

## Substrate scope in the olefin cyclopropanation reaction catalyzed by $\mu$ -oxo-bis[(salen)iron(III)] complexes\*

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**Abstract:** The cyclopropanation of various alkenes with different diazoester compounds was investigated using two different  $\mu$ -oxo-bis[(salen)iron(III)] complexes, [Fe(3,3',5,5'-<sup>t</sup>Bu<sub>4</sub>salen)]<sub>2</sub>O and [Fe(salen)]<sub>2</sub>O. Ethyl diazoacetate (EDA), *tert*-butyl diazoacetate (<sup>t</sup>BDA), and ethyl diazoacetoacetate (EDAA) were used with mono- and disubstituted terminal olefins (styrene and 1,1-diphenyl ethylene, respectively), internal olefin (*trans*- $\beta$ -methyl styrene), and an electron-rich alkene (*n*-butyl vinyl ether). Moderate-to-good cyclopropanation yields were obtained for most substrates.

### INTRODUCTION

In recent years, the versatility of the cyclopropyl fragment has received considerable importance due to its wide applicability in chemistry and biochemistry, ranging from critical synthetic intermediates and natural products, to being used in the production of insecticides and modern pharmaceuticals [1–4]. Many methods have been developed for the preparation of compounds containing the cyclopropyl moiety, but the most facile synthesis is the metal-mediated cycloaddition of a carbene fragment to an olefin, the olefin cyclopropanation reaction. Numerous metal complexes have been utilized either as stoichiometric metal carbene transfer reagents [5] or as catalysts [3,6]. Iron in particular has been an effective metal in both stoichiometric [5,7–16] and catalytic [17–20] olefin cyclopropanation reactions.

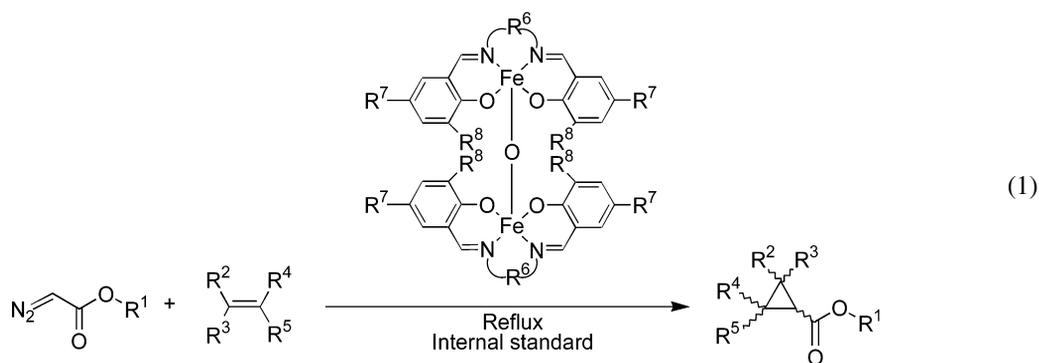
Among the first iron-based cyclopropanation catalysts was the Lewis acid complex [CpFe(CO)<sub>2</sub>(THF)](BF<sub>4</sub>), which was effective for various olefins with ethyl diazoacetate (EDA) or phenyl diazoacetate, as reported by Hossain's group [17,21,22]. Woo, Kodadek, and coworkers utilized various iron(II) and iron(III) porphyrins for olefin cyclopropanation initially with just EDA as the carbene source [18]. A follow-up study showed the application of various other bulky aryl diazo compounds, such as *p*-tolyl diazomethane, mesityl diazomethane, and trimethylsilyl diazomethane, with various porphyrins and related tetradentate iron(II) catalysts [19]. Another class of iron catalysts included the tri-dentate iron(III) and iron(IV) corroles, which catalyzed the cyclopropanation of styrene with EDA and a camphorsulfonic acid-derived carbenoid [20,23]. Generally, all of these reactions had to be carried under an inert atmosphere.

Recently, we reported the successful olefin cyclopropanation with EDA as the carbene source, catalyzed by several  $\mu$ -oxo-bis[(salen)iron(III)] complexes (eq. 1) [24]. This system did not require an inert atmosphere, which made it a convenient and facile route to obtain cyclopropanes. Our catalysts were synthesized from a variety of salen ligands following a literature procedure for the preparation of

\*Plenary and invited lectures presented at the 12<sup>th</sup> IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-12), Toronto, Ontario, Canada, 6–10 July 2003. Other presentations are published in this issue, pp. 453–695.

