Pergamon

Tetrahedron 54 (1998) 349–358

TETRAHEDRON

Iron Lewis Acid Catalyzed Reactions of Phenyldiazomethane with Aromatic Aldehydes

Syed J. Mahmood, Anjan K. Saha and M. Mahmun Hossain*

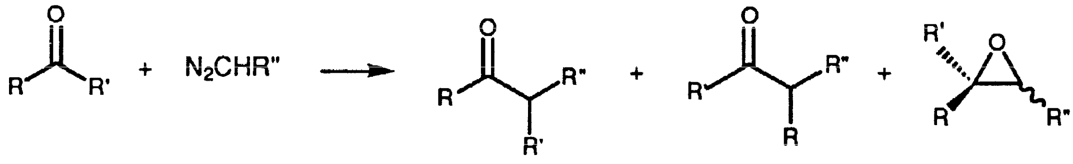
Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI 53201

Received 23 June 1997; revised 5 October 1997; accepted 28 October 1997

Abstract: The iron Lewis acid **1** was found to catalyze reactions of phenyldiazomethane and aromatic aldehydes to give *cis*-epoxides along with the corresponding ketones. The yield of the epoxide increased with electron-withdrawing substituents on the aldehyde, while little or no epoxide was formed with electron-donating substituents. The reaction was found to go through the coordination of the aldehyde to the iron Lewis acid instead of a carbene intermediate. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

In general, diazo compounds are known to react with aldehydes and ketones with or without a catalyst to form homologated carbonyl products and epoxides (eq. 1).[1] The reaction was not synthetically useful until recently, when Anselme et al. reported[2] the lithium bromide catalyzed homologation of aldehydes with aryldiazomethane to give only β-diketones in excellent yield. Later, Roskamp[3] reported that aldehydes also react with ethyldiazoacetate to form mainly β-ketoesters with moderate to fairly good yields (eq. 2). This reaction was catalyzed by a variety of Lewis acids (e.g., BF_3, $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $SnCl_2$, $GeCl_2$, $SnCl_4$).



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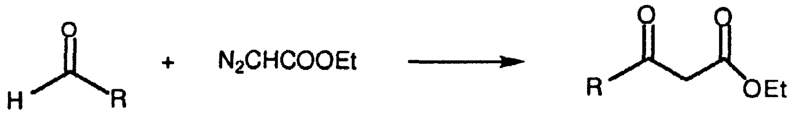

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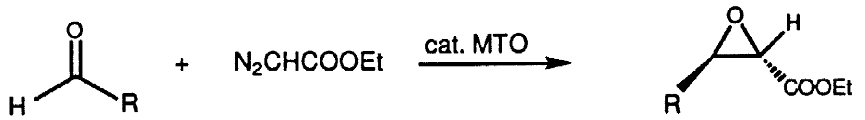
* Corresponding author. E-mail: mahmun@csd.uwm.edu

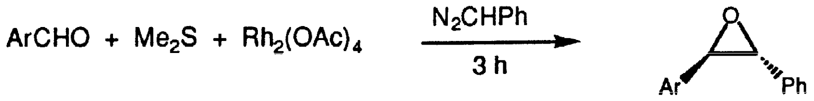
PII: S0040-4020(97)10287-3

The reaction of diazo compounds with aldehydes was also investigated in the presence of transition-metal catalysts and, recently, Espenson et al. reported[4] the synthesis of *trans*-epoxides from aldehydes and ethyldiazoacetate using methylrhenium trioxide as a catalyst (eq. 3).



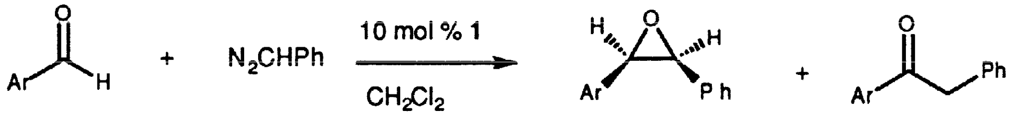
(3)

Later, Aggarwal et al.[5] reported direct synthesis of asymmetric epoxides from aldehydes and phenyldiazomethane using catalytic amounts of enantiomerically pure sulfides and $Rh_2(OAc)_2$ (eq. 4).



