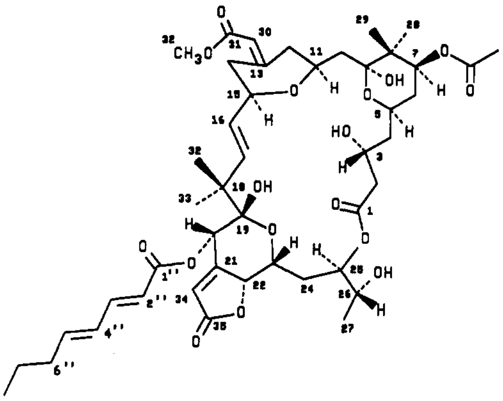

2, BRYOSTATIN 3

at C-20 and C-23 are presumably the same. The stereochemistry at C-22 of bryostatin 3 was assigned with NOE difference spectroscopy results: irradiation on the resonance of H-20 (δ 5.87) enhanced H-33 (δ 1.13) and H-22 (δ 4.61); irradiation on H-22 enhanced H-23 and H-20; irradiation on H-23 enhanced the H-22 and a signal at δ 5.68 (C-19 OH). These NOE results indicate that H-20, H-22, and H-23 are all above the pyran ring; therefore, H-22 is assigned the β configuration. The otherwise minor revision to a five-membered lactone versus the earlier six-membered lactone involving the C-19 hydroxy group is very important for various biochemical mechanistic reasons.[9] The heteronuclear molecular bond correlations (HMBC) summarized in Table I were crucial to assigning structure 2 to bryostatin 3.

The advances in bryostatin chemistry summarized here will simplify a number of on-going chemical and biological investigations in this important field.

Experimental Section[12]

General Procedures. All chromatographic solvents were redistilled. Commercial sources of silica gel (E. Merck, Darmstadt, 70–230 mesh) uniplates (Analtech, Inc., Newark, DE) were used for thin layer chromatography (TLC). The TLC plates were viewed with UV light and developed with anisaldehyde–sulfuric acid spray reagent followed by heating. The NMR spectra were measured on a Bruker AM-400 instrument, with an ASPECT 3000 computer, with $CDCl_3$ employed as solvent, and on a Varian VXR-500S instrument with a Sun 4/260 computer.

Bryostatin 2 7-(*p*-Bromobenzoate) (1d). To a solution of bryostatin 2 26-(*tert* butyl dimethyl silyl ether) (4.6 mg)[12] in CH_2Cl_2 (150 μL) were added *p*-bromobenzoic acid (1.5 mg), dicyclohexylcarbodiimide (3.0 mg), and 4-pyrrolidinopyridine (0.8 mg). The mixture was stirred at room temperature for 2 h. The *N*,*N*-dicyclohexylurea was collected and the filtrate dried. The residue was purified by silica gel column chromatography (1:1 hexane–ethyl acetate) to afford bryostatin 2 7-(*p*-bromobenzoate) 26-(*tert* butyl dimethyl silyl ether) (5.0 mg, 92%). The silyl ether group was removed by treatment with 1:20 48% hydrochloric acid–acetonitrile (250 μL, 0–5 °C, 4 h), solvent evaporated, and product purified by silica gel (1:1 hexane–ethyl acetate) column chromatography. Bryostatin 2 7-(*p*-bromobenzoate) (2.7 mg, 60%) was recrystallized from CH_2Cl_2–CH_3OH: mp 192–193 °C dec; $\alpha^{25}{}_{D}$ = +10° (2 mg/mL, CH_3OH); UV $\lambda^{CH_3OH}{}_{max}$ 243 mμ (ε 6430); IR (thin film) 3440, 2900, 1715, 1625, 1565, 1437, 1310, 1250, 1152, 1085 cm^{-1}. The high resolution (400 MHz) proton NMR spectrum was as expected for bryostatin 2 7-(*p*-bromobenzoate).

