373. (e) Appel, R.; Morbach, W. *Synthesis* **1977**, 699.

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10.1021/jo050455c CCC: \$30.25

SCHEME 1

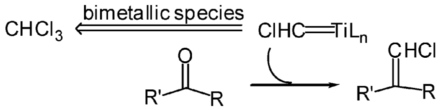
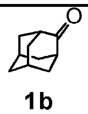
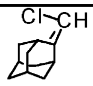
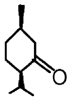
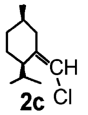
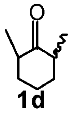
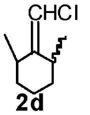
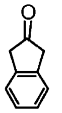
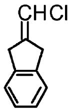
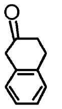
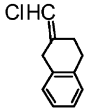
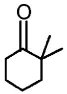
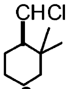
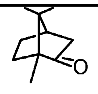
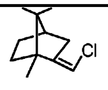
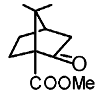
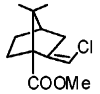
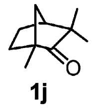
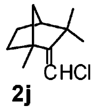


TABLE 1. Chloromethylenation via Activation of CHCl$_3$ by a Ti–Mg Bimetallic System[a]

Entry	Carbonyl Compd	TiC$_4$/Mg	Methylene Product	Yield (*E/Z*)
1	 **1b**	2/8	 **2b**	80% -
2	 **1c**	3/8	 **2c**	78% (1/1)
3	 **1d**	3/8	 **2d**	85% -
4	 **1e**	3/12	 **2e**	63% -
5	 **1f**	3/12	 **2f**	71% (1/1)
6	 **1g**	3/8	 **2g**	72% (85/15)

[a] Reactions were performed in CH$_2$Cl$_2$ and THF for 1 h at 10–25 °C.

TABLE 2. Chloromethylenation of Sterically Congested Ketones[a]

Entry	Carbonyl Compd	TiC$_4$/Mg	Methylene Product	Yield (*E/Z*)
1	 **1h**	3/8	 **2h**	92% (98/2)
2*	 **1i**	5/10	 **2i**	91% (92/8)
3*	 **1j**	3/8	 **2j**	60%[b,c] (14/86)

[a] Reactions were performed in CH$_2$Cl$_2$ and THF for 1 h at 10–25 °C. [b] Reaction was run at 50 °C. [c] Plus starting material **1j** (40%).

ratio in chloroform to give the desired vinyl chloride **2b** in 80% isolated yield (Table 1, entry 1).

Enolizable ketones also presented no difficulties (Table 1, entries 2–6). Using α-substituted derivative **1c** gave satisfactory results with the chloroform–TiCl$_4$–Mg system, giving a 78% yield of **2c** as a 1:1 *E*/*Z* mixture (entry 2). The α,α′-disubstituted derivatives **1d** gave an analogous result wherein two pairs of enantiomeric vinyl chlorides (four stereoisomers) were observed in a 4:1 ratio (85% yield). Indanone **1e** and *β*-tetralone **1f** gave 63% and 71% yields (entries 4 and 5), respectively, of the desired chloromethylenation products.[1] A particularly interesting example illustrating the selectivity of this process is the chloromethylenation of α,α-disubstituted cyclohexanone **1g** (entry 6). In contrast to the Tebbe–Grubbs methylenation reagent, which had been noted to act as a base to undergo the enolization of **1g**,[10,11] the CHCl$_3$–TiCl$_4$–Mg-derived chloromethylene carbenoid showed higher reactivity toward addition to the carbonyl group, leading to a good yield (72%) of vinyl chloride **2g** as an 85:15 *E*/*Z* mixture. The presence of the *Z*-isomer as a minor product was confirmed by the observation of a positive NOE between the vinyl proton and the allylic protons.

Most pleasingly, sterically congested ketones such as camphor **1h** and keto ester **1i** reacted exceedingly well with this carbenoid (Table 2, entries 1–2), highlighting the extraordinary nucleophilicity as well as the chemoselectivity of the TiCl$_4$–Mg-derived chlorocarbenoid.

