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Demonstration of a Phosphazirconocene as a Catalyst for the Ring Opening of Epoxides with TMSCl

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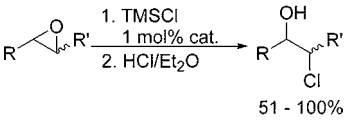
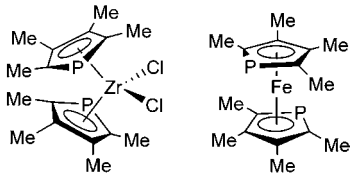
ABSTRACT



In this study, it was demonstrated for the first time that a phosphazirconocene catalyzes the ring opening of epoxides with TMSCl. This reactivity leads to a facile preparation of chlorohydrins. The late transition metal Fe analogue was found to catalyze the reaction at rates and stereoselectivity comparable to those of the Zr complex.

Upon beginning our investigations of the chemistry of early transition metal phosphametallocenes, we decided to evaluate the nucleophilicity of the phosphorus lone pair. Garrett and Fu had reported recently the ring opening of epoxides in the presence of TMSCl catalyzed by a phosphaferrocene.[1] The reaction was first reported to be catalyzed by PPh_3.[2] A study allowing the direct comparison of a phosphazirconocene and a phosphaferrocene as a catalyst for this reaction was designed, and the preliminary results are reported here.



1

2

We were interested in demonstrating the nucleophilic nature of the phosphorus atom in the phosphazirconocene **1**. Despite Fu's report, it was not assured that the Zr analogue, 2,2′,3,3′,4,4′,5,5′-octamethyl-1,1′-diphosphazirconocene dichloride **1**, $(TMP)_2ZrCl_2$, would have similar reactivity. The d^0 zirconium(IV) fragment of **1** is significantly more electron withdrawing than the d^6 Fe(II) fragment in the analogue, 2,2′,3,3′,4,4′,5,5′-octamethyl-1,1′-diphosphaferrocene **2**, $(TMP)_2Fe$. This difference can be seen in the 145 ppm downfield shift in the ^{31}P resonance of **1** compared to that of **2**, (**1**,^{31}P NMR 88.0 ppm; **2**, ^{31}P NMR −57.0 ppm).[3] We report here the catalytic activity of **1** and **2**, which allowed evaluation of the metal on the reactivity of the phospholyl ligand in the ring opening of epoxides.

There has been much interest in the ring opening of epoxides, and several examples of enantioselective nucleophilic catalysis have been reported recently.[4,5] Denmark has shown that chiral phosphoramides will nucleophilically and enantioselectively catalyze the ring opening of epoxides in the presence of $SiCl_4$.[6] Jacobsen[7] and Nugent[8] have each

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(1) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 4534−4535.
(2) Andrews, G. C.; Crawford, T. C.; Contillo, L. G., Jr. *Tetrahedron Lett.* **1981**, *22*, 3803−3806.
(3) Nief, F.; Mathey, F.; Richard, L. *Organometallics* **1988**, *7*, 921−926.
(4) For recent examples of phosphorous-based nucleophilic catalyses, see: Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836−3837. Vedejs, E.; Dauglis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813−5814.
(5) Nucleophilic catalysis: Tao, B.; Ruble, C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091−5092.
(6) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428−2429.
(7) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086−6087.

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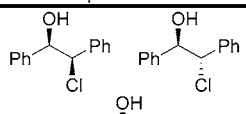
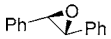
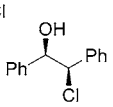
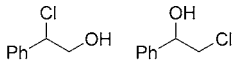
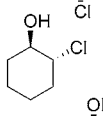
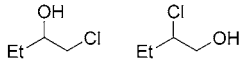
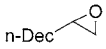
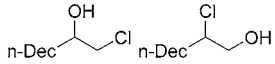
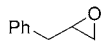
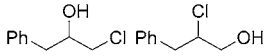
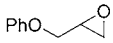
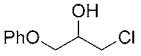
Table 1. Ring Opening of Epoxides with TMSCI and 1 mol % Catalyst[a]

		catalyst[b]			
entry	substrates	$(TMP)_2ZrCl_2$ (**1**)	$(TMP)_2Fe$(**2**)	none[c]	products[d]
1		6 h[e] (70%)[f] (7 : 1)[g]	1 h (51%) (3 : 1)	(<5%)	
2		2 d (82%)	4 d (72%)	(<5%)	
3		1 h (57%) (23 : 1)	1 h (64%) (49 : 1)	(<5%)	
4		1 h (82%)	1 h (78%)	(50%)[h]	
5		4 h (78%)	7 h (73%)	(8%)	
6		5 h (92%)	2 h (86%)	(<5%)	
7		2 h (100%)	1 h (96%)	(<5%)	
8		3 h (78%) (5 : 1)	7 h (65%) (4 : 1)	(5%)	
9		9 h (98%) (8 : 1)	15 h (87%) (7 : 1)	(<5%)	
10		3 h (90%) (19 : 1)	4 h (80%) (19 : 1)	(<5%)	
11		14 h (100%)	18 h (100%)	(6%)	

[a] Reaction conditions: epoxide (0.5 M), TMSCl (0.5 M), catalyst (1 mol %), $CDCl_3$ followed by treatment with HCl/Et_20. [b] TMP = 2,3,4,5-tetramethylphospholyl. [c] Percent completion of uncatalyzed reaction at the longest catalytic time. [d] Major product illustrated first. [e] Time required for 90% completion as determined by ^1H NMR. [f] Isolated yield of chlorohydrin. [g] Where applicable, the stereochemical or regiochemical results obtained with each catalyst are presented. [h] Uncatalyzed reaction slows dramatically, reaching only 66% after 6.5 h.

disclosed highly enantioselective catalysts for the ring opening of epoxides, as well as elegant mechanistic work elaborating the details of these reactions.

