Enantioselective Cyclopropanation of Allylic Alcohols. The Effect of Zinc Iodide

Scott E. Denmark* and Stephen P. O'Connor

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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The effect of zinc iodide on the catalytic, enantioselective cyclopropanation of allylic alcohols is examined with bis(iodomethyl)zinc as the reagent and bis-methanesulfonamide **7** as the catalyst. Significant rate enhancement was observed when 1 equiv of zinc iodide was present, but more importantly, the enantiomeric excess of the product cyclopropane increased from 80% to 89% for the substrate cinnamyl alcohol. Reaction studies and spectroscopic investigations show that this remarkable influence is the result of reagent modification via a Schlenk equilibrium that produces the more reactive and selective species (iodomethyl)zinc iodide.

Introduction

In 1958, Simmons and Smith reported a simple method for the cyclopropanation of olefins using a zinc−copper couple and diiodomethane in refluxing diethyl ether.[1] This paper was to herald an era of ready access to three-membered carbocycles. Furukawa later found that the zinc−copper couple could be replaced by diethylzinc, which provided better reproducibility, greater substrate variety, and faster reactions.[2] Wittig independently described an alternative process that uses zinc iodide and diazomethane.[3] The nature of the cyclopropanating reagents in these reactions has been addressed but was never clearly established.[4] However, the Lewis basic nature of the reagents was suggested by the strong directing effects of suitably placed hydroxyl groups or derivatives thereof.[5]

The obvious importance of enantiopure cyclopropanes as end products or synthetic intermediates led to the development of enantioselective versions of this reaction. There are numerous auxiliary-based methods such as the tartrate-derived acetal **1** pioneered by Yamamoto that illustrate the high levels of diastereoselectivity that can be obtained (Figure 1).[6] The use of stoichiometric quantities of chiral additives to modify the reagent has also met with considerable success.[7] Perhaps the best example of this type of reaction is that described by Charette wherein the dioxaborolane **2** is used. A third means of effecting an enantioselective process is that of catalysis, using substoichiometric amounts of a chiral modifier. Unfortunately, to date, catalytic methods have not been as selective. Both Kobayashi[8] and our own group[9] have reported enantioselective cyclopropanation procedures for allylic alcohols using bis-sulfonamides such as **3**. However, the enantiomeric excesses are in general 10−15% lower than the auxiliary-based or stoichiometric reagent methods. A very recent addition to the catalytic procedures currently available for enantioselective cyclopropanation has been reported by Charette.[10] When 25 mol % of the TADDOL reagent **4** was used, the cyclopropanation of cinnamyl alcohol was affected in 90% ee. However, substrate generality was limited as seen in the cyclopropanation of prenyl alcohol, which proceeded in only 60% ee.

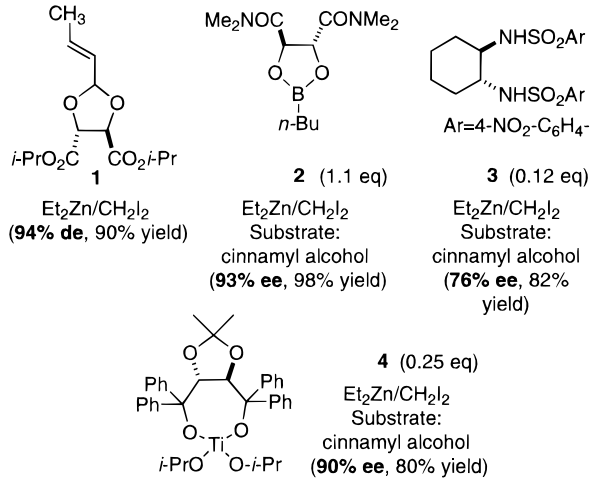

Figure 1. Reagents for stereoselective cyclopropanation with methylene transfer agents.

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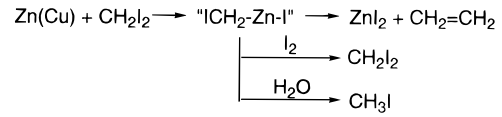
Scheme 1



Metal carbenes also react with olefins to yield cyclopropanes and in the presence of chiral ligands are highly selective and catalytic. However, the delivery of methylene (CH_2) is not enantioselective with these systems as diazo esters or diazo ketones must be used.[11]

Despite its widespread application as the premier methylene transfer agent, the exact composition of the Simmons−Smith reagent has never been unambiguously demonstrated. Our interest in a more precise formulation of reagent structure and deeper understanding of its mechanism of action derive from the belief that such information is crucial for the design of improved ligands for enantioselective cyclopropanation. Our studies on the chiral bis-sulfonamide-promoted cyclopropanation of allylic alcohols have uncovered some remarkable effects of added zinc iodide when used in conjunction with bis(iodomethyl)zinc. We report herein our studies, which suggest that this is the result of reagent modification by a Schlenk equilibrium. Both reaction studies and spectroscopic investigations indicate that, in the presence of zinc iodide, bis(iodomethyl)zinc is rapidly converted to (iodomethyl)zinc iodide. We believe that this species is a more reactive and more selective reagent under these reaction conditions.

Background

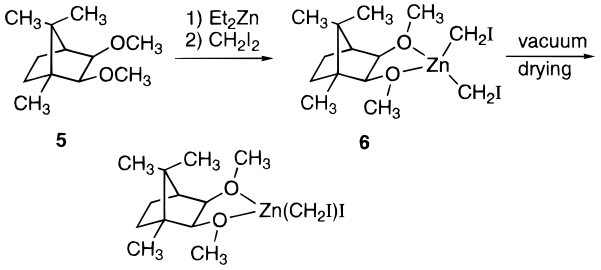
Chemical Insights. In 1929, Emschwiller[12] first reported the reaction of a zinc−copper couple with diiodomethane. The organozinc species formed by heating these reagents in Et_2O decomposed slowly at room temperature over several days with the concomitant evolution of ethylene, presumably the result of a coupling process. In addition, it was observed that methyl iodide was liberated upon hydrolysis while diiodomethane was regenerated by the addition of iodine (Scheme 1). These observations led Emschwiller to propose that (iodomethyl)zinc iodide had been formed.

In their landmark studies, Simmons and Blanchard[4a] examined cyclopropanation of olefins with $Zn-Cu/CH_2I_2$ in the presence of alcohols and have interpreted the results in terms of a Schlenk equilibrium (eq 1). In the

$$Zn(CH_2I)_2 + ZnI_2 \rightleftharpoons 2\ ICH_2ZnI \qquad (1)$$

Schlenk process, (iodomethyl)zinc iodide (ICH_2ZnI) disproportionates to bis(iodomethyl)zinc ($Zn(CH_2I)_2$) and zinc iodide. Dauben and Berezin have addressed this question as well but arrived at a conclusion supporting (iodomethyl)zinc iodide as the reagent.[13] In similar studies, Rickborn and Chan[14] have examined cyclopropanation of *cis*- and *trans*-5-methyl-2-cyclohexenols under the conditions of Simmons and Smith. The relative rates for the cyclopropanation of the two diastereomeric, cyclic allylic alcohols suggested that the complex between bis(iodomethyl)zinc and zinc iodide [$Zn(CH_2I)_2 \cdot ZnI_2$] was the actual reagent. The disparity between these conclusions reveals the difficulty in establishing reagent structure.

Scheme 2



Spectroscopic Insights. In 1984, Mitchell and Fabisch[15] reported a spectroscopic study on bromo analogs of the Simmons−Smith reagent. They reported that, in THF-d_8, the treatment of zinc metal or a zinc−copper couple with 1 equiv of dibromomethane produced a compound that they assigned as (bromomethyl)zinc bromide ($BrCH_2ZnBr$). However, upon standing, two new sets of signals appeared. Comparison of the relative peak positions to those reported for the corresponding mercury compounds $BrCH_2HgBr$ and $Hg(CH_2Br)_2$ led the authors to propose that one of the new species was $Zn(CH_2Br)_2$. It was concluded that the Schlenk equilibrium shown in eq 1 for the corresponding bromo analogs lies to the left.

Related studies from these laboratories[16] have also addressed the question of the Schlenk equilibrium for ICH_2ZnI. The formation of $Zn(CH_2I)_2$ under Furukawa conditions (1 equiv of Et_2Zn + 2 equiv of CH_2I_2) in acetone-d_6 followed by in vacuo removal of the solvent resulted in the formation of compounds that had lost ~50% of the original $ZnCH_2I$ units as determined iodometrically. Furthermore, if this process is carried out in the presence of 1 equiv of the bis-ether **5** (Scheme 2), the solid obtained after evaporation gave the correct elemental analysis for the compound of empirical formula **5**·ICH_2ZnI. However, ^1H and ^{13}C spectra of the complexes both before and after removal of the volatiles indicated a single ICH_2Zn-containing entity that appeared to be the same as **5**·$Zn(CH_2I)_2$. Our original interpretation was that the ICH_2ZnI formed by vacuum treatment underwent equilibration to $Zn(CH_2I)_2$ and zinc iodide, but the similarity of NMR signals for related carbenoid reagents has already been noted.

In a previous paper, we reported that zinc iodide had a beneficial effect on the rate and enantioselectivity of the bis-sulfonamide-catalyzed cyclopropanation of allylic alcohols with $Zn(CH_2I)_2$.[9b] In light of the studies mentioned above, the potential effect of zinc iodide on a Schlenk process under these reaction conditions was obvious. We were intrigued by the opportunity to use a combination of rate and selectivity data together with additional spectroscopic studies to elucidate the role of zinc iodide. We describe herein the results of that investigation in full and provide evidence that the actual cyclopropanating agent under these conditions is indeed ICH_2ZnI.

