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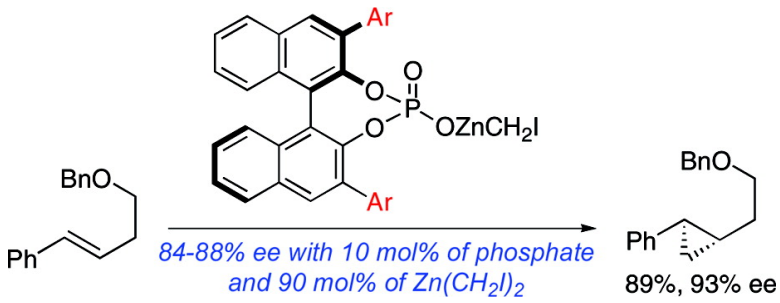

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Iodomethylzinc Phosphates: Powerful Reagents for the Cyclopropanation of Alkenes

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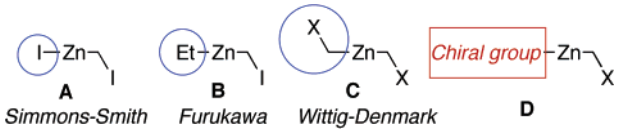
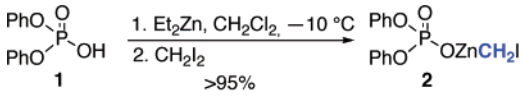
Since the first use of the Zn/Cu couple by Simmons and Smith for the cyclopropanation of C=C, several new improved reagents have been developed to increase the scope for the formation of the cyclopropane unit.[1] The reagent modification typically involves the replacement of the iodide substituent of the Simmons−Smith reagent (**A**)[2] by either an ethyl (**B**)[3] or halomethyl substituent (**C**).[4] Our group has been involved in the past few years in synthesizing, characterizing, and studying newly developed organo(iodomethyl)-zinc reagents that are still effective cyclopropanating reagents with novel properties.[5,6] Ultimately, the goal of this approach is to introduce a chiral organic group (**D**) that will lead to high enantioselectivities for the cyclopropanation of unfunctionalized alkenes and use this reagent in catalytic amounts.[7]



Since the electrophilicity of the iodomethylzinc species is intimately related to the electron-withdrawing ability of the attached group, we reasoned that the corresponding iodomethylzinc phosphate reagent should be sufficiently electrophilic to react with alkenes in a (2+1) addition mode. To test this hypothesis, commercially available diphenyl phosphate (**1**) was treated with 1 equiv of diethylzinc followed by 1 equiv of CH_2I_2 (eq 1). Iodomethylzinc phosphate **2** was formed in quantitative yield within 60 min (NMR monitoring). Evaporation of the solution led to a white solid that was stable for several weeks at 4 °C when protected from oxygen and moisture.



(1)

^{1}H NMR: 1.3 ppm (bs)
^{13}C NMR: -25.4 ppm

The atom connectivity was unambiguously established by the X-ray crystal structure of the THF complex (Figure 1), which indicated that the reagent crystallized as a dimeric structure having tetrahedral zinc centers. The bond lengths and angles are consistent with those reported in the literature.[8]

The reactivity of **2** as a cyclopropanating agent was then tested with representative substrates. Sequential treatment of diphenyl phosphate with diethylzinc, diiodomethane, and an alkene led to the cyclopropane in high yields (Table 1). Allylic alcohols and ether reacted smoothly with 1.2 equiv of the reagent to generate the corresponding cyclopropane in high yield (Table 1, entries 1−3). It is quite remarkable that the cyclopropanation reaction of allylic alcohols proceeded in such high yield, considering that the reagent excess was only 20 mol %. Typically, at least 2 equiv of the classical zinc carbenoids is necessary to get quantitative conversion for this class of substrates.

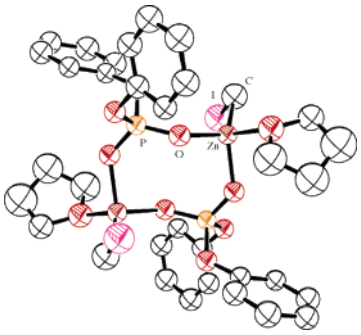
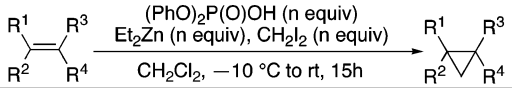
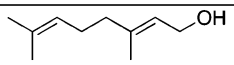
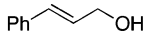
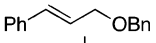


Figure 1. ORTEP drawing of **2**·THF dimer.

