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Unusual Ambiphilic Carbenoid Equivalent in Amide Cyclopropanation

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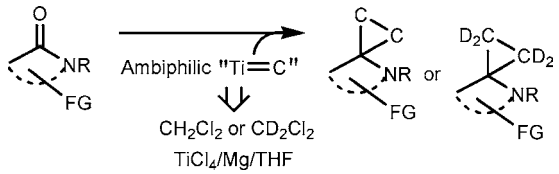
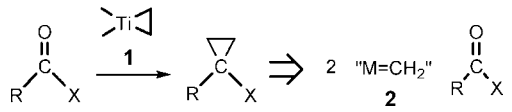
ABSTRACT



The titanium–methylene complexes derived from the $TiCl_4$–Mg–CH_2Cl_2 system serve as a novel class of ambiphilic carbenoid equivalents, which not only efficiently effect cyclopropanations of a variety amides but also exhibit high chemoselectivity.

The importance of cyclopropane rings as valuable building blocks for further structural elaboration[1] and as important skeletons in a variety of biologically active compounds[2] has stimulated the development of new methods for their construction. Among the most useful recently developed methods are carbonyl cyclopropanations (Scheme 1),[3] which

Scheme 1. Carbonyl Cyclopropanation



involve the reductive coupling of carbonyl compounds with the presumed titanacyclopropane intermediate **1** formed via the direct coupling of a suitable Grignard reagent with Ti-$(O\text{-}i\text{Pr})_4$.[3,4] To develop new strategies based on the concept of simple tandem methylene transfer reactions, we were attracted to the carbonyl cyclopropanations promoted by an ambiphilic carbenoid **2**, which not only could function as a Schrock-type carbene complex to effect carbonyl methylenation[5] but also played the role of a Fischer-type carbene complex to promote further cyclopropanation of the alkene.[6] To our knowledge, despite the vast number of metallocarbene-mediated carbonyl olefinations and olefin cyclopropanations, progress in metallocarbene-promoted carbonyl cyclopropanations has been slow to evolve.[7] The reason stems

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(2) (a) Liu, H.-W.; Walsh, C. T. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Eds.; Wiley: Chichester, 1987; p 1010ff. (b) Liu, H.-W.; Auchus, R.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 5335. (c) Adams, D. O.; Yang, S. F. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 170. (d) Burroughs, L. F. *Nature* **1957**, *179*, 360. (e) Pirrung, M. C.; Cao, J.; Chen, J. *J. Org. Chem.* **1995**, *60*, 5790.

(3) For reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759. (c) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (d) Kulinkovich, O. G. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 1065.

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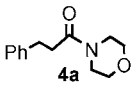
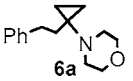
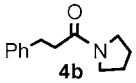
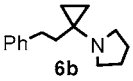
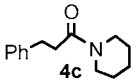
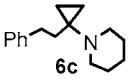
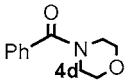
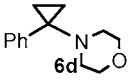
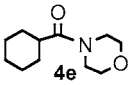
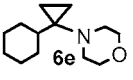
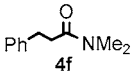
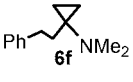
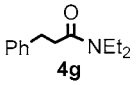
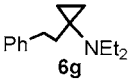
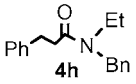
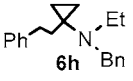
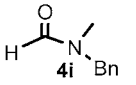
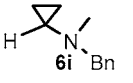
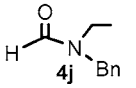
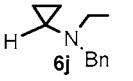
from the nature of the metallocarbenes. We report that the titanium−methylene complexes derived from the $TiCl_4$−Mg−CH_2Cl_2 system[5f,g] serve as a novel class of ambiphilic carbenoid equivalents, which not only efficiently effect cyclopropanations of a variety of amides but also exhibit high chemoselectivity.

The indication that such an ambiphilic methylene complex may exist came as a result of our probing the effect of the amount of Mg relative to $TiCl_4$ on the CH_2 transfer reaction of CH_2Cl_2. The reaction of a simple amide **4a** with CH_2Cl_2 was chosen to test the feasibility of the process (Table 1).

