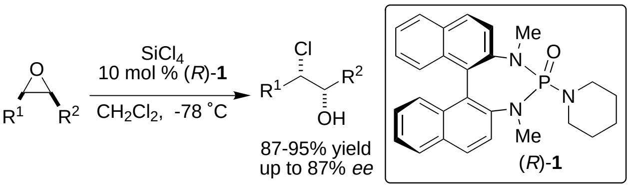
Beneficial Effect of *ortho*-Methoxy Groups in the Asymmetric Ring Opening of *meso* Epoxides with Silicon Tetrachloride Catalyzed by Chiral *ortho*-Methoxyphenyldiazaphosphonamide Lewis Bases

Response to the Communication by G. Buono et al.**

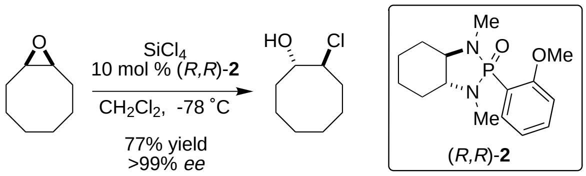
Scott E. Denmark,* Thomas Wynn, and Bradley G. Jellerichs

A 1998 report from these laboratories disclosed the enantioselective opening of *meso* epoxides with silicon tetrachloride in the presence of a catalytic amount of a chiral phosphoramide (Scheme 1).[1] The resulting chlorohydrins were formed in good yield and variable enantioselectivities which depended on the structure of the epoxide. For example, whereas *cis*-stilbene oxide afforded 2-chloro-1,2-diphenylethanol in 87 % *ee*, the opening of cyclopentene oxide produced the chlorohydrin in nearly racemic form. Moreover, we found that the reaction rate was also highly structure-dependent; for example, cyclohexene oxide required 20 min at $-75\,^\circ$C for complete conversion (52 % *ee*), whereas cyclooctene oxide required 5.5 days under the same conditions and produced the racemic chlorohydrin.



Scheme 1.

We were therefore surprised to read the recent report by Buono et al. in this journal which described the use of a phosphonamide-type catalyst for the same transformations that gave generally much higher enantioselectivities and at enhanced rates.[2] Although there was no reason a priori to question the results, we were particularly struck by the remarkable facility and selectivity reported for opening of cyclooctene oxide which was used to optimize the conditions and catalyst structure. The authors claimed that catalyst (*R*,*R*)-**2** gave a 77 % yield of the 2-chlorocyclooctanol in >99 % *ee* after 4 h at $-78\,^\circ$C (Scheme 2).



Scheme 2.

If true, these results represent a significant advance in the asymmetric synthesis of enantiopure chlorohydrins. However, the claims were so contrary to our own experience that we felt compelled to repeat the experiments as described by Buono et al. We describe herein the details of that exercise. Despite multiple repetitions with different experimentalists we have been unable to authenticate the results published by those authors.

We first prepared the catalyst (*R*,*R*)-**2** according to the published procedures.[2] The phosphonamide was purified to microanalytical standards and has been fully characterized spectroscopically.[3] Although there was a small discrepancy in the optical rotations, the enantiomeric purity of (*R*,*R*)-**2** we employed was assured by chiral stationary phase (CSP) supercritical CO_2 chromatographic (SFC) analysis of the bis(*p*-toluamide) derivative of the cyclohexane-1,2-diamine employed.

To evaluate the experimental results, we selected three substrates, namely *cis*-stilbene oxide (**3**), cyclohexene oxide (**4**) and cyclooctene oxide (**5**), which represented a range of structural classes and also corresponded to those results that were most at variance with our experience. Although we had previously described in detail the analytical methods employed in our work, we repeated this task to be certain of the veracity of our claims. Thus, freshly prepared samples of authentic racemic products were prepared by opening the

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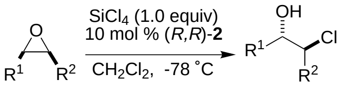
epoxides with silicon tetrachloride in the presence of HMPA. As described previously, 2-chloro-1,2-diphenylethanol (**6**) could be analyzed directly by CSP-SFC with baseline separation (Chiralpak AS column).[3] However, both *trans*-2-chlorocyclohexanol (**7**) and *trans*-2-chlorocyclooctanol (**8**) were first derivatized to their trifluoroacetates which gave baseline separation by CSP GC analysis (Chiraldex G-TA and B-PH columns).

