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Novel Ambiphilic Dichlorocarbenoid Equivalent in Alkene Cyclopropanation and Carbonyl Olefination

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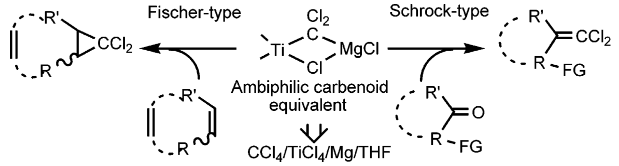
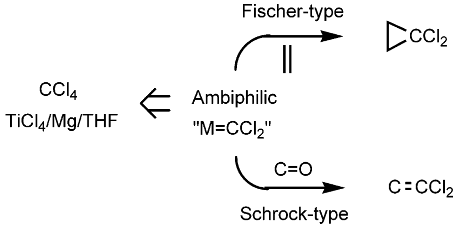


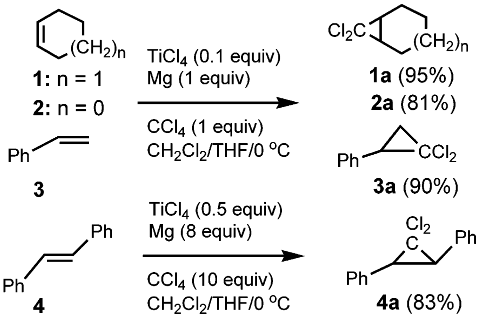
The Ti−Mg−dichloromethylene complexes derived from the oxidative addition of CCl_4 to the Mg−$TiCl_4$ bimetallic species serve as a novel class of ambiphilic dichlorocarbenoid equivalents. Not only is Ti−Mg−dichlorocarbenoid highly selective but also it seems highly reactive in both alkene cyclopropanations and carbonyl dichloromethylenations.

Dichlorocarbenoids exhibit reactivity ranging from electrophilic to nucleophilic. All reported examples of dichlorocarbenoid-mediated coupling reactions record it as participating as either a nucleophile[1] in carbonyl olefinations or an electrophile[2] in olefin cyclopropanations. For there to be no discontinuity between electrophilic and nucleophilic behavior, there must exist ambiphilic dichlorocarbenoids, which act as a Fischer-type complex[3] toward alkenes and as a Schrock-type complex[4] toward carbonyl compounds (Scheme 1). Changing the reaction profile whereby the same readily available carbenoid can be channeled into a different adduct greatly expands synthetic flexibility. Extensive interest in titanium−carbenoid-mediated reactions led us to record the first examples of the Ti−Mg−dichloromethylene complex participating as an ambiphilic dichlorocarbenoid, which not only efficiently effected highly selective cyclopropanation of alkenes but also displayed highly nucleophilic reactivity, leading to the dichloromethylenation of readily enolizable or sterically hindered carbonyls.

SCHEME 1. Novel Ambiphilic Dichlorocarbenoid in Alkene Cyclopropanation and Carbonyl Olefination



SCHEME 2. Optimized Conditions for the $TiCl_4$−Mg-Promoted Dichlorocarbene Transfer of CCl_4



For the alkene cyclopropanation, we examined the use of the Ti−Mg bimetallic species[5,6] to promote dichlorocarbene transfer of CCl_4. Adding the simple cyclohexene **1** to CCl_4 (10 equiv), $TiCl_4$ (1 equiv), and Mg (4 equiv) in 1,2-dichloroethane followed by THF at 0 °C did indeed complete cyclopropanation within 0.5 h, leading to the desired dichlorocyclopropane **1a** (Scheme 2, method A).

Remarkably, even a catalytic amount of $TiCl_4$ sufficed to completely effect cyclopropanation of **1a** albeit in a slower reaction. Thus, after 1∼2 h, using 5−10 mol % of $TiCl_4$ and stoichiometric quantities of CCl_4 and Mg gave a 95% yield of adduct **1a**. Cyclopentene **2** gave similar results under our standard conditions. Cyclopropanation onto styrene **3** also led