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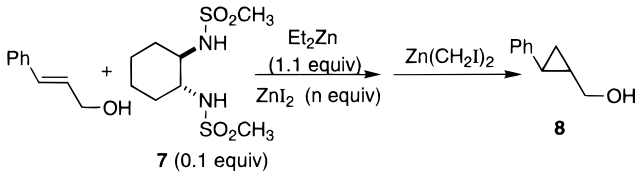
Scheme 3



While this paper was in preparation, Charette and Marcoux reported the results of a similar study on the existence and position of the Schlenk equilibrium in eq 1.[17] Reaction studies on the chiral, racemic compound 4-phenyl-3-butenol and also on a chiral, nonracemic allyl ether of a glucose-derived auxiliary were carried out. These investigations showed that reagent stoichiometries were critical in obtaining the highest diastereomeric excesses. The combination of equimolar amounts of diethylzinc and diiodomethane provided the highest diastereomeric excesses, suggesting that $EtZnCH_2I$ was the most selective reagent. Reagent combinations that should provide $Zn(CH_2I)_2$ and ICH_2ZnI led to successively lower de's. Utilizing the same bis-ether **5** that was used in our own work (*vide infra*), VT NMR studies verified the presence of these compounds using the appropriate reagent combinations. Unfortunately, the species $EtZnCH_2I$, the putatively more selective reagent, was revealed by NMR to coexist with substantial amounts of the $Zn(CH_2I)_2$ and Et_2Zn complexes, presumably the result of another Schlenk equilibrium (eq 2).

$$\mathbf{5}\cdot EtZnCH_2I \rightleftharpoons 1/2\ [\mathbf{5}\cdot Zn(CH_2I)_2 + \mathbf{5}\cdot Et_2Zn] \quad (2)$$

Of more relevance to this report, the authors showed spectroscopically that the complex of **5** with bis(iodomethyl)zinc undergoes reaction with the corresponding zinc iodide complex to yield the iodomethylzinc iodide complex $\mathbf{5}\cdot ICH_2ZnI$ (eq 3).[18]

$$1/2\ [\mathbf{5}\cdot Zn(CH_2I)_2 + \mathbf{5}\cdot ZnI_2] \rightleftharpoons \mathbf{5}\cdot ICH_2ZnI \quad (3)$$

Although the reactions investigated therein were diastereoselective cyclopropanations as opposed to the catalytic, enantioselective ones described here, the conclusions concerning reagent composition and the Schlenk equilibria are in agreement with our results. While the reagent ICH_2ZnI was the least selective for the diastereoselective cyclopropanations examined, we have found it to be far superior to $Zn(CH_2I)_2$ in catalytic, enantioselective cyclopropanations of allylic alcohols using chiral bis-sulfonamides as the promoters. The ability of zinc iodide to promote the formation of this reagent from bis(iodomethyl)zinc is examined in this report using both reaction selectivities and spectroscopy studies.

Results

Zinc Iodide and Enantioselective Cyclopropanation. In the course of our studies on the optimization of the catalytic, enantioselective cyclopropanation of cinnamyl alcohol with bis(iodomethyl)zinc and **7**[9] (Scheme 3), we noted an unusual kinetic profile (Figure 2, solid line). Specifically, the reaction displayed a marked induction period, followed by a rapid appearance of the product **8**. This behavior was exhibited at various temperatures with and without chiral catalysts. We surmised that this profile resulted from the slow formation of an active cyclopropanating species different from bis(iodomethyl)zinc. Once the reaction begins, a byproduct caused the formation of a more active cyclopropanating reagent leading to faster reaction. Thus, an autocatalytic process (with characteristic sigmoidal kinetics) was postulated. The only necessary byproduct of the cyclopropanation is zinc iodide (eq 4), and in our previous paper we noted the significant rate-enhancing effects of this salt if it is present at the beginning of the reaction. Indeed, the kinetic profile of an identical cyclopropanation of cinnamyl alcohol in the presence of zinc iodide (Figure 3, solid line) shows no induction period and a rapid appearance of product.

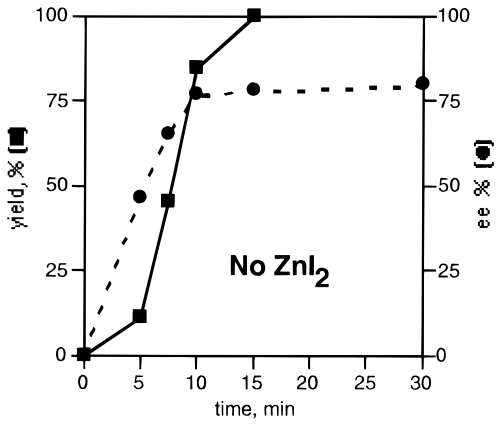


Figure 2. Yield and enantiomeric excess as a function of conversion without ZnI_2.

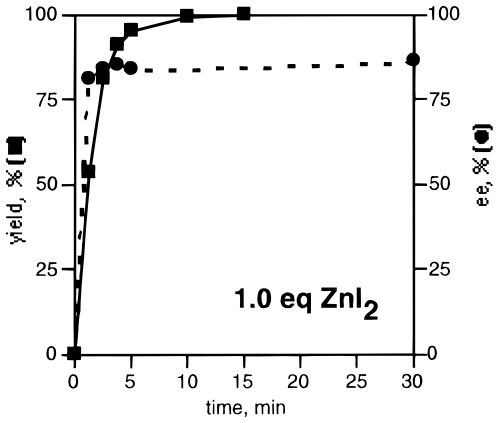


Figure 3. Yield and enantiomeric excess as a function of conversion with ZnI_2.

$$\text{olefin} + 1/2\ Zn(CH_2I)_2 \rightarrow \text{cyclopropane} + 1/2\ ZnI_2 \quad (4)$$

Additional evidence in support of the hypothesis of an autocatalytic process was forthcoming for the *conversion-dependent enantioselectivity* of the reaction. The dashed lines in Figures 2 and 3 depict the enantiomeric composition of the product as a function of reaction conversion. In the absence of zinc iodide, the enantiomeric excess of the product changes over the time course of the reaction from 46 to 76% ee. However, in the presence of zinc iodide, the enantiomeric excess is high (81−86%) and constant throughout the reaction time span.

(17) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539.

(18) Charette has recently described the solid-state structure of ICH_2ZnI as complex with 18-crown-6: Charette, A. B.; Marcoux, J.-F.; Bélanger-Gariépy, F. *J. Am. Chem. Soc.* **1996**, *118*, 6792.

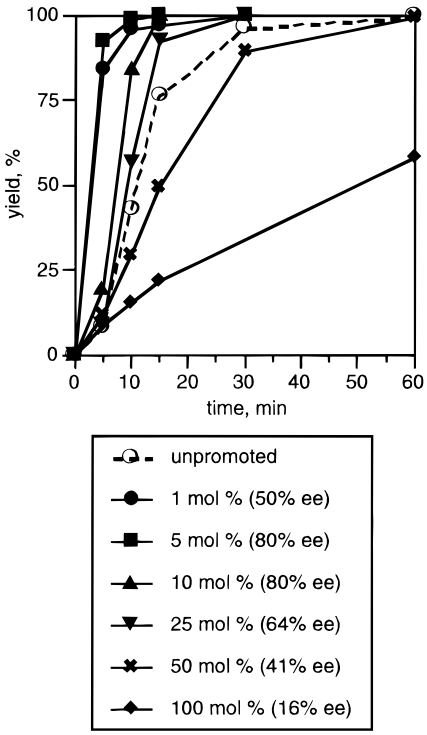


Figure 4. Dependence of rate and enantioselectivity of cyclopropanation of cinnamyl alcohol on loading of catalyst **7** (10 mol % zinc iodide added).

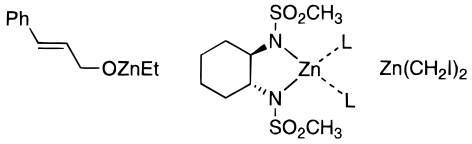


Figure 5. Zinc-containing species in the reaction mixture.

Another perplexing facet of the asymmetric cyclopropanations provides additional indirect evidence that zinc iodide is somehow incorporated into the catalytic complex. As part of the overall optimization, we examined the effect of catalyst loading on the rate and enantioselectivity of the cyclopropanation. This provided the astonishing results that are combined in Figure 4 (10 mol % zinc iodide added; see Scheme 3, $n = 0.1$). First, we discovered that the rate of reaction was *inversely* related to the loading of the catalyst **7**! With 1−5 mol % of **7**, we observed no induction period, and with 50−100 mol % of **7**, the reactions were actually *slower* than in the absence of the catalyst. Even more striking was the dependence of enantioselectivity on catalyst loading, which also decreased steadily beyond the 10% loading. We surmised that the zinc complex Zn(**7**-2H) (see Figure 5) was acting as a zinc iodide scavenger preventing the salt from generating whatever active species is actually responsible for the enantioselective cyclopropanation. This hypothesis was supported by an experiment identical to that with 25 mol % of **7** but with 1.25 equiv of zinc iodide added as well. The reaction rate and selectivity were restored (no induction period, 78% ee). Taken together, these three studies provide strong evidence that zinc iodide is necessary for the formation of the catalytically active species.

Survey of Metal Halides. Clearly, understanding the origin of the remarkable zinc iodide effect is critical for an accurate mechanistic picture of this process. However, before embarking on more detailed mechanistic experiments, we chose to establish if this behavior is unique to zinc iodide or if it is general for other metal salts. To do so, we developed a set of reaction conditions that have been found to give good, reproducible results (Scheme 4).[19] First, as noted before, it was necessary to form the ethylzinc alkoxide of the substrate allylic alcohols prior to reaction to obtain high selectivities.[9] Furthermore, contrary to our previously reported conclusions, the formation of the zinc complex of promoter **7** was important for high enantioselectivities. The protocol shown in Scheme 4 was used to survey other metal salts in the cyclopropanation reaction. A number of such additives were selected, and reactions were run using 1 equiv of the anhydrous solids in each case, Table 1.

Scheme 4

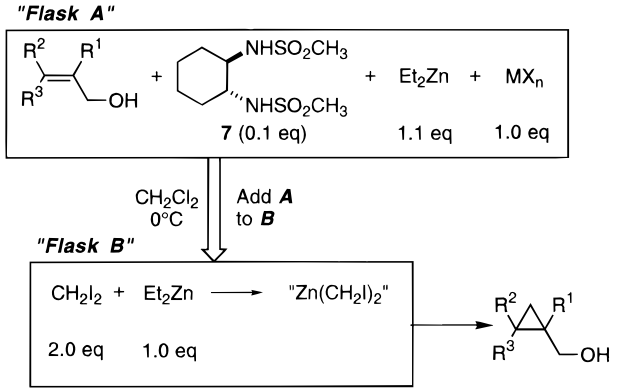


Table 1. Cyclopropanation of Cinnamyl Alcohol Using Various Additives

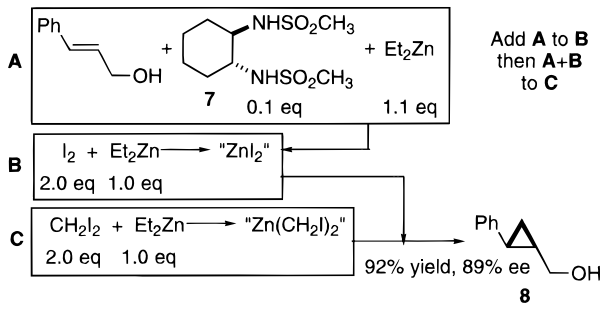
entry	additive[a]	$t_{1/2}$,[b] min	ee (**8**),[c] %
1		8	80
2	ZnI_2	<3	86
3	$ZnBr_2$	<3	80
4	$ZnCl_2$	4	76
5	ZnF_2	10	72
6	$Zn(OAc)_2$	10	45
7	$CdCl_2$	11	83
8	CdI_2	11	75
9	MgI_2	50[e]	23
10	PbI_2	8	72
11	MnI_2	12[e]	32
12	HgI_2	15	39
13	GaI_3	*d*	*d*

[a] 1.0 equiv. [b] Estimated half-lives from GC analysis of reaction progress. [c] Determined by chiral HPLC. [d] Decomposition of starting material. [e] Reaction faster than without **7**.

