be noted here. The reduction of **9** with sodium borohydride at −15 °C afforded a mixture of the *cis*- and *trans*-hydroxy acid (99%, ca. 80:20). The pure cis compound was obtained by lactonization of the reaction mixture (165 °C, 20 min), extraction of the trans acid, and hydrolysis of the pure lactone (mp 118–119.5 °C). Methylation (93%) and esterification (95%) afforded **10c**. Application of Vedejs'[15] procedure for ester enolate hydroxylation yielded, after silica gel chromatography, **11** (74%). This was smoothly converted to a mixture of ketones that could readily be separated by silica gel chromatography to afford **12a** (55%) and its isomer **12b** (7%). Since a chromatographic separation was required at this stage, we have carried the steps **9** → **12** without separation of isomers (overall yield 32% from **9**). While ketalization methods involving heating proved unacceptable owing to partial aromatization and epimerization of **12a**, a mixture of ethylene glycol and trimethyl orthoformate at room temperature for 16 min afforded **13** with minimal aromatization or epimerization of the methoxy group.[16] Execution of the same reaction sequence as for **6** afforded **15** in 63% overall yield after recrystallization from methanol. This compound was identical in melting point and spectroscopic properties with those previously reported.[2] Since **15** is readily converted to 4-demethoxydaunomycinone,[2,3,6] this completes the synthesis.

This chemistry effects the formation of the C ring of the anthracyclinone system from an AB- and D-ring component under sufficiently mild conditions that the thermally and acid-labile A ring can be incorporated directly into a tetracyclic framework. By using modified AB- and D-ring components, the route would afford convergent syntheses of a variety of anthracyclinone analogues. Finally, the strategy documented herein may be applicable to the syntheses of related antibiotic aglycones: aklavinones, citromycinones, and even olivomycins.

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(18) We wish to thank the National Science Foundation (CHE76-80381 A81) and the National Institutes of Health (CA 17712-01A2) for generous support. D.K.J. is an Ohio State University Dissertation Fellow (1978–1979); L.N. is an American Oil Fellow (1977–1978). Our thanks to C. M. Wong for an authentic sample of **15** and R. B. Garland (G. D. Searle Co.) for authentic samples of 4-demethoxydaunomycinone and its 7-epi isomer.

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Novel Copper–Pyridine Catalyzed Ring Opening Reactions of Aryl Oxiranes. An Asymmetric Synthesis of (+)-Indene 1,2-Oxide and (+)-*cis*-1,2-Indandiol

Sir:

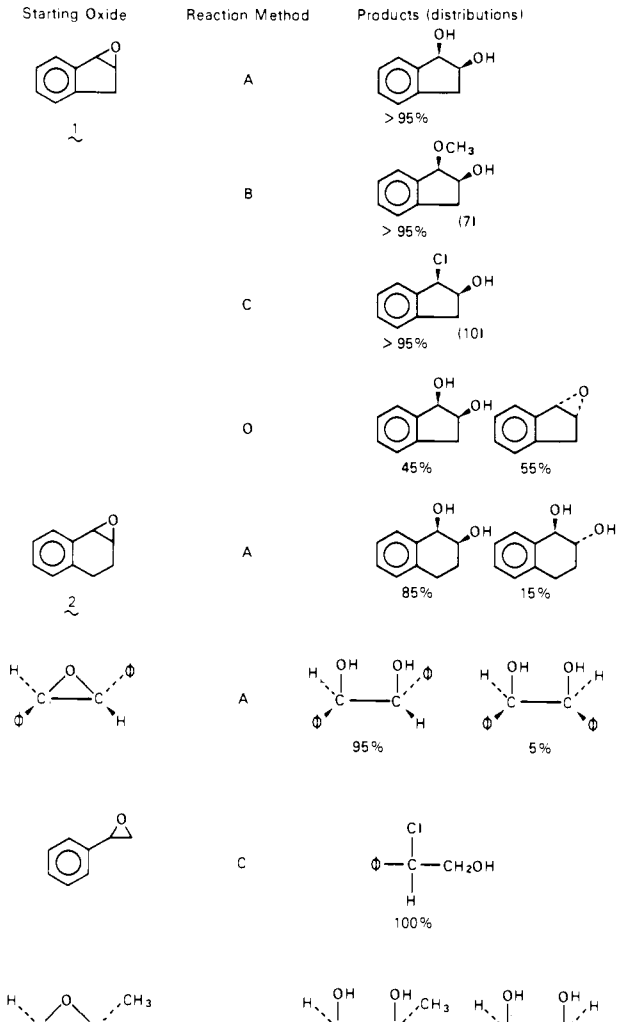
Aryl oxiranes have proved to be important intermediates in synthetic chemistry,[1] and certain of their hydroxylated derivatives have been described as the ultimate carcinogens of aromatic compounds.[2] While their behavior in acidic and basic media is reasonably well understood,[3] their reactivity under neutral conditions has been little investigated. Kinetic studies in several laboratories[4] have shown that these compounds undergo spontaneous ring opening reactions at pH 7, producing materials of unknown stereochemistry. Recently, Hanzlik and Michaely[5] reported on the rate of Cu^{2+}-catalyzed oxirane opening of 2-pyridylethylene oxide and on the products formed. While the pH optimum for the catalyzed process was 4.5, the rate was still significant at pH 7. Hoping to effect aryl oxirane ring opening under neutral conditions, we examined the reactivity of indene oxide (**1**) in the presence of $CuSO_4$ in an aqueous phosphate buffer (pH 7). Under these conditions, the oxirane was rapidly destroyed, but no diols were formed. The potent effect of $CuSO_4$ prompted us to explore the possibility that the nitrogen atom in 2-pyridylethylene oxide complexed with copper, with formation of a species that can promote hydration of an aryl oxirane. When **1** was added to an aqueous solution containing pyridine and $CuSO_4$ buffered with phosphate buffer at pH 7, *cis*-1,2-indandiol formed rapidly and cleanly (i.e., without detectable quantities of the trans isomer or other products). The results of a study of the effect of the absence of one or more components in the reaction mixture are summarized in Table I. The study also established that the presence of NaCl or NaBr increases the reaction rate. The successful hydration of **1** under these very mild conditions stimulated us to explore the copper–pyridine catalyzed reactivity of several oxiranes with methanol, water, and chloride ion. The results of this study (summarized in Table II) demonstrate that aryl oxiranes react regioselectively at the benzylic carbon to yield exclusively or predominantly cis products: glycols, glycol monomethyl ethers, and chlorohydrins. This regioselectivity differs from that noted by Hanzlik and Michaely[5] for 2-pyridylethylene oxide, where reaction occurred at the less substituted carbon. Alkyl oxiranes do not react under