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(1) (a) Speziale, A. J.; Ratts, K. W. *J. Am. Chem. Soc*. **1962**, *84*, 854. (b) Rabinowitz, R.; Marcus, R. A. *J. Am. Chem. Soc*. **1962**, *84*, 1312. (c) Isaacs, N. S.; Kirkpatrick, D. *J. Chem. Soc., Chem. Commun*. **1972**, 443. (d) Seyferth, D.; Marmor, R. S. *J. Organomet. Chem*. **1973**, *59*, 237. (e) Harrison, C. R.; Hodge, P.; Hunt, B. T.; Khoshdel, E.; Richardson, G. *J. Org. Chem*. **1983**, *48*, 3721. (f) Vinczer, P.; Struhar, S.; Novak, L.; Szantay, C. *Tetrahedron Lett*. **1992**, *33*, 683. (g) Carran, J.; Waschbusch, R.; Marinetti, A.; Savignac, P. *Synthesis* **1996**, 1494. (h) Waschbusch, R.; Carran, J.; Marinetti, A.; Savignac, P. *Chem. Rev*. **1997**, *97*, 3401. (i) Takeda, T.; Endo, Y.; Reddy, A. C. S.; Sasaki, R.; Fujiwara, T. *Tetrahedron* **1999**, *55*, 2475.

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(3) For some examples of a Fischer-type carbene complex-promoted cyclopropanation of olefins, see: (a) Fischer, E. O.; Dotz, K. H. *Chem. Ber*. **1972**, *105*, 1356. (b) Casey, C. P.; Albin, L. D.; Burkhardt, T. J. *J. Am. Chem. Soc*. **1977**, *99*, 2533. (c) Casey, C. P.; Polichnowski, S. W. *J. Am. Chem. Soc*. **1977**, *99*, 6097. (d) Casey, C. P.; Polichnowski, S. W.; Shusterman, S. J.; Jones, C. R. *J. Am. Chem. Soc*. **1979**, *101*, 7282. (e) Pfeiffer, J.; Dotz, K. H. *Angew. Chem., Int. Ed. Engl*. **1977**, *36*, 2828.

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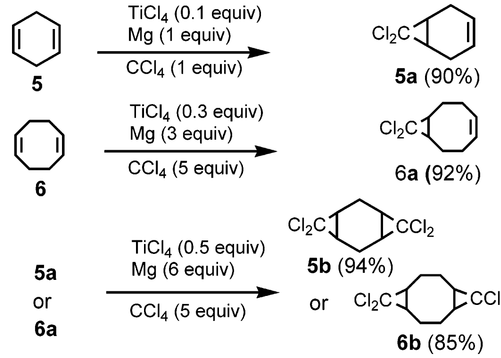
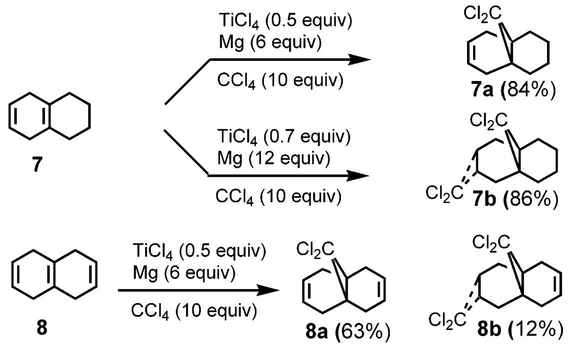
(6) (a) Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett*. **2004**, *6*, 4961. (b) Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett*. **2004**, *6*, 4965.

10.1021/jo052610t CCC: $33.50

SCHEME 3. Mono- vs Dicyclopropanation of Dienes



SCHEME 4. Chemoselective Cyclopropanation of Dienes

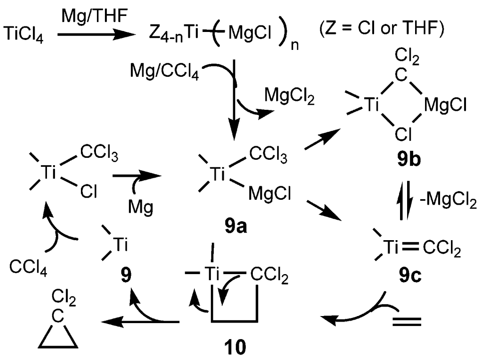


to equally gratifying results. Thus, the addition of $TiCl_4$ (method B) to a mixture of **3**, CCl_4, and Mg in $ClCH_2CH_2Cl$/THF produced the desired dichloride **3a** in 90% yield. Even in the case of the stilbene **4** which is of low reactivity toward dichlorocarbene derived from $CHCl_3$/base,[7] an excellent yield of adduct **4a** was obtained.

