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First Evidence for the Formation of a Geminal Dizinc Carbenoid: A Highly Stereoselective Synthesis of 1,2,3-Substituted Cyclopropanes

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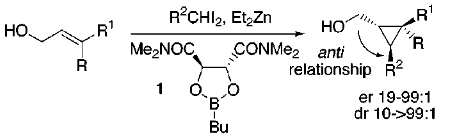
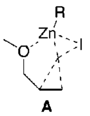
1,2,3-Substituted cyclopropanes are found widely in natural products and biologically active molecules.[1] Our interest in developing enantioselective methods for their synthesis using zinc carbenoids prompted us to look at novel organometallic species for their formation. We recently reported one approach to 1,2,3-substituted cyclopropanes which involved using substituted 1,1-diiodoalkanes as precursors to substituted zinc carbenoids (eq 1).[2]



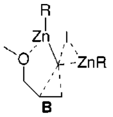
(1)

High levels of diastereo- and enantiocontrol were achieved in these reactions and in all the cases, an anti relationship was obtained between the R^2 group and the hydroxymethyl substituent. An intriguing complementary approach to the other diastereomeric cyclopropane **2** would involve generating a *syn*-cyclopropylzinc **3** (M = ZnR), which could then directly be used as the nucleophilic partner in subsequent reactions with electrophiles (Scheme 1).

Cyclopropylzinc derivatives have been prepared by using various procedures[3] including the cyclopropanation of an alkenylzinc.[4] However, this approach has not yet been extended to the synthesis of 1,2,3-substituted cyclopropane. The basic strategy reported in this communication involves the expedient synthesis of a cyclopropylzinc unit in a cyclopropanation reaction involving a novel *gem*-dimetallic carbenoid reagent **4** (M = ZnR). In principle, these unprecedented reagents should be amenable to directed processes since either Lewis acidic zinc atom of the *gem*-dizinc carbenoid could interact with a proximal basic group. It is widely accepted that directed electrophilic cyclopropanation reactions occur through complexation of the metal carbenoid with a proximal basic group (**A**).[5] However, it is anticipated that the stereochemical outcome of a directed reaction involving a *gem*-dizinc carbenoid should be governed by complexation of the zinc center that is *not* involved in the electrophilic carbenoid delivery (**B**). As a result, the reaction between these reagents and an allylic alcohol or ether would be predicted to lead to the *syn*-diastereomer **3**.



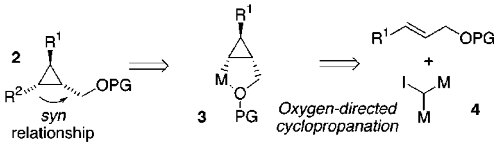
A



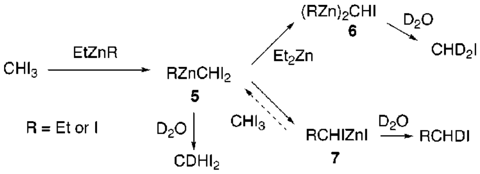
B

Our initial efforts were directed toward the demonstration that the formation of these novel *gem*-dizinc reagents was possible. Although *gem*-dimetallic compounds have become quite common reagents in the synthetic organic chemist's arsenal,[6] the related *gem*-dimetallic carbenoids are still elusive species. Such a reagent (when M = Cr) has been postulated to be the reactive species in the Takai olefination reaction[7] but there is no precedence thus far of a dizinc analogue of this reagent. Theoretically, the dizinc reagent could be prepared by the reaction between iodoform and diethylzinc and our initial efforts were focused toward obtaining evidence that this species could be formed.[8]