Table I. Reaction of **1** (1 mmol in 5 mL of THF) in Phosphate Buffer (25 mL, pH 7) at Room Temperature for 8 h

reactants	results
1. $CuSO_4$ (0.5 mmol), pyridine (1 mL), and NaBr (5 mmol)[a]	*cis*-diol >95%
2. $CuSO_4$ (0.5 mmol), pyridine (1 mL)	*cis*-diol 25% unreacted oxide 75%
3. $CuSO_4$ (0.5 mmol)	dimeric products no diol
4. pyridine (1 mL)	no reaction
5. phosphate buffer	no reaction

[a] Halohydrins were not detected at the end of the reaction period.

Table II. Copper–Pyridine Catalyzed Reactions of Aryl Oxiranes[a]



[a] A, $CuSO_4$/pyridine/phosphate buffer (pH 7.0); B, $CuSO_4$/pyridine/methanol; C, $CuSO_4$/pyridine/LiCl/THF; D, $CuSO_4$/nicotine/phosphate buffer (pH 7.0). In each of the above reactions, 0.5–1 equiv of $CuSO_4$ and ~5 equiv of NaCl or NaBr were used. The reaction mixture in each case, except for *trans*-stilbene oxide (70 °C), was stirred at room temperature until TLC indicated that the aryl oxirane had completely reacted (8–12 h). Yields were determined by NMR.

these conditions.

The cis stereospecificity of the copper sulfate–pyridine catalyzed reaction differs from both the acid- and base-catalyzed processes. Berti et al.[6] investigated acid-catalyzed openings of **1** and found approximately 2:1 mixtures of *trans*- to *cis*-diols. The only product we were able to isolate from the reaction of **1** with dry methanol-KOH was *trans*-1-methoxy-2-indanol; i.e., trans addition occurred. Similar results were recently reported by Posner and Rogers.[7] Both pyridine and Cu^{2+} (sulfate or other ions) are essential for the stereospecific cis opening. An excess of Cu^{2+} is not desirable, since side reactions appear. Pyridine derivatives can be substituted for pyridine; however, other tertiary amines, e.g., triethylamine, result in very little or no reaction. The results imply that a Cu^{2+}–pyridine complex of undetermined structure effects the cleavage.

To determine whether this reaction could be employed for an asymmetric resolution, nicotine was substituted for pyridine, and the hydration of **1** was allowed to proceed for approximately 1 half-life.[8] The reaction yielded (+)-(1*R*,2*S*)-*cis*-indandiol in 45% yield, enantiomeric excess (ee) 23% (α^{25}_D +11.72° (*c* 0.34, $CHCl_3$)) and reisolation of unreacted **1** yielded (+)-(1*S*,2*R*)-indene oxide in 55% yield, ee 18% (α^{25}_D +3.13° (*c* 0.30, $CHCl_3$)).

The consequences of these copper-catalyzed ring opening reactions for synthetic chemistry are apparent; however, since the neutral and mild reaction conditions approximate those present in biological systems, an examination of the reactivity of arene and arenediol oxides with this reagent is indicated and planned.

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