Crystal Structure Determination of Bryostatin 2 7-(*p*-Bromobenzoate) (1d): molecular formula $C_{52}H_{69}O_{17}Br$, F.W. 1046.01, *F*(000) 2208, space group $P2_12_12_1$, crystal dimensions 0.26 × 0.24 × 0.40 mm, radiation, Cu Kα, λ = 1.541 84 Å, temperature 26 ± 1 °C, cell constants *a*, 12.999 (2) Å, *b*, 19.947 (4) Å, and *c*, 21.641 (4) Å, $V = 5611.8$ Å^3, $Z = 4$, $\rho_o = 1.237$ g/cm^3, $\rho_c = 1.238$ g/cm^3, and $\mu = 15.24$ cm^{-1}. **Collection parameters**: instrument Enraf-Nonius, CAD4 diffractometer; monochromator graphite crystal incident beam; attenuator Ni foil, factor = 11.7; take-off angle 2.0°; detector aperture 1.8 mm horizontal, 4.0 mm vertical; crystal detector distance 21 cm; scan type ω–2θ, scan rate 0.8 to 5.5°/min (in ω); scan width 0.8 + 0.15 tan θ deg; maximum 2θ 150.0°; and number of reflections measured, one octant + Friedels, 12 159 total, 9715 unique. **Corrections made**: Lorentz-polarization, ϕ scan empirical absorption (0.979 to 0.999 on F_o), linear decay (0.987 to 1.000 on F_o), and anisotropic decay (0.871 to 1.351 on F_o). **Solution and refinement**: direct methods structure solution was accomplished by means of SHELXS-86: Sheldrick, G. Institut für Anorganische Chemie der Universität, Tammannstrasse 4, D-3400 Göttingen, Federal Republic of Germany, using the TEXP feature for partial structure expansion until all 70 non-hydrogen atoms in the molecule were located. All least-squares block-diagonal refinement calculations were performed by using the CRYSTALS computing package: Watkin, D. J.; Carruthers, J. R.; Betteridge, P. W., 1985, Chemical Crystallography Laboratory, University of Oxford, Oxford, OX1 3PD, England. Due to instability noted during initial refinements, the Robust–Resistant (Tukey and Prince) weighting scheme option was used until convergence occurred, then the weighting scheme was changed to $1/\sigma^2(F_o)$ for the final cycles of refinement. Final steps of refinement were done with 5890 reflections in which $F_o{}^2 > 2\sigma(F_o{}^2)$. All non-hydrogen atoms (with the exception of the atoms C38 and C43–46) were refined anisotropically. Hydrogen atom coordinates were calculated with fixed thermal parameters ($U_{iso} = 0.08$ Å^2). They were included but not refined.

Acknowledgment. With appreciation for financial support we thank the Outstanding Investigator Grant OIG CA44344-01A1 and Grant CA-16049-10-12 awarded by the Division of Cancer Treatment, NCI, DHHS, National Cooperative Drug Discovery Grant No. AI-25696-02 and 03, the Fannie E. Rippel Foundation, Virginia Piper, the Arizona Disease Control Research Commission, the Robert B. Dalton Endowment Fund, Eleanor W. Libby, the Waddell Foundation (Donald Ware), and Herbert K. and Dianne Cummings (The Nathan Cummings Foundation, Inc.). We also appreciate assistance provided by Dr. Thomas Groy and Dr. Ronald A. Nieman.

Supplementary Material Available: Table of atomic coordinates and isotropic displacement parameters and 400-MHz ^{1}H NMR spectrum for bryostatin 2 7-(*p*-bromobenzoate) (4 pages). Ordering information is given on any current masthead page.

Synthesis of Chiral α-Alkyl Phenethylamines via Organometallic Addition to Chiral 2-Aryl-1,3-oxazolidines

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Received May 1, 1990

Introduction

In order to fulfill a supply requirement for an optically active pure pharmaceutical candidate, we required substantial quantities of (*R*)-α-methyl-*p*-bromophenethylamine on a continual basis. Normally, this class of amines is readily available for small-scale use, but the commercial availability of large quantities is severely limited. We therefore sought an alternative synthesis that would permit facile access to these amines in high optical purity in a manner that would be amenable to pilot-plant scale. Many of the published routes to α-alkyl phenethylamines require a tedious resolution of the corresponding racemate.[2] The

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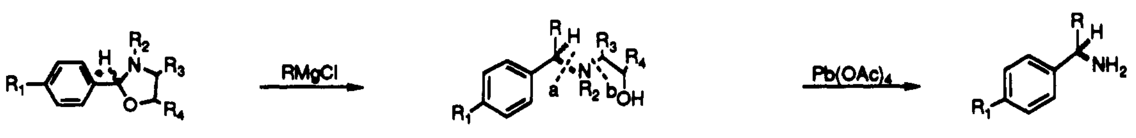
[1] SmithKline Beecham Postdoctoral Fellow, 1989–1990.

