1,2-Ferrocenediylazaphosphinines 2: A New Class of Nucleophilic Catalysts for Ring-Opening of Epoxides[1]

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Abstract: 1,2-Ferrocenediylazaphosphinines (**1a**–**c**) have been successfully employed as a new class of nucleophilic catalysts for ring-opening of a range of epoxides, their catalytic efficiency in terms of regioselectivity as well as chemical yield comparing well with the existing catalysts in the literature. In contrast, low enantiomeric excesses have been obtained from the reactions of *meso*-epoxides catalyzed by (*R*)-**1**.

Key words: ferrocenediylazaphosphinines, nucleophilic catalysts, ring-opening, epoxides

We have recently shown that the reaction of 1-(α-aminoalkyl)-2-diphenylphosphinoferrocene with glyoxals results in, via an unusual cyclization, 1,2-ferrocenediylazaphosphinines (**1**, Figure 1) rather than the expected bisferrocenyldiimine products.[1] These compounds constitute a new class of planar chiral ferrocenes that are of intense current research interest in the field of asymmetric catalysis.[2,3] For instance, Fu has demonstrated that ferrocenes of the type (π-heterocycle)FeCp can be successfully employed not only as ligands but also as nucleophilic catalysts in a number of asymmetric catalytic reactions.[3h,4] In particular, he recently established that a phosphaferrocene catalyzes the ring opening of epoxides with TMSCl,[5] and more recently the same author reported very high enantiomeric excesses (up to 98% ee) for the enantioselective ring opening of *meso*-epoxides catalyzed by a series of ferrocene-fused planar-chiral N-oxides.[6] Denmark had earlier accomplished an enantiomeric excess up to 87% ee for the same reaction by employing a chiral HMPA as a nucleophilic catalyst.[7] In this regard, it is worth noting that our new compounds **1a**–**c** are powerful ligands in a Cu-catalyzed cyclopropanation of styrene to achieve a complete diastereocontrol.[1] We have thus reasoned that our new compound **1**, carrying in principle two donor sites of sp^2-nitrogen and carbonyl oxygen, would also function as a suitable nucleophilic catalyst for the same reaction.

In this communication, we describe our discovery that a variety of epoxides undergo ring-opening with TMSCl (or $SiCl_4$) by the action of **1a**–**c** as Lewis base catalysts. Thus, treatment of an epoxide with 1.2 equivalents of TMSCl (or $SiCl_4$) and 5 mol% of **1** in CH_2Cl_2 at room temperature, followed by deprotection of the resulting TMS (or

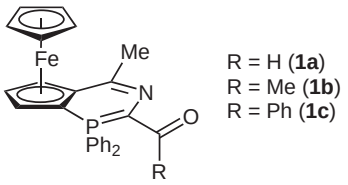

Figure 1

$SiCl_3$) ether with acid, cleanly affords a chlorohydrin (Table 1).[8] Representative procedure for Table 1, including monitoring the background reaction: a solution was prepared of hex-1-ene oxide (0.148 g, 1.48 mmol) and TMSCl (0.230 ml, 1.81 mmol) in CH_2Cl_2 (4.52 ml) in a Schlenk tube. After degassing the solution by the freeze-and-thaw method three times, a portion of this stock solution was transferred to a 5 mL screw-capped vial (background reaction), and 1.69 mL of the stock solution (0.49 mmol of epoxide, 0.60 mmol of TMSCl) was transferred to a Schlenk tube containing catalyst **1a** (11.3 mg, 0.025 mmol). The two reactions were allowed to proceed at room temperature and monitored by GC. After 70 minutes, the catalyzed reaction was complete and the background reaction had not proceeded (<5% conversion). For the catalyzed reaction, the solvent was removed in vacuo, and the TMS ether was treated with HCl (1 M in Et_2O) for 1 hour at room temperature. The resulting chlorohydrins were purified by flash chromatography on silica gel (20% Et_2O/pentane), and their NMR identifications were made by comparison with literature data.[5–7]

All reactions went to completion with inversion of configuration at the carbon undergoing substitution as verified by comparison with the known chlorohydrins.[5–7] *Cis*-stilbene oxide reacted at the lowest rate than any of the substrates employed (runs 1–3 vs. 4–15). This is most likely due to hindered approach to the TMS-nucleophile intermediate (cf. Figure 2). The regioselectivity in the reaction of unsymmetrical epoxides is governed by both steric and electronic effects. This is illustrated in the high level but opposite sense of regioselectivity in the opening of styrene oxide (runs 7–9) and other terminal epoxides (runs 10–18). For example, in the case of alkene oxide [R^1 = Bu, Bn, CH_2Cl, CH_2OBn, $CH_2OC(O)Pr$], displacement occurs preferentially at the less hindered carbon (runs 10–18), barring an overriding electronic effect observed with styrene oxide (runs 7–9). Fu and Denmark independently have also made parallel observations.[5,7] Structural change in the catalyst plays also a certain role in the regioselectiv-

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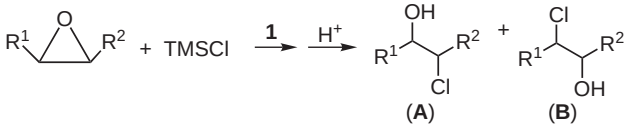
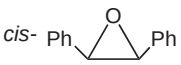
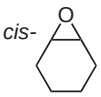
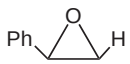
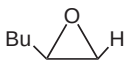
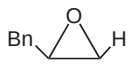
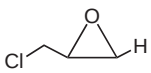
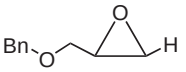
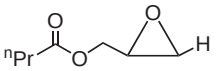
ity, thus **1a** giving the highest and in some cases a perfect regiocontrol (runs 7, 10, and 13). The catalyst **1c** also exhibits near perfect regiocontrol for some substrates carrying other functional groups (runs 16–19).