The reaction exhibits exceptional selectivity. In contrast to the traditional dichlorocarbene transfer via pyrolysis of trichloroacetate derivatives or base-induced decomposition of $CHCl_3$, which had been noted to be indiscriminate in its cyclopropanation of dienes,[2c,2h] the dichlorocarbenoid system described above could stop at the monocyclopropanation stage. Thus, reacting cyclohexadiene **5** with $TiCl_4$–Mg–CCl_4 complexes at 0 °C using method A led to complete consumption of **5** within 1 h to give only the bicyclic adduct **5a** in 90% yield (Scheme 3). Monocyclopropanation onto an eight-membered ring **6** was equally effective. In these cases, cyclopropanation of the initial dichloroadduct **5a** or **6a** to tetrachlorotricyclooctane appears to be quite slow. We believe that the relatively low temperature required to generate the dichloromethylene complex by Ti–Mg bimetallic species may explain our high selectivity. It is interesting to note that increasing the amount of $TiCl_4$ and Mg dramatically enhanced the cyclopropanation of the initial adducts **5a** and **6a**. Thus, exposure of **5a** and **6a** to 0.5 equiv of $TiCl_4$ and 6 equiv of Mg produced the corresponding tetrachlorides **5b** and **6b**, both possessing only anti configuration, in 94% and 85% yields, respectively.

Changing the diene to the bicyclic substrate **7**[2d] with two different alkene moieties led to equally gratifying results as illustrated in Scheme 4. Thus, addition of THF (5 equiv) to $TiCl_4$ (0.5 equiv) and Mg (6 equiv) in a 2:1 $ClCH_2CH_2Cl/CCl_4$ mixture of solvent (method C) followed by diene **7** at 0 °C gave a single adduct **7a** in 84% yield. Increasing the amount of $TiCl_4$ and Mg effected complete dicyclopropanation to **7b** (86% yield). Surprisingly, employment of bicyclotriene **8** as the test substrate with Ti–Mg–dichlorocarbenoid could not be stopped at the monocyclopropanation stage wherein a 75% yield of a 63:12 ratio of adducts **8a** and **8b** was obtained.

SCHEME 5. Mechanistic Rationale for an Olefin Cyclopropanation with the Ti–Mg–CCl_4 System



These results implicate a metathesis-like mechanism as shown in Scheme 5, wherein the reductive elimination of the presumed titanacyclobutane **10** formed via an electrophilic addition of the Fischer-type Ti–Mg–dichlorocarbenoid **9c**, which may be derived from **9a** or **9b**, to the double bond accounts for the formation of product and the generation of an active chain-propagating titanium species **9**. Although this scheme accounts for some of our current observations, further mechanistic work is clearly required before any definite conclusions can be reached.

Having established the feasibility of a Ti–Mg–dichlorocarbenoid as an electrophilic dichlorocarbene equivalent in alkene cyclopropanation, we then established its nucleophilic behavior with respect to the carbonyl compounds. The dichloromethylenation of adamantanone **11** with CCl_4 was chosen to test the feasibility of the process. Exposure of **11** to the Ti–Mg–dichloromethylene complex at 0 °C produced the desired vinyl dichloride **11a** (Table 1, entry 1). Thus, addition of a THF–CCl_4 solution of **11** (1 equiv) to a mixture of $TiCl_4$ (2 equiv) and magnesium powder (8 equiv) in CH_2Cl_2 at 0 °C gave **11a** (92% isolated yield, method D) in addition to a trace amount of the reduction product readily identified as adamantanol by its spectroscopic properties. Using 2-methylcyclohexanone **12** gave an analogous result with the $TiCl_4$–Mg–CCl_4 system, affording an 86% yield of **12a** (entry 2). The aromatic ketone **13** also gave satisfactory results (entry 3).

Extension of these observations to highly enolizable ketones[8] confirms their generality. Thus, adding THF to a mixture of β-tetralone **14** (method E), $TiCl_4$ (4 equiv), and magnesium (8 equiv) in CH_2Cl_2–CCl_4 at 0 °C produced the desired dichloride **14a** (80% isolated yield, entry 4). For olefination of 2-indanone **15**, use of a 4:12 $TiCl_4$–Mg ratio proves most satisfactory, giving an 85% yield of adduct **15a** (entry 5). More dramatically, increasing the degree of steric hindrance at the carbonyl group does not impede carbonyl olefination. The Ti–Mg–dichloromethylene complexes showed higher reactivity toward addition to the carbonyl group of 2,2-dimethylcyclohexanone **16** in contrast to the Tebbe–Grubbs methylenation reagent, which had