0022-3263/91/1956-1340$02.50/0

Scheme I



	R_1	R_2	R_3	R_4
1 a,	H	H	Ph	H
b,	Br	H	Ph	H
c,	OMe	H	Ph	H
d,	Br	H	Me	Ph
e,	Br	Me	Me	Ph

	R	R_1	R_2	R_3	R_4
2 a,	C_2H_5	H	H	Ph	H
2 b,	C_4H_9	H	H	Ph	H
2 c,	CH_3	H	H	Ph	H
2 d,	CH_2Ph	H	H	Ph	H
2 e,	CH_3	Br	H	Ph	H
2 f,	CH_3	MeO	H	Ph	H
2 g,	CH_3	Br	H	CH_3	Ph
2 h,	CH_3	Br	Br	CH_3	Ph

	R	R_1
3a,	C_4H_9	H
3b,	CH_3	H
3c,	C_2H_5	H
3d,	CH_2Ph	H
3e,	CH_3	Br
3f,	CH_3	MeO

Scheme II

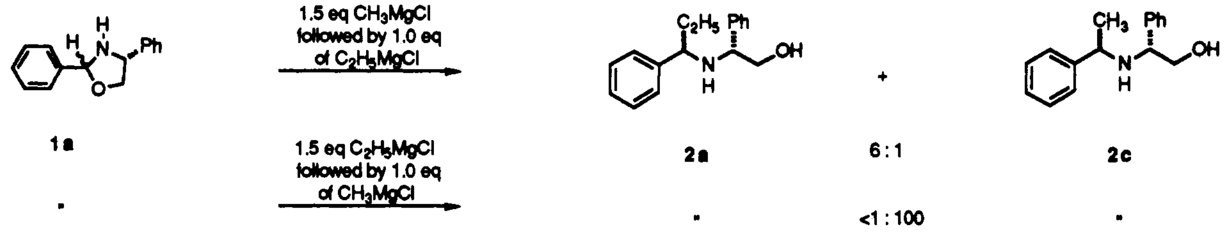


Table I. Yield and Selectivities for Grignard Additions to Oxazolidines 1 and Cleavage Yields of 3

entry	substrate	RMgCl	yield, %[a]	diastereoselectivity[b]		cleavage yield, %		$[\alpha]^{25}_D$, deg (c, $CHCl_3$)	% ee[h]
1	**1a**	Et	62	98:2	**2a**	–		–	–
2	**1a**	Bu[21]	47	98:2	**2b**	52	**3a**	+11.7 (1.0)	92
3	**1a**	Me	56	95:5	**2c**	50	**3b**	+28.8 (1.0)[c]	94
4		Et (3 equiv, $CeCl_3$)[20]	85	>99:1	**2a**	46	**3c**	+35.2 (1.2)[d]	95
5	**1a**	Me [1eq,$MgBr_2 \cdot O(Et)_2$]	31[b]	96:4	**2c**	–		–	–
6	**1a**	benzyl	87	94:6	**2d**	–		–	–
7	**1a**	benzyl (3 equiv, $CeCl_3$)	78	98:2	**2d**	59	**3d**	−10.9 (1.6)[e]	>99
8	**1b**	Me	60	95:5	**2e**	65	**3e**	+24.1 (1.6)[f]	98
9	**1c**	Me	45	97:3	**2f**	46	**3f**	+24.6 (1.0)[g]	96
10	**1d**[6a]	Me	51	94:6	**2g**	–			–
11	**1e**[6c]	Me	77	60:40	**2h**	–			–
12	**1a**	MeLi (−78 °C)	48	95:5	**2c**	–			–
13	**1a**	MeLi (25 °C)	49	77:23	**2c**	–			–
14	*i*	Me	50	87:13	*j*	–			–

