amine was purified by Kugelrohr distillation or flash column chromatography.

Acknowledgment. We are indebted to the Analytical and Physical & Structural Chemistry Departments for the analytical data: Ms. E. Reich for combustion analyses, Mr. L. Killmer for mass spectral data, and Mr. G. Zuber for FT/IR data. We are particularly indebted to Professor Gawley for communicating to us the details of his procedure for oxidative cleavage and to Drs. Conrad Kowalski and Vance Novack for their very helpful suggestions at the beginning of this work.

Supplementary Material Available: General experimental procedures for the synthesis of oxazolidines **1a–c** (including spectral data); spectral data for phenethylamines **3a–f**; and ^{1}H NMR spectra for **2a,c–e,h** (8 pages). Ordering information is given on any current masthead page.

Catalysis of Aryl–Halogen Exchange by Nickel(II) Complexes Using NaOCl

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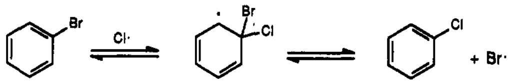
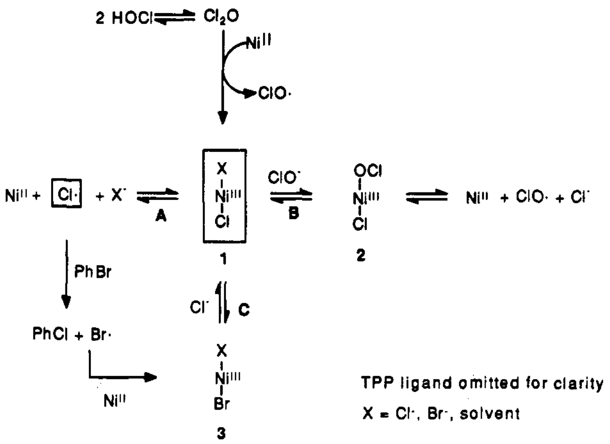
Due to the ease with which aryl–halogen bonds are activated by transition metals, aryl halides have become important precursors to a wide variety of synthetically useful compounds.[1] One successful method for the synthesis of haloarenes is the halogen exchange reaction. Although Ni^0, Ni^{II}, and Cu^I are commonly employed today to effect this transformation, reactions of this type were originally conducted photochemically.[1–5] One of the first examples was the conversion of PhBr to PhCl with $Cl_2/h\nu$. Studies by Miller and Walling[6a] and Milligan[6b] revealed that this reaction most likely proceeds via free radical ipso substitution of $Br^\bullet$ by $Cl^\bullet$ (eq 1).[6c] Since aryl halides have this intrinsic propensity to undergo ipso substitution reactions,[6c] we became intrigued by the possibility of developing a nonphotochemical method that could generate halogen radicals catalytically; this could then potentially serve as an efficient, catalytic, and inexpensive method for the synthesis of haloarenes.



(1)


Scheme I

TPP ligand omitted for clarity

X = Cl⁻, Br⁻, solvent

Recent studies in our laboratory on the mechanism of Ni^{II}-catalyzed epoxidation reactions revealed that when employing NaOCl as terminal oxidant at reduced pH under phase-transfer conditions, chlorine radicals could be produced catalytically.[7] This facile generation of $Cl^\bullet$ might arise from a radical chain mechanism or from homolytic bond cleavage of the Ni–Cl bond of **1**; we previously proposed[7] that **1** is formed by the reaction of a macrocyclic Ni^{II} complex with Cl_2O (Scheme I, pathway A). Pathway B was previously proposed to explain rapid epoxidation when olefins are the substrate.[7]

Also postulated in Scheme I are the equilibria between **1**, **2**, and **3**, which might be attained in the presence of a phase-transfer catalyst (PTC) (pathways B and C). This would then suggest that the formation of **2** and **3** should not limit the success of this approach since anion exchange would regenerate **1**. Although a Ni^{III}–Cl bond should be relatively long-lived, eventual homolytic cleavage to regenerate the more stable Ni^{II} would also liberate a chlorine radical. If a sufficient concentration of $Cl^\bullet$ could be generated before catalyst degradation, such a system should render the transformation of aryl bromides to the corresponding chlorides *catalytic* in Ni^{II}, would obviate the use of gaseous chlorine, and should be complimentary to the already existing methods. While the actual mechanism of Ni^{II}-catalyzed generation of chlorine radicals remains speculative, the reaction was put into practice as described below.