Rates and enantiomeric excesses were measured both with (10 mol %) and without promoter **7**. Shown in Table 1 are the times to 50% conversion ($t_{1/2}$) and enantiomeric excesses where cinnamyl alcohol was the model substrate. The results shown are for those reactions run in the presence of **7**. Duplicate reactions were also run with each metal salt but in the absence of promoter, and in all cases except for magnesium iodide and manganese iodide (Table 1, entries 9 and 11, respectively) the promoted reactions were faster. Only zinc bromide and cadmium chloride (Table 1, entries 3 and 7, respectively) provided enantiomeric excesses equal to or greater than that which was obtained in the absence of an additive (Table 1, entry 1). However, zinc iodide was unique in providing not only the best selectivity but also a very high reaction rate ($t_{1/2} = <3$ min). Our attention was therefore focused on zinc iodide as the ideal additive.

(19) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584.

Scheme 5



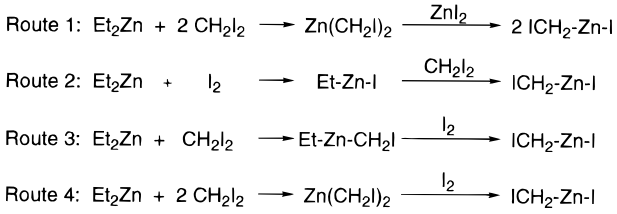
In situ Generation of Zinc Iodide. Having demonstrated the critical role played by zinc iodide, we became concerned about reproducibility due to the hygroscopic nature of this salt and the extreme moisture sensitivity of organozinc reagents. Indeed, repeated use of zinc iodide from the same container led to progressively lower enantiomeric excesses in the cyclopropanation of cinnamyl alcohol, eventually approaching 70% ee. Furthermore, a control experiment in which 1 equiv of water was added to the reaction mixture led to a slow reaction in which the product was obtained in only 31% ee.

A possible solution to this problem is to generate zinc iodide in situ from nonhygroscopic reagents. The route envisioned involved the addition of 1 equiv of diethylzinc to a suspension of 2 equiv of iodine in dichloromethane (eq 5). A three-flask protocol was developed to incorporate this modification (Scheme 5). The allylic alcohol and promoter **7** (0.1 equiv) were treated with 1.1 equiv of diethylzinc in flask A, zinc iodide was generated in flask B, and bis(iodomethyl)zinc was prepared in flask C. The contents of flask A were added to flask B, and this mixture then transferred to flask C. As a further improvement, we chose to distill the diethylzinc prior to use.[20] The benefits became apparent when the cyclopropanation of cinnamyl alcohol using this new procedure gave the product reproducibly in 89% enantiomeric excess. These results should be contrasted to those obtained when 1 equiv of solid zinc iodide was used, where the selectivities ranged from 86% ee at best down to a low of 70% ee.[21]

$$Et_2Zn + 2\ I_2 \rightarrow ZnI_2 + 2\ EtI \qquad (5)$$

Zinc Iodide and the Schlenk Equilibrium. In a multicomponent system such as that shown in Scheme 4, there is a multitude of interactions possible for zinc iodide. Zinc iodide could influence any or all of the three main components of the reaction, which not coincidentally are all present as zinc-containing species. As shown in Figure 5, these are the substrate (ethylzinc alkoxide), the catalyst (zinc−sulfonamide complex), and the reagent (bis(iodomethyl)zinc). The interaction of zinc iodide with the oligomeric ethylzinc alkoxide could form a mixed aggregate that is highly reactive. In addition, we cannot rule out an interaction of zinc iodide with the zinc promoter, although the inverse dependence of rate and selectivity on catalyst loading suggest that this interaction is not favorable. At this stage of our investigation we chose to concentrate on the role of zinc iodide in reagent composition.

Scheme 6



The combination of zinc iodide with bis(iodomethyl)zinc represents the Schlenk equilibrium of eq 1. If this process does occur, (iodomethyl)zinc iodide would be formed, which could serve as the active cyclopropanation reagent. Our approach to the question of reagent composition has been two-fold involving both reagent studies and spectroscopic investigations.

Reagent Studies. To address the question of reagent composition, specifically $Zn(CH_2I)_2$ vs ICH_2ZnI, we chose to independently generate (iodomethyl)zinc iodide by four distinct reactions and use it under our standard conditions for the cyclopropanation of cinnamyl alcohol in the presence of promoter **7**. Shown in Scheme 6 are the four proposed routes to make (iodomethyl)zinc iodide. Route 1 is the Schlenk process in question. Routes 2 and 3 are simple permutations of the same conceptual approach that is founded on the lability of the zinc−carbon bonds in diethylzinc. The addition of 1 equiv of iodine to diethylzinc followed by the addition of 1 equiv of diiodomethane should yield the desired product (iodomethyl)zinc iodide by the sequential replacement of the reactive ethyl groups (route 2). Likewise, reversal of reagent addition order, namely 1 equiv of diiodomethane first and then 1 equiv of iodine to diethylzinc, should also give (iodomethyl)zinc iodide (route 3). A fourth route was envisioned whereby bis(iodomethyl)zinc, generated from 2 equiv of diiodomethane and 1 equiv of diethylzinc, undergoes iodinolysis with 1 equiv of iodine to yield (iodomethyl)zinc iodide.[22]

Since the proposed Schlenk equilibrium of eq 1 and route 1 would give 2 equiv of (iodomethyl)zinc iodide, the stoichiometries for routes 2−4 were adjusted accordingly; i.e., reagents were used such that 2 equiv of ICH_2ZnI would be produced in each case. The reagent mixtures were all heterogeneous, containing either white precipitate or a slurry of purple hue indicating residual iodine. We note this to illustrate the difficulty of performing spectroscopic investigations of such compounds (vide infra). Our standard procedure for the individual steps of each route was to wait 5 min at 0 °C after the addition of each reagent before continuing with the sequence. The four reagents were used under a standard set of reaction conditions similar to that shown in Scheme 4 for the promoted cyclopropanation of cinnamyl alcohol. However, for routes 2−4 the reactions taking place in the B and C flasks are carried out in one flask (B) to generate the reagent (iodomethyl)zinc iodide as shown in Scheme 7. The progress of the reactions was monitored by GC and the enantiomeric excess of the cyclopropanes was established after workup by chiral HPLC. The results are shown in Figure 6.

(20) While neat diethylzinc is a highly pyrophoric liquid, the in vacuo distillation of 5 mL quantities was uneventful. From the slightly yellow commercial material was obtained a clear and colorless distillate that was superior by ^{1}H-NMR analysis.

(21) It should also be noted that while we have been able to regenerate the "dry" solid ZnI_2 by slow sublimation at 200 °C/0.1 mm (as shown by the 86% ee obtained when using this material), the use of Et_2Zn and I_2 to generate ZnI_2 in situ avoids this tedious procedure.

(22) A fifth route was attempted following the method of Wittig[3] (diazomethane and zinc iodide) but proved impractical due to the difficulty of obtaining dry diazomethane.

Scheme 7

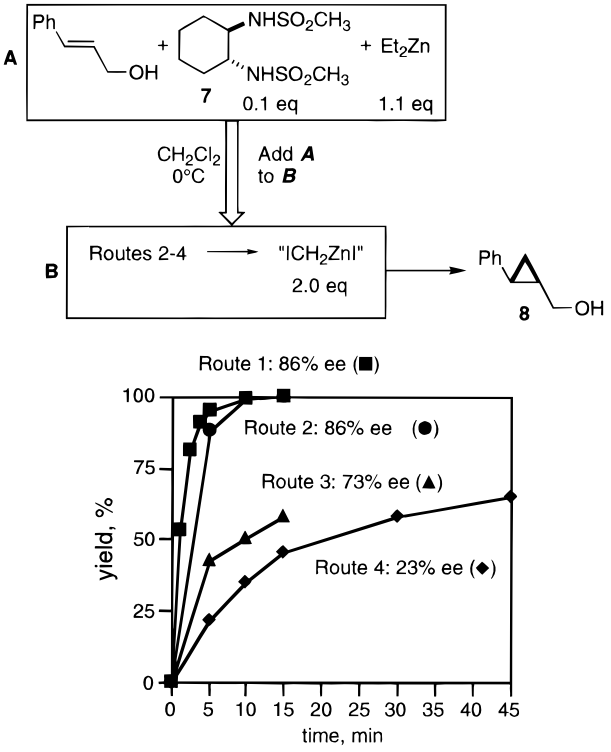


Figure 6. Rate and selectivity data for the four routes to (iodomethyl)zinc iodide.

The reactions with reagents formed using route 1 (the Schlenk process) and route 2 had essentially the same rates and gave the product **8** in the same enantiomeric excess (86% ee). This suggests that the same species must be formed by these two procedures and that the Schlenk equilibrium lies on the side of (iodomethyl)zinc iodide (eq 1). However, the reagents from routes 3 and 4 were both slower and less selective (73% and 23% ee, respectively). Since our initial assumption was that routes 2−4 should all give (iodomethyl)zinc iodide, the discrepancy in the reaction results necessitated investigations of the actual species formed under each set of conditions. This was addressed by the spectroscopic studies described below. Not only should this support our contention that zinc iodide and bis(iodomethyl)zinc react to form (iodomethyl)zinc iodide by showing that the species formed with routes 1 and 2 are the same, but it should also provide insights into reasons for the lower reaction rates and selectivities observed with routes 3 and 4.

