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New development in the enantioselective ring opening of *meso*-epoxides by various chloride ion silicon sources catalyzed by an *o*-methoxyaryldiazaphosphonamide Lewis base

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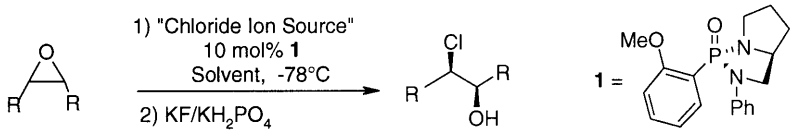
Abstract

New developments in the enantioselective ring opening of *meso*-epoxides catalyzed by a chiral Lewis base have been achieved using various chloride ion silicon sources. Thus, the use of TMSCl led to enantioselectivities varying from 6 to 98% ee depending on the nature of the considered epoxide.

1. Introduction

Since it establishes two contiguous stereogenic centers, the desymmetrization of *meso*-epoxides appears to be a method of choice for producing valuable intermediates for the stereocontrolled preparation of non-racemic chiral organic compounds.[1] In this area, numerous asymmetric methodologies have been developed using halide ions as nucleophiles leading to the synthesis of enantiomerically enriched halohydrins.[2] Recently, we have reported the synthesis of various *o*-methoxyaryldiazaphosphonamide Lewis bases and their successful use in the asymmetrization of *meso*-epoxides with silicon tetrachloride.[3] Moreover, a beneficial secondary ligand interaction effect has been demonstrated as well as the passage via a hexacoordinate stabilized silicon intermediate.[4] In the context of our studies, we report here the enantioselective ring opening of *meso*-epoxides catalyzed by an *o*-methoxyaryldiazaphosphonamide Lewis base using various halide ion silicon sources.



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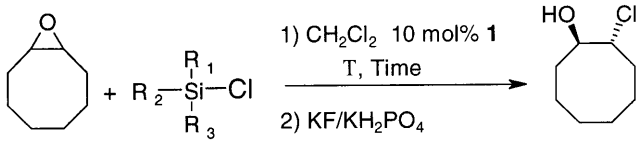
2. Results and discussion

Numerous silicon chloride compounds are now easily available and may constitute an interesting alternative versus the use of silicon tetrachloride because of their lower reactivity and their easier handling. On the basis of such considerations, we have investigated the use of such reagents in the enantioselective ring opening of cyclooctene oxide in dichloromethane catalyzed by 10 mol% of Lewis base **1**. The results are summarized in Table 1.

Table 1
Enantioselective catalyzed ring opening of cyclooctene oxide using various chloride ion silicon sources[5]



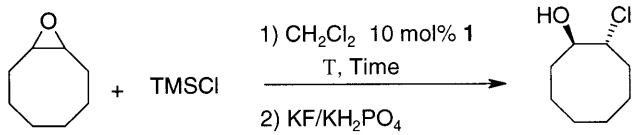
Entry[a]	$R_1R_2R_3SiCl$	T (°C)	Time (h)	Yield (%)[c]	E.e. (%)[d]
1	$MeSiCl_3$	−78	4	73	>**98**
2	$PhSiCl_3$	−78	4	61	>**98**
3	$C_6H_{11}SiCl_3$	0	48	80[e]	34
4	*n*-$BuSiCl_3$	0	48	80	48
5	Ph_2SiCl_2	0	48	75	20
6	$MePhSiCl_2$	0	48	79	86
7	Me_2SiCl_2	0	48	85	60
8	*n*-$BuMe_2SiCl$	0	48	83[e]	64
9	$PhMe_2SiCl$	0	48	70	56
10	*tert*-$BuMe_2SiCl$	−78	4	49	60
11	$C_6H_{13}SiMe_2Cl$	−78	4	21	>**98**
12	*tert*-$BuPh_2SiCl$	−78	4	50	62
13[b]	TMSCl	0	48	57[e]	>**98**

[a] Reactions performed on 1.2 mmol scale at −78°C using 1.5 equiv. of chloride ion silicon source.
[b] Reaction performed using freshly distilled TMSCl.
[c] Isolated yield after flash chromatography.
[d] Ee determined by GC analysis using a Lipodex E column, the major enantiomer possessing (1*R*,2*R*) absolute configuration.
[e] No reaction occurred at −78°C.

Thus, whatever the nature of the source of chloride used, the formation of the expected chlorohydrin was observed in isolated yields varying from 21 to 83%. Furthermore, the enantiomeric excesses observed are highly chloride source dependent. Thus, enantiomeric excesses (ee) up to 98% for (1*R*,2*R*)-2-chlorocyclooctan-1-ol were obtained only using $MeSiCl_3$, $PhSiCl_3$, $C_6H_{13}SiMe_2Cl$ and Me_3SiCl (TMSCl) sources (Table 1, entries 1, 2, 11 and 13), whereas low enantioselectivities have been measured in all the other cases. Nevertheless, the result obtained using TMSCl as the chloride source appeared to be the most interesting in terms of enantioselectivity due to its easy handling with respect to Me_3SiCl_3 or $PhSiCl_3$.