[a] Isolated (flashed or recrystallized) yields. [b] The lower yield may be attributed to low solubility of the reagents in THF. [c] Literature[2f] value is +38.8° (neat). [d] Literature[2g] value is +20.2° (neat). [e] Literature[2h] −11.8° (neat). [f] Literature[2k] +25° (neat). [g] Literature +36.1° (neat). [h] Optical purities were determined by the NMR method of Shapiro.[18] The configuration of the final amine product **3** was verified by comparison with authentic samples. [i] The substrate amine in this case was the methoxy derivative of the imine **1B**. [j] This product is the methoxy analogue of **2e** [−9.7° (c 1.0, $CHCl_3$)]. [k] Diastereomeric isomer ratios were determined by using 400-MHz ^1H NMR spectroscopy.

few reported asymmetric approaches are unacceptable for a number of reasons, such as high cost, multiple steps, low chemical yields, or low diastereoselectivity.[3] On the basis of Takahashi's asymmetric synthesis of *optically pure N*-alkyl-1-cyclohexyl-2-phenethylamines by stereoselective addition of benzylmagnesium chloride to (4*R*)-2-cyclohexyl-4-phenyl-1,3-oxazolidine,[4] and the fact that Grignard additions to chiral oxazolidines have enjoyed widespread success in asymmetric systhesis,[5] we decided to explore the use of the analogous 2-aryl-4-phenyl-1,3-oxazolidine **1** as a general substrate for organometallic additions (Scheme I). Since Takahashi[4a] reported only benzylic Grignard addition to 2,4-disubstituted oxazolidines, we sought to explore the scope of this reaction with the ultimate intention of employing the adduct as a source of chiral α-substituted phenethylamines. This report summarizes our efforts to that end.

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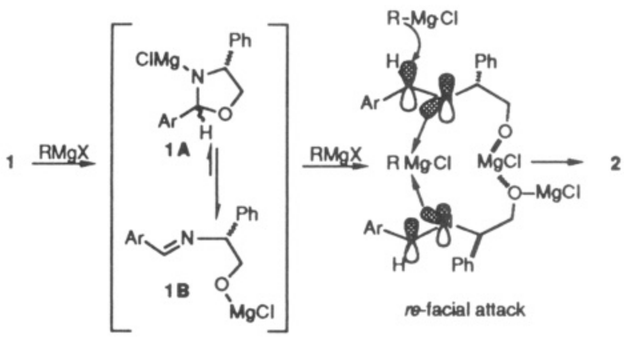
(5) (a) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185. (b) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475. (c) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (d) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron Lett.* **1988**, *29*, 6949. (e) Alcaide, B.; Lopez-Mardomingo, C.; Perez-Ossorio, R.; Plumet, J. *J. Heterocycl. Chem.* **1982**, *19*, 45. (f) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2253. (g) Neelakantan, L. *Ibid.* **1971**, *36*, 2256.

Scheme III



Results and Discussion

Table I outlines our results in the stereoselective organometallic nucleophilic addition to **1**.

All substrate oxazolidines were readily synthesized by condensation of the appropriate aldehyde with the prerequisite chiral amino alcohol.[6] Most of our reactions were done utilizing the readily available (*R*)- or (*S*)-phenylglycinol, prepared in bulk via our recently reported BH$_3$/DME amino acid reduction procedure.[7] Grignard addition to oxazolidine **1** occurred quite readily under THF reflux (4–24 h) with usually very high diastereoselection for **2** (averaging $\sim$96% de) as determined by 400-MHz ^{1}H NMR spectroscopy. Typically, 2.5–3.0 equiv of Grignard reagent was required to force the reaction to completion *and* achieve high diastereoselectivity. In fact Grignard addition would not occur cleanly until at least $\sim$1.5 equiv of the organometallic had been added.