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$[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})]_2\text{O}$  [salcen = 1,2-cyclohexanediamino- $N,N'$ -bis(salicylidene)] [25]. The optimized reaction conditions were found to be 5 equiv of olefin and 5 mol% catalyst loading, relative to EDA, under reflux conditions in benzene. The tetra-*tert*-butyl salen catalyst with ethylene backbone,  $[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})]_2\text{O}$ , was gauged as the most efficient catalyst out of the series of tetra-substituted  $[\text{Fe}(\text{salen})]_2\text{O}$  catalysts possessing different diamine backbones. Herein, we supplement our earlier report on this catalyst system with a study of other diazoesters as the carbene source. We also expand the substrate scope with the use of a variety of olefins, which includes terminal and internal alkenes, such as styrene and *trans*- $\beta$ -methyl styrene, respectively, as well as 1,1-disubstituted alkenes such as 1,1-diphenylethylene (DPE) and electron-rich olefins such as *n*-butyl vinyl ether (*n*BVE). Two different catalysts have been investigated: the more sterically bulky  $[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})]_2\text{O}$  complex and the less sterically hindered, less soluble, and unsubstituted  $[\text{Fe}(\text{salen})]_2\text{O}$  complex.



## RESULTS AND DISCUSSION

In a typical reaction, the catalyst (5 mol%) and the olefin (5 equiv) were dissolved in benzene (2 or 5 ml, depending on the scale of the diazo precursor, *vide infra*) in a 25-ml, two-neck round-bottom flask equipped with a water-cooled reflux condenser and a magnetic stirbar. A benzene (2 ml) solution containing the diazo compound (0.56 mmol for EDA and  $^t\text{BDA}$  or 0.32 mmol for EDAA) and a gas chromatography internal standard was then slowly added to the reaction over 30 min via a syringe pump. After complete addition of the reagents, the flask was immersed in a preheated oil bath and allowed to reflux. Aliquots (0.2 ml) were periodically taken, passed through a silica gel plug (2.5  $\times$  0.8 cm) to remove the catalyst, rinsed with  $\text{CH}_2\text{Cl}_2$  (10–20 ml), and the combined eluents were analyzed using gas chromatography.

The two different catalysts chosen for this study included  $[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})]_2\text{O}$  and  $[\text{Fe}(\text{salen})]_2\text{O}$ . In our previous work [24], we ascertained that optimal yields for the cyclopropanation of styrene with EDA were obtained when  $[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})]_2\text{O}$  was used, making it an obvious choice. We rationalized that  $[\text{Fe}(\text{salen})]_2\text{O}$ , being a sterically less hindered catalyst, would be more appropriate for bulkier carbene source where the lack of substituents on the salen ligand would make it easier for the diazo compound to access the metal center of the catalyst. However, we found that  $[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})]_2\text{O}$  was actually the better catalyst, giving higher yields of cyclopropanes for all the different diazo compounds (see Table 1). This may be attributed to the better solubility of  $[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})]_2\text{O}$  under our reaction conditions. On the other hand, the use of  $[\text{Fe}(\text{salen})]_2\text{O}$  resulted in slightly better diastereoselectivities than with the more sterically hindered catalyst. We note that in all cases the background reaction with no catalyst gave the lowest yields and diastereoselectivities.

**Table 1** Substrate scope of the olefin cyclopropanation reaction catalyzed by  $\mu$ -oxo-bis[(salen)iron(III)] complexes<sup>a</sup>.

Olefin	Carbene source	Time (h)	[Fe(salen)] <sub>2</sub> O <sup>b</sup>		[Fe(3,3',5,5'-tBu <sub>4</sub> salen)] <sub>2</sub> O <sup>b</sup>		No catalyst	
			Yield (%) <sup>c</sup>	<i>cis:trans</i> <sup>d</sup>	Yield (%) <sup>c</sup>	<i>cis:trans</i> <sup>d</sup>	Yield (%) <sup>c</sup>	<i>cis:trans</i> <sup>d</sup>
Styrene	EDA	15	75(3) <sup>e</sup>	1:2.6	85(8)	1:2.5	25(1)	1:1.8
	<sup>t</sup> BDA	15	57(1)	1:4.1	83(1)	1:4.0	23(3)	1:1.9
	EDAA <sup>f</sup>	46	36(1)	1:2.5	67(7)	1:3.1	6(1)	1:1.9
1,1-Diphenyl ethylene	EDA	8	73(1)	N/A	97(1)	N/A	5(1)	N/A
	<sup>t</sup> BDA	31	69(5)	N/A	74(6)	N/A	11(1)	N/A
	EDAA <sup>f</sup>	46	9(4)	N/A	4(1)	N/A	0	N/A
<i>n</i> -Butyl vinyl ether	EDA <sup>f</sup>	24	56(0)	1:2.4	72(4)	1:2.2	6(1)	1:0.9
	<sup>t</sup> BDA <sup>f</sup>	44	62(11)	1:4.7	94(8)	1:3.6	4(1)	0:1
<i>Trans</i> - $\beta$ -methyl styrene	EDA	23	24(1)	1:4.7	28(0)	1:2.8	2(2)	0:1
	<sup>t</sup> BDA	30	14(1)	0:1	27(3)	1:12.0	0	0
	EDAA <sup>f</sup>	46	<5 <sup>g</sup>	1:1.3 <sup>h</sup>	<5 <sup>g</sup>	1:1.8 <sup>h</sup>	0	0

<sup>a</sup>Diazo compound (1 equiv), olefin substrate (5 equiv), undecane (1 equiv), or dodecane (1 equiv) as the internal standard, in refluxing undistilled benzene.

