

Improved Protocol for the Diastereoselective Cyclopropanation of Alkenes using Geminal Dizinc Carbenoids: A Study on the Effect of Zinc Iodide

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A mixture of ZnI_2 , $\text{EtZnI} \cdot 2\text{OEt}_2$ and CHI_3 produces a *gem*-dizinc carbenoid that is an efficient cyclopropanating reagent. The presence of ZnI_2 allows for shorter reaction times and cleaner reactions, particularly with less reactive sub-

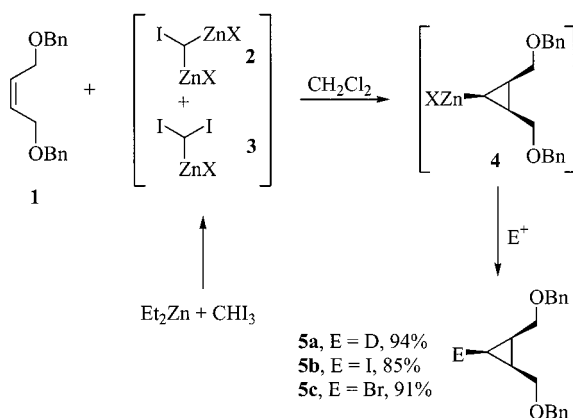
strates. This modification improves the scope of the reaction and it raises important mechanistic issues about this reaction. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2004)

Introduction

1,2,3-Substituted cyclopropanes are widely found in natural products and other biologically active molecules.^[1] Our interest in developing enantioselective methods for their synthesis using zinc carbenoids^[2] prompted us to look at novel organometallic species that would complement existing methods.^[3] Recently, an approach was developed that relied on the synthesis and reactivity of novel *gem*-dizinc carbenoids **2**, which led to a cyclopropylzinc intermediate **4**. This intermediate could then be further functionalized by treatment with a suitable electrophile (Scheme 1).^[4] This approach is highly efficient with 2-butene-1,4-diol derivatives, such as **1**. However, lower yields are observed with other protected or unprotected disubstituted allylic al-

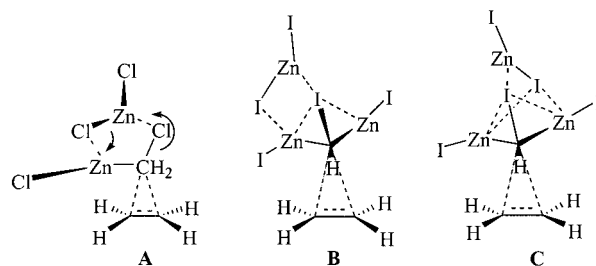
cohols, since the competing reaction involving the (diiodomethyl)zinc reagent **3** becomes important, leading to iodo-substituted cyclopropanes.

The effect of zinc halides in the Simmons-Smith reaction with zinc carbenoids has been the subject of several investigations. For example, Denmark has shown that addition of ZnI_2 increases the reaction rate, as well as the enantioselectivities, when the reaction is run in the presence of a chiral disulfonamide catalyst.^[5,6] He concluded that ZnI_2 undergoes the Schlenk equilibrium with $\text{Zn}(\text{CH}_2\text{I})_2$ to yield the more reactive IZnCH_2I reagent, but ZnI_2 was not involved in the postulated transition structure. A recent theoretical investigation by Nakamura led to a novel suggestion about the role of zinc halides in these reactions.^[7] DFT calculations led to the finding that the activation energy of the cyclopropanation of alkenes with ClZnCH_2Cl is significantly lowered in the presence of ZnCl_2 . Presumably, the Lewis acid acts as a chloride shuttle via a five-centered transition structure **A**.^[8] Although the positive effect of Lewis acids in the Simmons-Smith cyclopropanation has been sporadically observed,^[9] their exact role still remains uncertain.



Scheme 1

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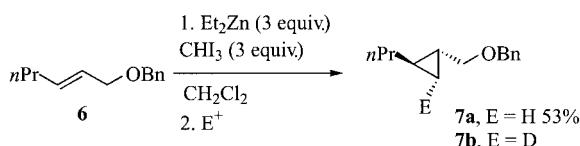
Phillips and co-workers recently reported a DFT investigation on the reactivity of the *gem*-dizinc carbenoid **2** as a cyclopropanation reagent.^[10] These calculations compared the geometry of different *gem*-dizinc carbenoids ($\text{RZnCHIZnR}'$, where $\text{R}, \text{R}' = \text{Et}, \text{I}$) and their respective

transition states in the cyclopropanation of alkenes. Phillips found that the energy of the transition state is lowered by 6.3 kcal/mol by adding 1 equiv. of ZnI_2 (transition state C). He also found the competing transition state B, which is 0.2 kcal/mol higher than C.

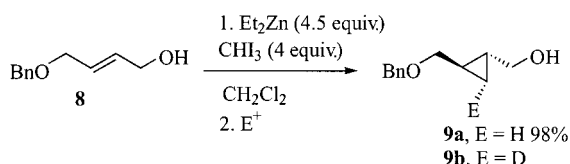
These calculations, combined with the observation that the scope of the reaction of *gem*-dizinc carbenoids is somewhat limited using our published protocol (without ZnI_2),^[4] prompted us to systematically investigate the effect of added ZnI_2 in these reactions.