The first attempts to reproduce the results using *cis*-stilbene oxide immediately raised our concerns. Three independent runs, rigorously following the conditions reported by Buono et al.,[3] did indeed produce **6**, but in nearly racemic form (Table 1, entries 1–3) and not 60% *ee* as reported. In all three runs, the products were isolated in a highly pure state by chromatography (as judged by 500 MHz ^{1}H NMR analysis), and no other signals were seen in the CSP-SFC traces.[3] The next case, cyclohexene oxide, behaved similarly (Table 1, entries 4–6) producing the chlorohydrin **7** in good yield, but again in nearly racemic form, not 82% *ee* as reported. Finally, we found the behavior of cyclooctene oxide to be completely disparate from the published results. In two independent experiments exactly following the experimental description (−75 °C, 3.5 h), we obtained only 3% of the chlorohydrin **8** along with 81–83% recovery of the epoxide (Table 1, entries 7 and 8). Derivatization of this small quantity revealed an essentially racemic product. In a third experiment, the reaction time was extended to three days in an attempt to increase conversion. Once again, we secured only 6% of **8** along with a 70% recovery of **5**. The enantiomeric composition of **8** from this experiment was only marginally improved suggesting that the small amount of **8** obtained in entries 7 and 8 may have arisen from ring opening upon workup.

Table 1. Attempted opening of *meso* epoxides with silicon tetrachloride and **2**.[a]



Entry	Epoxide	t [h]	Product	Yield [%][b]	*ee* [%][c]
1	**3**	3.5	**6**	87	5
2	**3**	3.5	**6**	75	5
3	**3**	3.5	**6**	65	8
4	**4**	0.33	**7**	90	5
5	**4**	0.33	**7**	90	6
6	**4**	0.33	**7**	75	5
7	**5**	3.5	**8**	3[d]	1
8	**5**	3.5	**8**	3[e]	3
9	**5**	72	**8**	6[f]	8

[a] Reactions all performed on 1.2 mmol scale. See Supporting Information for full experimental details. [b] Yield of chromatographically homogeneous material. [c] Enantiomeric excess determined by CSP-SFC or CSP-GC as described in the Supporting Information. [d] 83% recovery of epoxide **5**. [e] 81% recovery of epoxide **5**. [f] 70% recovery of epoxide **5**.

Clearly there is a serious discrepancy between the results reported by Buono et al. and what we have found. Although we have made no attempt to adumbrate the origin of the problems, the data given in their Supporting Information provide reason for concern. For example, the determination of enantiomeric composition of **7** is described as being done by ^{13}C analysis of the derived fluorolactate according to Heumann et al.[4] This is most disturbing since the original authors use ^{19}F NMR spectroscopy; it is difficult to accurately integrate ^{13}C{^{1}H} spectra.[5] Also of concern is the analytical method employed for determination of the enantiopurity of **8**. The authors describe their sample of **8** as having >99% *ee* on the basis of CSP-GC analysis (Lipodex E) of the trifluoroacetate of **8**. It is remarkable that the enantiomers of this compound are reported to have retention times that differ by nearly 8 min. Whereas one would assume that this method would have been calibrated with the racemate, these data are not provided.

In conclusion, the reported ability of chiral phosphonamide **2** to effect the enantioselective opening of *meso* epoxides with silicon tetrachloride has not withstood experimental verification. Although we have not attempted to repeat all of the examples in which this catalyst (or others claimed in the paper) is purported to give enantiomerically enriched chlorohydrins, until the questions raised herein are appropriately addressed, all the results described by Buono et al. should be viewed with skepticism.[6,7]

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[1] S. E. Denmark, P. A. Barsanti, K.-T. Wong, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 2428.

[2] J. M. Brunel, O. Legrand, S. Reymond, G. Buono, *Angew. Chem.* **2000**, *112*, 2654; *Angew. Chem. Int. Ed.* **2000**, *39*, 2554.

[3] See Supporting Information for all spectral and analytical data.

[4] A. Heumann, R. Faure, *J. Org. Chem.* **1993**, *58*, 1276.

[5] E. Breitmaier, W. Voelter, *Carbon-13 NMR Spectroscopy*, 3rd ed., VCH, Weinheim, **1987**, pp. 43–55.

[6] Since the time these control experiments were completed, the same group has published "further developments" in which they claim, inter alia, the ability to use a variety of chlorosilanes to open cyclooctene oxide (S. Reymond, J. M. Brunel, G. Buono, *Tetrahedron: Asymmetry* **2000**, *11*, 4441). Among the most incredible of the results is the report that *tert*-butyldimethylchlorosilane can open this epoxide in 4 h at −78 °C with 60% *ee*. In our first communication, we explicitly state that other chlorosilanes were competent reaction partners, but all of the products were racemic.

[7] **Note added in proof** (May 8, 2001): The inability of (R,R)-**2** to enantioselectively promote the opening of cyclooctene oxide as we describe, has been independently confirmed by Professor Gregory Fu and Beata Tao (MIT) with catalyst samples provided by both us and Professor Buono. We thank Professor Fu and Miss Tao for their gracious assistance.

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