(4)

Herein, we wish to discuss our results from the iron Lewis acid **1** catalyzed reactions of aromatic aldehydes **2** with phenyldiazomethane **3** in the formation of *cis*-epoxides **4** and corresponding ketones **5**, respectively (eq. 5).



(5)

2a, Ar=Ph **3** **4** **5**
2b, Ar=*p*-ClPh
2c, Ar=*p*-NO_2Ph
2d, Ar=*p*-CF_3Ph
2e, Ar=*p*-CH_3Ph
2f, Ar=*p*-OCH_3Ph

Results and Discussion

The Lewis acid (η^5-C_5H_5)$Fe^+(CO)_2(THF)BF_4^-$ was prepared by protonation[6] of the known methyl complex at -78° C in THF, which, in turn, was easily synthesized in two steps in high yield from the commercially available iron dimer.[7] In the initial stages we studied the reactions of benzaldehyde with phenyldiazomethane to optimize the conditions of the reaction. Recent results are summarized in Table 1. In the absence of the catalyst, no epoxide was formed, although we got 17 % of the corresponding ketone (Run 1). When phenyldiazomethane was added all at once rather than dropwise in the presence of 10 mol % catalyst, trace amounts of *cis*-epoxide and 65 % of the ketone were isolated (Run 2). Dropwise addition of phenyldiazomethane improved the yield of *cis*-epoxide to 28%. Runs

3, 8 and 9 were performed to find the optimum catalyst concentration for the highest yield of epoxides from benzaldehyde and phenyldiazomethane, a 10 mol % catalyst concentration was found to be the best. In our effort to improve epoxide yield, we decided to run the reaction at different temperatures (Runs 3-7). At 45^0 C no epoxide was formed. As we lowered the temperature, the yield of epoxide gradually decreased. The best results were obtained when the reaction was run at room temperature. Increase of aldehyde concentration decreased the yield of epoxide but increased the yield of the ketone (Run 10, 11), and ease in epoxide formation (30%) was observed when 1.4 -2 equiv. of diazo was used (Runs 12, 13).

Table 1: Isolated Yield of Epoxides and Ketones From Reaction of Benzaldehyde and Phenyldiazomethane Catalyzed by $(\eta^5\text{-}C_5H_5)Fe^+(CO)_2(THF)BF_4^-$.

RUN	Mol% catalyst	Aldehyde (eq)	Diazo (eq)	Time of add^n	(Hrs.) after add^n	Temp (^{0}C)	% Epoxide[b]	Yield[a] Ketone[b]
1	0	1	1	1 time	18	RT	-	17
2	10	1	1	1 time	18	RT	trace	65
3	10	1	1	6-7	12	RT	28	45
4	10	1	1	6-7	12	45	0	45
5	10	1	1	6-7	12	-78	4	55
6	10	1	1	6-7	12	-30	10	55
7	10	1	1	6-7	12	0-(-5)	17	45
8	20	1	1	6-7	12	RT	24	57
9	40	1	1	6-7	12	RT	24	45
10	10	2	1	6-7	12	RT	14	55
11	10	5	1	6-7	12	RT	12	60
12	10	1	1.4	6-7	12	RT	30	55
13	10	1	2	6-7	12	RT	30	56

