Acyloxymethylzinc Reagents: Preparation, Reactivity, and Solid-State Structure of This Novel Class of Cyclopropanating Reagents

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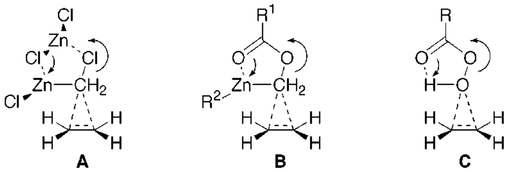
Cyclopropanes are the focus of much interest as they are found in many natural and unnatural products possessing interesting biological activities.[1] They are also useful synthetic intermediates[2] and can serve as mechanistic probes in many organic reactions.[3] Surprisingly, however, the number of approaches to access cyclopropanes from alkenes is limited to methodologies developed a few decades ago. These include free carbenes,[4] transition metal-catalyzed diazo decomposition,[5] Simmons−Smith reaction,[6] and Michael initiated ring closure.[7] The development of a reagent that would overcome the inherent limitations of these classical approaches would be of great value. Indeed, the use of a large excess of reagent (>5 equiv) is often required and so far only the Simmons−Smith reaction is capable of an efficient enantioselective methylene transfer, in cases where allylic alcohols are used as substrates.[6] In this perspective, we were interested in the development of a new concept of metal carbenoids that could show increased reactivity and/or provide new avenues to perform enantioselective cyclopropanation reactions. Herein, we report conceptually different carbenoids, the acyloxymethylzinc carbenoids, which are reactive and promising cyclopropanating reagents. Furthermore, these reagents are the first examples of zinc carbenoids that can cyclopropanate alkenes without involving the breaking of a carbon−halogen bond in the methylene transfer process.[8]

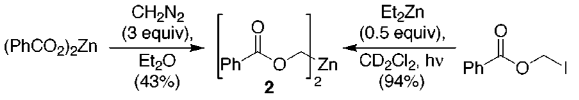
Drawing on the experimental evidence for Lewis acid catalysis in the Simmons−Smith reaction[9] and Nakamura's reported five-membered, cyclic transition state model **A**,[10] we reasoned that a carbenoid with internal Lewis acid activation could be an efficient methylene transfer reagent. We therefore became interested in the versatile carbenoid template **B** since this family of reagents is the methylene transfer equivalent of peracids in epoxidation reactions (**C**).



With this model in mind, the R^1 group should be electron withdrawing to increase the electrophilicity of the carbenoid, which is expected to be enhanced through intramolecular coordination to the zinc atom (Scheme 1, **B**). Gratifyingly, it was found that a 1:1 mixture of iodomethyl perfluoropentanoate **1**[11] and diethylzinc affords a reactive carbenoid. Furthermore, ^{1}H NMR analysis indicated that the zinc−iodine exchange had occurred as Et-I was formed quantitatively, thus affording the carbenoid of the general structure **B**. More conveniently, the desired alkylzinc reagent can be prepared in the presence of the alkene, using photoinduced zinc−iodine exchange.[12,13] The reactivity of this carbenoid was examined mainly by its reaction with a variety of unfunctionalized olefins (Table 1),[14] since these substrates are generally poorly reactive under the existing Simmons−Smith protocols.[15]

As illustrated in Table 1, this reagent cyclopropanates efficiently a variety of unfunctionalized alkenes (entries 1−4). Interestingly, *trans*-stilbene, which is often unreactive under most Simmons−Smith protocols, gives the desired product in modest yield (entry 5).[16] As expected, the cyclopropanation of functionalized substrates proved also efficient (entry 6). While the reaction conditions are not optimized,[17] the data presented in Table 1 unambiguously demonstrate the synthetic potential of zincmethylesters as efficient cyclopropanating reagents. Although this type of reagent is precedented, the parent zincmethylbenzoate compounds have been shown to be poorly reactive as either electrophiles[18] or nucleophiles.[19]

The structure of a member of this class of carbenoids was confirmed by X-ray crystallography. The bis(benzoyloxymethyl)zinc analogue **2** was prepared using both the reported[18] and photoinduced[12] routes (eq 1). An ORTEP drawing of **2** is shown in Figure 1 and selected bond lengths and angles are presented in Table 2.[20]



(1)

In contrast with other carbenoid complexes in which the zinc center displays a tetrahedral geometry,[21] the zinc center in **2** resides in a distorted square-bipyramidal environment. The Zn−C

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[1] Salaün, J. *Curr. Med. Chem.* **1995**, *2*, 511.

[2] (a) *Small Ring Compounds in Organic Synthsis VI*; de Meijere, A., Ed.; Springer: Berlin, Germany, 2000; Vol. 207. (b) Houblen-Weyl, *Methods of Organic Chemistry*; Thieme: Stuttgart, 1997; Vol. E 17c.

[3] Nonhehel, D. C. *Chem. Soc. Rev.* **1993**, *22*, 347.

[4] Doering, W. v. E.; Hoffman, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162.

[5] (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Lydon, K. M.; McKervey, M. A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. II, p 539. (c) Pfaltz, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol II, p 513.