Experiments revealed that the optimum reaction conditions for the *quantitative* conversion of PhBr to PhCl were those in which 6 mol % of nickel catalyst was employed in conjunction with domestic bleach adjusted to pH 9, and the reactions were run under phase-transfer conditions using $CHCl_3$ as the organic phase and benzyltributylammonium bromide as the phase-transfer catalyst (PTC). Omission of the nickel catalyst produced only 1–2% PhCl and confirmed the feasibility of this approach. Furthermore, in the absence of PTC, only a 57% yield of PhCl was obtained, which suggested that interconversion of **1**, **2**, and **3** was crucial for the complete conversion of bromide to chloride.

Table I lists the results obtained with several substituted aryl bromides using NiTPP as the catalyst. The yields ranged from good to excellent and in all cases only ipso substitution of $Br^\bullet$ was observed. Almost identical yields were obtained with $[Ni(cyclam)](NO_3)_2$,[9] but Ni(salen)[10]

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[1] Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267–2273, and references therein.

[2] Ksuo, T. T.; Kochi, J. K. *J. Org. Chem.* **1980**, *45*, 1930–1937, and references therein.

[3] (a) Hardy, W. B.; Fortenbaugh, R. B. *J. Am. Chem. Soc.* **1958**, *80*, 1716–1718. (b) Bacon, R. G. R.; Hill, H. A. *J. Chem. Soc.* **1964**, 1097–1112.

[4] Takagi, K.; Hayama, N.; Okamoto, T. *Chem. Lett.* **1978**, *2*, 191–192.

[5] (a) Srpek, O. *Monatsh. Chem.* **1890**, *11*, 429–32. (b) Asinger, F. *Monatsh. Chem.* **1934**, *64*, 153. (c) Voegtli, W.; Lauger, P. *Helv. Chim. Acta* **1954**, *37*, 1627–1633.

[6] (a) Miller, B.; Walling, C. *J. Am. Chem. Soc.* **1957**, *79*, 4187–4191. (b) Milligan, B.; Bradow, R. L.; Rose, J. E.; Hubbert, H. E.; Roe, A. *J. Am. Chem. Soc.* **1962**, *84*, 158–162. (c) For a general review of free radical ipso substitution reactions, see: Traynham, J. G. *Chem. Rev.* **1979**, *79*, 323–330.

[7] Yoon, H.; Wagler, T. R.; O'Connor, K. J.; Burrows, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4568–4570.

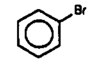
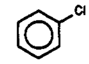
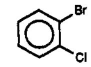
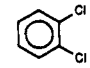
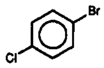
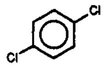
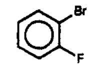
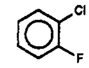
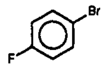
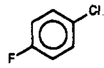
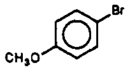
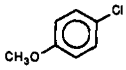
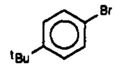
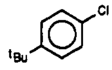
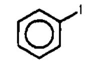
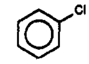
[8] Abbreviations used: salen, *N,N'*-ethylenebis(salicylideneamine); cyclam, 1,4,8,11-tetraazacyclotetradecane; TPP, 5,10,15,20-tetraphenylporphyrin.

[9] Easily prepared from cyclam (Lancaster) and $Ni(NO_3)_2$. See: Kinneary, J. F.; Albert, J. S.; Burrows, C. J. *J. Am. Chem. Soc.* **1988**, *110*, 6124–6129.

