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LETTERS

Exploring New Reactive Species for Cyclopropanation

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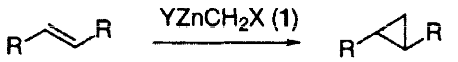
Abstract: An organozinc species $RXZnCH_2I$ generated by reacting $Zn(CH_2I)_2$ with RXH was found to be an efficient reagent for the cyclopropanation of olefins at room temperature. A 50.7% ee was obtained for the cyclopropanation of *trans*-β-methylstyrene when a chiral alcohol was used.

The Simmons-Smith reaction is a powerful method for synthesizing cyclopropanes from olefins (eq. 1).[1] A variety of versions of this reaction have been developed in the past.[2] A (halomethyl)zinc $YZnCH_2X$ (**1**) is believed to be the reacting species in the Simmons-Smith reaction, but the Y substituent is usually limited to a halogen, Et, or ICH_2 group, depending upon the protocol used (eq. 1). As a part of our general interest in the area of small ring synthesis from unfunctionalized olefins, we have been investigating the reaction properties of new (iodomethyl)zinc species $RXZnCH_2I$ generated by modifying the Y group. Herein we wish to report our preliminary studies in this area.



X = Br, Cl, I; Y = halogen, Et, ICH_2 **(eq. 1)**

We began our studies by generating a series of new (iodomethyl)zinc species from alcohols and acids to study their reactivities. The active reagent $RXZnCH_2I$ (**3**) could be generated by two methods shown in eqs. 2 and 3, differing in order of reagent addition. The method outlined in eq. 3 requires less CH_2I_2. For our initial studies the method outlined in eq. 2 was used with *trans*-β-methylstyrene as the substrate. The results obtained (Figure 1) show that the reactivity of $RXZnCH_2I$ is highly dependent upon the R group. When RXH was EtOH or $ClCH_2CH_2OH$, no reaction occurred after stirring 24 h at room temperature. It was found that, in general, as RXH became more acidic, the reactivity increased.

$$Et_2Zn + 2\,CH_2I_2 \longrightarrow 2EtI + (ICH_2)_2Zn \xrightarrow[\mathbf{2}]{RXH} \underset{\mathbf{3}}{RXZnCH_2I} + CH_3I \qquad \textbf{(eq. 2)}$$

$$Et_2Zn + \underset{\mathbf{2}}{RXH} \longrightarrow EtH + RXZnEt \xrightarrow{CH_2I_2} \underset{\mathbf{3}}{RXZnCH_2I} + EtI \qquad \textbf{(eq. 3)}$$

Among the RXH investigated, CF_3CO_2H accelerated the cyclopropanation reaction dramatically compared to the typical cyclopropanation conditions (i.e. no RXH was added). The reaction was complete within 30 min at

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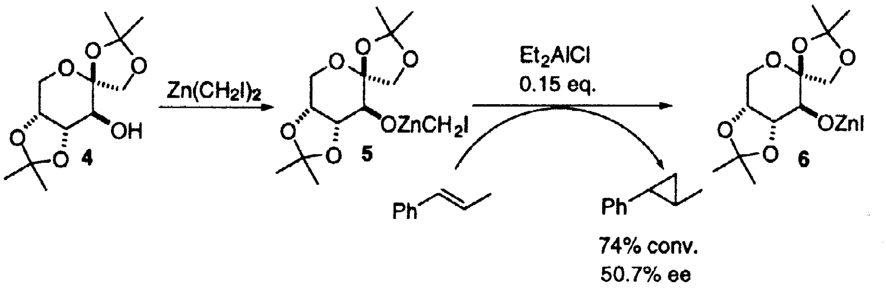
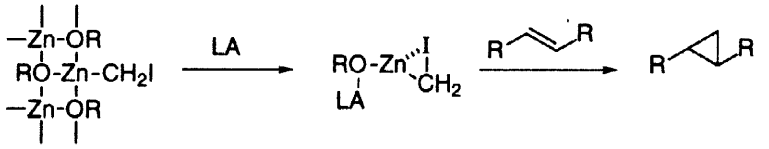
room temperature for *trans*-β-methylstyrene, and was very clean as judged by the ^{1}H NMR of the crude reaction mixture. Intrigued by this result, we decided to examine more substrates with this cyclopropanation reagent. The results summarized in Table 1 show that a variety of substrates can be converted into cyclopropanes efficiently within a short period of time.[3] For CF_3CO_2H the reagents generated by both methods provided similar results. Considering that many cyclopropanation protocols require refluxing and long reaction times, the current reagent should provide an attractive alternative, particularly for the substrates which have been unreactive in the past, such as stilbene.

Having discovered that $RXZnCH_2I$ is effective for cyclopropanation, we were anxious to investigate whether a chiral (iodomethyl)zinc species (RX^*ZnCH_2I) could induce any enantioselectivity for the cyclopropanation. For our preliminary test, chiral (iodomethyl)zinc reagent **5** was prepared from alcohol **4**, which was prepared in one step from fructose (eq. 4).[4] With *trans*-β-methylstyrene as the substrate no cyclopropanation occurred, but upon addition of a Lewis acid the reaction took place.[5] A 50.7% ee was obtained for the cyclopropane product. Zinc alkoxides (ROZnR') are likely to form aggregates,[6] and the Lewis acid may facilitate the reaction by breaking down the proposed $(ROZnCH_2I)_n$ aggregates. After the aggregate is broken, the zinc has a vacant orbital for iodine to coordinate, thus activating the methylene group toward cyclopropanation (eq. 5).