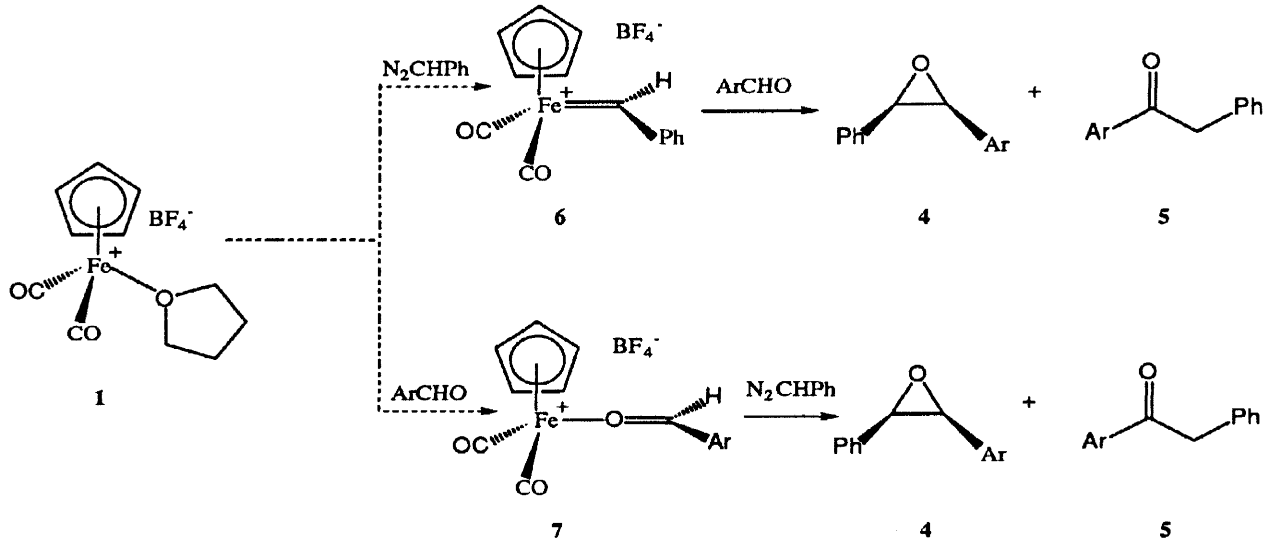
[a] Isolated yield. [b] Identified by comparing the ^{1}H NMR spectra to those of known compounds[8,9]

Next, we decided to see if the yield of epoxide could be improved by putting electron-withdrawing or electron-donating substituents on the aldehyde. These results are summarized in Table 2. Runs 1-3 clearly demonstrate that electron withdrawing groups on the aldehyde enhance the yield of epoxide, and the opposite trend is observed with electron-donating substituents (Runs 4 and 5). The reactions with electron-donating aldehydes were found to be slow and 20-30% of starting aldehydes were isolated from the reaction mixtures and no decomposed products from corresponding epoxides were isolated.

Table 2 : Isolated Yield of Epoxides and Ketones from Reactions of Substituted Benzaldehydes and Phenyldiazomethane Catalyzed by $(\eta^5\text{-}C_5H_5)Fe^+(CO)_2(THF)BF_4^-$.

RUN	Aldehyde (eq)	Diazo (eq)	Time of add^n	(Hrs) after add^n	Temp (^{0}C)	% Epoxide	Yield^a Ketone
1	*p*-Cl	1.4	6-7	6	RT	36^b	50^c
2	*p*-NO_2	1.4	6-7	6	RT	42^b	43^c
3	*p*-CF_3	1.4	6-7	6	RT	42^d	44^e
4	*p*-CH_3	1.4	6-7	6	RT	trace	52^{c,e}
5	*p*-OCH_3	1.4	6-7	6	RT	-	55^{c,e}

[a] Isolated yield. 5-10% of *cis/trans* stilbenes along with 10-15% of azine were also isolated.[10] [b,c,e] Identified by comparing ^1H NMR spectra to those of known compounds.[8,9,11] [d] Identified from ^1H NMR and CH analysis: ^1H NMR ($CDCl_3$): δ 4.43 (1 H, J= 4.25 Hz), 4.39 (1 H, d, J= 4.25 Hz), 7.10-8.20 (9H, m). CH analysis: C, 68.39%; H, 3.94%; calculated C, 68.18%; H, 4.19%. [e] 20-30% of unreacted aldehydes were also isolated from the reaction.