[6] Charette, A. B.; Beauchemin, A. *Org. React.* (*N.Y.*) **2001**, *58*, in press.

[7] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867.

[8] Motherwell reported a superb route to zinc carbenoids using Zn/Hg, carbonyl compounds (or their equivalents), and TMSCl. However, the proposed intermediate for these reactions is the chloro-alkylzinc reagent, see: Motherwell, W. B.; O'Mahony, D. J. R.; Popkin, M. E. *Tetrahedron Lett.* **1998**, *39*, 5285 and cited references.

[9] Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367.

[10] Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844.

[11] This iodide was selected for its physical properties. As described in the Experimental Section, it can be purified by distillation, without being hydrophilic and/or volatile enough to jeopardize product isolation.

[12] The zinc−iodine exchange reaction is slow and it is inhibited by the presence of alkenes. For a similar observation, see: (a) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1895. The use of a UV−vis source is required to achieve quantitative formation of the carbenoid, see: (b) Charette, A. B.; Beauchemin, A.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1998**, *120*, 5114.

[13] The photolysis is performed using a GE 275W sunlamp or a 300W OSRAM Ultra-Vitalux lamp.

[14] In contrast to diiodomethane, irradiation of iodide **1** in the absence of Et_2Zn does not lead to cyclopropane formation, see: Kropp, P. J. *Acc. Chem. Res.* **1984**, *17*, 131 and references therein.

[15] For superior reagents to cyclopropanate unfunctionalized alkenes, see: (a) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974. (b) Yang, Z. Q.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621. (c) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *112*, 4539.

[16] Zn/Cu, CH_2I_2 (6 equiv), Et_2O: 24%, see: (a) Brown, R. S.; Traylor, T. G. *J. Am. Chem. Soc.* **1973**, *95*, 8025. $EtZnI/CH_2I_2$ (3 equiv), Et_2O: 48%, see: (b) Sawada, S.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2669. $Et_2Zn/TFA/CH_2I_2$ (4 equiv), CH_2Cl_2: 70%, see ref 15b.

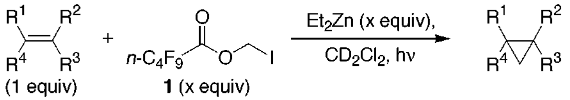
[17] A significant amount of the carbenoid decomposition is due to homologation to form n-$C_4F_9CO_2Zn$(n-Pr), as in the case of $EtZnCH_2I$: Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539.

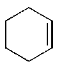
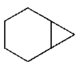
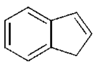
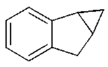
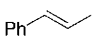
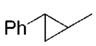
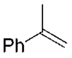
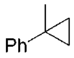
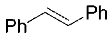
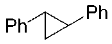
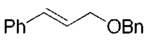
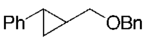
[18] Wittig, G.; Jautelat, M. *Liebigs Ann. Chem.* **1967**, *702*, 24.

[19] Knochel, P.; Chou, T.-S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202.

10.1021/ja0109287 CCC: $20.00

Table 1. Cyclopropanation of Unfunctionalized Alkenes Using Ethylzincmethyl Perfluoropentanoate



Entry	Alkene	x	Product	Conversion (%)[a,b]
1		1.5		>99
2		1.5		88
3		1.5		78
4		1.5		>99
5		4		41 (35)
6		1.5		>99

[a] Determined by ^{1}H NMR and by GC using *n*-nonane as the internal standard. [b] Isolated yields are shown in parentheses.

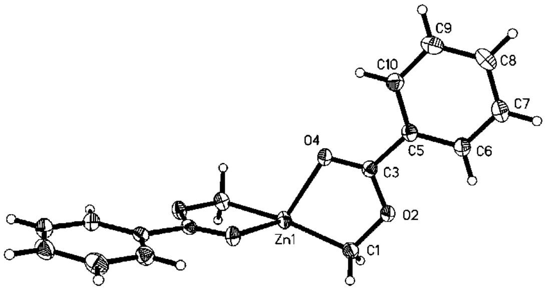


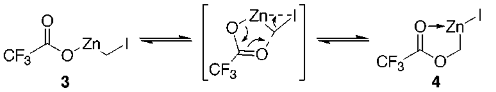
Figure 1. ORTEP view of $(PhCO_2CH_2)_2Zn$. Ellipsoids are drawn at the 30% probability level.