Results and Discussion

In our previous communication, we established that the optimal stoichiometry for generation of the reagent was a 1:1 ratio of Et_2Zn and CHI_3 . Two substrates were chosen for the purpose of this study. The benzyl ether **6** reacted under our optimal protocol to give the 1,2,3-substituted cyclopropane **7a** in only 53 % yield (Scheme 2).^[11] Alcohol **8** was also included in this study, although it led to the desired cyclopropane in good yield (98 %, Scheme 3).

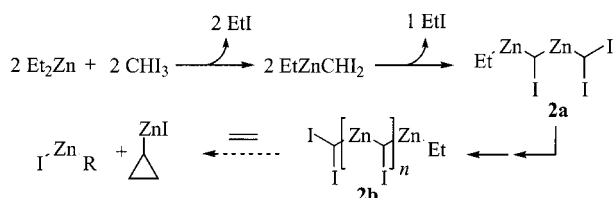


Scheme 2



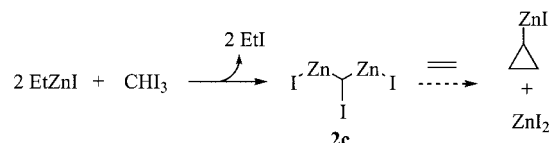
Scheme 3

Given the stoichiometry used in these reactions, a more accurate representation of **2** is probably the oligomeric form **2b**, in which one end of the oligomer consists of an ethyl group and the other of a (diiodomethyl)zinc carbenoid (Scheme 4). This reagent should not lead to the formation of any ZnI_2 upon cyclopropanation, but to an alkylzinc iodide.



Scheme 4

For the purpose of our studies, we have also prepared the *gem*-dizinc reagent **2c** from 2 equiv. of EtZnI and 1 equiv. of CHI_3 (Scheme 5). Although we were unable to characterize this species due to its instability, trapping experiments have shown that two C–I bonds are exchanged to generate **2c**. This reagent is particularly interesting, since ZnI_2 is the by-product of the cyclopropanation reaction and Schlenk equilibration is not an issue with this reagent upon ZnI_2 addition.



Scheme 5

Four protocols in which various amounts of ZnI_2 were added or formed in situ were tested with both substrates (Figure 1). The reactions with alkene **6** are much more efficient when the reagent is prepared from ethylzinc iodide instead of diethylzinc (Protocols A, B vs. C, D). The conversions were not only incomplete with Et_2Zn , but also significant amounts of the iodocyclopropanes resulting from the reaction involving reagent **3** were produced, in addition to extensive decomposition. For comparison purposes, the reaction was also run using Protocol A, but in the presence of added diethyl ether (Protocol B), since the addition of a complexing solvent (which is present during EtZnI formation in Protocols C and D) may influence the reaction profile. Although the reaction was cleaner using Protocol B, the conversion was still quite low. Finally, the addition of extra ZnI_2 (Protocol D) led to a very clean reaction that compared favorably with that of Protocol C, leading to the complete consumption of the alkene within 25 min, instead of 45 min. However, although the reaction using Protocol D reaches completion more quickly than using Protocol C, a significant difference in conversion is only observed after about 15 min. It is thus still not clear whether ZnI_2 allows

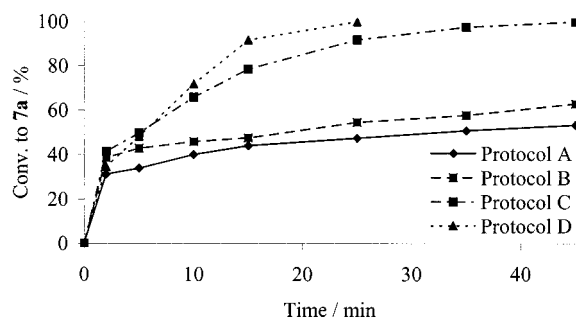


Figure 1. Comparison of the reaction conditions for the cyclopropanation of the benzyl ether **6**; all the reactions were run in CH_2Cl_2 at 0 °C, and each data point is an average of 3 reactions; Protocol A: Et_2Zn (3 equiv.) + CHI_3 (3 equiv.); Protocol B: Et_2Zn (3 equiv.) + CHI_3 (3 equiv.) + Et_2O (6 equiv.); Protocol C: EtZnI (3 equiv.), CHI_3 (1.5 equiv.) + Et_2O (6 equiv.); Protocol D: EtZnI (3 equiv.) + ZnI_2 (1.5 equiv.) + CHI_3 (1.5 equiv.) + Et_2O (9 equiv.); see supporting information for further details

for a lower transition state energy (as suggested by Phillips), or if it simply stabilizes the reagent throughout the reaction (either through slower reagent formation or through reagent stabilization).^[12]

The same beneficial effect of ZnI_2 is also observed in the cyclopropanation of the allylic alcohol **8** (Figure 2). It is interesting to note that in this case, the reagent combination $\text{EtZnI} + \text{CHI}_3$ (Protocol G) is not more effective than those involving Et_2Zn and CHI_3 (Protocols E and F). However, Protocol H, which uses 2 equiv. of added ZnI_2 , is the most efficient; the reaction is complete within 25 min. It is important to mention that the presence of less than 1 equiv. of ZnI_2 is not sufficient to achieve a faster consumption of starting material. This observation, and the fact that Protocol G is not optimal in this case, may be accounted for by the fact that the ZnI_2 formed initially is trapped by the basic zinc alkoxide, and therefore is unavailable for the activation or stabilization of the reagent. The true activating or stabilizing effect takes place only when more than 1 equiv. of ZnI_2 is present in solution.