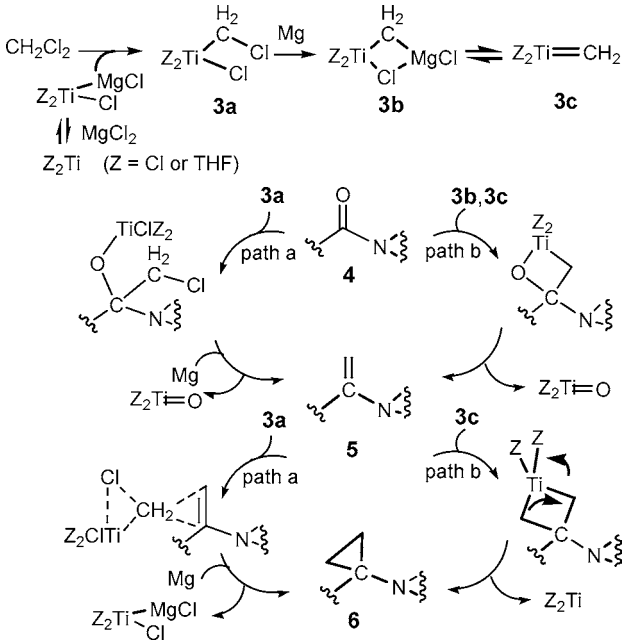
Table 1. Typical Amide Cyclopropanation with CH_2Cl_2[a]

entry	substrate	$TiCl_4$: Mg	product	yield (%)[b]
1	 **4a**	0.8 : 8	 **6a**	81
		2.8 : 30[c]		72
2	 **4b**	0.8 : 8	 **6b**	71
3	 **4c**	0.8 : 8	 **6c**	76
4	 **4d**	0.8 : 8	 **6d**	64
5	 **4e**	0.8 : 12	 **6e**	73
6	 **4f**	0.8 : 8	 **6f**	75
7	 **4g**	0.8 : 12	 **6g**	67
8	 **4h**	0.8 : 12	 **6h**	62
9	 **4i**	0.8 : 8	 **6i**	51
10	 **4j**	0.8 : 8	 **6j**	50

[a] Reactions were run on a 1 mmol scale in CH_2Cl_2/THF (1 mL) at 0−25 °C, unless otherwise noted. [b] Isolated yield. [c] Cyclopropanation performed on a 5 mmol scale.

Exposing morpholine amide **4a** to 2 equiv of $TiCl_4$ and 8 equiv of Mg did indeed produce the cyclopropanation adduct but only in less than 5% yield. Remarkably, using less than 1 equiv of $TiCl_4$ dramatically improved the nucleophilic and electrophilic additions, leading to smooth amide cyclopropanations. Thus, reacting **4a** with CH_2Cl_2 at 0−25 °C using 0.8 equiv of $TiCl_4$ effected complete carbonyl methylenation and alkene cyclopropanation within 4 h to give the desired cyclopropylamine **6a** in 81% yield (entry 1). The reaction directly scales up; thus, adduct **6a** was obtained in 72% yield on a 5 mmol scale using 2.8 equiv of $TiCl_4$ and 30 equiv of Mg. Pyrrolidine amide **4b** and piperidine amide **4c** gave similar results under our standard conditions (entries 2 and 3). The reaction is best envisioned as involving interception of the enamine **5** formed via a nucleophilic attack of a presumed titanium chloromethylene complex **3a** (path a) or methylene complexes **3b** and **3c**[5] (path b) on the carbonyl carbon by a Simmons−Smith-type complex **3a**[8] or an electrophilic titanium methylidene **3c** followed by reductive elimination to product **6** as shown in Scheme 2. Although

Scheme 2. Proposed Mechanism for Amide Cyclopropanation



this scheme accounts for our current observations, we cannot rule out the involvement of some titanacyclopropane complex as the active entity. Further mechanistic work is clearly required before any definite conclusions can be reached.

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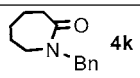
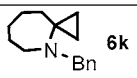
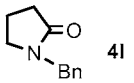
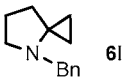
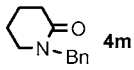
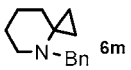
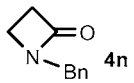
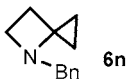
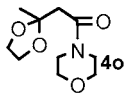
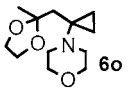
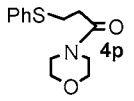
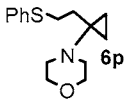
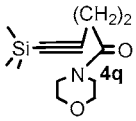
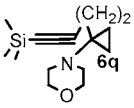
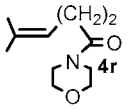
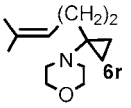
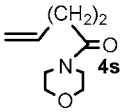
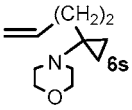
Table 2. Direct Cyclopropanation of Cyclic Amides and Amides Containing Functional Groups[a]