[10] Yoon, H.; Burrows, C. J. *J. Am. Chem. Soc.* **1988**, *110*, 4087–4089.

0022-3263/91/1956-1344$02.50/0

Table I. Product Yield in Ni(TPP)-Catalyzed Halogen Exchange Reactions[a]

aryl bromide	product	yield[b] (%)	selectivity[c] (%)
		100	100
		85	85
		85	85
		95	95
		100	100
		50	61
		47	68
		10	48

[a] Reaction conditions: 30 min reaction time at 25 °C using reactant ratio, Ni catalyst/PTC/aryl bromide/NaOCl (pH 9.0) = 1:1:17:500. [b] Yields based on starting ArBr determined by GC. [c] Selectivity = % yield of corresponding aryl chloride/% disappearance of starting material.

afforded slightly lower yields. In the case of PhBr as substrate, the reaction rates were consistently about 1 turnover min^{-1}, and the reaction was complete in 20 min.

Clearly, fluoro and chloro substituents already present on the aromatic nucleus are quite stable to the reaction conditions. Unfortunately, aryl iodides gave poor yields of aryl chlorides (5–10%), since the alternative pathway to produce iodoarene dichloride seems to be preferred.[6] One additional limitation is that haloarenes possessing alkyl substituents undergo facile benzylic chlorination to afford a mixture of bromo and chloro benzylic chlorides.[5] This was not surprising since chlorine radicals had previously been shown to exhibit low levels of chemoselectivity.[11] *t*-Bu and CH_3O substituents gave lower yields and selectivity for halogen exchange, presumably due to some reaction of these groups giving water-soluble products. For example, *p*-bromoanisole was converted to *p*-bromophenol in a nearly 30% yield while the halogen exchange pathway accounted for about 50% of the product.

Given the intrinsic ability of macrocyclic Ni^{II} complexes to homolytically cleave Cl_2O under phase-transfer conditions, it was informative to examine the results of direct addition of Cl_2O to the haloarene. Indeed, addition of a CCl_4 solution of chlorine monoxide[12] to PhBr in the presence of 1 mol % Ni^{II}TPP resulted in a 38% yield of PhCl! (In the absence of catalyst no PhCl was produced.) The low yield could be attributed in part to degradation of the porphyrin ring by Cl_2O. A compilation of these results with a variety of Ni^{II} catalysts can be found in Table II.

Table II. Comparison of Ni(II) Catalysts for Reaction of Bromobenzene with Cl_2O

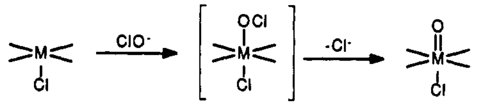
catalyst[a]	PhCl yield (%)	$E_{1/2}$ (V)[13]
[Ni(cyclam)]$(NO_3)_2$[b]	57	0.6
NiTPP	38	1.0
Ni(salen)	18	1.5
none	0	

[a] 1 mol % catalyst used relative to PhBr. [b] Solvent = 1:1 CH_2Cl_2/CCl_4. CCl_4 was used in all other cases.

[Ni(cyclam)]$(NO_3)_2$ proved to be the most successful catalyst in effecting halogen exchange under these homogenous reaction conditions (57% PhCl). The strong correlation between the yield of PhCl and the $E_{1/2}$ values[13] for the catalysts studied supports our hypothesis for the one-electron oxidation of Ni^{II} to Ni^{III} (i.e., formation of 1). Hence, it seems reasonable to assume that chlorine radicals are catalytically generated via homolytic cleavage of 1.

Additional studies were conducted to determine whether catalysis could be achieved with simple inorganic Ni^{II} salts. Interestingly, $NiCl_2$, $Ni(OAc)_2$, and $Ni(BF_4)_2$ all produced a 33–35% yield of PhCl when subjected to the same reaction conditions used for Ni^{II}(TPP).[14] As a control, we verified that the macrocyclic ligands alone did not result in any production of PhCl. These results are in complete agreement with previous experiments, which suggested that the role of the macrocycle is to stabilize higher oxidation states of nickel ($Ni^{II} \rightarrow Ni^{III}$).[7] Clearly, simple anions cannot offer the same degree of stability and consequently afford lower yields of PhCl.