Spectroscopy Studies. The insolubility as well as instability of the zinc-containing compounds of interest in $CDCl_3$ necessitated the use of solubilizing and stabilizing agents. It had previously been shown that some of the organozinc species under investigation were solubilized and stabilized in benzene-d_6 and acetone-d_6 when ether-type ligands were present.[16] Unfortunately, for the purposes at hand, neither dimethoxyethane, THF, nor diethyl ether provided sufficient solubilization in either $CHCl_3$ or CH_2Cl_2. However, these same studies revealed that equimolar amounts of the bis-methyl ether **5** allowed significant solubilization (0.8−1.0 M) of bis(iodomethyl)-zinc at room temperature in benzene-d_6.[16] We were gratified to discover that this compound solubilized bis-(iodomethyl)zinc in $CDCl_3$ at a concentration adequate for our purposes (0.6 M). Furthermore, variable-temperature NMR studies allowed us to reduce the equilibration of the bound and unbound zinc−ether complexes such that the two diastereotopic zinc-bound methylenes could be observed as separate signals in the ^{13}C spectrum at −70 °C while still maintaining complete solubility even at 0.6 M. We thus undertook the spectroscopic examination of the processes shown in Scheme 6 by both ^1H and ^{13}C NMR using 1 equiv of **5** per zinc. Our goal was to establish what species were formed with each route and to determine the reasons for the differences in rates and selectivities.

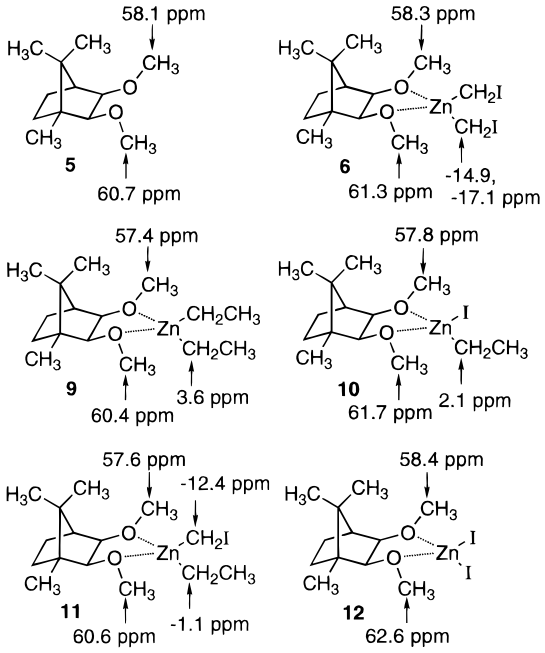


Figure 7. Diagnostic ^{13}C resonances for **5** and its complexes **6** and **9**−**12** ($CDCl_3$, 0.6 M, −70 °C).

The ^1H NMR spectra were found to be useful for determining the extent of some of the reactions examined. However, the broadness of the peaks at low temperatures as well as the presence of many overlapping signals made interpretation difficult. The ^{13}C NMR spectra were much more informative. Thus, analysis of each of the components formed using the four routes shown in Scheme 6 was carried out in $CDCl_3$ at −70 °C in the presence of **5** (1.0 equiv).

Some of the diagnostic ^{13}C resonances for the various compounds of interest when complexed with **5** are collected in Figure 7. The peaks for the bornane carbons did not vary by much more than 1−2 ppm for all of the compounds examined. The signals for the carbons attached to zinc were more diagnostic as shown by the wide range of chemical shifts. Once each of the complexes for starting materials (Et_2Zn, ZnI_2) and intermediates (EtZnI, $EtZnCH_2I$, $Zn(CH_2I)_2$) were assigned and established to be distinguishable, we felt that the complexes of the reagents formed by each of the four routes in Scheme 6 would then be examined.

The spectra for the first intermediates in each of the four routes revealed important information. For routes 1 and 4 the clean and quantitative formation of complex **6** was observed as had been previously reported.[16] However, it was also clear that the expected products from routes 2 and 3 were not being formed exclusively. The ^1H and ^{13}C NMR spectra for the expected complexes of EtZnI (**10**) and $EtZnCH_2I$ (**11**) contained multiple sets

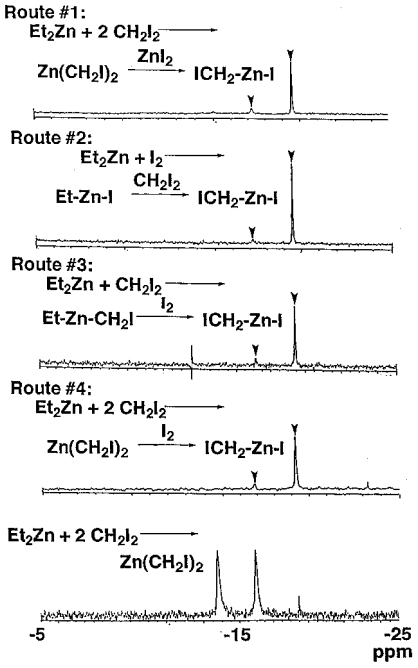


Figure 8. Partial ^{13}C-spectra for the four routes to (iodomethyl)zinc iodide and of bis(iodomethyl)zinc as complexes with **5** in $CDCl_3$ at −70 °C.

of resonances. For **10**, it was conceivable that the Zn−epimeric complexes of EtZnI with **5** were not interconverting at the temperature of acquisition (−70 °C). While the spectrum indicated that the two diastereomeric EtZnI complexes were the major species present, minor species were also detected.

For **11**, the situation was not as easily explained. Examination of the ^1H and ^{13}C spectra indicated the presence of both the diethylzinc complex **9** and the bis(iodomethyl)zinc complex **6**, in addition to the signals that have tentatively been assigned to **11**. The overall transformation for the first step of route 3 therefore appeared to be as follows (stoichiometries of products not indicated):

$$Et_2Zn + CH_2I_2 \rightarrow EtZnCH_2I + Zn(CH_2I)_2 + Et_2Zn \quad (6)$$

This was obviously not the intended outcome, namely the unique formation of $EtZnCH_2I$ as indicated by a clean spectrum of **11**. It was apparent that the addition of 1 equiv of iodine, the second step of route 3, to this reagent mixture would not yield the complex between (iodomethyl)zinc iodide and **5** as the exclusive product. The reason for the lower reaction rate and selectivity (73% ee) with route 3 was likely a manifestation of incomplete reagent formation and inhomogeneity.

Spectroscopic analysis of the end product from each of the four routes provided a wealth of information. We first analyzed the diagnostic region of the ^{13}C spectrum where the ZnCH_2I signals appeared. Shown in Figure 8 are the ^{13}C spectra (−5 to −25 ppm) for the compounds made by each of the four routes to (iodomethyl)zinc iodide (the spectrum of the bis(iodomethyl)zinc complex (**6**) is shown for comparison). All four routes appeared to give the same species. Two signals were visible in all of the spectra: a small peak at approximately −17.2 ppm and a larger one at approximately −19.6 ppm. These were different from those for **6**, which displayed resonances

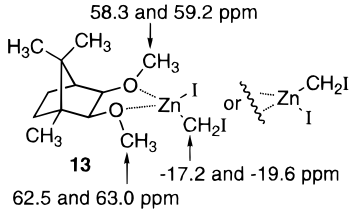


Figure 9. Complex **13** (**5**·ICH_2ZnI).

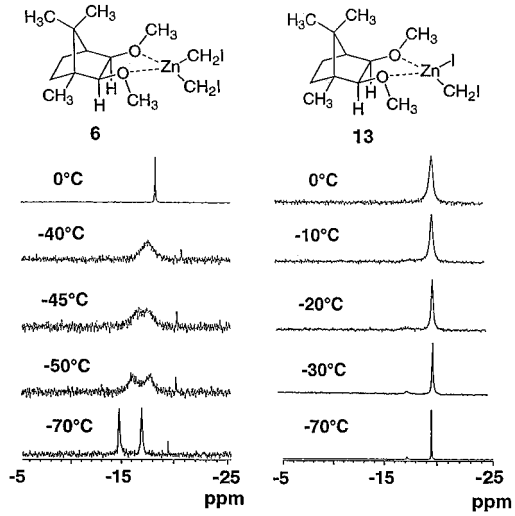


Figure 10. Variable temperature studies of **6** (**5**·$Zn(CH_2I)_2$) and **13** (**5**·ICH_2ZnI) in $CDCl_3$.

of approximately equal intensity at approximately −14.9 ppm and approximately −17.1 ppm. Clearly, a new and unique species was formed from each of the four routes. We suspected this new species was **13**, the complex of **5** and (iodomethyl)zinc iodide, and that the two signals were due to the Zn−epimeric complexes (Figure 9). In support of this hypothesis, we demonstrated that the signals corresponded to two species in equilibrium. By raising the temperature to 0 °C and then recooling to −70 °C the two peaks at −17.2 and −19.6 ppm coalesced and then reappeared (Figure 10). Likewise, the coalescence of the bis(iodomethyl)zinc complex was observed, albeit at a lower temperature (approximately −45 °C), as one might expect for a less Lewis acidic species. Why one diastereomer should so heavily predominate was not obvious, and no attempt to assign the individual isomers was made.

Full examination of the spectra for the end products of each route provided further insights. The use of route 1 (the Schlenk equilibrium) and route 2 provided the cleanest spectra with near-quantitative formation of the new species, which we have assigned as **13** (Figure 9). This supported our contention that the addition of zinc iodide to bis(iodomethyl)zinc leads to (iodomethyl)zinc iodide via a Schlenk process. While we were initially concerned with additional peaks in the spectrum for the first step of route 2, this was simply due to the presence of both diastereomeric complexes. Thus, we have supported the notion that the effect of zinc iodide on the enantioselective cyclopropanation of allylic alcohols was one of reagent modification.

The spectra for the reagent formed using route 3 were much more complicated. As described above, the mixture from the first step of route 3 contained $EtZnCH_2I$ along with diethylzinc and bis(iodomethyl)zinc. When reacted with 1 equiv of iodine (per zinc) in the second step it also

yielded a number of species. Two major complexes were evident, and we have assigned these as the desired (iodomethyl)zinc iodide complex **13** and, tentatively, the zinc iodide complex **12**. Surprisingly, there were no signals for ethylzinc species in the ^{1}H NMR spectrum and no evidence in the ^{13}C spectrum for any residual bis(iodomethyl)zinc.

In route 4, the addition of 1 equiv of iodine to bis(iodomethyl)zinc clearly produced (iodomethyl)zinc iodide as shown in Figure 8. However, there appeared to be at least one other major zinc-containing complex present as evidenced by a second set of ^{13}C signals as well as multiple resonances in the ^{1}H spectrum. We have tentatively assigned these additional peaks to the zinc iodide complex **12**.