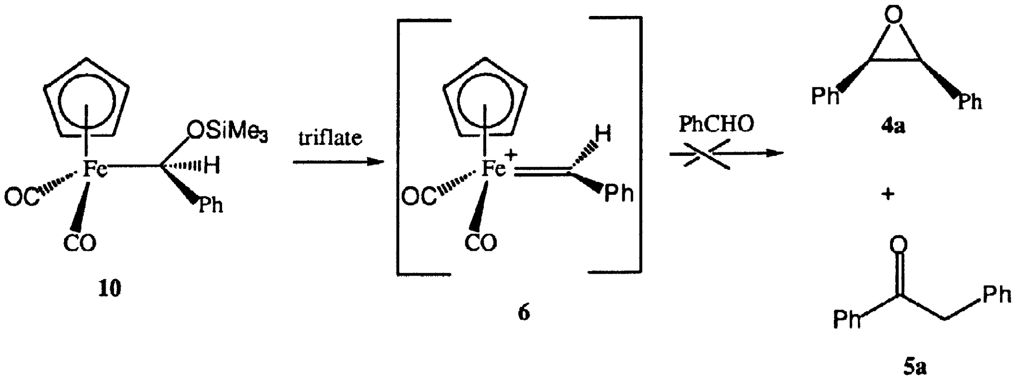


Scheme I

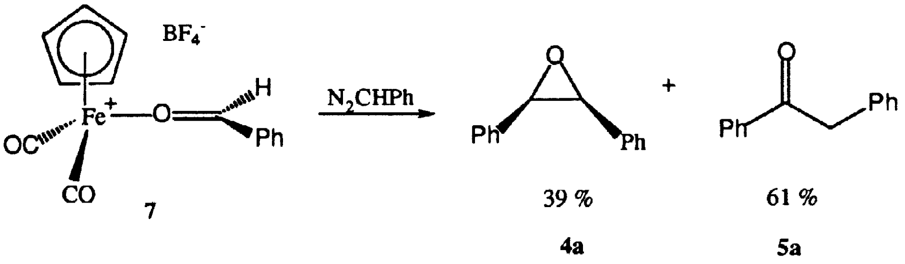
In this catalytic reaction, two possible routes exist for the synthesis of epoxides and corresponding ketones. The first possibility is the formation of metal carbene complex **6** (Scheme I) from the reaction between iron Lewis acid **1** and the diazo compound **3**,[10a,b] then the carbene **6** reacts with an aldehyde **2** to produce epoxide **4** and ketone

5. The other possibility is the formation of an aldehyde adduct **7**, from the Lewis acid **1** and the aldehyde, and the subsequent reaction with the diazo compound produces epoxide **4** and ketone **5**, respectively (Scheme I).

In order to verify the involvement of a possible carbene mechanism, we synthesized the benzylidine carbene complex **6** (Scheme II) using the procedure developed in our laboratory.[12] The carbene was purified by crystallization at -78°C and then treated with benzaldehyde. The reaction mixture was slowly warmed to room temperature. Formation of either epoxide **4a** or ketone **5a** was not observed (Scheme II). Consequently, the known benzaldehyde complex **7**[13] (Scheme III) was prepared by the reaction between benzaldehyde and iron Lewis acid **1** in CH_2Cl_2. The σ-benzaldehyde complex **7** was then treated with the phenyldiazomethane. The reaction resulted in the formation of both epoxide **4a** and ketone **5a** in about 1:2 ratio, which was same as observed from catalytic reactions (runs 12,13; Table 1). This strongly implicates a benzaldehyde coordination mechanism rather than a carbene mechanism.



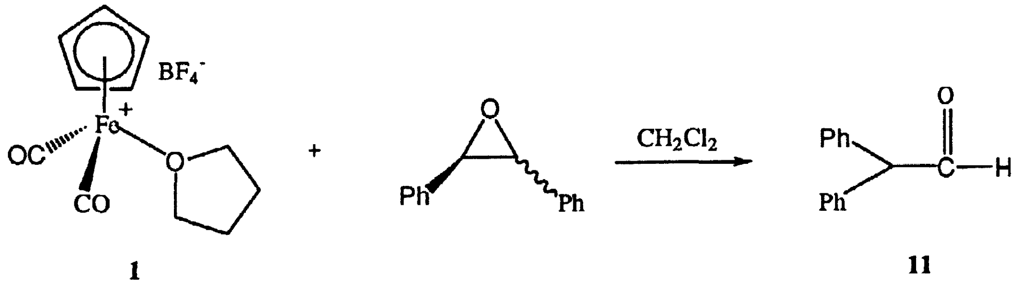
Scheme II



Scheme III

The next question was whether the ketone was forming via a ring-opening rearrangement reaction[14] of the epoxide or as a side product of the reaction from a common intermediate . When the *cis*-epoxide or *trans*-epoxide was treated in presence of the 10 mole% iron Lewis acid at room temperature, formation of only aldehyde **11** in 91-