Table 1. Cyclopropanation Using Achiral Phosphoric Acid **2**



entry	substrate	product	n	yield (%)
1		**3**	1.2	> 95 (98%)[a,b]
2		**4**	1.2	> 95 (98%)[a]
3		**5**	1.2	> 95 (98%)[a]
4		**6**	1.5	95[c]
5		**7**	1.5	62[c]

[a] Determined by ^{1}H NMR using an internal standard. Isolated yield in parentheses. [b] Only the allylic alcohol double bond reacted. [c] Determined by GC analysis using an internal standard.

The carbenoid was reactive enough so that alkenes bearing no proximal basic groups could also be cyclopropanated (entries 4−5).

We then turned our efforts toward the design of a chiral zinc phosphate reagent for the enantioselective cyclopropanation of unfunctionalized alkenes. We envisioned that the use of a chiral phosphoric acid derived from a 3,3′-disubstituted BINOL derivative to efficiently project the chirality toward the carbenoid's reactive center would lead to efficient enantiodiscrimination. After considerable screening, chiral phosphoric acid **8**[9] proved to be the best precursor for this transformation. Treatment of **8** with diethylzinc followed by CH_2I_2 and protected allylic alcohols led to good yields of the cyclopropane (Table 2). Only 1.2 equiv of the chiral zinc carbenoid that is formed in situ were enough to achieve high conversions for the reaction of allylic ethers[10] (Table 2). 1,2-Dichloroethane (DCE) was the best solvent for this reaction, allowing better reactivity and selectivity than dichloromethane. The enantioselectivity is good, ranging from 85 to 91% ee for substrates bearing methyl, benzyl, MOM, and nonbulky silyl protecting groups (entries 1−5). Bulkier silyl protecting groups led to lower reaction rates. The selectivity could be further improved by running the reaction at −20 °C, although the reaction rate was lower (entry 6). The cyclopropanation of a homoallylic benzyl ether led to complete

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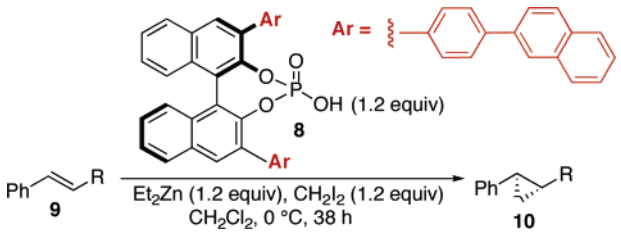
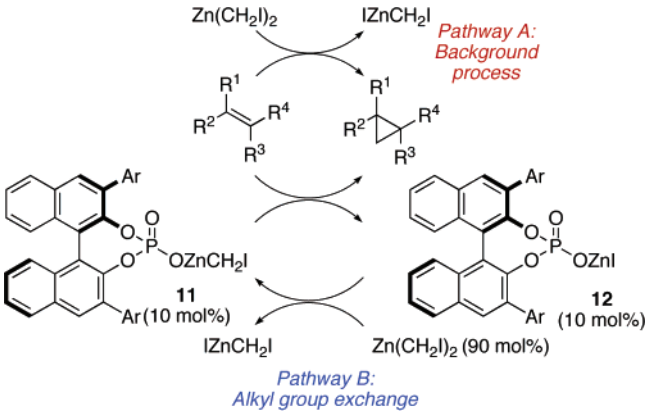
Table 2. Cyclopropanation with Chiral Phosphoric Acid **8**



entry	R		yield (%)[a]	ee (%)[b]
1	CH_2OMe	**(9a)**	>95 (73)	91
2	CH_2OBn	**(9b)**	>95 (89)	90
3	CH_2OPMB	**(9c)**	95 (78)	85
4	CH_2OMOM	**(9d)**	75 (47)	90
5	CH_2OTES	**(9e)**	>95 (79)[c]	87
6[d]	CH_2OTES	**(9e)**	>95 (84)[c]	92
7	CH_2CH_2OBn	**(9f)**	>95 (85)	93
8	CH_2OZnEt	**(9g)**	>95 (80)	39[e]