Our initial hypothesis for the poor selectivity observed with route 4 (23% ee) related to diiodomethane, the byproduct, which should be formed upon iodinolysis of $Zn(CH_2I)_2$. It could conceivably convert the ethylzinc alkoxide of cinnamyl alcohol (EtZnOR) into the corresponding (iodomethyl)zinc alkoxide (ICH_2ZnOR).[23] However, subsequent spectroscopic investigations revealed that metathesis of the ethylzinc alkoxide with diiodomethane to yield the (iodomethyl)zinc alkoxide does not occur. The addition of 1 equiv of CH_2I_2 to the preformed ethylzinc alkoxide of cinnamyl alcohol in $CDCl_3$ at room temperature showed no change in the ^{1}H NMR spectrum after 20 min. This result as well as the spectroscopic studies for route 4 described above suggests that the reason for poor selectivity with this procedure is the production of byproduct(s) that interfere with the reaction between bis(iodomethyl)zinc and iodine.

The spectroscopic studies for routes 1 and 2 clearly showed that the Schlenk equilibrium lies on the side of (iodomethyl)zinc iodide. However, all of the NMR investigations on reagent composition described above were conducted using equimolar amounts of **5**. We were very cognizant of the influence of ligands and solvents on Schlenk equilibria,[24] and attempts were made to assess if the bis-ether **5** was responsible for shifting the equilibrium of eq 1 in favor of (iodomethyl)zinc iodide over bis(iodomethyl)zinc and zinc iodide.

Solutions of complexes **6** (**5**·$Zn(CH_2I)_2$) and **12** (**5**·ZnI_2) were prepared separately in $CDCl_3$, cooled to −70 °C, and then combined. At −70 °C, spectra were acquired at 15, 45, and 150 min after mixing (see the Supporting Information). The two peaks in the ^{13}C spectrum for **6** (at −14.9 and −17.1 ppm) were slowly replaced by those assigned to **13**, the (iodomethyl)zinc iodide complex (at −17.2 and −19.6 ppm). The immediate appearance of complex **13** showed that equilibration occurred even at −70 °C but the half-life was on the order of 30−40 min. Thus, while the Schlenk equilibration of **6** and **12** to give **13** does occur at −70 °C, it is slow enough that it might be possible to assess what effect the bis-ether **5** has on this process.

Despite the technical difficulties we nonetheless made an attempt to determine if the Schlenk equilibrium could be established *in the absence of* ***5***. Thus, suspensions of bis(iodomethyl)zinc and zinc iodide were prepared at 0 °C in $CDCl_3$ (0.6 M). They were then combined and maintained for 5 min at 0 °C following which the white slurry was cooled to −70 °C. Two equivalents of the bis-ether **5** (1 equiv for each zinc equiv) was then added. Unfortunately, only minimal solubilization occurred at this reduced temperature as large amounts of precipitate still remained. An acquisition time of 60 min was required to obtain ^{13}C spectra with a signal-to-noise ratio of only ∼3:1. As observed above, this was sufficient time for the Schlenk equilibrium to have occurred by at least 50% at this temperature ($t_{1/2}$ = ∼30−40 min). Between −10 and −25 ppm in the ^{13}C spectrum, a single peak at approximately −19 ppm was discernible above the noise, indicative of the presence of **13**. The time required for data acquisition as well as the poor signal-to-noise ratio make interpretation of this result very questionable. However, it does suggest that even in the absence of **5**, the Schlenk process of eq 1 lies on the side of (iodomethyl)zinc iodide.

Discussion

Reaction Studies with Zinc Iodide and Other Metal Salts. The graphs in Figures 2−4 clearly establish that zinc iodide improves the enantiomeric excess for the cyclopropanation of allylic alcohols by making the process highly selective throughout the entire course of the reaction. Thus, while zinc iodide accelerates the reaction for the promoted *and* unpromoted events, the enantiomeric excess is increased not by making the promoted reaction *faster* but by making it *consistently more selective*.

The presence of a substantial background reaction, which occurs in the absence of promoter, has been a limiting factor in improving the enantiomeric excesses under these conditions. As mentioned above, the rate acceleration observed upon the addition of 1 equiv of zinc iodide manifests itself in the presence of promoter **7** but unfortunately also in its absence. Obviously, if the difference in rate between the promoted and unpromoted reactions can be increased, the reaction should become more selective.

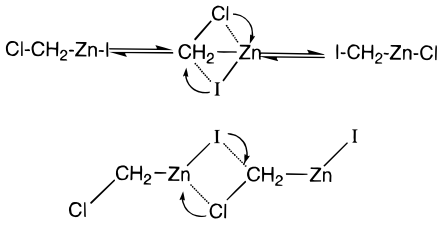
Indeed, the effect of zinc iodide on the enantioselective pathway is dramatic. With as little as 1 mol % of **7**, the product cyclopropane **8** is obtained quantitatively in less than 30 min with 50% ee. Raising the amount of **7** slows down the reaction and decreases the enantioselectivity by sequestering the zinc iodide produced throughout the reaction. Without zinc iodide available, the formation of (iodomethyl)zinc iodide from bis(iodomethyl)zinc is a much slower process. Clearly, the zinc species added at the outset of the reaction are not uniquely responsible for the high rates and enantioselectivities observed.

The results in Table 1 show clearly the benefits of the use of zinc iodide over the other metal salts examined. Both rate and enantiomeric excess were optimal with zinc iodide. Each of the additives in Table 1 may enter into a Schlenk equilibrium process with bis(iodomethyl)zinc

(23) Independent generation of the iodomethylzinc alkoxide of cinnamyl alcohol followed by cyclopropanation under standard conditions using 10 mol % of **7** led to **8** in a very unselective manner (2% ee). This suggested that the reason route 4 was so poorly selective resulted from the formation of diiodomethane and that this compound reacted with the ethylzinc alkoxide of cinnamyl alcohol to form the (iodomethyl)zinc alkoxide.

(24) For the Schlenk equilibrium between $Et_2Zn + ZnI_2$ and EtZnI, in the presence of coordinating solvents such as THF or ether the following references support EtZnI as the more stable species: (a) Abraham, M. H.; Rolfe, P. H. *J. Chem. Soc., Chem. Commun.* **1965**, 325. (b) Evans, D. F.; Wharf, I. *J. Organomet. Chem.* **1966**, *5*, 108. (c) Evans, D. F.; Wharf, I. *J. Chem. Soc. A* **1968**, 783. (d) Abraham, M. H.; Rolfe, P. H. *J. Organomet. Chem* **1967**, *7*, 35. (e) Evans, D. F.; Fazakerley, G. V. *J. Chem. Soc. A* **1971**, 182. In the absence of coordinating solvents, the following references suggest that the equilibrium favors $Et_2Zn + ZnI_2$: (f) Boersma, J.; Noltes, J. G. *J. Organomet. Chem.* **1967**, *8*, 551. (g) Boermsa, J.; Noltes, J. G. *Tetrahedron Lett.* **1966**, 1521. (h) Evans, D. F.; Maher, J. P. *J. Chem. Soc.* **1962**, 5125.

Scheme 8



as shown in eq 7. In the case where M = Zn, 2 equiv of

$$Zn(CH_2I)_2 + MX_n \rightleftharpoons ICH_2ZnX + ICH_2MX_{n-1} \quad (7)$$

the species ICH_2ZnX would be formed. For the reaction where 1 equiv of a metal iodide MI_n is used 1 equiv each of ICH_2ZnI and ICH_2MI_{n-1} would be produced. The assumption that the Schlenk process for each metal salt lies to the right may not necessarily be true, but our results support this contention. If this were not the case, then the metal salts should all have had no effect on rate and selectivity. As can be seen from Table 1, each metal salt provided results different from the case where no additive was used (entry 1).

Simmons and Blanchard have examined the species $ClCH_2ZnI$ formed by the reaction of zinc−copper couple and chloroiodomethane.[4a] Initial insertion of zinc into the carbon−iodine bond is assumed to occur since the analogous reaction with dichloromethane does not lead to a reagent capable of olefin cyclopropanation. Furthermore, if $ClCH_2ZnCl$ is formed using the method of Wittig (diazomethane and zinc chloride),[3] cyclopropanation of olefins does occur. Thus, since $ClCH_2ZnCl$ is an active cyclopropanation reagent but zinc−copper couple and dichloromethane do not lead to a species capable of adding methylene to olefins, it can safely be concluded that zinc does not readily insert into carbon−chlorine bonds. It was therefore not unreasonable for Simmons and Blanchard to propose that $ClCH_2ZnI$ is formed from zinc−copper couple and chloroiodomethane by zinc insertion into the carbon−iodine bond. However, upon hydrolysis of this putative species, methyl iodide was formed with only trace quantities of methyl chloride in evidence. An equilibrium such as that shown in Scheme 8 must be occurring whereby $ClCH_2ZnI$ is converted to ICH_2ZnCl by an intramolecular or intermolecular process. Thus, while $ClCH_2ZnI$ is formed initially, the thermodynamically more stable isomer is probably ICH_2ZnCl. Conceivably, the longer carbon−iodine vs carbon−chlorine bond as well as the fact that iodide is a better bridging group than chloride may make the (iodomethyl)zinc chloride species more favorable. It may also be that the (iodomethyl)zinc chloride species is more reactive than the corresponding (chloromethyl)zinc iodide both toward hydrolysis as well as methylene delivery to olefins. These events may be activated by a zinc−iodine interaction of either an inter- or intramolecular nature.

The conclusion one draws is that the species ICH_2ZnX (X = Cl or Br), obtained by the Schlenk process (eq 7) from $Zn(CH_2I)_2$ and ZnX_2, are stable relative to the corresponding compounds XCH_2ZnI, due to the greater ability of iodine to coordinate with zinc in an intramolecular manner. The nature of the X group in ICH_2ZnX must have little influence on the reactivity of the reagent since reactions in the presence of ZnI_2, $ZnBr_2$, and $ZnCl_2$ proceed at approximately the same rate yet significantly faster than the case when no additive is used. It appears that the presence of a halogen, whether iodine, bromine, or chlorine, on the zinc atom, when coupled with the internally activated ICH_2Zn unit, is responsible for the faster reactions compared to $Zn(CH_2I)_2$.

