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New, General, and Practical Enamine Cyclopropanation Using Dichloromethane

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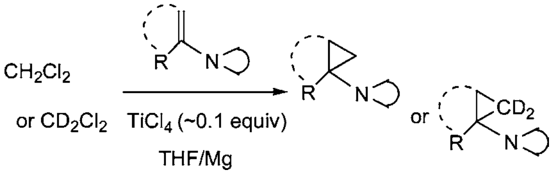
ABSTRACT



Dichloromethane serves as a novel electrophilic carbene equivalent which adds to an enamine double bond. The presence of other alkene moieties in the enamine partner is well tolerated. Even enamines derived from sterically hindered ketones react readily with dichloromethane promoted by $TiCl_4$–Mg.

The utility of cyclopropylamines as valuable building blocks for molecular construction[1] and the ease of access to enamines make the conversion of the latter into the former a useful transformation. The most common method for the preparation of these cyclopropane derivatives involves the addition of methylene to the enamine double bond induced by diazomethane−CuCl[1a,2a] or diiodomethane−$ZnEt_2$.[1a,2b,c] However, the requirement of the use of potentially unstable and expensive reagents to generate carbenoids greatly limits the general utility of the method. The direct cyclopropanation of alkenes with *gem*-dibromides promoted by Cu[3] or Zn−Cu[4] constitutes a useful cyclopropane ring forming process. However, this process does not generally extend to enamines. The reported metal carbenoid generated from dibromomethane−Zn−Cu[4] added to a simple enamine of cyclohexanone in yields ranging from 8 to 22%. In searching for new strategies based on a simple metathesis-like mechanism, we turned our attention to evaluating the feasibility of an enamine cyclopropanation via an electrophilic Fischer-type carbene complex.[5] To our knowledge and despite the vast number of carbonyl olefinations mediated by nucleophilic titanium carbenoids,[6,7] no enamine cyclopropanations promoted by titanium−methylene complexes have been recorded. Earlier work from our laboratories established the feasibility of the CH_2Cl_2−$TiCl_4$−Mg system as a highly nucleophilic carbene complex to effect carbonyl methylena-

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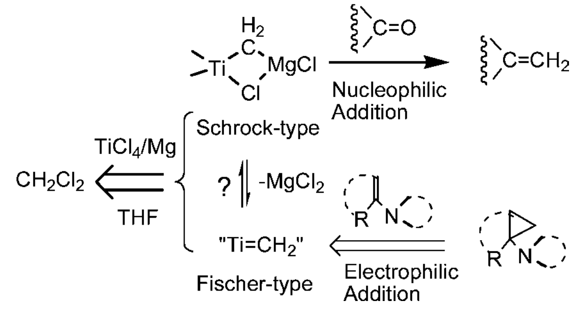
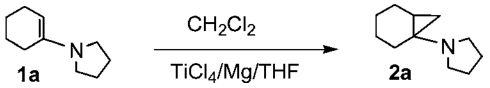
tion.[7] To expand the scope of titanium carbenoid-mediated reactions, we considered the prospect of a $TiCl_4$−Mg bimetallic complex-promoted cyclopropanation of enamine with CH_2Cl_2 as a possibility (Scheme 1). In this communication, we report a new, practical, and general approach for the construction of cyclopropylamines which is based on the use of CH_2Cl_2 to generate an electrophilic carbenoid equivalent.