We have examined two additional metalloporphyrins in order to compare their potential as catalysts in this system. Both Mn(TPP)Cl and Fe(TPP)Cl produced only 10 and 1% yields of PhCl from PhBr, respectively. This suggests that Mn^{III} and Fe^{III} porphyrins show preference for O–Cl bond cleavage after reaction with hypochlorite to generate metal–oxo species (eq 2).[15,16] This contrasts with the Ni^{II} porphyrins, which apparently facilitate homolytic M–O cleavage to produce ClO•. Hence, aryl bromides should find widespread application as mechanistic probes for the identification of reaction intermediates formed in these and other systems that were designed to mimic the catalytic properties of cytochrome P-450.[15]



(2)

As expected, attempts to carry out the reverse reaction, conversion of aryl chlorides to aryl bromides using sodium hypobromite and nickel catalysts, were unsuccessful. Owing to the higher stability of the carbon–chlorine bond compared to the carbon–bromine bond, decomposition of the intermediate (eq 1) favors formation of chlorobenzene in the absence of other driving forces.[6]

As a result of this and previous research in this area,[7] we view macrocyclic Ni^{II} complexes as versatile catalysts for a wide variety of synthetically useful transformations. In addition to catalyzing the epoxidation of olefins with high turnover numbers,[7] the synthesis of haloarenes can now be conducted under conditions that employ readily available Ni^{II} catalysts and an inexpensive oxidant such as domestic bleach.

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[11] (a) Russel, G. A. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. I, pp 275–331. (b) Huyser, E. S. In *The Chemistry of the Carbon-Halogen Bond*; Patai, S., Ed.; Wiley: London, 1973; Part I, pp 549–608.

[12] For the preparation of Cl_2O, see: Cady, G. H. *Inorg. Synth.* **1957**, *5*, 156.

[13] Koola, J. D.; Kochi, J. K. *Inorg. Chem.* **1987**, *26*, 908–916.

[14] Increasing the amount of Ni^{II} salt to 60 mol % did *not* result in increased yields of PhCl.

[15] Various mechanistic proposals for the reaction of metalloporphyrins with NaOCl with/without PTC have been reported. See: Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 1850–1859, and references therein.

[16] The reactions of metalloporphyrins with Cl_2O are well precedented. See: Rodgers, K. R.; Goff, H. M. *J. Am. Chem. Soc.* **1988**, *110*, 7049–7060.

These findings are significant for two additional reasons. First, they suggest the use of simple aryl halides as chlorine radical traps in investigations that employ NaOCl as an oxidant, thus providing useful mechanistic information. Second, they are suggestive of additional synthetic applications that utilize this intrinsic ability of Ni^{II} catalysts to homolytically cleave Cl_2O or similar species. Efforts are presently underway to fine-tune this catalysis for the formation of carbon–carbon bonds via intramolecular radical cyclization reactions.

Experimental Section

Solvents (HPLC grade) and aryl halides were obtained from commercial sources and used without further purification. Ni[cyclam]$(NO_3)_2$,[9] Ni(salen),[10] and chlorine monoxide[12] were synthesized according to literature procedures. Ni(TPP), Fe(TPP)Cl, Mn(TPP)Cl, and benzyltributylammonium bromide were obtained from Aldrich. NaOCl (pH 9.0) was obtained by adding concentrated HCl to commercial bleach (determined to be 0.77 M in NaOCl by iodometric titration).