We propose that the first three additives, ZnI_2, $ZnBr_2$, and $ZnCl_2$, increase reaction rates by forming highly reactive cyclopropanating reagents ICH_2ZnX (X = I, Br, Cl). However, in the presence of 10 mol % of chiral sulfonamide **7**, the different reagents afford the product cyclopropane with different enantiomeric excesses of (Table 1): ZnI_2 (86% ee), $ZnBr_2$ (80% ee), $ZnCl_2$ (76% ee). It is obvious that the reagents become less sensitive to the influence of the chiral promoter **7** in the order I > Br > Cl. Thus, while the proposed reagents ICH_2ZnI, ICH_2ZnBr, and ICH_2ZnCl all contain the (iodomethyl)zinc unit, the nature of the halogen attached *directly* to the zinc atom is obviously critical for an effective interaction with the promoter. Since the promoter is present as the zinc derivative (formed by prior treatment with 1 equiv of diethylzinc), it is reasonable to propose that X in ICH_2ZnX coordinates to the zinc of the promoter complex. The ability of the atom X to do this must decrease in the direction I > Br > Cl. The larger size, longer zinc−iodine bond lengths, and increased polarizability of iodine relative to bromine and chlorine are factors that may contribute to this phenomenon. As Simmons and Smith showed that iodine is the best X group of I−, Br−, and Cl− in XCH_2Zn for cyclopropanation, we suggest that iodine in the ZnX portion of the reagent is the best halogen for interacting with the promoter.[4a,25]

Reagent Studies of the Schlenk Equilibrium. Of the four routes examined for the independent production of (iodomethyl)zinc iodide (Scheme 6), only routes 1 and 2 gave clearly interpretable results regarding the Schlenk equilibrium. Since both the rate and enantioselectivity of cyclopropanation with the reagent prepared by route 1 were essentially identical to those obtained with route 2, we suggest that the Schlenk equilibrium does exist and that ICH_2ZnI is the active agent.

The results for routes 3 and 4 were not as straightforward. Both the rates of reaction and the enantiomeric excesses of the products were much lower. As all four routes were actually heterogeneous mixtures of highly reactive organometallic reagents, it was impossible to assess the degree of completion for each step in these processes as well as to establish how cleanly the desired reagents were made. Given these limitations, we offer the tentative conclusion that while ICH_2ZnI is formed in each route (vide infra), there are other species present that reduce the effective concentration or interfere with the cyclopropanation process.

Spectroscopy Studies. From the partial ^{13}C spectra NMR provided in Figure 8 it could be seen that each of the four routes shown in Scheme 6 produced the same new species characterized by the signals at −17.2 and −19.6 ppm. That these two resonances were observed in this region of the ^{13}C spectrum suggested that they are for methylenes bonded to both iodine and zinc. Further, their temperature-dependent line shape suggested that they are interconverting species present in unequal amounts that belong to the two diastereomeric (iodomethyl)zinc iodide complexes **13** shown in Figure 9. The observation that the Schlenk mixture $Zn(CH_2I)_2/ZnI_2$ also gave these two peaks (route 1) was a strong indica-

(25) For a discussion of transition structure proposals for the cyclopropanation see ref 19.

tion that the effect of zinc iodide under the standard reaction conditions for the cyclopropanation of allylic alcohols was to drive the equilibrium process to the reagent (iodomethyl)zinc iodide. The nearly identical spectra for the reagents obtained with both routes 1 and 2 is the strongest support for this contention.

The full spectra for routes 3 and 4 revealed the presence of **13** for both of these routes, albeit compromised by other species. The observation of these other species helped us rationalize why reactions using the reagents produced with route 3 and 4 were not as selective. The active agent (iodomethyl)zinc iodide was formed but in reduced amounts leading to slower and less effective catalysis.

In the case of route 3, the lower yield of (iodomethyl)-zinc iodide could be due to poor chemical selectivity in both steps. In the first step, 1 equiv of CH_2I_2 is added to Et_2Zn, and three species were detected spectroscopically (Et_2Zn, $EtZnCH_2I$, $Zn(CH_2I)_2$). It is likely that $EtZnCH_2I$ is produced but undergoes Schlenk equilibration itself to form a mixture containing Et_2Zn and $Zn(CH_2I)_2$ (eq 8).

$$EtZnCH_2I \rightleftharpoons 1/2\ [Et_2Zn + Zn(CH_2I)_2] \qquad (8)$$

It is also possible that the reaction of $EtZnCH_2I$ with CH_2I_2 is faster than the reaction of Et_2Zn with CH_2I_2. This would produce the same three species. Whichever the case, subsequent addition of I_2 does not cleanly produce ICH_2ZnI as we could detect the ZnI_2 complex **12** as an additional major component. Thus, for route 3, an unproductive side reaction gives ZnI_2 and removes this zinc equiv from the potential for methylene delivery.

Route 4 also led to lower than expected quantities of (iodomethyl)zinc iodide complex **13**. It was apparent from the spectra that the problem was in the iodinolysis step, namely the addition of 1 equiv of iodine to the bis-(iodomethyl)zinc complex **6**. While **13** was formed, it appeared that substantial amounts of the zinc iodide complex **12** had also been produced. Again, a puzzling observation was that none of the bis(iodomethyl)zinc complex **6** remained. Since equimolar quantities of iodine and the complex of $Zn(CH_2I)_2$ were reacted, it is difficult to rationalize the production of ICH_2ZnI and ZnI_2 while completely consuming the $Zn(CH_2I)_2$.

A major caveat in these spectroscopic studies is the role of the bis-ether **5** in the position of the Schlenk equilibrium. While **5** is essential for solubilization and stabilization to allow spectroscopic observation of the various zinc species, it is well known that the position of the Schlenk equilibrium is strongly medium dependent.[24] An attempt to address what effect the bis-ether **5** had on the Schlenk equilibrium was thwarted by low solubility of the species at −70 °C. The evidence obtained supported the hypothesis that the zinc equilibrium, *even in the absence of the bis-ether* ***5***, favored (iodomethyl)zinc iodide. However, the low signal-to-noise level in the ^{13}C spectrum (~3/1) resulting from the limited low-temperature solubility of the species present make this conclusion less than firm.

Summary

The results presented here have served to clarify the favorable effect of zinc iodide in the bis-sulfonamide-promoted cyclopropanation of allylic alcohols. It has been proposed and the supporting evidence provided that (iodomethyl)zinc iodide is formed by the action of zinc iodide upon the reagent bis(iodomethyl)zinc. Furthermore, it is concluded that (iodomethyl)zinc iodide is the actual cyclopropanation reagent both with and without chiral promoters. While complications due to instability and insolubility of many of the zinc compounds were encountered and potentially compromising modifications were required to perform the spectroscopic studies, the combination of all of the results obtained lead us to conclude that the Schlenk equilibrium of eq 1 lies predominantly if not exclusively on the side of (iodomethyl)zinc iodide. We have further demonstrated that, for allylic alcohols, in situ zinc iodide generation under the conditions of bis-sulfonamide **7**-promoted cyclopropanation leads to a highly selective reaction (89% ee).

Experimental Section

General Methods. ^1H and ^{13}C NMR and 2D NMR spectra were recorded at field strengths of 400 or 500.1 MHz (^1H) and 100 or 125.8 MHz (^{13}C). Data are reported in the following order: chemical shifts in ppm (δ); multiplicities are indicated (bs (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); coupling constants, *J*, are reported in hertz; integration is given; and assignment is indicated. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Optical rotations are reported as follows: $[\alpha]^{temp}_D$ (solvent, concentration in g/100 mL). Diiodomethane (Aldrich) was washed with $Na_2S_2O_3$ (aq), dried ($MgSO_4$), distilled from CaH_2 (88 °C/40 Torr), stored over copper, and protected from light. Neat diethylzinc was used as purchased from Strem in protocol A. In protocol B, diethylzinc was distilled (0 °C/0.03 Torr). Zinc iodide (Aldrich) of 99.99+% and 99.999% grades was stored over P_2O_5. Iodine was obtained from Mallinckrodt and used as is. Reagent-grade dichloromethane was distilled from P_2O_5 prior to use in the reactions. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light, iodine, or phosphomolybdic acid solution (5% in ethanol). Column (flash) chromatography was performed using 32−63 mm silica gel. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying reagents: hexane ($CaCl_2$), dichloromethane ($CaCl_2$), ethyl acetate (K_2CO_3). Analytical gas chromatography was performed on a Hewlett-Packard 50 m Ultra Phenyl Methyl Silicone (U2) or a Hewlett Packard 50 m phenyl methyl silicone (HP-5) column. Analytical high-pressure liquid chromatography (HPLC) was performed using Daicel Chiralcel OJ column with the detector wavelength at 254 nm. The flow rate and solvent system were as denoted. The syntheses of **5**[16c] and **7**[9a,19] have been previously described. Cinnamyl alcohol was obtained from Aldrich and recrystallized from pentane/ether.

NMR Studies. General Procedure for the Preparation of Samples. All of the NMR tubes used were Wilmad 528, dried for 2 h at 125 °C, and then allowed to cool to rt over P_2O_5. The septum-capped NMR tubes were evacuated and then filled with argon. All additions of liquids were performed with gas-tight syringes or with cannulas. Solid zinc iodide was added to NMR tubes while in a glovebox. Where noted, degassing involved three freeze−pump−thaw cycles. Chloroform-d_1 was distilled from P_2O_5 and then passed through basic alumina immediately prior to sample preparation.

NMR Spectra of (*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane (5). A sample of **5** (60 mg, 0.30 mmol) in a septum-capped NMR tube under argon was dissolved in $CDCl_3$ (0.5 mL). The sample was degassed, the tube was sealed with Teflon and parafilm, cooled to −70 °C, and the spectra were acquired. Data for **5**: ^1H NMR (500 MHz, $CDCl_3$, −70 °C) 3.38 (s, 3 H, $H_3C(12)$), 3.33 (s, 3 H, $H_3C(11)$), ~3.34 (HC(2), this signal was obscured by the C-11 methyl signal), 3.13 (d, J = 6.7, 1 H, HC(3)), 1.79 (d, J = 5.1, 1 H, HC(1)), 1.58 (tt, J = 9.0, 12.4, 1 H, $HC(6_x)$), 1.37 (dt, J = 3.4, 12.4, 1 H, $HC(5_x)$), 0.97 (s, 3 H, $H_3C(8)$), 0.90 (dt, J = 3.9, 11.2, 1 H, $HC(5_n)$), 0.83 (s, 3 H, $H_3C(10)$), 0.83 ($HC(6_n)$, this

signal was obscured by the C-10 methyl signal), 0.68 (s, 3 H, $H_3C(9)$); ^{13}C NMR (125.8 MHz, $CDCl_3$, −70 °C) 89.91 (C(3)), 86.19 (C(2)), 60.68 (C(12)), 58.26 (C(11)), 48.83 (C(4)), 46.72 (C(1)), 46.21 (C(7)), 33.19 (C(5)), 23.77 (C(6)), 20.90 (C(9)), 20.07 (C(8)), 11.42 (C(10)).