Scheme 1



Scheme 2



Our initial control experiments involving the mixing of iodoform and diethylzinc under various reaction conditions and stoichiometries are shown in Scheme 2. A first alkyl exchange process between CHI_3 and Et_2Zn would lead to zinc carbenoid **5** (R = Et). In principle, this reagent can either undergo a second alkyl group exchange with Et_2Zn to generate the *gem*-dizinc carbenoid **6** (R = Et) or it can decompose to generate zinc carbenoid **7** (R = Et).[9] Alternatively, **7** can react further with CHI_3 to generate the zinc carbenoid **5** (R = I). To obtain evidence for the formation of the *gem*-dizinc carbenoid **6**, the reagents were mixed and aliquots were quenched with D_2O. The presence of a *gem*-dizinc carbenoid **6** would lead to the formation of CD_2HI whereas the presence of the monozinc carbenoid **5** would produce $CDHI_2$. GC/MS analysis revealed that upon mixing equimolar amounts of Et_2Zn and CHI_3 in $(CH_2Cl)_2$, at 0 °C and in the absence of a complexing ligand, a rapid consumption of iodoform was observed within 5 min. Its subsequent quench with D_2O indicated that the main species present was the zinc carbenoid **5** as evidenced by the amount of $CDHI_2$ formed (Table 1, entry 1). More importantly, significant quantities of CHD_2I were also detected, thus confirming that the *gem*-dizinc carbenoid **6** was also present. The same experiment carried out this time with 1 equiv of a complexing ligand produced similar results but with a slightly higher yield (entry 2). When the stoichiometry between the reactants was increased to 2:1 (Et_2Zn:CHI_3), the amount of the *gem*-dizinc reagent **6** surpassed that of **5** as evidenced by the amount of deuterated material obtained (entry 3). However, the low yield indicated that the carbenoids rapidly decomposed under these conditions and its confirmation was obtained by the detection of 1-iodopropane by GC/MS (via **7** in Scheme 2). Finally, **6** was also formed in substantial quantities when EtZnI was used instead of Et_2Zn (entry 4). Consequently, the data in Table 1 indicate that

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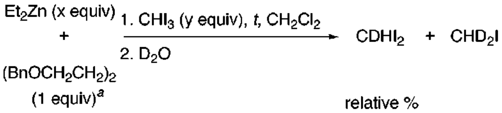
Table 1. Trapping Experiments of Zinc Carbenoid Reagents **5** and **6**

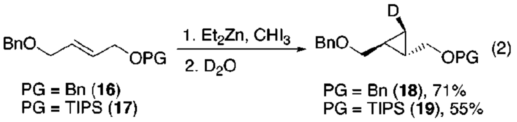


$$\mathrm{Et_2Zn}\ (x\ \text{equiv}) + (\mathrm{BnOCH_2CH_2})_2\ (1\ \text{equiv})^{a} \xrightarrow[\text{2. } \mathrm{D_2O}]{\text{1. } \mathrm{CHI_3}\ (y\ \text{equiv}),\ t,\ \mathrm{CH_2Cl_2}} \mathrm{CDHI_2} + \mathrm{CHD_2I}$$

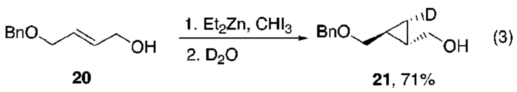
					relative %		
Entry	x	y	t (min)	%[b]	CHI_3	$CDHI_2$	CHD_2I
1[c]	1	1	5	71	<1	77	23
2	2	2	5	85	1	81	18
3	2	1	5	13	<1	31	69
4[d]	3	1.5	5	76	<1	57	42

[a] The diether was used as a stabilizing ligand. [b] Percent determined by the following: $[[CHI_3] + [CHDI_2] + [CHD_2]]/[CHI_3] \times 100$. Heptane was used as the internal standard. A small percentage means that **5** and **6** have decomposed before the quench. [c] The reagents were mixed without any complexing agent. [d] EtZnI was used in place of Et_2Zn.

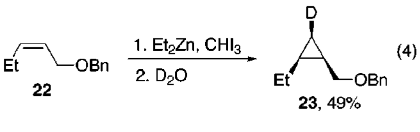
gem-dizinc reagent **6** can be formed under a variety of conditions but the zinc carbenoid **5** is also present. The next issues were to determine whether reagent **6** could react preferentially over **5** in a cyclopropanation process and whether it was possible to trap the resulting cyclopropylzinc with electrophiles. After surveying a number of allylic alcohols and their protected derivatives, we found that protected 2-butene-1,4-diols were ideal candidates to test the synthetic potential of the *gem*-dizinc carbenoid reagents and to evaluate the stereochemical outcome of the reactions. After extensive experimentation, we found that the optimal reaction conditions consisted of mixing 2 equiv of Et_2Zn and CHI_3 with the allylic ether at 0 °C.[10] The cyclopropanation was rapid (<15 min) and a subsequent addition of the electrophile (5 equiv) produced the corresponding cyclopropane in excellent yields.[11,12] Iodo- (**11**), bromo- (**12**), and phenylseleno-substituted (**13**) cyclopropanes can be prepared very efficiently by using this very simple procedure. The NMR analysis of the crude reaction also revealed that in all the cases, the *syn* diastereomer was formed exclusively (>99:1).[13] As expected, based on literature background, the resulting cyclopropylzinc **9** was not sufficiently reactive to give the addition product with allyl or acyl halides. In those cases, transmetalation with CuCN•2LiCl followed by the addition of the electrophile proved to be effective.[14,15] We have also shown that this reagent reacts with other allylic ethers or alcohols and that the stereochemical outcome is highly dependent upon the nature of the proximal directing group (eqs 2−4). For example, benzyl ethers **16** and **22** were converted to the deuteriocyclopropanes **18** and **23** in 71% and 49% yield, respectively. Interestingly, when one of the benzyl ether groups was replaced by a triisopropylsilyl group, deuterium incorporation occurred exclusively syn to the best directing group (eq 2). Conversely, the monoprotected butenediol **20** afforded the cyclopropylzinc syn to the alkoxide, showing the versatility and the flexibility of this approach (eq 3).