In this case, the experimental conditions have been optimized varying the nature of the solvent, the temperature and the reaction time (Table 2).

Table 2
Enantioselective catalyzed ring opening of cyclooctene oxide using TMSCl as chloride ion silicon source



Entry[a]	Solvent	T (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	CH_2Cl_2	25	48	60	40
2	CH_2Cl_2	0	48	57	>98
3	CH_2Cl_2	0	96	86	70
4	CH_2Cl_2	0	48	76	34[d]
5	THF	0	48	66	56
6	CH_3CN	0	48	90	70

[a] Reactions performed on 1.2 mmol scale at −78°C using 1.5 equiv. of freshly distilled TMSCl.
[b] Isolated yield after flash chromatography.
[c] Ee determined by GC analysis using a Lipodex E column, the major enantiomer possessing (1*R*,2*R*) absolute configuration.
[d] Reaction performed using 10 mol% of catalyst and 10 mol% of HMPA.

It clearly appears that CH_3CN is the best solvent in terms of chemical yield (Table 2, entry 2, 90%), whereas only an enantioselectivity up to 70% ee has been encountered. On the other hand, THF led to poor yield and low enantioselectivity (Table 2, entry 5, 66 and 56%, respectively). The best enantiomeric excess up to 98% was obtained using CH_2Cl_2 at 0°C, but in this case the chlorohydrin has been isolated in only 57% yield (Table 2, entry 2).

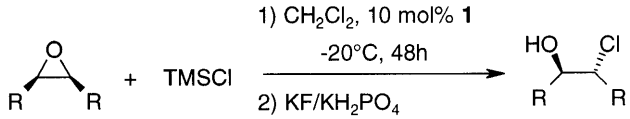
Under these best experimental conditions in terms of enantioselectivity, a range of *meso*-epoxides have been subjected to the enantioselective ring opening reaction using TMSCl as the chloride silicon source (Table 3).

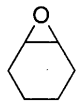
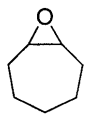
In all cases, the expected chlorohydrins have been obtained in good yields varying from 60 to 85%. Nevertheless, poor enantiomeric excesses have been observed varying from 0 to 80% depending on the nature of the epoxide. Thus, *cis*-stilbene oxide afforded the (2*S*,3*S*)-2-chloro-1,2-diphenylethan-1-ol in 60% yield and 80% ee. As an extension of this reaction, we have used trimethylsilylbromide or trimethylsilyliodide in the enantioselective ring opening of *meso*-epoxides, but whatever the experimental conditions no significant enantioselectivity (up to 10% ee) has been detected whereas a total conversion into bromo- and iodohydrins has been achieved.[7]

3. Conclusion

In conclusion, new developments in the enantioselective ring opening of *meso*-epoxides catalyzed by a chiral Lewis base have been achieved using various chloride ion silicon sources. Further studies dealing with mechanistic features are under current investigations.

Table 3
Catalytic asymmetric ring opening of various *meso*-epoxides using TMSCl as chloride silicon source



Entry[a]	Epoxide	Yield (%)[b]	Ee (%)
1		85	40[c]
2		70	12[c]
3		80	22[d]
4		79	6[d]
5		60	80[e]
6		78	0[e]

[a] Reactions performed on 1.2 mmol scale at −78°C using freshly distilled TMSCl (1.5 equiv.).
[b] Isolated yield after flash chromatography.
[c] Ee determined by GC analysis using a Lipodex E column.
[d] Ee determined by ^{31}P NMR analysis using a chiral organophosphorus derivatizing agent (Ref. 6).
[e] Ee determined by HPLC analysis on a Daicel Chiralcel OD-H column.

Acknowledgements

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3. Brunel, J. M.; Legrand, O.; Reymond, S.; Buono, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2554.
4. Reymond S.; Legrand, O.; Brunel, J. M.; Buono, G. *Eur. J. Org. Chem.* **2000**, in press.
5. *General procedure for the preparation of chiral chlorohydrins*: To a stirred solution of catalyst 1 (0.1 equiv.) in CH_2Cl_2 or THF (6 mL) at −78°C under argon is added the desired chloride ion source (1 equiv.). After 5 min, epoxide (1 equiv.) is added. After the addition is completed, the mixture was stirred at −78°C for 4 to 48 hours (depending on the nature of the chloride ion source) and then quenched by pouring into cold (−78°C), rapidly stirring sat. $NaHCO_3$ or 1/1 sat. KF/sat. KH_2PO_4 (15 mL) and allowed to warm to rt. The resulting mixture was extracted with CH_2Cl_2 (2×15 mL) and the combined organic extracts were washed with water (10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue is purified by silica gel chromatography.
6. Reymond, S.; Brunel, J. M.; Buono, G. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1273.
7. The same reaction performed using trimethylsilylazide in the enantioselective ring opening of cyclohexene oxide at room temperature for 2 days catalyzed by **1** led to the synthesis of the racemic azido alcohol in only 30% yield.