(eq. 4)



(eq. 5)

Great progress has been made in the asymmetric cyclopropanation of allylic alcohols.[7-12,5] However, a direct asymmetric cyclopropanation of unfunctionalized olefins by transferring a simple methylene group from (halomethyl)zinc reagents is an unsolved, yet challenging, problem. Only two reports have appeared in the literature for asymmetric cyclopropanation of olefins in the absence of hydroxy groups using (halomethyl)zinc reagents. In one case, (-)-menthol was used as chiral inducer, and <4% ee was obtained.[13] In the other case L-leucine was used as chiral inducer, and a $[\alpha]^{25}_D$ of -0.77 was reported (no ee was mentioned).[14] The 50.7% ee obtained in the current study provides an encouraging start.

In conclusion, we have found that certain new (iodomethyl)zinc species generated using an external modifier could efficiently cyclopropanate olefins. A reasonable level of enantioselectivity was obtained for the cyclopropanation of an unfunctionalized olefin when a chiral (iodomethyl)zinc species was used, which demonstrates the great potential of such a process for the asymmetric cyclopropanation of unfunctionalized olefins. Further studies are currently underway.

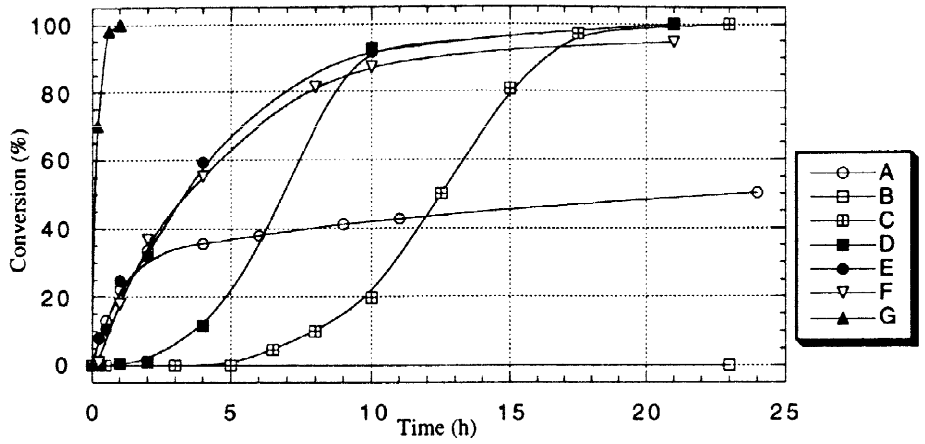
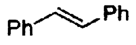
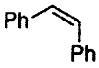
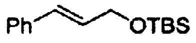
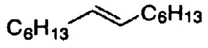
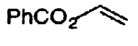
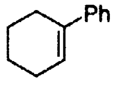
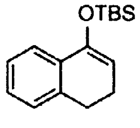


Figure 1. Plot of the conversion of *trans*-β-methylstyrene against time (h). The curves presented are: (**A**) No RXH, (**B**) EtOH or $ClCH_2CH_2OH$, (**C**) Cl_2CHCH_2OH, (**D**) CCl_3CH_2OH, (**E**) CF_3CH_2OH, (**F**) $PhCO_2H$, (**G**) CF_3CO_2H.

Table 1. Cyclopropanation of Representative Olefins Accelerated by CF_3CO_2H[a]

Entry	Substrate	time (min)	Conv. (%)[b]	Yield (%)[c]
1		30	100	77
2		60	>90	70[d]
3		60	nd	72[d]
4		30	100	95
5		40	100	80
6		40	100	99
7		20	100	85
8		30	>97	88
9		150	>90	90
10		30	100	78
11		25	100	50[e]

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[a] All reactions were carried out at rt with a 2/1 ratio of Zn/olefin except entries 2 & 3 where the Zn/olefin ratio was 4/1. [b] The conversion was determined from the crude reaction mixture either by GC or ^{1}H NMR. [c] Isolated yield. [d] *Trans*-stilbene gave *trans*-cyclopropane and *cis*-stilbene gave *cis*-cyclopropane. [e] The yield was for the product after desilylation by TBAF.

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3. **A typical procedure**: To freshly distilled CH_2Cl_2 (20 mL) was added Et_2Zn (1.0 M in hexanes)(20 mL, 20 mmol) under N_2 (it is best to use an inlet adapter for the nitrogen line since needles often become clogged). The solution was cooled in an ice bath and a solution of trifluoroacetic acid (1.54 mL, 20 mmol) in CH_2Cl_2 (10 mL) was then dripped very slowly into the reaction mixture via syringe. Upon stirring for 20 min, a solution of CH_2I_2 (1.61 mL, 20 mmol) in CH_2Cl_2 (10 mL) was added. After an additional 20 min stirring, a solution of the TBS ether of cinnamyl alcohol (2.60 g, 10 mmol) in CH_2Cl_2 (10 mL) was added, and the ice bath was removed. After an additional 30 min stirring, the reaction mixture was quenched with 0.1 N HCl (50 mL) (or sat. aqueous NH_4Cl) and hexanes (25 mL) and the layers separated. The aqueous layer was extracted with hexanes. The combined organic layers were washed with sat. $NaHCO_3$, H_2O, and brine, then dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography (hexanes/ether = 50/1) to yield the cyclopropane product (2.61 g, 95.3%).
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