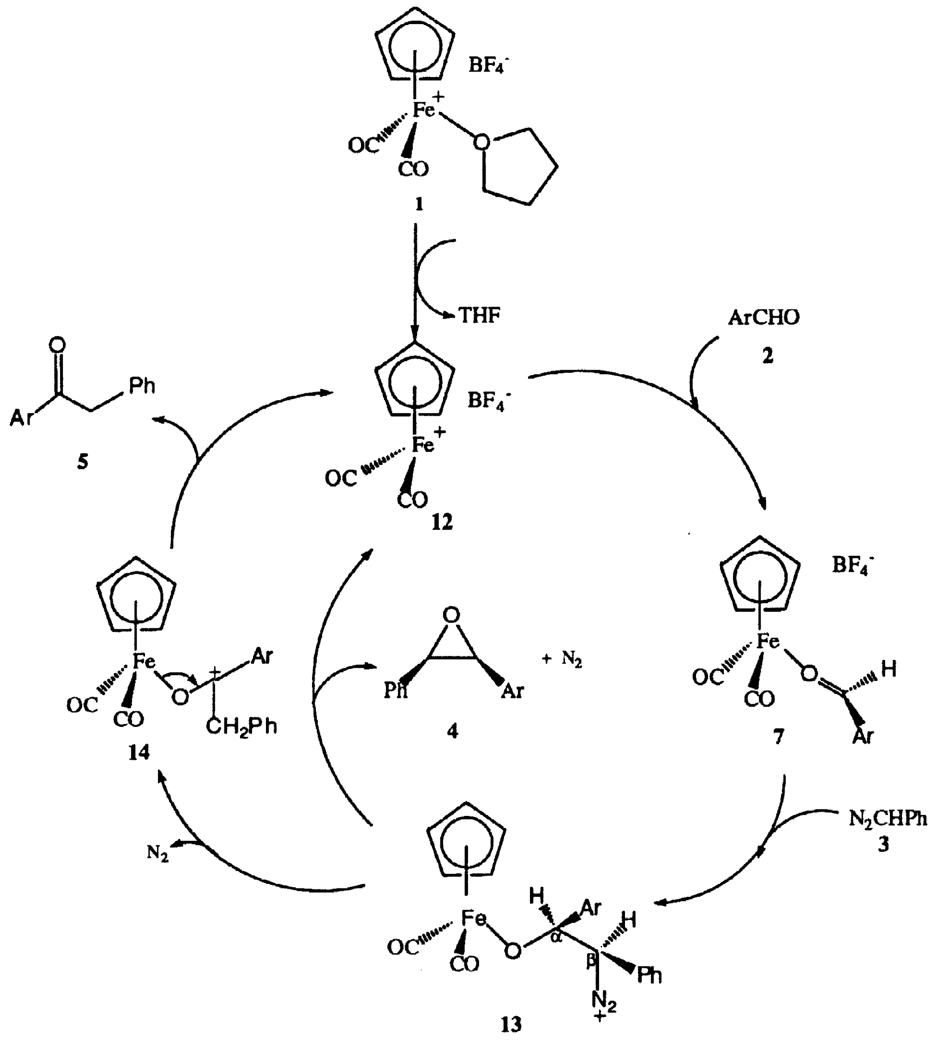
98% was observed, no ketone **5a** was isolated from the reaction (Scheme IV). This strongly suggests that the formation of ketones is a competitive reaction, rather than a by-product from the corresponding epoxides.