Analytical gas chromatography was performed on a 5% phenyl methyl silicone column (10 m × 0.53 mm), using a Hewlett-Packard 5890A gas chromatograph with thermal conductivity detection; a linear oven temperature program initiated at 35 °C and increased at 10 °C/min to 180 °C was employed. Low resolution GC/MS spectra were obtained on a Hewlett-Packard 5980A spectrometer with 70-eV electron impact ionization. The pH of the NaOCl was determined with a Corning 250 pH meter and was calibrated before use. All reactions were run in stoppered round-bottom flasks (10 mL).

General Procedure for Halogen Exchange. To a vigorously stirred $CHCl_3$ (6 mL) solution containing Ni^{II}TPP (8.0 mg, 0.012 mmol), *p*-bromochlorobenzene (38 mg, 0.20 mmol), and benzyltributylammonium bromide (3.0 mg, 0.0084 mmol) was added pH 9.0 NaOCl (7.8 mL, 6.0 mmol, 0.77 M). After 30 min, the stirring was stopped and the organic layer was passed through a short column of neutral alumina (activity III). Rotary evaporation of the solvent afforded a 75% yield (22 mg, 0.15 mmol) of pure *p*-dichlorobenzene. For analytical experiments (results reported in Table I), a similar reaction was carried out on half scale, using various aryl bromides and an internal standard, typically *o*-dichlorobenzene. An aliquot of the organic layer was passed through a short column of alumina and analyzed by GC. Higher yields were typically observed by GC analysis compared to preparative isolation and weighing. Co-injection of the reaction with an authentic sample of the aryl chloride allowed for the unambiguous identification of products. Low resolution GC/MS analysis was also performed.

Acknowledgment. We thank the National Science Foundation for a grant (CHE-9006684) supporting this research.

Additions and Corrections

Vol. 55, 1990

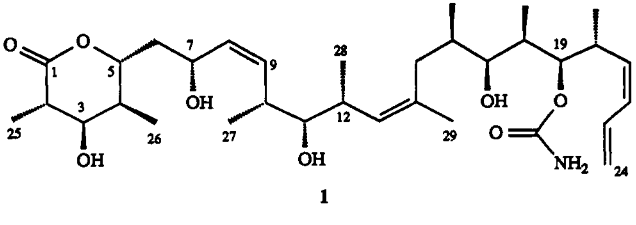
Hson Mou Chang,* Kwok Ping Cheng, Tai Francis Choang, Hak Fun Chow, Kuk Ying Chui,* Po Ming Hon, Fan Wah Lau Tan, Yun Yang, Zeng Pei Zhong, Chi Ming Lee,* Hing Leung Sham,* Chun Fei Chan, Yu Xin Cui, and Henry N. C. Wong*. Structure Elucidation and Total Synthesis of New Tanshinones Isolated from *Salvia miltiorrhiza* Bunge (Danshen).

Page 3538, ref 4 should read as follows: Zhang, H.-Y.; Ouyang, R. *Acta Pharm. Sinica* **1979**, *14*, 288.

Page 3539, column 1, line 30: $H_{6\beta}$ should be $H_{6\alpha}$.

Sarath P. Gunasekera,* Malika Gunasekera, Ross E. Longley, and Gayle K. Schulte. Discodermolide: A New Bioactive Polyhydroxylated Lactone from the Marine Sponge *Discodermia dissoluta*.

Page 4912. The relative stereochemistry of the structures 1 and 2 was transposed incorrectly from the URANUS drawing. The correct relative stereochemistry of the structures 1 and 2 are given below.



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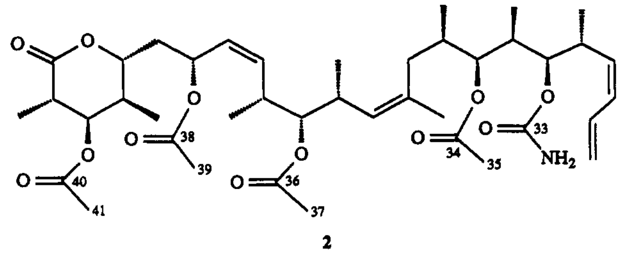

2