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Catalytic Enantioselective Cyclopropanation with Bis(halomethyl)zinc Reagents. I. Optimization of Reaction Protocol

Scott E. Denmark*, Beritte L. Christenson, Diane M. Coe and Stephen P. O'Connor

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

***Key Words** : Allylic alcohol, diethylzinc, bis(iodomethyl)zinc, cyclopropanation*

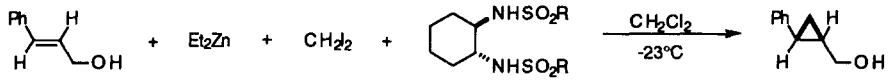
***Abstract:** The rate and selectivity of catalytic enantioselective cyclopropanation of cinnamyl alcohol utilizing bis-iodomethyl zinc and **4a/4b** is greatly dependent on the order of addition of the reagents. The independent pre-formation of the ethylzinc cinnamyloxide and bis(iodomethyl)zinc was found to be crucial. The reaction displayed autocatalytic behavior which was shown to be due to the generation of zinc iodide.*

The development of catalytic enantioselective carbon-carbon bond forming reactions is arguably one of the most important challenges in organic synthesis. Within this vast subclass, those transformations capable of creating two carbon-carbon bonds, e.g. cycloadditions ([4+2], [2+2], [2+1]), are of particular interest. Because of their importance as synthetic targets and intermediates and in physical organic studies, cyclopropanes have attracted a great deal of attention.[1] Our efforts have been focused on the development of reagents for catalytic, enantioselective cyclopropanation using the Furukawa modification[2] of the Simmons-Smith reaction.[3] In laying the groundwork for this enterprise we have disclosed: (1) structural studies of the species present in solution,[4] (2) the first X-ray crystallographic analysis of a bis(iodomethyl)zinc compound,[4] (3) solvent effects, substrate generality, reagent types [$Zn(CH_2Cl)_2$ vs. $Zn(CH_2I)_2$], and heteroatom-directing effects,[5] and (4) a preliminary study of the influence of chiral amino alcohols on the cyclopropanation of cinnamyl alcohol.[6]

The modest selectivity obtained in these early studies with chiral amino alcohols revealed that strongly Lewis basic ligands are not practical as catalysts for cyclopropanation. We then turned our attention to less Lewis basic species such as chiral bis(sulfonamides) in cyclopropanation where bis(iodomethyl)zinc is the active methylene-delivering reagent. Early studies with the bis(benzenesulfonamide) and bis(4-nitrobenzene-sulfonamide) (**4a**) of (*R*,*R*)-1,2-cyclohexanediamine were also disappointing (25-30% e.e.). A report by Kobayashi et. al. of much higher enantioselectivities (75-80% e.e.) using the same promoters clearly implicated the importance of reaction protocol on selectivity.[7] In view of the potential complexity of the catalytic process and the multiplicity of species involved, we have initiated an extensive study of the effect of experimental variables (methylene source, solvent, additives, temperature, order of addition, reagent combinations) on the rate and selectivity of reaction. A portion of that study is described herein. The following Letter describes an extensive survey of the promoter structure and its effect on rate and selectivity using one of the standard protocols developed in the present investigation.

Cinnamyl alcohol was used as the test substrate since both the optical rotation[8] and an HPLC method[7] for the determination of the enantiomeric excess of product **5** are known. The overall reaction entails the combination of cinnamyl alcohol (**1**), diethylzinc (**2**), diiodomethane (**3**), and a promoter (**4a**, **4b**) as shown in Table I. A number of combination protocols of these compounds were investigated, some of which are shown below. All reactions were carried out at -23°C under an atmosphere of argon in either methylene chloride or 1,2-dichloroethane with either promoter **4a** or **4b** at 10 mol % loading. The determination of product enantiomeric excess (HPLC)[9] and analysis of the rate of reaction (GC)[10] were used to assay each protocol.

Table I. Asymmetric cyclopropanation of cinnamyl alcohol with different protocols.