Scheme IV

On the basis of our experimental observations, we propose the following plausible catalytic cycle (Scheme V) for the formation of epoxides and ketones from the iron Lewis acid **1**, aromatic aldehydes and phenyldiazomethane. In the proposed cycle, the iron Lewis acid **1** dissociates the weakly bound THF ligand to produce highly reactive 16 e$^-$ complex **12**, which has a vacant coordination site for the aldehyde to bind, producing the σ-bonded aldehyde complex **7**. The absence of epoxide formation using THF as a solvent strongly suggests an initial dissociation of the THF ligand to form **12** as a key step in the catalytic cycle. Nucleophilic attack of phenyldiazomethane to the coordinated aldehyde complex results in the formation of **13**. Expulsion of nitrogen from **13** followed by either ring closure or hydride migration results in the formation of epoxide **4** and ketone **5**, respectively. At this point, we are unable to explain the lack of formation of a corresponding aldehyde by an aryl group migration from the intermediate **13**.

The most important aspect of this reaction was the stereoselectivity of the reaction; only *cis*-epoxide was isolated from the reaction. To the best of our knowledge, these are the first examples of overwhelming *cis* preference in these epoxidation reactions under catalytic conditions. For a benzaldehyde complex, a more stable conformation will be the Ar group *anti* to the Cp group as shown in Scheme V. This is also confirmed by the X-ray diffraction studies done by Protasiewicz on some bezaldehyde iron complexes.[13] The reaction of iron benzaldehyde complex **7** with phenyldiazomethane could lead to the formation of iron-diazo complex **13** where both Ph and Ar would be *cis* to each other but *anti* to the big Cp group, which could collapse very rapidly before any rotation about the C_β-C_α bond to form the *cis*-epoxide. A similar type of mechanism was proposed by Brookhart, Casey and also by us to explain the *cis*-selectivity in cyclopropanation reactions from an iron carbene complex and an alkene.[15]



Scheme V

It is noted that the ratio of epoxide *vs.* ketone formation depends on the nature of the substitutents on benzaldehyde. No epoxide formation was observed with electron-donating substituents on bezaldehyde, but the formation of epoxide was observed with benzaldehyde and yields were increased with electron-withdrawing substituents. The presence of an electron-donating substituent would enhance the hydride migration from the complex **13**, because it would stabilize the resulting carbocation **14**.[16] Whereas, the rate of ring-closure reaction to form epoxides would not be affected by the nature of the substituents. As a result, only ketones are likely to be formed from electron-donating aldehydes. With an electron-withdrawing substituent, the hydride migration will be slower and could be competitive with the rate of the ring-closure reaction. Therefore, both the epoxide and the ketone are likely to be formed.

Conclusion

From our studies, we conclude that cyclopentadienyl dicarbonyl iron Lewis acid also acts as a catalyst for the formation of epoxides from aromatic aldehydes and phenyldiazomethane. The formation of epoxides is stereoselective, i.e. only *cis* -epoxides are formed, no evidence is found for formation of a *trans*-epoxide. All previous examples of epoxidation resulted in the more sterically favored *trans*-epoxides or a mixture of *cis*- and *trans*-epoxides. Currently, work is underway to improve the yield of epoxides using other solvent systems or diazo compounds.

Experimental

General considerations: Infrared spectra were recorded using a Nicolet MX-1 FT-IR spectrometer. Proton and Carbon 13 spectra were obtained on a Bruker 250 MHz NMR spectrometer. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane and $CDCl_3$ was used as the solvent. All organometallic operations were performed under a dry nitrogen atmosphere using standard Schlenk techniques. All of the glass flasks were flamed under vacuum and filled with nitrogen prior to use. Column chromatography was performed using silica gel (40-140 mesh). HPLC reagent grade CH_2Cl_2 was distilled under nitrogen from P_2O_5. HPLC reagent grade pentane was distilled from sodium under an inert atmosphere immediately prior to use. Reagent grade diethyl ether and tetrahydrofuran was freshly distilled under a nitrogen atmosphere from sodium benzophenone ketyl. Benzaldehyde, *p*-tolualdehyde and *p*-anisaldehyde were purified by extraction with sodium bicarbonate solution, washed with water, dried over sodium sulfate and distilled under vacuum. *p*-Nitrobenzaldehyde and *p*-chlorobenzaldehyde were purified by recrystallization from ethanol and then dried under vacuum for several days. α,α,α-Trifluro-*p*-tolualdehyde was purified by distillation. Phenyldiazomethane was synthesized from benzaldehyde following the procedure described by Creary.[17]