(2)



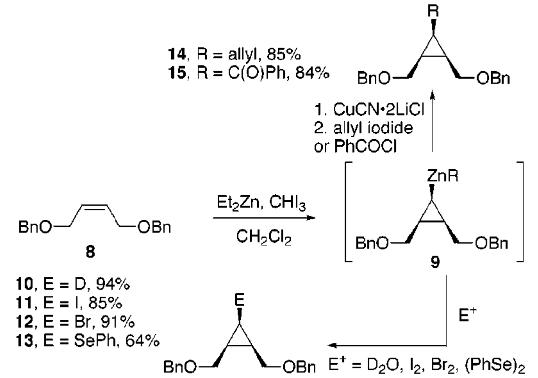
(3)



(4)

In summary, we have reported the synthesis and reactivity of a novel *gem*-dizinc carbenoid which provides an expedient access to substituted cyclopropanes. The study of the scope of this new reagent is underway and will be reported in due course.

Scheme 3



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Supporting Information Available: Experimental procedures and spectral data of selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Small Ring Compounds in Organic Synthesis VI*; de Meijere, A., Ed.; Springer: Berlin, 2000; Vol. 207. (b) Houblen-Weyl, *Methods of Organic Chemistry*; Thieme: Stuttgart, 1997; Vol. E 17c.
(2) Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1090−1092.
(3) (a) Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075−5078. (b) Béruben, D.; Marek, I.; Labaudinière, L.; Normant, J. F. *Tetrahedron Lett.* **1993**, *34*, 2303−2306. (c) Béruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *Tetrahedron Lett.* **1993**, *34*, 7575−7578. (d) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179−1180. (e) Béruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488−2501. (f) Martin, S. F.; Dwyer, M. P. *Tetrahedron Lett.* **1998**, *39*, 1521−1524.
(4) Yachi, K.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2515−2517.
(5) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370 and references therein.
(6) (a) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241−3267. (b) Normant, J. F. *Acc. Chem. Res.* **2001**, *34*, 640−644. (c) Matsubara, S.; Oshima, K.; Utimoto, K. *J. Organomet. Chem.* **2001**, *617*, 39−46 and references therein.
(7) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.
(8) Literature reports of low yields (<60%) of iodocyclopropanes are possible when an alkene is treated with diethylzinc and iodoform: (a) Nishimura, J.; Furukawa, J. *Chem. Commun.* **1971**, 1375−1376. (b) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1500−1503.
(9) This is the main pathway of decomposition of zinc carbenoids, see: Charette, A. B.; Marcoux, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4539−4549.
(10) No additive was used in this case since the substrate can stabilize the carbenoids.
(11) The formation of cyclopropylzinc **9** from iodide **11** under the reaction conditions was ruled out by showing that **11** was stable when treated with Et_2Zn and CHI_3.
(12) When D_2O was used as electrophile, <5% of the iodo-substituted cyclopropane was observed, which indicates that *gem*-dizinc carbenoid **6** is substantially more reactive than carbenoid **5**.
(13) The relative configurations of all the compounds were determined by nOe experiments.
(14) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390−2392. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188. (c) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056−8066.
(15) Pd- or Ni-catalyzed cross coupling reactions are also possible: (a) Piers, E.; Coish, P. D. G. *Synthesis* **2001**, 251−261. (b) de Lang, R.-J.; Brandsma, L. *Synth. Commun.* **1998**, *28*, 225−232.

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