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Preparation and Reactivity of Some Functionalized Halomethylzinc Carbenoids.

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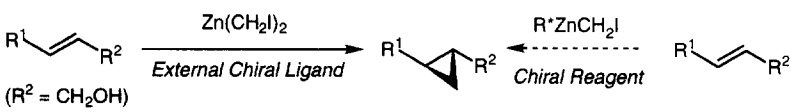
Abstract: Various mixed diorganozinc reagents were prepared by the irradiation of diethylzinc and functionalized alkyl iodides. These species were shown to react with dihalomethane to form zinc carbenoids in a highly regioselective manner. In some cases, the latter reagents proved to be effective cyclopropanating reagents.

The enantioselective cyclopropanation of alkenes using the Simmons-Smith[1] or related reagents[2] ($EtZnCH_2I$, $Zn(CH_2I)_2$) has so far exclusively relied on the use of stoichiometric[3] or catalytic[4] amounts of external chiral ligands to control the stereochemical outcome of the reaction (Scheme 1). The inherent limitation of this approach is that only allylic alcohols produce good enantioselectivities since the hydroxy group (or its zinc alkoxide) is acting as a linker between the reagent and the chiral additive.

Scheme 1



As part of our research program directed towards the development of efficient methods for the enantioselective cyclopropanation of alkenes, we became interested in generating functionalized chiral reagents of the general structure R^*ZnCH_2I. This paper presents our initial findings on the feasibility of their synthesis as well as on their efficiency as cyclopropanating reagents. Since such reagents have not been prepared thus far, several fundamental issues needed to be addressed before an enantioselective version of this reaction is to be developed. The method for the efficient preparation of R^*ZnCH_2I is based on our recent report that showed that mixed diorganozinc reagents could be prepared by irradiating a stoichiometric mixture of a functionalized alkyl iodide and Et_2Zn.[5] For example, the trimethylsilylmethyl ethyl zinc is formed in quantitative yield when an equimolar amount of trimethylsilylmethyl iodide and diethylzinc is irradiated in CH_2Cl_2 (Scheme 2). Furthermore, more complex mixed diorganozinc reagents containing the non-transferable group, TMSM[6] are easily prepared when a mixture of an alkyl iodide, trimethylsilylmethyl iodide and Et_2Zn is irradiated for 2 h at room temperature. This method is simple, compatible with a variety of solvents and more importantly, it does not lead to any by-products that would jeopardize the subsequent chemistry of the functionalized iodomethylzinc reagents since these reagents will have to be made *in situ*.

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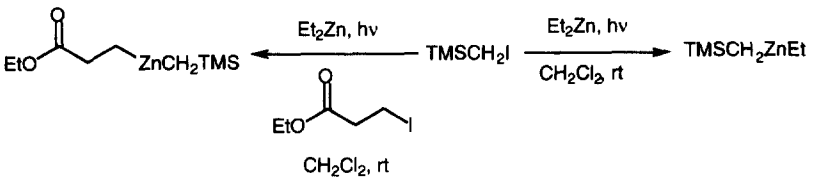
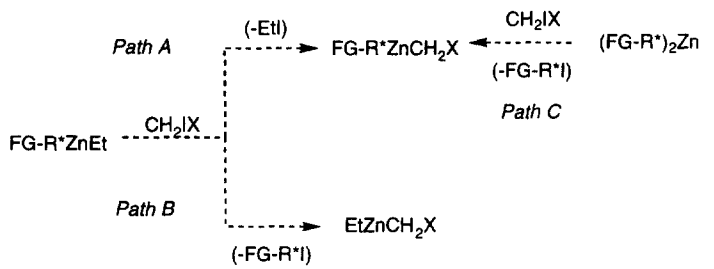
Scheme 2



Our interest in mixed dialkylzinc chemistry originates from the assumption that these species should produce a zinc carbenoid (R^*ZnCH_2X) when treated with XCH_2I (X=Cl,I). Furthermore, we hoped that the exchange reaction would proceed with high regioselectivity if R* contains a basic or an electron-withdrawing group, (Scheme 3, Path A). This is an essential requirement of the methodology if chiral zinc carbenoids are to be sought since the undesired pathway (Path B) would lead to the achiral Furukawa reagent, $EtZnCH_2X$. Obviously, an alternative approach to the desired zinc carbenoid would involve the reaction of the diorganozinc $(FG\text{-}R^*)_2Zn$ with CH_2IX (Scheme 3, Path C). However, in doing so, one equivalent of a potentially expensive alkyl group would be converted into the corresponding alkyl iodide.