In an interesting experiment, we added 1.5 equiv of methyl Grignard to **1** in THF at room temperature followed shortly by 1.0 equiv of ethyl Grignard and then warmed the reaction mixture to reflux temperature. The resulting product was that predominately from addition of the ethyl group rather than methyl (6:1 ratio). Reversing the order of addition led to a reversal of product selectivity (Scheme II), but with an even greater disparity in the ratio of products (>100:1). This unprecedented high level of asymmetric induction for Grignard addition to the normally tautomeric oxazolidine/imino functionality may be attributed to a highly ordered transition state resulting from significant chelation of the alkoxy substituent and imino nitrogen to at least one magnesium cation. The Grignard reagent then attacks the *re* face of C-2 of either **1A** or **1B**[4a,8] from the less hindered side, distal to the *R* substituent of the amino alcohol moiety (Scheme III). This observation appears to support the postulate of Hauser[9-11] who suggested that amino ethers form a 2:1 strongly coordinated nitrogen/oxygen to magnesium complex, which in our case forms after deprotonation with the first equivalent of Grignard. Consequently, 1.5 equiv of Grignard is unavailable for addition to carbon. This mode of addition is not very dissimilar to the one invoked by Takahashi[12] and Koga[13] in their reported chelation-controlled nucleophilic addition to chiral valinol derived hydrazones and *tert*-leucine derived α,β-unsaturated aldimines, respectively.

In attempts to further exploit this "chelation handle" and also possibly decrease the quantity of Grignard reagent required, we explored the use of Lewis acid chelators. For example, when we used either ZnCl$_2$, TiCl$_4$, BF$_3$·O(Et)$_2$, CuI, or CuBr$_2$·S(CH$_3$)$_2$ with methyl Grignard, we obtained at best a 77:23 ratio of isomeric products. However, with a 1:1 ratio of cerium chloride to Grignard reagent (3 equiv) under our standard reaction conditions, essentially one stereoisomer was obtained. Thus, the stronger chelating ability of cerium has enhanced the selectivity of the organometallic addition to the extent that a single diastereomer may be produced.[14,20] The methoxy analogue of imine **1B** gave a diminished ratio of isomers ($\sim$87:13) as did the (*p*-bromophenyl)oxazolidine analogue of ephedrine (compare entries 10, 11, and 14). Takahashi[4b,c,e] and Davidsen[15] obtained comparable or worse results with chiral N-substituted valinol derived oxazolidines. Thus, at least one of the nitrogen– or oxygen–magnesium bonds in Scheme III should be covalent in order to produce the higher selectivity.[21,22]

Unlike the Takahashi example, which contained only one benzylic amine bond susceptible to reductive cleavage,[4a] we anticipated the need to devise a hydrogenolysis procedure to selectively cleave the ethanolamine carbon–nitrogen bond (b) of **2** (Scheme I). All of our attempts to hydrogenolyze **2** to **3** were without much success, at least up to hydrogen pressures of 80 psi. We also attempted to exploit the hydrogenolysis conditions of Bringman[16] but

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[8] Our data to date does not allow us to discern whether or not Grignard addition is preceded by ring opening since the stereochemical result would be equivalent. However, the NMR (CDCl$_3$) solution spectrum of **1a** indicates that the oxazolinyl/imino tautomeric equilibrium lies predominately toward the imine.[4a,6a,e]

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[20] We have extensively explored the use of cerium organometallics in nucleophilic additions to **1** and closely related analogues. In related work in this laboratory just recently published,[23] we report a synthesis of chiral homoallylamines employing the highly selective allylcerium organometallic reagent. Unlike other organometallic reagents that we investigated, the cerium organometallic is highly regioselective for C-2 of **1** and is the reagent of choice in a nucleophilic addition to **1**. In due course, we will report our results employing this reagent, and others, in Michael-type conjugate additions to α,β-unsaturated analogues of **1**.

[21] A referee suggested that we extend the scope of our study to include 2-aliphatic oxazolidines. However, the pioneering work of Takahashi[4] and later Davidsen[15] has already amply demonstrated the applicability of those substrates, albeit on 2,3,4-trisubstituted oxazolidines. Nevertheless, we employed (4*R*)-2-*n*-butyl-4-phenyloxazolidine as a substrate in a reaction with phenyl Grignard and obtained a 9:91 ratio of **2b**. As expected, the minor isomer in Table I (entry 2) is now major. Thus, with the exception of the unstable 2-methyl-4-phenyloxazolidine, both aliphatic and aryl 2-oxazolidines may be employed in this reaction.