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)diethylzinc (9). To a septum-capped NMR tube containing **5** (60 mg, 0.30 mmol) in $CDCl_3$ (0.5 mL) at 0 °C was added Et_2Zn (31 μL, 0.30 mmol). The sample was degassed, the tube was sealed with Teflon and parafilm and cooled to −70 °C, and the spectra were acquired. Data for **9**: ^1H NMR (500 MHz, $CDCl_3$, −70 °C) 3.41 (s, 3 H, $H_3C(12)$), ∼3.41 (HC(2), this signal was obscured by the C-12 methyl signal), 3.33 (s, 3 H, $H_3C(11)$), 3.22 (d, J = 7.6, 1 H, HC(3)), 1.86 (d, J = 4.8, 1 H, HC(1)), 1.61 (m, 1 H, $HC(6_x)$), 1.39 (dt, J = 4.3, 12.3, 1 H, $HC(5_x)$), 1.05 (t, J = 8.5, 3 H, CH_3CH_2Zn), 0.99 (s, 3 H, $H_3C(8)$), 0.90 (s, 3 H, $H_3C(10)$), 0.70 (s, 3 H, $H_3C(9)$), −0.49 (q, J = 8.2, 2 H, H_2CZn); ^{13}C NMR (125.8 MHz, $CDCl_3$, −70 °C) 89.92 (C(3)), 86.16 (C(2)), 60.43 (C(12)), 57.39 (C(11)), 49.20 (C(4)), 46.39 (C(1)), 45.61 (C(7)), 33.05 (C(5)), 23.57 (C(6)), 20.97 (C(9)), 19.85 (C(8)), 11.78, 11.64 (C(10), CH_3CH_2Zn)), 3.64 (CH_2Zn).

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)ethylzinc Iodide (10). The contents of a septum-capped NMR tube containing **9** (0.30 mmol) in $CDCl_3$ (0.5 mL) at 0 °C was tranferred via cannula to a second septum-capped NMR tube containing I_2 (76 mg, 0.30 mmol) at 0 °C. After being mixed at 0 °C for 1 min, the sample became clear and colorless. It was allowed to warm to rt for 30 min and then cooled to −70 °C for acquisition of the spectra. Only partial spectral assignments are given for **10** due to complexities arising from the presence of diastereomeric complexes. Data for **10**: ^1H NMR (500 MHz, $CDCl_3$, −70 °C) 0.11 (q, J = 8.0, CH_2Zn); ^{13}C NMR (125.8 MHz, $CDCl_3$, −70 °C) 61.78 (C(12)), 57.78 (C(11)), 2.09 (CH_2Zn).

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)bis(iodomethyl)zinc (6). To a septum-capped NMR tube containing **9** (0.30 mmol) in $CDCl_3$ (0.5 mL) at 0 °C was added CH_2I_2 (48 μL, 0.60 mmol). The tube was sealed with Teflon and parafilm and placed in the NMR probe at 0 °C. Observation of the ^{13}C spectrum indicated that ∼60 min were required for complete formation of the bis(iodomethyl)zinc species. The probe was then cooled to −70 °C, and the spectra were acquired. Only partial spectral assignment could be made for the ^1H NMR spectrum at −70 °C due to the broadness of the signals. Data for **6**: ^1H NMR (500 MHz, $CDCl_3$, −70 °C) 1.20 (bs, 2 H, H_2CZn); ^{13}C NMR (125.8 MHz, $CDCl_3$, −70 °C) 90.37 (C(3)), 86.87 (C(2)), 61.28 (C(12)), 58.28 (C(11)), 49.48 (C(4)), 46.73 (C(1)), 44.18 (C(7)), 32.45 (C(5)), 23.02 (C(6)), 20.86 (C(9)), 20.32 (CH_3CH_2I), 19.63 (C(8)), 11.88 C(10), 1.17 (CH_3CH_2I), −14.85, −17.05 (ICH_2Zn).

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)ethyl(iodomethyl)zinc (11). To a septum-capped NMR tube containing **9** (0.30 mmol) in $CDCl_3$ (0.5 mL) at −78 °C was added CH_2I_2 (24 μL, 0.30 mmol), and the tube sealed with Teflon and parafilm. After the contents were mixed at −78 °C, the tube was warmed to 0 °C for 5 min and then cooled back to −70 °C for the acquisition of the spectra. The spectra indicated the presence of both **9** and **6** along with the complex of $EtZnCH_2I$ (**11**). Partial assignment of the spectra for **11** are given. Data for **11**: ^1H NMR (500 MHz, $CDCl_3$, −70 °C) −0.03 (q, J = 7.8, 1 H, CH_3CH_2Zn), −0.10 (q, J = 8.1, 1 H, CH_3CH_2Zn); ^{13}C NMR (125.8 MHz, $CDCl_3$, −70 °C) −1.09 (CH_3CH_2Zn), −12.37 (ICH_2-ZnEt), −15.0, −17.2 ($Zn(CH_2I)_2$).

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)zinc Iodide (12). To a septum-capped NMR tube containing ZnI_2 (96 mg, 0.30 mmol) were added $CDCl_3$ (0.5 mL) and **5** (60 mg, 0.30 mmol). The sample was degassed and the tube sealed with Teflon and parafilm. Approximately 1 h at room temperature with occassional mixing was required to affect complete solution. The sample was then cooled to −70 °C for the acquisition of the spectra. Data for **12**: ^1H NMR (500 MHz, $CDCl_3$, −70 °C) 3.82 (d, J = 6.81, 1 H, HC(2)), 3.74 (s, 3 H, $H_3C(12)$), 3.68 (d, J = 6.7, 1 H, HC(3)), 3.60 (s, 3 H, $H_3C(11)$), 2.11 (d, J = 3.9, 1 H, HC(1)), 1.74 (b, 1 H, $HC(6_x)$), 1.48 (d, J = 9.3, 1 H, $HC(5_x)$), 1.05 (s, 3 H, $H_3C(8)$), 0.99 (s, 3 H, $H_3C(10)$), 0.77 (s, 3 H, $H_3C(9)$); ^{13}C NMR (125.8 MHz, $CDCl_3$, −70 °C) 89.97 (C(3)), 85.41 (C(2)), 62.59 (C(12)), 58.38 (C(11)), 49.86 (C(4)), 47.17 (C(1)), 44.01 (C(7)), 32.33 (C(5)), 22.68 (C(6)), 20.85 (C(9)), 20.01 (C(8)), 12.17 (C(10)).

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)(iodomethyl)zinc Iodide (13) via Route 1. To a septum-capped NMR tube containing a solution of **6** in $CDCl_3$ (0.6 M) at −78 °C was added via cannula an equimolar solution of **12** also in $CDCl_3$ (0.6 M) at −78 °C. The sample was placed in the NMR probe precooled to −70 °C, and spectra were acquired at 8, 48, and 150 min from mixing. At 48 min approximately 50% of **6** and **12** remained while by 150 min the conversion to **13** was complete. Data for **13**: ^1H NMR (500 MHz, $CDCl_3$, −70 °C) 3.78 (s, 3H, $H_3C(12)$), 3.71 (s, 3H, $H_3C(11)$), 3.12 (q, J = 7.6, CH_3CH_2I), 2.02 (d, J = 5.0, 1 H, HC(1)), 1.745 (t, J = 7.6, CH_3CH_2I), 1.35 (bs, 2 H, $ZnCH_2I$), 1.00 (s, 3 H, $H_3C(8)$), 0.91 (s, 3 H, $H_3C(10)$), 0.73 (s, 3 H, $H_3C(9)$); ^{13}C NMR (125.8 MHz, $CDCl_3$, −70 °C) 89.49 (C(3)), 85.37 (C(2)), 63.00 (C(12)), 59.21 (C(11)), 49.52 (C(4)), 46.90 (C(1)), 43.94 (C(7)), 32.27 (C(5)), 22.61 (C(6)), 20.70 (C(9)), 20.28 (CH_3CH_2I), 20.11 (C(8)), 12.06 (C(10)), 1.14 (CH_3CH_2I), −17.19, −19.56 ($ZnCH_2I$).

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)(iodomethyl)zinc Iodide (13) via Route 2. To a septum-capped NMR tube containing **10** (0.30 mmol) in $CDCl_3$ (0.6 M) at −78 °C was added CH_2I_2 (24 μL, 0.30 mmol). Three hours at room temperature was required for complete conversion to **13**. Spectra (^1H and ^{13}C NMR) were then acquired at −70 °C and were essentially the same as those obtained with route 1.

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)(iodomethyl)zinc Iodide (13) via Route 3. The sample of **11** (0.30 mmol) from above at 0 °C was added via cannula to a septum-capped NMR tube under argon containing I_2 (76 mg, 0.30 mmol) at 0 °C. Complete dissolution of the I_2 required ∼5 min at 0 °C, at which point the sample was cooled to −70 °C for the acquisition of ^1H and ^{13}C NMR spectra. These indicated the presence of both **11** and **13**.

NMR Spectra of ((*R*)-(1*l*,2*l*,3*u*,4*u*)-2,3-Dimethoxy-4,7,7-trimethylbicyclo[2.2.1]heptane)(iodomethyl)zinc Iodide (13) via Route 4. The sample of **6** (0.30 mmol) from above at −78 °C was added via cannula to a septum-capped NMR tube under argon containing I_2 (76 mg, 0.30 mmol) at −78 °C. The contents of the tube were warmed to 0 °C and mixed for 2−3 min, at which point complete dissolution of the I_2 occurred. After 5 min at 0 °C, the tube was placed in the NMR probe at −70 °C, and the spectra were acquired. While **13** was present, the was an appreciable amount of **12** as well as a small quantity another compound which was not assignable.