1 **2** **3** **4a** R = 4-NO_2-C_6H_4 **4b** R = CH_3 **5**

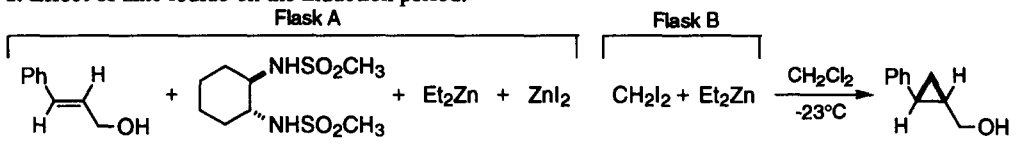
protocol	flask A[a]	flask B[a]	flask C	addition order	promoter	$t_{1/2}$(min)[b]	ee, %[c]
I	**1** (1.0 eq)	**4** (0.1 eq)	**3** (2.0 eq)	(i) B to C	**4b**	120	26
		2 (0.1 eq)	**2** (1.0 eq)	(ii) A to C			
II	**1** (1.0 eq)	**3** (2.0 eq)	-	(i) A to B	**4b**	>330	0
	4 (0.1 eq)	**2** (1.0 eq)			**4b**[f]	118	36
III	**1** (1.0 eq)	**4** (0.1 eq)	**3** (2.0 eq)	(i) B to C	**4b**	45	74
	2 (1.0 eq)	**2** (0.1 eq)	**2** (1.0 eq)	(ii) A to C			
IV	**1** (1.0 eq)	**4** (0.1 eq)	**3** (2.0 eq)	(i) A to B	**4b**	40	75
	2 (1.0 eq)		**2** (1.0 eq)	(ii) (A + B) to C			
V	**1** (1.0 eq)	**3** (2.0 eq)	-	(i) A to B	**4a**	60	76
	4 (0.1 eq)	**2** (1.0 eq)			**4b**	55	80
	2 (1.1eq)				**4a**[d]	35	45
VI	**1** (1.0 eq)	**4** (0.1 eq)	-	(i) A to B	**4b**	85	74
	2 (1.0 eq)	**3** (2.0 eq)					
		2 (1.0 eq)					
VII	**1** (1.0 eq)	-	-	-	**4a**	95	71
	4 (0.1 eq)				**4a**[d]	270	47
	2 (2.0 eq)				**4a**[e]	300	47
	3 (3.0 eq)				**4b**	72	68

[a] Added in descending order. [b] Time to 50% conversion. See ref. 10. [c] See ref. 9. [d] $ClCH_2I$ was used. [e] $(CH_2Cl)_2$ was the solvent. [f] Used 2.0 equiv **2** and 4.0 equiv **3**.

Our initial objective (as manifest in Protocols I and II) was to investigate the ability of **4** to promote the cyclopropanation of **1**. Control experiments revealed that reactions in the absence of **4** were considerably slower. The major difference between our procedure and that of Kobayashi (Protocol VII) was that our methods always employ preformed $Zn(CH_2I)_2$; in Protocol VII the CH_2I_2 is added last. In addition, we surmised that formation of the zinc alkoxide of cinnamyl alcohol might be necessary for optimum selectivity and reproducibility. This

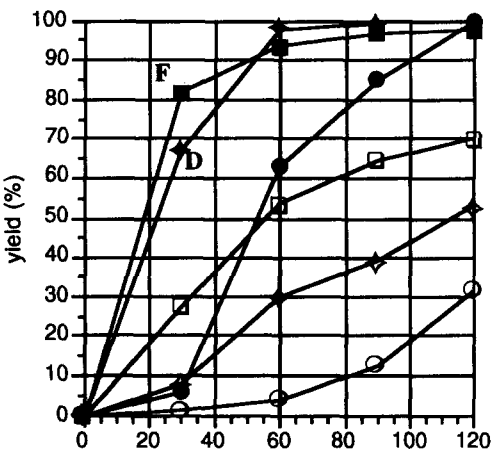
hypothesis was borne out by the success of Protocols III and IV which also served to illustrate that **4** need not be deprotonated. Protocols V and VI showed that the promoter **4** could be added to either the substrate flask or the reagent flask with minimal effect on the results. Protocol V (with **4** in the substrate flask) was slightly superior and more reproducible. While we could at times achieve reasonable levels of enantioselectivity with Protocol VII,[7a] in our hands this one-pot procedure led to variable results. In all of the Protocols surveyed, the use of $Zn(CH_2Cl)_2$ led to significantly lower selectivity. Examination of other solvents (1,2-dichloroethane, toluene, Et_2O, CH_3CN) was similarly unproductive as reactions were much slower or less selective. Under similar conditions **4b** was marginally superior to **4a** (see accompanying Letter).