<sup>b</sup>5 mol% of catalyst relative to the diazo compound.

<sup>c</sup>Determined by GC analysis. Products identified by GC/MS.

<sup>d</sup>Determined by GC analysis. Isomers identified by comparison with results from earlier work [24].

<sup>e</sup>The values in parenthesis are standard deviations in the yields based on at least two runs.

<sup>f</sup>Dodecane used as the internal standard.

<sup>g</sup>Trace amounts detected in very concentrated samples.

<sup>h</sup>Reported within experimental error associated with trace amounts detected.

Varying the alkyl group on the diazo ester from ethyl to *tert*-butyl, in the case of EDA and <sup>t</sup>BDA, respectively, affected the yields and diastereoselectivities tremendously. With all the electron-poor olefins, it was observed that the less bulky EDA gave higher final yields (cf. 75 vs. 57 % for [Fe(salen)]<sub>2</sub>O in the case of styrene). For DPE and *trans*- $\beta$ -methyl styrene, the reaction with <sup>t</sup>BDA both required longer time and afforded lower yield. However, for the electron-rich *n*BVE, we observed that the use of <sup>t</sup>BDA resulted in higher yields over a longer period of time. Curiously, in the first 22 h of the reaction with <sup>t</sup>BDA, only about 5 % yields of the cyclopropane were obtained with both catalysts (data not shown in Table 1), and most of the catalytic activities observed for this combination of reagents were the result of longer reaction time. Having a bulkier carbene source, however, induced higher diastereoselectivity in favor of the *trans* cyclopropane. This was expected as the *trans* configuration results in the least steric repulsion around the cyclopropyl framework.

In the presence of the commercially available and highly functionalized carbene source ethyl diazoacetoacetate (EDAA), both the substituted and unsubstituted catalysts were able to cyclopropanate all the olefins that we studied, albeit with variable yields. In general, the more substituted carbene source EDAA gave lower cyclopropane yields than either EDA or <sup>t</sup>BDA. *Trans*- $\beta$ -methyl styrene gave trace amounts of the cyclopropane products under the catalytic conditions.

Interestingly, both Rh<sub>2</sub>(OAc)<sub>4</sub> and [Cu(OTf)]<sub>2</sub>·C<sub>6</sub>H<sub>6</sub> did not work with EDAA. In our hands, when Rh<sub>2</sub>(OAc)<sub>4</sub> was used to cyclopropanate styrene and [Cu(OTf)]<sub>2</sub>·C<sub>6</sub>H<sub>6</sub> was used to catalyze the cyclopropanation of DPE, both with EDAA as the carbene source, very little or no cyclopropane product was observed even after three days. That both rhodium and copper complexes, which are known to be very efficient cyclopropanation catalysts, do not work with EDAA makes the catalytic activity of our complexes noteworthy.

Preliminary studies of styrene cyclopropanation with other noncommercial diazo compounds showed considerable success using our  $[\text{Fe}(\text{salen})_2\text{O}]$  catalysts.  $[\text{Fe}(3,3',5,5'\text{-}^t\text{Bu}_4\text{salen})_2\text{O}]$  could efficiently catalyze the transfer of the carbene from phenyl diazomethane and diphenyl diazomethane. However, no cyclopropanation product was observed when the bulky ethyl diazomalonate was used to cyclopropanate styrene. The steric bulk of this carbene source might impede the ability of this compound to approach the metal center.

## CONCLUSIONS

To summarize, our study of various commercially available diazo compounds showed that they can successfully cyclopropanate a variety of olefins when catalyzed by  $\mu$ -oxo-bis[(salen)iron(III)] complexes. In the case of EDAA, to the best of our knowledge no literature precedence existed for catalytic olefin cyclopropanation with iron catalysts. Moderate-to-good cyclopropanation yields were obtained for terminal olefins while even difficult internal olefins, such as *trans*- $\beta$ -methyl styrene [26], could be cyclopropanated. Moreover, the degree of synthetic tunability of the  $\mu$ -oxo-bis[(salen)iron(III)] catalysts, their ease of synthesis and handling, and the simple reaction conditions make this an attractive catalyst system for olefin cyclopropanation.

## ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the NSF and the DOE through a grant to the Northwestern University Institute for Environmental Catalysis. Partial support from the Dupont Company and the Packard Foundations through young investigator grants are gratefully acknowledged. STN is an Alfred P. Sloan fellow.

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