Table 2. Selected Bond Lengths and Angles for the $(PhCO_2CH_2)_2Zn$ Comple

	Bond Lengths (Å)		
Zn(1)–C(1)	1.978(2)	Zn(1)–O(4)	2.1816(15)
C(1)–O(2)	1.490(2)	C(3)–O(4)	1.227(2)
O(2)–C(3)	1.320(2)	C(3)–C(5)	1.482(3)
	Bond Angles (deg)		
$C(1)^{i}$–Zn(1)–C(1)	159.35(13)	O(2)–C(3)-O(4)	124.01(18)
$C(1)^{i}$–Zn(1)–O(4)	113.53(8)	C(1)–Zn(1)-O(4)	80.66 (7)
Zn(1)–C(1)–O(2)	109.43(13)	$O(4)^{i}$–Zn(1)–O(4)	97.22(8)
Zn(1)–O(4)–C(3)	109.00(12)	Zn(1)–C(1)-O(2)–C(3)	2.7(2)
C(1)–O(2)–C(3)	116.83(15)	O(2)–C(3)-C(5)–C(6)	−2.4(3)

bond length of 1.978 Å,[21] the C═O bond length of 1.227 Å, and the Zn–O–C bond angle of 109.00° are in agreement with literature data and the Zn–O bond length of 2.1816 Å is slightly longer than those found in other complexes.[22] X-ray crystal structure analyses of α-heteroatom-substituted dialkylzinc compounds are rare,[23] and to the best of our knowledge this is the first structure of an α-oxygenated derivative.[24]

Finally, the data presented in Table 1 provide substantial evidence that the increased reactivity of Shi's Carbenoid[15b] ($CF_3CO_2ZnCH_2I$, **3**) might be attributed to in situ equilibration leading to formation of iodomethylzinc trifluoroacetate **4** under the reaction conditions (eq 2). The acyloxymethylzinc **4** was observed



(2)

both by ^{1}H NMR and by GC analysis of hydrolyzed reaction aliquots.[25] The proposed equilibrium is precedented and appears to be general to mixed zinc carbenoids ($XZnCH_2Y \leftrightarrow XCH_2ZnY$).[26]

In conclusion, we have shown that acyloxymethylzinc derivatives are promising cyclopropanating reagents for unfunctionalized alkenes. The application of these reagents in directed and enantioselective cyclopropanation reactions and the development of a more reactive, storable, solid carbenoid[21d] within this family of reagents are currently under investigation. Application of this new concept to other metals will also be reported in due course.

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Supporting Information Available: Typical experimental procedures, experimental details, and spectra data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Intensity data were measured on a Enraf-Nonius CAD-4 diffractometer using copper Kα radiation and the $\omega/2\theta$ scan technique. Crystals of $(PhCO_2CH_2)_2Zn$ belong to the monoclinic space group $C2/c$ with $a = 11.781$ (5) Å, $b = 9.066$ (2) Å, $c = 13.780$ (4) Å, $\beta = 103.15$ (3)°, $V = 1433.2$ (8) Å^3, $Z = 4$, and $D_{calcd} = 1.5556$ mg/m^3. Data were collected at 220 K, and the structure was solved by direct methods and refined to $R_f = 0.0318$ and $R_w = 0.0948$ for 1311 reflections with $I = 2\sigma(I)$.

(21) (a) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 723. (b) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592. (c) Charette, A. B.; Marcoux, J.-F.; Bélanger-Gariepy, F. *J. Am. Chem. Soc.* **1996**, *118*, 6792. (d) Charette, A. B.; Marcoux, J.-F.; Molinaro, C.; Beauchemin, A.; Brochu, C.; Isabel, E. *J. Am. Chem. Soc.* **2000**, *122*, 4508.

(22) For the crystal structure of other five-membered complexes with chelation of a C═O oxygen on the zinc atom, see: (a) Braibanti, A.; Pellinghelli, M. A.; Piripicchio, A.; Tiripicchio Camellini, M. *Acta Crystallogr.* **1971**, *B27*, 1240. (b) Göttlicher, S.; Paulus, H. *Chem. Ber.* **1982**, *115*, 393. (c) van Vliet, M. R. P.; van Koten, G.; Modder, J. F.; van Beek, A. M.; Klaver, W. J.; Goubitz, K.; Stam, C. H. *J. Organomet. Chem.* **1987**, *319*, 285. (d) Balogh-Hergovich, E.; Kaizer, J.; Speier, G.; Huttner, G.; Rutsch, P. *Acta Crystallogr.* **1999**, *C55*, 557.

(23) Gais, H.-J.; Bülow, G.; Raabe, G. *J. Am. Chem. Soc.* **1993**, *115*, 7215 and references therein.

(24) For the X-ray crystal structure of a 2-zincio-1,3-oxazole ($Zn-C_{sp^2}-O$), see: Boche, G.; Bosold, F.; Hermann, H.; Marsch, M.; Harms, K.; Lohrenz, J. C. W. *Chem. Eur. J.* **1998**, *4*, 814.

(25) The **3**:**4** ratio was evaluated to be varying between ca. 2:1 (NMR) and 4:1 (GC analysis). Since 2 equiv of the carbenoid are used, a significant fraction of the cyclopropane formation could be attributed to the zincmethylester **4**. See the Experimental Section for details.

(26) (a) $IZnCH_2Cl$ vs ICH_2ZnCl: Simmons, H. E.; Blanchard, E. P.; Smith, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 1347. (b) $MeOCH_2ZnCl$ vs $MeOZnCH_2Cl$: Taeger, E.; Bergk, K. H. *J. Prakt. Chem.* **1967**, *35*, 1. (c) $EtZnCH_2I$ vs *n*-PrZnI (irreversible): see ref 17.