Scheme 3

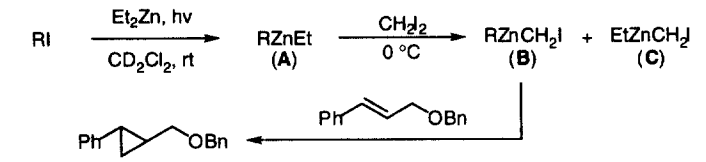


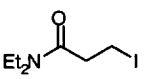
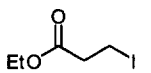
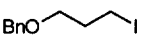
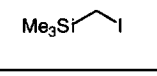
Several alkyl iodides possessing different functional groups were initially converted into the corresponding mixed diorganozinc reagents (Table 1). In all the cases, the conversion were excellent as determined by ^1H NMR (formation of EtI) and by GC. The mixed reagent was then directly treated with CH_2IX to form the zinc carbenoid. The regioselectivity of the exchange was determined by measuring the relative integration (^1H NMR) of ethyl iodide and of the starting iodide. Alternatively, an aliquot was taken and the quenched mixture was analyzed by GC using decane as the internal standard. After the exchange reaction had taken place, the benzyl ether of cinnamyl alcohol was added to evaluate the relative reactivity of the resulting zinc carbenoid. The results obtained for different alkyl halides are summarized in Table 1.

Entry 1 clearly demonstrates that, although the presence of an amide group ensures the regioselective exchange of the ethyl group for CH_2I, the resulting carbenoid is a totally ineffective cyclopropanation reagent. Conversely, replacement of the amide group by an ester allows the exchange to be partially regioselective, but the carbenoid was a slightly more reactive cyclopropanating reagent (entry 2). The addition of 2 equiv of Et_2O produced an increase in regioselectivity but, as expected, the carbenoid was slightly less electrophilic due to the additional complexation (entry 3). The use of $ClCH_2I$ in the absence of a complexing solvent provided excellent regioselectivity in the exchange reaction and good reactivity of the carbenoid towards the

benzyl ether of cinnamyl alcohol (entries 4 and 5). Although the 3-benzyloxypropyl group led to a relatively efficient zinc reagent, the regioselectivity in the exchange reaction is too low for it to be synthetically useful (entry 6).[7] The most effective functionalized carbenoid reagent was derived from trimethylsilylmethyl iodide (entries 7 and 8). The trimethylsilylmethyl group provided both, improved regioselectivity and excellent reactivity in the subsequent cyclopropanation reaction.

Table 1. Regioselective preparation and reactivity of mixed iodomethylzinc reagents.[8]



Entry	RI	%Mixed (**A**)[a]	Regioselectivity (**B**:**C**)[a]	%Cyclopropane[a]
1		>99	>98:2	0
2		95	87:13	40
3[b]		98	>97:3	21
4[c]		95	>97:3	42
5[c-e]		>98	>98:2	81
6[d,e]		92	72:28	≥90
7		>99	84:16	>95
8[c]		>99	94:6	>95

[a]Determined by ^{1}H NMR and GC with decane as internal standard. [b]2 equiv of Et_2O were added. [c]CH_2ICl was used instead of CH_2I_2. [d]The mixed dialkylzinc had to be irradiated with a GE 275W Sunlamp in order to perform the halogen-metal exchange reaction. [e]2 equiv of $RZnCH_2X$ were used.

Overall, these results tend to demontrate that the presence of a basic group is necessary to have a good regioselectivity in the halogen-metal exchange reaction. Conversely, the reactivity of the resulting functionalized carbenoid reagent as a cyclopropanating reagent is higher when it contains less basic groups..

In summary, we developed a new approach to stabilized Furukawa type zinc carbenoids from mixed dialkylzincs. Application of this work towards the synthesis of chiral zinc carbenoids will be reported in due course.

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7. In this case, the reaction mixture had to be irradiated in order to push the metal-halogen exchange process between the mixed diorganozinc and chloroiodomethane to completion: (a) Miyano, S.; Yamashita, J.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1946. (b) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892-897.
8. Typical experimental procedure: A vacuum-dried pyrex NMR tube, sealed with a septum and Teflon tape was purged several times with an inert gas (N_2 or Ar). The starting iodide (0.70 mmol) and CD_2Cl_2 (0.70 mL) were added and the tube was carefully shaken. Decane (20.0 mg) and Et_2Zn (1.00 equiv) were added and the tube was carefully shaken twice. The clear solution was then irradiated with a 275W sunlamp (GE) placed at about 20 cm away from the solution in order to avoid sample warming and loss of solvent. The exchange process took between 2 and 4 h depending on the substrate and it was monitored by ^1H NMR and GC. When the synthesis of the mixed diorganozinc was complete (NMR), the tube was cooled to 0 °C and CH_2I_2 (0.9 equiv) was added. The NMR tube was carefully shaken and the alkene (0.75 equiv) was added. The solution was allowed to stand overnight at room temperature. The crude reaction mixture was analyzed by ^1H NMR, quenched and analyzed by GC.