Catalytic epoxidation: In a typical experiment, the catalyst was dissolved in 5-6 mL of freshly distilled methylene chloride under nitrogen, then, an appropriate amount of aldehyde was added. Phenyldiazomethane was diluted with 3-4 mL of freshly distilled dichloromethane and was drawn into a gas-tight syringe. It was then added into the reaction mixture dropwise over a period of 6-7 h. with the help of a syringe pump. After the addition was complete, the reaction mixture was allowed to stir for another 6-12 h. The reaction was stopped by adding 9-10 mL of diethyl ether, which caused the catalyst to precipitate from the solution. Any remaining metal moiety was removed by filtration through a plug of silica. The solvent was removed by rotary evaporation and the products were isolated by column chromatography (2-10 % ether in pentane). The products were finally identified by comparing the ^{1}H NMR spectra to those of known compounds.[8,9,11]

Synthesis and reaction of iron carbene with benzaldehyde: A 0.1213 g (0.340 mmol) of the siloxy complex **10** was dissolved in 3 mL of CH_2Cl_2 and cooled to -78^0 C. To this solution 0.490 mL (0.8 equiv) of trimethylsilyltriflate was added. The change of color from yellow to pink suggested the formation of benzylidine carbene complex **6**. The reaction mixture was allowed to stir for 0.5 h at -78^0 C. Pentane was added to precipitate out the carbene complex and the solvent was removed by filter stick. The carbene that formed was repeatedly recrystallized with CH_2Cl_2/pentane at -78^0 C. 3 mL of CH_2Cl_2 was added to dissolve the carbene and 0.1045 g (0.340 mmol) of benzaldehyde was added. The reaction mixture was stirred at -78^0 C and slowly warmed to room temperature. Diethyl ether was added and the metal moiety was removed through a plug of silica. Removal of the solvent gave a red/yellow oil. ^{1}H NMR showed no trace of either *cis*-stilbene oxide **4a** or deoxybenzoin **5a**.

Synthesis and reaction of benzaldehyde complex with phenyldiazomethane: A 0.1245 g (0.370 mmol) sample of iron Lewis acid **1**, 0.786 g (7.41 mmol) of benzaldehyde and 7 mL of CH_2Cl_2 were stirred for 3 h at room temperature. Subsequently, the solvent was removed under reduced pressure and the remaining residue was repeatedly washed with diethyl ether to obtain the σ-bonded complex **7**.[13] ^{1}H NMR (CD_2Cl_2): δ 9.65 (1H, s); 7.61-7.96 (5 H, m) and 5.50 (5 H, s). 1 equiv. of phenyldiazomethane was added all at once to this σ-bonded complex **7** and the resultant mixture was stirred at room temperature for 12 h. From ^{1}H NMR, the product of the reaction was found to be *cis*-stilbene oxide **4a** and deoxybenzoin **5a** in 1:2 ratio.

Reaction of iron Lewis acid with *cis*-or *trans*-stilbene oxide: A 0.0220 g (0.0112 mmol) sample of *cis*-stilbene oxide was added to a solution of the iron Lewis acid (0.0038 g, 0.0011 mmol) in degassed CD_2Cl_2 (0.7 mL) in NMR tube. The reaction was monitored by ^{1}H NMR. After 3 h, the characteristic ^{1}H NMR peak at 4.29 ppm for *cis*-stilbene oxide completely disappeared. The reaction mixture was transferred into a round-bottomed flask and pentane was added to it. It was then chromatographed on a column of silica gel and eluted with diethyl ether. Removal of the solvent gave 0.0215 g (98 %) of 2,2-diphenylacetaldehyde.[14a] The reaction was repeated with *trans*-stilbene oxide and only 2,2-diphenylacetaldehyde was isolated in 91% yield.

Acknowledgement: We gratefully thank the NIH for the partial support of this research.

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