The chloromethylenation products **2h** (92% yield) and **2i** (91% yield) were isolated on a 1 mmol scale using 3 mmol of TiCl$_4$ and 8 mmol of Mg. The stereochemistry is assigned as depicted on the basis of the NOESY spectrum. The reaction directly scales up; thus vinyl chloride **2h** was obtained in 89% yield on a 15 mmol scale using 30 mmol of TiCl$_4$ and 80 mmol of Mg. Remarkably, this bimetallic carbenoid reacted even with the sterically more hindered fenchone **1j** (Table 2, entry 3), which by virtue of the steric shielding of two quaternary carbon atoms adjacent to the carbonyl group demands a very good nucleophile.[12] Thus, chloromethylenation of **1j** at 50 °C gave the desired alkene **2j** in a remarkable 60% yield (with starting material remaining) and tentatively assigned as a 14:86 *E*/*Z* mixture based upon steric strain considerations.

Acyclic ketones that bear Lewis basic sites can also serve as satisfactory acceptors, as shown by **1k** and **1l** giving the corresponding vinyl chlorides **2k** and **2l** in 82% and 60% yields, respectively (Table 3, entries 1 and 2).

Notably, either ketal, alkene, or sulfide unit is well tolerated. Changing the carbonyl compounds to alde-

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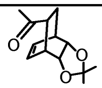
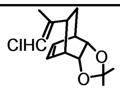
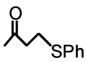
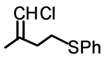
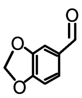
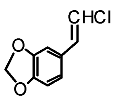
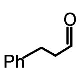
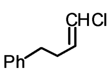
(10) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

(11) Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733.

(12) Corey, E. J.; Kang, J.; Kyler, K. *Tetrahedron Lett.* **1985**, *26*, 555.

TABLE 3. Chloromethylenation of Acyclic Ketones and Aldehydes[a]

Entry	Carbonyl Compd	TiC_4/Mg	Methylene Product	Yield (E/Z)
1	 **1k**	3/8	 **2k**	82% (6/4)
2	 **1l**	3/12	 **2l**	60% (6/4)
3	 **1m**	5/16	 **2m**	78% (3/1)
4	 **1n**	3/12	 **2n**	85% (12/5)

[a] Reactions were performed in CH_2Cl_2 and THF for 1 h at 10−25 °C.

hydes, which are particularly prone to reduction and/or dimerization, led to equally gratifying results. Thus, exposure of **1m** to a 5:16 $TiCl_4$/Mg ratio afforded a 3:1 mixture of (E)- and (Z)-vinyl chlorides **2m**[13a] in 78% yield with most of the remainder being dimerization and reduction products (entry 3). The aliphatic aldehyde **1n** also gave satisfactory results. Thus, reacting **1n** with chloroform using a 3:12 $TiCl_4$/Mg ratio led to smooth chloromethylenation to give **2n**[13b] in 85% yield as a 12:5 E/Z mixture.

In conclusion, this Mg−Ti bimetallic complex promoted oxidative addition of $CHCl_3$ not only represents an extremely simple, practical, and efficient synthesis of vinyl chlorides, but also offer opportunities for discovery of other halomethylenetitanium complexes.[14] Not only is this chlorocarbenoid nonbasic but it also seems highly nucleophilic. The novel nucleophilicity involved suggests several intriguing directions which are currently under active investigation.