[a] Determined by ^{1}H NMR using an internal standard. Isolated yield in parentheses. [b] Determined by HPLC on chiral stationary phase. [c] The corresponding alcohol was obtained after deprotection with 1.0 M H_3PO_4 and NH_4F at 40 °C. [d] The reaction was performed at −20 °C for 48 h. [e] The opposite (*S*,*S*)-enantiomer was obtained.

Scheme 1. Catalytic Cycle for the Cyclopropanation Reaction

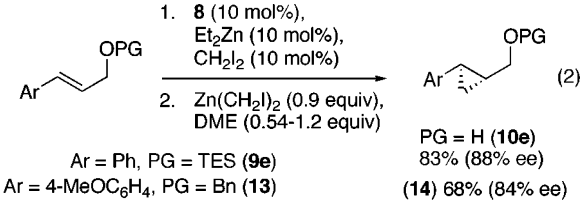


conversion and 93% ee (entry 7). This constitutes the highest enantioselectivity ever reported for a homoallylic substrate in enantioselective zinc-mediated reaction.[11] However, the use of the less reactive bis(homo)allylic benzyl ether as the substrate proved to be detrimental to both conversions and ee.[12] Finally, the preformation of a zinc alkoxide is detrimental to the enantioselectivities (entry 8). This observation is quite significant since, unlike in previously developed systems from our laboratories and others,[10] the preformation of a zinc alkoxide is not required to obtain high conversions and enantioselectivities.

The main drawback of this reaction is the use of an expensive chiral phosphoric acid in stoichiometric amounts. We thus explored the possibility of regenerating the chiral iodomethylzinc species from bis(iodomethyl)zinc through a Schlenk equilibration according to Scheme 1. Unfortunately, only 68% ee was obtained if silyl ether **9e** was treated with 10 mol % of **11** and 90 mol % of $Zn(CH_2I)_2$, presumably because of the competing background reaction between the substrate and the achiral reagent.

To minimize the background cyclopropanation that could arise from pathway A, we envisioned that the addition of a Lewis basic additive in less than stoichiometric amount (≤90 mol %) that would selectively complex $Zn(CH_2I)_2$ or $IZnCH_2I$ would not only decrease the rate of the background cyclopropanation but also increase the rate of the iodomethyl group exchange (pathway B). Several additives were tested, and 0.5 equiv of 1,2-dimethoxyethane (DME) was sufficient and optimal to significantly decrease the rate of the cyclopropanation between the alkene and the achiral reagent.

We then tested the reaction using 10 mol % of the chiral phosphoric acid **8** (eq 2). Gratifyingly, 88% ee was observed when allylic ether **9e** was treated with 10 mol % of **8** and 90 mol % of $Zn(CH_2I)_2$ in the presence of DME. The cyclopropanation of the more reactive olefin **13** required more DME to slow the background reaction but it also lowered the rate of the asymmetric process. It should be pointed out that in all the cases, it is possible to recover the phosphoric acid reagent.[13]



In conclusion, we have developed a new powerful family of zinc carbenoids derived from phosphoric acids for the cyclopropanation of alkenes. The reagents can be used in stoichiometric amounts or in catalytic amounts if more complex phosphate reagents are used. Further work is in progress to increase the scope of the reaction and to develop better chiral discriminating reagents.

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Supporting Information Available: Experimental procedures and characterization of new compounds including spectral data. X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The cyclopropanation of alkyl- or alkenyl-substituted allylic ethers in the presence of **8** provided the corresponding cyclopropane in high conversions but in ≤79% ee. However, we found that the level of enantioselection was highly dependent upon the nature of the groups at 3 and 3′ and that ligand screening is necessary. In the case of polyenes, high regiocontrol was observed to favor the allylic ether double bond.
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(12) The cyclopropanation of benzyl (4*E*)-5-phenylpent-4-enyl ether in the conditions reported in Table 2 led to 39% conversion and 50% ee.
(13) See Supporting Information for details.

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