Scheme 1. Ti−Mg-Promoted CH_2 Transfer of CH_2Cl_2



The cyclopropanation of cyclohexanone enamine **1a** with CH_2Cl_2 was chosen to test the feasibility of the process (Table 1). Using a 1:1 Mg/$TiCl_4$ ratio did not promote CH_2 transfer from CH_2Cl_2. Increasing the amount of Mg did indeed produce cyclopropylamine **2a** but only in less than 10% conversion with most of the remainder being a hydrolysis product derived from **1a**. On the other hand, simply decreasing the amount of $TiCl_4$ dramatically improved the cyclopropylamine formation, with the yield varying from 8 to 85% (entries 2−4). Most revealing was the catalytic effect of $TiCl_4$, in that as little as 15% can effect complete cyclopropanation to **2a**. The addition of a solution of **1a** (2 mmol) in THF (1.5 mL) to a suspension of $TiCl_4$ (0.3 mmol) and Mg (10 mmol) in CH_2Cl_2 at 25 °C was adopted as the standard protocol, and it produced the desired cyclopropylamine **2a**. More gratifyingly, the reaction directly scales up; thus, adduct **2a** was obtained in 84% yield on a 10 mmol scale using 0.1 equiv of $TiCl_4$ and 4 equiv of Mg.

Table 1. Reaction Conditions for Cyclopropanation of Enamine **1a**[a] with CH_2Cl_2

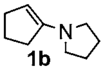
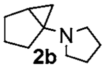
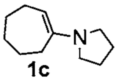
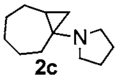
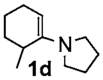
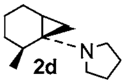
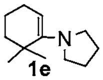
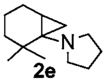
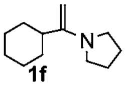
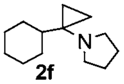
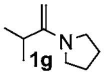
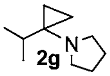
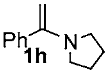
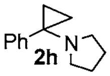
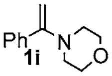
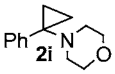
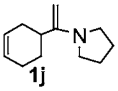
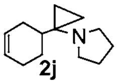
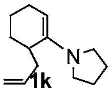
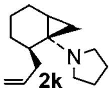


entry	$TiCl_4$/Mg (mmol)	THF/CH_2Cl_2 (mL)	reaction temp (°C)	conv (%)[b]	yield (%)[c]
1	2:2	1.5/7.0	25	0	0
2	2:5	1.5/7.0	25	5	5
3	2:10	1.5/7.0	25	8	8
4	1:10	1.5/7.0	25	50	32
5	0.3:10	1.5/5.0	25	100	85
6	0.3:10	1.0/5.0	25	90	67
7	0.3:10	0.5/5.0	25	80	56
8	0.3:10	1.5/5.0	0	85	63

[a] All reactions were performed on a 2 mmol scale. [b] The conversion was determined by NMR analysis of the corresponding crude product. Most of the remainder was a hydrolysis product derived from **1a**. [c] Isolated yield.

Having established the feasibility of the cyclopropanation, we studied its generality with respect to the enamine partner. The variation of the ring size was briefly explored. Switching from the six-membered ring cyclohexenylamine to either the five- or seven-membered analogue had little effect (Table 2, entries 1 and 2). Thus, both **1b** and **1c** reacted efficiently with CH_2Cl_2-derived titanium carbenoid to give the desired cyclopropanation products **2b** (72%) and **2c** (83%), respec-

Table 2. Cyclopropanation of Enamines (2 mmol) with CH_2Cl_2 Promoted by Ti−Mg Bimetallic Complexes

entry	enamine	$TiCl_4$/Mg (mmol)	cyclopropylamine	yield[a] (%)
1	 **1b**	0.3:10	 **2b**	72
2	 **1c**	0.3:10	 **2c**	83
3	 **1d**	0.3:10	 **2d**	85
4	 **1e**	0.3:12	 **2e**	85
5	 **1f**	0.3:10	 **2f**	73
6	 **1g**	0.3:10	 **2g**	70
7	 **1h**	0.2:16[b]	 **2h**	65
8	 **1i**	0.2:16[b]	 **2i**	70
9	 **1j**	0.3:12	 **2j**	50
10	 **1k**	0.3:10	 **2k**	76

[a] Isolated yield. [b] To a suspension of $TiCl_4$ and magnesium powder in THF (2 mL) at 0 °C was added a solution of enamine (2 mmol) in THF (6 mL)/CH_2Cl_2 (1 mL). [c] The reaction was performed at 0−5 °C.