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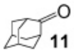
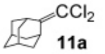
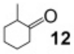
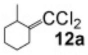
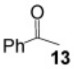
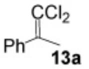
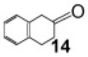
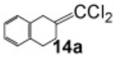
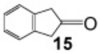
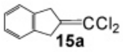
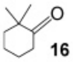
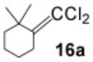
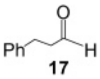
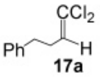
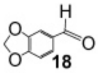
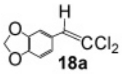
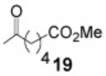
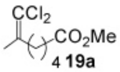
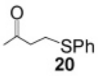
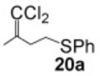
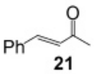
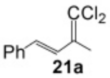
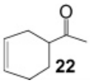
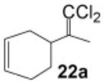
[7] (a) Komrsova, H.; Farkas, J. *Collect. Czech. Chem. Commun.* **1960**, *25*, 1977. (b) Hausser, J. W.; Uchic, J. T. *J. Org. Chem.* **1972**, *37*, 4087.

[8] Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

TABLE 1. Typical Examples of the Nucleophilic Addition of the Ti−Mg−Dichloromethylene Complex to Form Vinyl Dichlorides

entry	substrate	method $TiCl_4$/Mg[a]	product	yield[b] (%)
1	 **11**	D 2/8	 **11a**	92
2	 **12**	D 2/8	 **12a**	86
3	 **13**	D 2/8	 **13a**	75
4	 **14**	E 4/8	 **14a**	80
5	 **15**	E 4/12	 **15a**	85
6	 **16**	E 2/8	 **16a**	81
7	 **17**	D 2/8 15/40[c]	 **17a**	61 64[c]
8	 **18**	E 15/40[c]	 **18a**	78[c]
9	 **19**	E 3/8	 **19a**	79
10	 **20**	E 3/12	 **20a**	76
11	 **21**	D 2/8	 **21a**	74
12	 **22**	E 1/8	 **22a**	62

[a] Olefination performed on 1 mmol of substrate. [b] Isolated yield. [c] Olefination performed on 10 mmol of substrate.

been noted to act as a base to undergo the enolization of **16**.[9] Thus, reacting **16** with $TiCl_4$−Mg−CCl_4 using method E led to the desired vinyl dichloride **16a** in 81% yield (entry 6). Switching from ketone to either the aliphatic or aromatic aldehyde was equally effective (entries 7 and 8). The reaction directly scales up; thus, adduct **17a** was obtained in 64% yield on a 10-mmol scale using 15 equiv of $TiCl_4$ and 40 equiv of Mg.

The chemoselectivity was explored with a series of ketones (entries 9−12). As expected, esters and sulfides have no effect (entries 9 and 10). A particularly interesting example illustrating the chemoselectivity of this process is the addition of substrates **21** and **22**. Only addition to the carbonyl group to give a carbonyl olefination adduct is observed (entries 11 and 12).

The Ti−Mg−dichloromethylene complexes serve as a novel class of ambiphilic dichlorocarbenoid equivalents. Not only is this Ti−Mg carbenoid highly selective but also it seems highly reactive in both alkene cyclopropanation and carbonyl dichloromethylenation. The novel nature involved suggests several intriguing directions which are currently under active investigation.

Experimental Section

Typical Procedure for the Cyclopropanation of Alkenes: Method A. To a 0 °C suspension consisting of Mg (240 mg, 10 mmol), $TiCl_4$ (188 mg, 0.11 mL, 1 mmol), cyclohexene **1** (0.82 g, 1 mL, 10 mmol), CCl_4 (1.54 g, 1 mL, 10 mmol), and $ClCH_2CH_2Cl$ (15 mL) was added THF (0.5 mL). After being stirred for 1−2 h at 0 °C, a solution of saturated potassium carbonate (10 mL) was added and the mixture was diluted with ether (30 mL). The organic layer was separated, dried, evaporated, and purified by chromatography on silica gel (elution with hexane) to give 7,7-dichlorobicyclo[4.1.0]heptane **1a** (1.58 g, 95% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.95−1.90 (m, 2 H), 1.68−1.61 (m, 4 H), 1.32−1.26 (m, 2 H), 1.21−1.15 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.0, 25.8, 20.2, 18.8; high-resolution MS *m*/*e* calcd for $C_7H_{10}Cl_2$ 164.0160, found 164.0155.