Presented in Table 1 are the results of combining 1 mol % **1** or **2** and 1.0 equiv of TMSCl with various epoxides in $CDCl_3$ at room temperature followed by cleavage of the trimethylsilyl group with HCl. We note that **1** and **2** catalyze the ring opening of epoxides at comparable rates, despite the large difference in the ^{31}P NMR shift (vide supra). The largest difference in rate was by a factor of 6 in favor of Fe catalyst **2** (entry 1). In other cases, the Zr catalyst **1** was faster (entry 2). Typically, there was a significant rate enhancement when using catalyst **1** or **2**. The exception is *cis*-2-butene oxide (entry 4), which in the first hour reacts almost as fast without catalyst. After the first hour, the uncatalyzed reaction slows dramatically, reaching only 66% at 6.5 h. *cis*-Epoxides reacted notably faster than *trans*-epoxides (entries 1 vs 2 and 4 vs 5). The stereoselectivity and regioselectivity of the ring opening are generally similar for these catalysts. The exception is the reaction of styrene oxide where the Fe catalyst **2** offers significantly higher regioselectivity (49:1 vs 23:1).[9]

The ring opening of aromatic epoxides gave clean conversion to the chlorohydrin. Styrene oxide showed a strong preference for the opposite regioselectivity to that observed in the aliphatic series, suggesting electronic control of the ring opening.[10] Styrene oxide was observed to yield chlorohydrin with the chlorine at the more substituted α-carbon atom in a ratio >20:1 (entry 3) with both catalysts. To our knowledge, these results represent the highest regioselectivity reported to date for nucleophilic catalytic ring opening of epoxides in the presence of TMSCl.

The stereochemistry of ring opening had several unexpected and unique features. The aliphatic epoxides were observed to yield products with *exclusive inversion* of stereochemistry (entries 4−7).[1] In contrast to the aliphatic epoxides, the ring opening of *trans*-stilbene oxide produced a single stereoisomer with *exclusive retention* of configuration. Additionally, *cis*-stilbene oxide produced a mixture of stereoisomeric chlorohydrins, with *net inversion* of configuration predominating. This inversion yields a predominant stereochemistry identical to that derived from *trans*-stilbene oxide. The stereochemistry of ring opening was confirmed

(8) McCleland, B. W.; Nugent, W. A.; Finn, M. G. *J. Org. Chem.* **1998**, *63*, 6656−6666.

(9) Determined by ^1H NMR (500 MHz) calibrated against the ^{13}C sidebands and authentic samples.

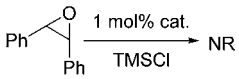
(10) For an example of similar results, see: Afonso, C. A. M.; Vieira, N. M. L.; Motherwell, W. B. *Synlett* **2000**, 382−384.

by in situ treatment of the silylated chlorohydrin with TBAF to regenerate the epoxide (>95%). We also noted the formation of *trans*-stilbene oxide (<5%) during the reaction of *cis*-stilbene oxide with catalysts **1** and **2**. While the formation of *trans*-stilbene oxide has important implications for the mechanism of the reaction, it does not account for the major stereoisomer observed. *trans*-Stilbene oxide does not react sufficiently fast to account for the reaction rate observed for *cis*-stilbene oxide (compare entries 1 and 2). Previously, a mechanism was proposed for this reaction that invoked nucleophilic attack by P at Si with the chloride then nucleophilically opening the epoxide.[1] Such a mechanism does not account for the stereochemical outcome of the reaction of stilbene oxides. Therefore, a mechanistic alternative that accounts for these results but does not necessitate *trans*-stilbene oxide as the common intermediate is required. Studies are underway to elucidate this mechanism.

We found that ring opening with PPh_3 was comparable to or slightly faster than catalysis with phospholyl complexes **1** or **2**.[2] The rates of reaction that we observed with our catalysts were also comparable with those reported by Garrett and Fu.[11]

It was established that the P atom of **1** and **2** was efficacious in these systems by attempting ring opening of *cis*-stilbene oxide with Cp_2ZrCl_2 or $FeCp_2$ under otherwise identical conditions. No reaction was observed in these control experiments (Scheme 1).

Scheme 1



Cat. = Cp_2ZrCl_2, Cp_2Fe

The results presented herein demonstrate that the Zr phospholyl complex **1** is comparable in reactivity to the Fe analogue **2** despite the significant difference in ^{31}P NMR signals (vide supra). The necessity of the P atom for catalysis was demonstrated (Scheme 1). Several mechanistic questions arise from this study, and our investigation of the mechanism will be reported shortly.

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(11) Garrett and Fu employed 5 mol % vs our 1 mol % for comparable rates; see ref 1.