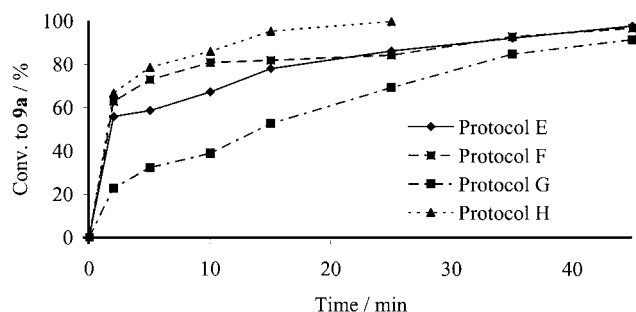


Figure 2. Comparison of the reaction conditions for the cyclopropanation of the alcohol **8**; all the reactions were run in CH_2Cl_2 at 0°C , and each data point is an average of 3 reactions; Protocol E: Et_2Zn (4.5 equiv.) + CHI_3 (4 equiv.); Protocol F: Et_2Zn (4.5 equiv.) + CHI_3 (4 equiv.) + Et_2O (9 equiv.); Protocol G: EtZnI (5 equiv.), CHI_3 (2 equiv.) + Et_2O (10 equiv.); Protocol H: EtZnI (5 equiv.) + ZnI_2 (2 equiv.) + CHI_3 (2 equiv.) + Et_2O (14 equiv.); see supporting information for further details

Using this new and improved protocol, we were able to cyclopropanate (*E*)-alkenes diastereoselectively with different substitution patterns, without undesired iodocyclopropanation from carbenoid **3** (Table 1).

Table 1. Cyclopropanation of various alkenes

Entry	R ¹	R ²	E ⁺	11/12 ^[a]	Yield [%] ^[b]
1	Pr	H	D ₂ O	> 95:5	85
2	H	Me	H ₂ O	96:4	76
3	H	Me	I ₂	96:4	76
4	H	H	H ₂ O	90:10	59
5	H	H	I ₂	90:10	74

[a] Ratio as determined by ^1H NMR spectroscopy. [b] Isolated yield of **11**.

Conclusions

In summary, a new and improved protocol for the cyclopropanation of alkenes using a *gem*-dizinc carbenoid has been developed. This protocol, involving carbenoid **2c** and ZnI_2 , has been shown to both have a broader scope of substrates, as well as achieving 100 % conversion more quickly than our previous protocol using carbenoid **2b**. However, whether this enhancement is due to reagent activation (as proposed by Phillips) or by reagent stabilization could not be demonstrated unequivocally. Further studies to exploit the full synthetic potential of these reagents will be reported in due course.

Experimental Section

Et_2Zn (291 μL , 2.838 mmol, 4.5 equiv.) was slowly added to a solution of iodine (960 mg, 3.784 mmol, 6.0 equiv.) and diethyl ether (589 μL , 5.676 mmol, 9.0 equiv.) in dry CH_2Cl_2 (3 mL) at 0°C . The ice bath was removed and the solution stirred for 10 min before recooling to 0°C . The benzyl ether (0.631 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) was then added by cannula to this clear colorless solution, followed by a solution of CHI_3 (372 mg, 0.946 mmol, 1.5 equiv.) in CH_2Cl_2 (6 mL) and of dry air (100 μL). After the appropriate reaction time (15–45 min), the cyclopropylzinc was quenched with either saturated aqueous NH_4Cl , 1 M DCl in D_2O , or (after cooling to -78°C) a solution of iodine (400 mg, 1.577 mmol, 2.5 equiv.) in THF (3 mL). After 1 min, saturated aqueous Na_2SO_3 (5 mL) was poured in. The aqueous layer was extracted with diethyl ether ($3 \times 4\text{ mL}$), the combined organic layers washed successively with saturated aqueous Na_2SO_3 (4 mL), saturated aqueous NaHCO_3 (4 mL) and brine (4 mL), dried with MgSO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired cyclopropane.

Acknowledgments

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- [11] The relative stereochemistry for the electrophile insertion is that shown in Schemes 2 and 3; it was established by deuteration of the cyclopropylzinc reagent, which led to **7b** and **9b** exclusively.
- [12] Detailed kinetic studies were inconclusive because of the heterogeneous nature of the reaction mixture, and the difficulty in controlling the exact initial concentration of **2c** (carbenoids of type **2** undergo decomposition and are subject to various equilibria).

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