Method B. To a 0 °C suspension consisting of Mg (240 mg, 10 mmol), styrene **3** (1.04 g, 10 mmol), CCl_4 (1.54 g, 10 mmol), THF (0.5 mL), and $ClCH_2CH_2Cl$ (15 mL) was added $TiCl_4$ (188 mg, 0.11 mL, 1 mmol). After being stirred for 1 h at 0 °C, a solution of saturated potassium carbonate (10 mL) was added and the mixture was diluted with ether (30 mL). The organic layer was separated, dried, evaporated, and purified by chromatography on silica gel (elution with hexane) to give 1,1-dichloro-2-phenylcyclopropane **3a** (1.68 g, 90% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5 H), 2.92 (dd, $J = 10.4$, 8.4 Hz, 1 H), 2.00 (dd, $J = 10.4$, 8.4 Hz, 1 H), 1.87 (t, $J = 8.4$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 128.9, 128.3, 127. 6, 60.7, 35.4, 25.6.

Method C. To a 0 °C suspension consisting of Mg (144 mg, 6 mmol), $TiCl_4$ (94 mg, 0.06 mL, 0.5 mmol), CCl_4 (1.54 g, 10 mmol), and $ClCH_2CH_2Cl$ (3 mL) was added THF (0.3 mL) dropwise, during which time a pale black color developed. After being stirred for 1∼2 min at 0 °C, a solution of bicyclodiene **7** (134 mg, 1 mmol) in $ClCH_2CH_2Cl$ (1 mL) was added. The black mixture was stirred for an additional 1 h, treated with a solution of saturated potassium carbonate (4 mL), and diluted with ether (10 mL). The organic layer was separated, dried, evaporated, and purified by chromatography on silica gel (elution with hexane) to give 11,11-dichlorotricyclo[4.4.1]undec-3-ene **7a** (182 mg, 84% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 5.50 (bs, 2 H), 2.48 (d, $J = 16.4$ Hz, 2 H), 2.18 (d, $J = 16.4$ Hz, 2 H), 1.92−1.29 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.5, 65.9, 30.4, 29.6, 26.1, 20.1; high-resolution MS *m*/*e* calcd for $C_{11}H_{14}Cl_2$ 216.0472, found 216.0466. Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.84; H, 6.50. Found: C, 60.51; H, 6.44.

General Procedure for the Dichloromethylenation of Carbonyl Compounds: Method D. At 0 °C, adamantanone **11** (150 mg, 1 mmol) in CCl_4 (3 mL) and THF (1 mL) was added to a suspension consisting of Mg (192 mg, 8 mmol) and $TiCl_4$ (2 mmol, 1 M in CH_2Cl_2, 2 mL). After the initial exotherm had ceased, the cooling bath was removed. 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 100:1 hexanes−ethyl acetate) to give dichloride 2-dichloromethyleneadamantane **11a** (198 mg, 92% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 3.09 (bs, 2 H), 1.93−1.71 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 107.1, 37.8, 36.4, 34.6, 27.4; high-resolution MS *m*/*e* calcd for $C_{11}H_{14}Cl_2$ 216.0473, found 216.0470.

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

Method E. To a 0 °C suspension consisting of Mg (192 mg, 8 mmol), $TiCl_4$ (4 mmol, 2 M in CH_2Cl_2, 2 mL), CCl_4 (5 mL), and β-tetralone **14** (146 mg, 1 mmol) was added THF (1 mL) dropwise. After being stirred for 1 h at 0 °C, a solution of saturated potassium carbonate (10 mL) was added. 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 100:1 hexanes−ethyl acetate) to give 2-dichloromethylene-1,2,3,4-tetrahydronaphthalene **14a** (170 mg, 80% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.07 (m, 4H), 4.86 (d, J = 1.2 Hz, 1 H, *H*C═C), 4.83 (d, J = 1.2 Hz, 1 H, *H*C═C), 3.52 (s, 2 H, (*H*2C)C═C), 2.84 (t, J = 6.4 Hz, 2 H, (*H*2C)2C═C), 2.46 (t, J = 6.4 Hz, 2 H, (*H*2C)2C═C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 137.0, 128.5, 128.3, 125.9, 125.8, 125.5, 108.2, 37.1, 31.8, 31.2; high-resolution MS *m*/*e* calcd for $C_{11}H_{10}Cl_2$ 212.0160, found 212.0168. Anal. Calcd for $C_{11}H_{10}Cl_2$: C, 61.99; H, 4.73. Found: C, 61.76; H, 4.65.

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Supporting Information Available: Experimental procedures and spectral data, including copies of ^{1}H and ^{13}C NMR spectra for dichlorocyclopropanes **1a**, **3a**, **4a**, **5a**,**b**, **6a**,**b**, **7b**, and **8a**,**b**, and vinyl dichlorides **11a**, **12a**, **13a**, **15a**, **17a**, **19a**, **20a**, **21a**, and **22a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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