Experimental Section

Typical Procedure for Chloromethylenation of 1a−d,f−i,k,n. Preparation of 2a. To a suspension consisting of Mg (192 mg, 8 mmol), $TiCl_4$ (570 mg, 0.31 mL, 3 mmol), and $CHCl_3$ (4 mL) at 10−15 °C was added a solution of 4-*tert*-butylcyclohexanone **1a** (154 mg, 1 mmol) in $CHCl_3$ (1 mL) and THF (1 mL). The black slurry was stirred for 1 h, cooled to 0 °C, and carefully poured into ice-cold saturated potassium carbonate solution (10 mL). The resulting mixture was stirred with 20 mL of ether, and the phases were separated. After this procedure was repeated twice, the combined extracts were dried, evaporated, and purified by chromatography on silica gel (elution with hexane) to give 4-*tert*-butyl-1-(chloromethylene)cyclohexane **2a** (123 mg, 66% yield) as a colorless oil: IR (neat) 3065, 2976, 2842, 1620, 1480, 1444, 1394, 1360 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 5.74 (t, J = 1.6 Hz, 1 H), 2.98−2.93 (m, 1 H), 2.35−2.30 (m, 1 H), 2.03−1.91 (m, 1 H), 1.90−1.85 (m, 2 H), 1.76−1.68 (m, 1 H), 1.20−1.16 (m, 1 H), 1.08−0.97 (m, 2 H), 0.85 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.1, 108.1, 48.0, 34.0, 32.4, 28.6, 28.4, 27.6. 27.4; high-resolution MS m/e calcd for $C_{11}H_{19}Cl$ 186.1172, found 186.1175.

Procedure for Chloromethylenation of 1e,l−m. Preparation of 2e. To a suspension consisting of Mg (288 mg, 12 mmol), $TiCl_4$ (570 mg, 0.31 mL, 3 mmol), and $CHCl_3$ (4 mL) at 10−15 °C was added a solution of indanone **1e** (132 mg, 1 mmol) in $CHCl_3$ (1 mL) and THF (0.5 mL). The mixture was stirred. After 15 min of stirring at room temperature, an additional 1 mL of THF was added. The black slurry was stirred for an additional 0.5 h, then cooled to 0 °C, and carefully poured into ice-cold saturated potassium carbonate solution (10 mL). The product was extracted into ether, and the combined extracts were dried and evaporated. Purification by flash chromatography (silica gel, hexane) afforded 103 mg (63%) of **2e** as a colorless oil: IR (neat) 3020, 2920, 1668, 1558, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.15 (m, 4H), 5.09 (quintet, J = 1.2 Hz, 1 H), 3.75 and 3.73 (2 d, J = 1.2 Hz, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.2, 141.1, 140.7, 126.8, 126.7, 124.7, 124.5, 110.9, 37.7, 37.6; high-resolution MS m/e calcd for $C_{10}H_9Cl$ 164.0392, found 164.0394.

Procedure for Chloromethylenation of Fenchone 1j: 2-(Chloromethylene)-1,3,3-trimethylbicyclo[2.2.1]-heptane 2j. To a suspension consisting of Mg (192 mg, 8 mmol), $TiCl_4$ (570 mg, 0.31 mL, 3 mmol). and $CHCl_3$ (4 mL) at 40−50 °C was added a solution of fenchone **1j** (152 mg, 1 mmol) in $CHCl_3$ (1 mL) and THF (1 mL). The reaction was stirred for 1 h at ambient temperature and recooled to 0 °C. Saturated potassium carbonate solution (10 mL) was added and the mixture was diluted with ether (20 mL). The organic layer was separated, dried, evaporated, and purified by chromatography on silica gel (elution with hexane) to give 110 mg (60%) of 2-(chloromethylene)-1,3,3-trimethylbicyclo[2.2.1]heptane **2j** as a 14:86 Z/E mixture along with recovered fenchone **1j** (60 mg). **2j**: IR (neat) 3050, 2980, 2860, 1636, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 and 5.58 (2 s, total 1 H, ratio 14:86), 1.76−1.68 (m, total 1 H), 1.59−1.53 (m, total 1 H), 1.52 and 1.44 (2 s, total 3 H), 1.53−1.40 (m, total 2 H), 1.25−1.14 (m, total 3 H), 1.28, 1.21, 1.05, and 1.03 (4 s, total 6 H); major isomer ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.3, 106.7, 51.5, 47.6, 45.9, 45.6, 35.1, 29.5, 26.6, 25.3, 20.4; high-resolution MS m/e calcd for $C_{11}H_{17}Cl$ 184.1019, found 184.1011.

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Supporting Information Available: Experimental procedures, spectra data for vinyl chlorides **2a−m**, and copies of ^1H NMR spectra of vinyl chlorides **2a−m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Further studies will determine whether these bimetallic-species promoted oxidative additions will be generally useful for employment with polyhaloalkanes and other trihaloalkanes and carbontetrahalides.