(1*R*,2*R*)-2-Phenylcyclopropanemethanol (8). In Situ Generation of Zinc Iodide. To a flame-dried, 15 mL, two-necked, round-bottom flask (flask A) equipped with a stir bar, septum, and argon inlet were added cinnamyl alcohol (134 mg, 1.00 mmol) and promoter **7** (27 mg, 0.10 mmol, 0.10 equiv). Vacuum (∼0.1 mm) was applied for ∼30 s, and then the flask was put under an atmosphere of argon. This was repeated twice followed by the addition of CH_2Cl_2 (3 mL). The solution was cooled under argon to 0 °C, and diethylzinc (113 μL, 1.10 mmol, 1.10 equiv) was added. The solution was stirred at 0 °C for 10 min. To a flame-dried, 25 mL, two-necked, round-bottom flask (flask B) equipped with a stir bar, septum, and argon inlet were added iodine (508 mg, 2.00 mmol, 2.00 equiv) and CH_2Cl_2 (10 mL). The suspension was cooled under argon to 0 °C, and diethylzinc (103 μL, 1.00 mmol, 1.00 equiv) was added. A thick, white precipitate immediately formed, occassionally exhibiting a purple tint. The slurry was stirred at 0 °C for 10 min. To a flame-dried, 100 mL, two-necked, round-bottom flask (flask C) equipped with a stir bar, septum, and argon inlet were added diiodomethane (161 μL, 2.00 mmol, 2.00 equiv) and CH_2Cl_2 (24 mL). The solution was cooled to 0 °C, and diethylzinc (103 μL, 1.00 mmol, 1.00 equiv) was added with subsequent stirring for 5 min (white precipitate formed

after ~2 min). The contents of flask A were added via cannula over ~30 s to flask B. The resulting thick, white slurry was stirred at 0 °C for 2 min and was transferred in like manner to flask C. The mixture was a thick white slurry and was maintained at 0 °C. Reaction progress was monitored periodically as follows: an aliquot (5-10 drops) was removed via cannula into a precooled (0 °C) solution of CH_2Cl_2 (0.5 mL) containing TMEDA (5 drops); after washing with 2 N HCl (0.5 mL), this solution was passed through a small plug of Florisil (~1/8 in.), followed by EtOAc (0.5 mL); this solution was then assayed by GC (U2, isothermal 180 °C, t_R 5.9 min). The reaction was quenched at 0 °C after 45 min with 2 N NaOH (13 mL). The organic layer was removed, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The product was then purified by flash chromatograpy (hexane/EtOAc, 3/1) followed by bulb-to-bulb distillation to yield 136 mg (92%) of product as a clear, colorless liquid. Data for **8**: (see ref 19 for full characterization of **8**) ^{1}H NMR (400 MHz, $CDCl_3$) 7.30−7.24 (m, 2 H), 7.20−7.14 (m, 1 H), 7.10−7.06 (m, 2 H), 3.67−3.56 (ddd, J = 6.8, J = 11.2, J = 18.1, 2 H), 1.86−1.79 (td, J_t = 4.6, J_d = 9.3, 1 H), 1.84−1.79 (t, J = 4.5, 1 H), 1.50−1.42 (m, 1 H), 1.01−0.90 (m, 2 H); HPLC t_R (1*R*,2*R*)-**8**, 23.1 min (94.9%); t_R (1*S*,2*S*)-**8**, 29.8 min (5.1%) (89% ee) (Daicel OJ, hexane/*i*-PrOH, 98/2, 1.0 mL/min). Anal. Calcd for $C_{10}H_{12}O$ (148.21): C, 81.04; H, 8.16. Found: C, 80.74; H, 8.26.

(1*R*,2*R*)-2-Phenylcyclopropanemethanol (8). General Procedure for Use with and without Additives. In a flame-dried, 25 mL, two-necked, round-bottom flask (flask A) equipped with a stir bar, septum, and argon inlet were combined cinnamyl alcohol (41 mg, 0.30 mmol), promoter **7** (9 mg, 0.03 mmol, 0.10 equiv), and 1.00 equiv of an anhydrous solid from Table 1. The corresponding reaction was also run in the absence of any additive. Vacuum (~0.1 mm) was applied for ~30 s, and then the flask was put under an atmosphere of argon. This was repeated twice followed by the addition of CH_2Cl_2 (4 mL). The suspension was cooled under argon to 0 °C, and diethylzinc (34 μL, 0.33 mmol, 1.10 equiv) was added and the mixture maintained at 0 °C for 30 min. To a second 25 mL, two-necked, round-bottom flask (flask B) similarly equipped were added CH_2Cl_2 (7 mL) and diiodomethane (49 μL, 0.60 mmol, 2.00 equiv) and the contents cooled under argon to 0 °C. Diethylzinc (31 μL, 0.30 mmol, 1.00 equiv) was added to give a white slurry after 1-2 min. After 5 min at 0 °C, the contents of flask A were transferred via cannula over ~30 s to flask B. The mixture was a thick slurry and was maintained at 0 °C with periodic assays as described above in the procedure for In Situ Generation of Zinc Iodide. After 30 min at 0 °C, as described above in the procedure for In Situ Generation of Zinc Iodide, the reaction was quenched, the product isolated and purified, and the enantiomeric excess determined. (See Table 1 for results).

(1*R*,2*R*)-2-Phenylcyclopropanemethanol (8). Route 1. In a flame-dried, 25 mL, two-necked, round-bottom flask (flask A) equipped with a stir bar, septum, and argon inlet were combined cinnamyl alcohol (41 mg, 0.30 mmol) and promoter **7** (9 mg, 0.03 mmol, 0.10 equiv). Vacuum (~0.1 mm) was applied for ~30 s, and then the flask was put under an atmosphere of argon. This was repeated twice followed by the addition of CH_2Cl_2 (4 mL). The suspension was cooled under argon to 0 °C, and diethylzinc (34 μL, 0.33 mmol, 1.10 equiv) was added to give a clear, colorless solution which was maintained at 0 °C for 30 min. To a second 25 mL, two-necked, round-bottom flask (flask B) similarly equipped were added iodine (152 mg, 0.60 mmol, 2.00 equiv) and CH_2Cl_2 (7 mL) and the contents cooled under argon to 0 °C. Diethylzinc (31 μL, 0.30 mmol, 1.00 equiv) was added to give a slurry with a slight purple tint. After 10 min at 0 °C, an additional quantity of diethylzinc (31 μL, 0.30 mmol, 1.00 equiv) was added followed by diiodomethane (40 μL, 0.60 mmol, 2.00 equiv). After an additional 5 min at 0 °C, the contents of flask A were transferred via cannula over ~30 s to flask B. The mixture was a thick white slurry and was maintained at 0 °C with periodic assays as described above in the procedure for In Situ Generation of Zinc Iodide. After 30 min at 0 °C, as described above in the procedure for In Situ Generation of Zinc Iodide, the reaction was quenched, the product isolated and purified, and the enantiomeric excess determined. Data for **8**: HPLC t_R (1*R*,2*R*)-**8**, 21.8 min (93.4%); t_R (1*S*,2*S*)-**8**, 28.4 min (6.6%) (86% ee) (Daicel OJ, hexane/*i*-PrOH, 98/2, 1.0 mL/min).

(1*R*,2*R*)-2-Phenylcyclopropanemethanol (8). Route 2. The contents of flask A were prepared as described above for route 1. To a second 25 mL, two-necked, round-bottom flask (flask B) similarly equipped were added iodine (152 mg, 0.60 mmol, 2.00 equiv) and CH_2Cl_2 (7 mL) and the contents cooled under argon to 0 °C. Diethylzinc (62 μL, 0.60 mmol, 2.00 equiv) was added to give a white slurry. After 5 min at 0 °C, diiodomethane (49 μL, 0.60 mmol, 2.00 equiv) was added, again producing a white slurry. After an additional 5 min at 0 °C, the contents of flask A were transferred via cannula over ~30 s to flask B. The mixture was a thick white slurry and was maintained at 0 °C with periodic assays as described above in the procedure for In Situ Generation of Zinc Iodide. After 30 min at 0 °C, as described above in the procedure for In Situ Generation of Zinc Iodide, the reaction was quenched, the product isolated and purified, and the enantiomeric excess determined. Data for **8**: HPLC t_R (1*R*,2*R*)-**8**, 21.6 min (93.1%); t_R (1*S*,2*S*)-**8**, 28.1 min (6.9%) (86% ee) (Daicel OJ, hexane/*i*-PrOH, 98/2, 1.0 mL/min).

(1*R*,2*R*)-2-Phenylcyclopropanemethanol (8). Route 3. The contents of flask A were prepared as described above for route 1. To a second 25 mL, two-necked, round-bottom flask (flask B) similarly equipped were added CH_2Cl_2 (7 mL) and diiodomethane (49 μL, 0.60 mmol, 2.00 equiv) and the contents cooled under argon to 0 °C. Diethylzinc (62 μL, 0.60 mmol, 2.00 equiv) was added. After 5 min at 0 °C, at which point a small amount of white precipitate had formed, iodine (152 mg, 0.60 mmol, 2.00 equiv) was added to give a thick slurry with a slight purple tint. After an additional 5 min at 0 °C, the contents of flask A were transferred via cannula over ~30 s to flask B. The mixture was a thick white slurry and was maintained at 0 °C with periodic assays as described above in the procedure for In Situ Generation of Zinc Iodide. After 30 min at 0 °C, as described above in the procedure for In Situ Generation of Zinc Iodide, the reaction was quenched, the product isolated and purified, and the enantiomeric excess determined. Data for **8**: HPLC t_R (1*R*,2*R*)-**8**, 21.8 min (86.9%); t_R (1*S*,2*S*)-**8**, 28.0 min (13.1%) (73% ee) (Daicel OJ, hexane/*i*-PrOH, 98/2, 1.0 mL/min).

(1*R*,2*R*)-2-Phenylcyclopropanemethanol (8). Route 4. The contents of flask A were prepared as described above for route 1. To a second 25 mL, two-necked, round-bottom flask (flask B) similarly equipped was added CH_2Cl_2 (7 mL) and diiodomethane (98 μL, 1.20 mmol, 4.00 equiv) and the contents cooled under argon to 0 °C. Diethylzinc (62 μL, 0.60 mmol, 2.00 equiv) was added to produce a thick white slurry in 1-2 min. After 5 min at 0 °C, iodine (152 mg, 0.60 mmol, 2.00 equiv) was added to give a thick slurry with a purple tint. After an additional 5 min at 0 °C, the contents of flask A were transferred via cannula over ~30 s to flask B. The mixture was a thick white slurry and was maintained at 0 °C with periodic assays as described above in the procedure for In Situ Generation of Zinc Iodide. After 30 min at 0 °C, as described above in the procedure for In Situ Generation of Zinc Iodide, the reaction was quenched, the product isolated and purified, and the enantiomeric excess determined. Data for **8**: HPLC t_R (1*R*,2*R*)-**8**, 22.4 min (61.8%); t_R (1*S*,2*S*)-**8**, 27.8 min (38.2%) (23% ee) (Daicel OJ, hexane/*i*-PrOH, 98/2, 1.0 mL/min).

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Supporting Information Available: The experimental procedures along with the ^{1}H and ^{13}C NMR spctra for the various complexes and exchange experiments are provided (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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