Figure 1. Effect of zinc iodide on the induction period.



	1	4a	2		3	2	5
reaction	**1**	**4a**	**2**	ZnI_2	**3**	**2**	**5**, e.e., %
A (○)	1.0	-	1.1	-	2.0	1.0	-
B (●)	1.0	0.1	1.1	-	2.0	1.0	80
C (◇)	1.0	-	1.1	0.1	2.0	1.0	-
D (◆)	1.0	0.1	1.1	0.1	2.0	1.0	78
E (□)	1.0	-	1.1	1.0	2.0	1.0	-
F (■)	1.0	0.1	1.1	1.0	2.0	1.0	86

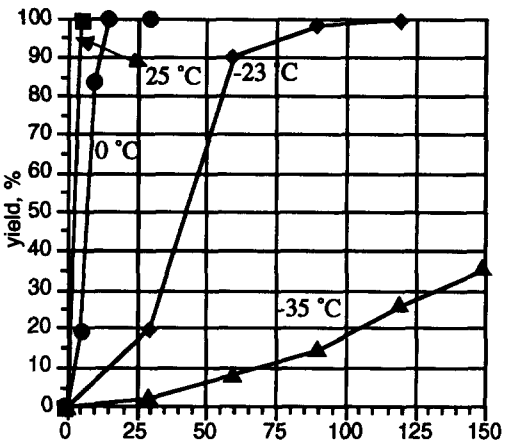
Careful monitoring of both the unpromoted and the promoted reactions revealed an early induction period during which little conversion was observed followed by rapid production of **5** (curves A and B, Figure 1). This led to the hypothesis of autocatalysis which implicated an important role for ZnI_2, the only by-product of the reaction. We reasoned that as the reaction proceeded, the zinc iodide produced aided in the generation of a catalytically active species. We were gratified to observe that the addition of 10 mol % of ZnI_2 eliminated the induction period for both the unpromoted (curve C) and the promoted (curve D) reactions. Surprisingly, despite the poor solubility of ZnI_2, a full equiv (curves E and F) had a still more pronounced rate effect, and also *increased the enantioselectivity to 86% ee!*



We have examined the effect of temperature upon reaction rate and selectivity. As expected, the rate, as indicated by $t_{1/2}$, was dramatically reduced at lower temperatures (see Figure 2). Unfortunately, the effect of lower reaction temperatures on selectivity was disappointing. At -35 °C, the selectivity actually dropped (64% ee), possibly reflecting a greater decrease in the rate of the promoted (enantioselective) process while leaving the background reaction less affected. However, we cannot rule out an unselective process, promoted by the sulfonamides, which becomes more dominant as the temperature is lowered. At -23°C, 0°C, and 25°C, the product enantiomeric excesses showed little variation (81, 80, and 78% ee, respectively).

Figure 2. Effect of temperature on rate and selectivity.

reaction	temperature	$t_{1/2}$ (min)	e.e., %
A (■)	25 °C	<3	78
B (●)	0 °C	7	80
C (◆)	-23 °C	43	81
D (▲)	-35 °C	185	64



In conclusion, we have established that both *prior formation of a zinc alkoxide and the use of added ZnI_2 are critical for effective catalytic enantioselective cyclopropanation of allylic alcohols using chiral bis(sulfonamides.* In the following paper the effect of promoter structure on reaction selectivity is presented.

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(9) HPLC detemination of enantiomeric excess: Daicel Chiralcel OJ (25 cm x 0.46 mm), hexane/isopropyl alcohol, 98/2, 1 mL/min; t_R ((*1R,2R*)-2-phenylcyclopropanemethanol) 27 min; t_R ((*1S,2S*)-2-phenylcyclopropanemethanol) 32-33 min; t_R (cinnamyl alcohol) 44-45 min.

(10) Reaction progress was monitored as follows: an aliquot (10-20 drops) was removed via cannula into a precooled (-23°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") followed by EtOAc (0.5 mL); GC analysis was then performed (Hewlett-Packard 5890, HP-U2 (50 m x 0.2 mm), 180°C isothermal; t_R (cinnamyl alcohol) 8.1 min, t_R (*trans*-2-phenylcyclopropanemethanol) 11.9 min).

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