entry	substrate	$TiCl_4$: Mg	product	yield (%)[b]
1	 **4k**	0.8 : 12	 **6k**	72[c]
2	 **4l**	0.8 : 12	 **6l**	74[c]
3	 **4m**	0.8 : 12	 **6m**	31 64[d]
4	 **4n**	0.8 : 12	 **6n**	34 67[d]
5	 **4o**	0.8 : 8	 **6o**	70
6	 **4p**	0.8 : 8	 **6p**	72
7	 **4q**	0.8 : 8	 **6q**	56
8	 **4r**	0.8 : 8	 **6r**	74
9	 **4s**	0.8 : 8	 **6s**	74

[a] Reactions were conducted on a 1 mmol scale in CH_2Cl_2/THF (1 mL) at 0−25 °C, unless otherwise noted. [b] Isolated yield. [c] 2.5−3 mL of THF was used. [d] Performing the reaction at −10 °C.

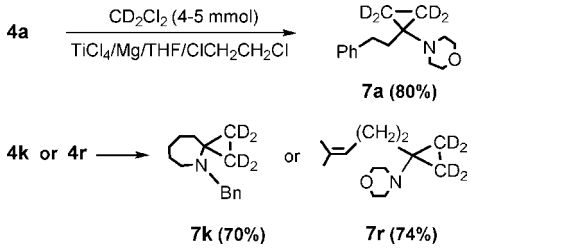
Changing the substrate to aromatic amide **4d** and cyclohexanecarbonyl amide **4e** led to equally gratifying results (entries 4 and 5). Variation of the substituents at nitrogen was briefly explored. Cyclopropanation onto the acyclic amine-derived amides **4f**−**h** (entries 6−8) was equally effective. Some dependence on the nature of the amide was observed because cyclopropanation on formamides **4i** and **4j** gave inferior results, giving a moderate yield of **6i**[9] and **6j** (entries 9 and 10).

Extension of these observations to other substrates such as lactams confirms their generality. The cyclic amide **4k** gave an analogous result with titanium−methylene complexes (Table 2, entry 1) wherein the spiro amine **6k** was obtained in 72% yield. Switching from the seven-membered ring lactam to the five-membered analogue also gave satisfactory results (entry 2). Notably, the ring size in the lactam substrate had some effect on cyclopropanation (entries 3 and 4). Surprisingly, performing the cyclopropanation on **4m** and **4n** at −10 °C for 16 h increased the yield of **6m** and **6n**[4j] to 64% and 67%, respectively.

The reaction exhibits good chemoselectivity. As expected, acetal and sulfide have no effect (entries 5 and 6). Remarkably, both acetylenes and alkenes are also tolerated (entries 7−9). The latter is particularly noteworthy because the reductive coupling of terminal olefins with carboxylates promoted by the titanacyclopropane intermediate had been noted previously.[3,4]

The efficiency and practicality of this chemistry is illustrated by the very simple synthesis of deuterated cyclopropylamines such as **7a**, **7k**, and **7r** by simple tandem Ti−Mg-promoted CD_2-transfer reactions of CD_2Cl_2 (Scheme 3).

Scheme 3. Synthesis of Deuterated Cyclopropylamines



Performing the reaction in $ClCH_2CH_2Cl$ allowed the use of only 4−5 mmol of CD_2Cl_2.

The $TiCl_4$−Mg-promoted tandem methylene transfer reactions of CH_2Cl_2 serve as a novel class of ambiphilic carbenoid equivalents that effect complete nucleophilic and electrophilic additions. Not only is this titanium−methylene complex highly reactive but it also seems highly selective in amide cyclopropanations and might become a practical cyclopropanation reagent. The novel nature involved suggests several intriguing directions which are currently under active investigation. Further studies will determine whether this carbenoid formation promoted by Ti−Mg complexes will be generally useful for other geminal dihalides such as 1,1-dichloroethane.

Acknowledgment. We thank the National Science Council of the Republic of China for generous support.

Supporting Information Available: Experimental procedures and spectral data, including copies of ^1H and ^{13}C NMR spectra for **6a**−**s**, **7a**, **7k**, and **7r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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