Our working hypothesis for the catalytic cycle may be the same as that proposed by others.[7] As such, the first step in the catalytic cycle is expected to be the formation of a cationic complex **C** or **D** between TMSCl (or $SiCl_4$) and **1** (Figure 2). Donor-stabilized silyl cations are ubiquitous,[9] and the structure and reactivity of resulting pentacoordinate silicon compounds are now well documented.[10] Subsequent complexation of the epoxide to the silicon cation followed by nucleophilic attack with the chloride ion in an S_N2 fashion will eventually lead to ring-opening.

Table 1 Ring-Opening of Epoxides with TMSCl in the Presence of **1**



Run	Epoxide	1	*t* (min)	Yield (%)[a]	Ratio (**A**:**B**)[b]
1		**1a**	600	95	–
2	*cis*- Ph, Ph	**1b**	600	95	–
3		**1c**	600	95	–
4		**1a**	60	97	–
5	*cis*-	**1b**	60	98	–
6		**1c**	60	97	–
7		**1a**	15	98	6:94
8	Ph, H	**1b**	15	98	10:90
9	R^1=Ph; R^2=H	**1c**	15	98	13:87[c]
10		**1a**	70	97	100:0
11	Bu, H	**1b**	70	97	92:8
12	R^1=Bu; R^2=H	**1c**	70	98	93:7
13		**1a**	60	98	100:0
14	Bn, H	**1b**	60	97	99:1
15	R^1=Bn; R^2=H	**1c**	60	97	96:4
16		**1c**	150	93	100:0
	Cl, H				
	R^1=CH_2Cl; R^2=H				
17		**1c**	180	91	96:4
	Bn, O, H				
	R^1=CH_2OBn; R^2=H				
18		**1c**	90	89	100:0
	^{n}Pr, O, O, H				
	R^1=CH_2OC(O)Pr; R^2=H				
19	*trans*-	**1c**	120	98	90:10
					
	Ph, Me				

[a] Overall isolated yield.
[b] Determined by GC.
[c] The ratio (**A**:**B**) becomes 0:100 in the presence of $SiCl_4$.

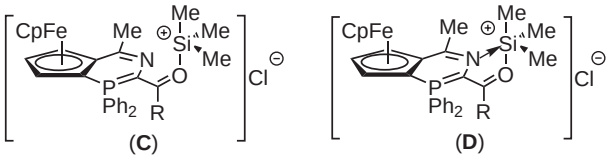
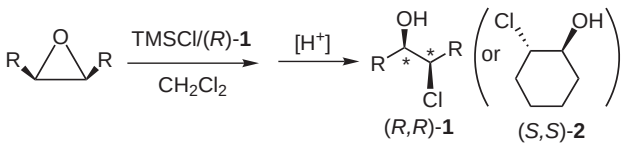


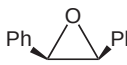
Figure 2

Encouraged by the exceptionally high regioselectivity of *rac*-**1**, we have decided to perform the asymmetric ring opening of *meso*-epoxides by employing (*R*)-**1** only to find disappointingly low enantiomeric excesses (% ee) regardless the types of catalysts or the substrates employed (Table 2). Lowering the reaction temperature to –78 °C has little effect on the enantiomeric excess.

In summary, we now put into entry 1,2-ferrocenediylazaphosphinines as a new class of nucleophilic catalysts for ring-opening of a variety of epoxides. Their catalytic efficiency in terms of regioselectivity as well as chemical yield compares well with such catalysts as phosphaferrocene and HMPA although enantioselectivity is far less efficient. Studies on fine-tuning of the catalysts to improve their enantioselection are currently underway and will be the subject of our future communication.

Table 2 Asymmetric Ring-Opening of *meso*-Epoxides Catalyzed by (*R*)-**1**[a]



Entry	Epoxide	Catalyst	Temp. (°C)	Product	ee (%) (config.)
1		(*R*)-**1a**	r.t.	**1**	1.1 (*R*,*R*)
2	Ph, Ph	(*R*)-**1a**	–78	**1**	5.4 (*R*,*R*)
3		(*R*)-**1b**	r.t.	**1**	<1 (*R*,*R*)
4		(*R*)-**1c**	r.t.	**1**	5.7 (*R*,*R*)
5		(*R*)-**1a**	r.t.	**2**	4.0 (*S*,*S*)
6		(*R*)-**1a**	–78	**2**	6.8 (*S*,*S*)
7		(*R*)-**1b**	r.t.	**2**	2.3 (*S*,*S*)
8		(*R*)-**1c**	r.t.	**2**	3.6 (*S*,*S*)

[a] (*R*) Refers to the planar chirality in the catalyst **1**.

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