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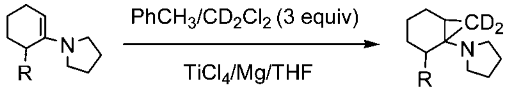
tively. Notably, the 2-methylcyclohexanone-derived enamine **1d** also gave satisfactory results with the CH_2Cl_2−Mg−$TiCl_4$−THF system (entry 3). The C_1−C_2 stereochemistry of the adduct **2d** was established by the presence of an NOE between the cyclopropyl methylene protons and the methyl protons.[8] Surprisingly, increasing the degree of steric hindrance at the enamine did not impede cyclopropanation. Thus, cyclopropanation onto the enamine **1e** derived from 2,2-dimethylcyclohexanone was equally effective, leading to **2e** in 85% yield (entry 4). To demonstrate the scope of this cyclopropane-forming method further, the utility of this protocol was examined in the cyclopropanation with the acyclic ketone-derived enamines: **1f** and **1g** gave the desired cyclopropylamines **2f** (73%) and **2g** (70%), respectively (entries 5 and 6). Changing the substrate to pyrrolidine and morpholine enamines of aromatic ketones led to equally gratifying results (entries 7 and 8) with formation of cyclopropylamines **2h** (65%) and **2i** (70%).

The use of enamines **1j** and **1k** (entries 9 and 10) highlights the possible chemoselectivity of the process. As expected, internal and terminal alkenes are completely unaffected. Only additions to the enamine double bonds to give adducts **2j** and **2k** were observed. An NOE experiment provided additional support for the assignment of the C_1−C_2 stereochemistry as depicted in **2k**.

To demonstrate the practicability of titanium−methylene complex-mediated enamine cyclopropanation further, a very simple preparation of deuterated cyclopropylamines **6a** and **6d** was carried out (Scheme 2). Performing the reaction in toluene allowed the use of only 3 equiv of CD_2Cl_2.

Scheme 2. Conversion of Enamine to Deuterated Cyclopropylamine

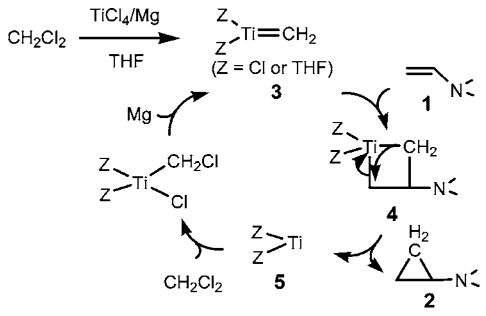


1a: R = H
1d: R = CH_3

6a: R = H (81%)
6d: R = CH_3 (78%)

The above results can be rationalized in terms of a metathesis-like mechanism as shown in Scheme 3, wherein the reductive elimination of the presumed titanacyclobutane **4** formed via an electrophilic addition of the Fischer-type titanium−methylene complex **3** to the double bond accounts for the formation of cyclopropylamine and the generation of an active chain-propagating titanium species **5**. Left unanswered by this proposal is the strong dependence of the formation of the Fischer-type methylene complex on the relative amount of $TiCl_4$ to Mg and THF. Further mechanistic work is clearly required before any definite conclusions can be reached.

Scheme 3. Enamine Cyclopropanation via Electrophilic Titanium−Methylene Complexes



The ability to elaborate CH_2Cl_2 into a novel class of electrophilic titanium−methylene complexes via titanium-catalyzed oxidative addition of an unactivated C−Cl bond should prove to be a particularly valuable method that enhances synthetic efficiency. The successful application of the CH_2Cl_2−Mg−$TiCl_4$-mediated cyclopropanation of various enamines highlights the unusual reactivity and selectivity of this new electrophilic titanium carbenoid, which serves as a practical reagent applicable to large-scale syntheses. The novel electrophilicity involved suggests several intriguing directions which are currently under active investigation.

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 ^{1}H and ^{13}C NMR spectra for **2a−k**, **6a**, and **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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