[22] In related work, organometallic additions to nitrones bearing stereogenic N-substituents were reported by Coates after the submission of this manuscript: (a) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464. (b) Chang, Z.-Y.; Coates, R. M. *Ibid.* **1990**, *55*, 3475.

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obtained the undesired bond cleavage at a (Scheme I). Only the carefully controlled oxidative conditions of Gawley[17] proved to be effective in obtaining the desired chiral phenethylamines, albiet in moderate yields.

Additional studies designed to further exploit the chelation-controlled stereoselectivity of nucleophilic additions to this chiral oxazolidinyl/imino system will be forthcoming.

Experimental Section

All commercially obtained solvents and reagents were used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Flash column chromatography was done on "Baker silica gel for flash column" (~40 μm average particle diameter). Melting points were measured on a capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken on a Brucker AM-400.

Starting Materials. All substrate oxazolidines were readily synthesized by condensation of the appropriate aldehyde with the prerequiste chiral amino alcohol.[6] The synthesis of oxazolidines **1a–c** are included as supplementary material. All Grignard reagents used in this study were purchased from Aldrich Chemical Co. and titrated by the method of Ogura.[19] Moisture-sensitive reactions were carried out in predried glassware and under a nitrogen atmosphere.

General Procedure A. Addition of Grignard Reagents to 2-Aryl-1,3-oxazolidines (1). To a THF solution of the oxazolidine (0.3–0.5 M) was added Grignard reagent (3 equiv) dropwise via an addition funnel. The resulting dark-red solution was magnetically stirred at reflux temperature for (4–24 h). After being cooled to room temperature, the reaction mixture was treated with a small quantity of water (1–2 mL) and the resulting white precipitate was removed by filtration. The filtrate was diluted with ether and dried over MgSO$_4$. The solvent was evaporated in vacuo, and the residue was purified by flash column chromatography.

General Procedure B. Addition of Organocerium Reagents to 2-Aryl-1,3-oxazolidines (1). The anhydrous CeCl$_3$[14] (3 equiv) was stirred in THF (5 mL per gram of CeCl$_3$) for 2 h. The suspension was cooled to -45 °C, treated with Grignard reagent (3 equiv), and stirred for 1 h at -45 °C. A solution of the oxazolidine in THF (0.5 M) was added into the stirred suspension dropwise via an addition funnel. The resulting solution was stirred at -45 °C for 3–6 h. The reaction mixture was then allowed to warm to room temperature, poured into ice–water, and extracted with ether. The ether extracts were dried (MgSO$_4$) and evaporated in vacuo. The residue was purified by flash column chromatography.

(2*R*,1′*R*)-2-[(1′-Phenylethyl)amino]-2-phenylethanol (2c). Prepared by general procedure A: flash chromatography (50% Et$_2$O in hexanes as eluent) yielded 3.0 g (56%) of an orange oil; $[\alpha]^{25}_{D}$ -20.3° (*c* 1.4, CHCl$_3$); IR (neat) 3250–3500 cm^{-1} (NH, OH); ^{1}H NMR (CDCl$_3$) δ 7.20–7.40 (m, 10 H), 3.88 (dd, 1 H, *J* = 7.8, 4.6 Hz), 3.70–3.76 (m, 2 H), 3.51 (dd, 1 H, *J* = 11.8, 7.8 Hz), 2.58 (br s, 1 H), 1.36 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (CDCl$_3$) δ 145.5, 140.8, 128.5, 128.4, 127.1, 126.5, 66.0, 61.4, 54.6, 22.2; MS (CI) [*m/e* (% RA)] 242 [(M + 1)$^+$, 100]; HRMS (CI) calcd for (M + 1)$^+$ $C_{16}H_{20}NO$ 242.1545, found 242.1535.

(2*R*,1′*R*)-2-[(1′-Phenylpropyl)amino]-2-phenylethanol (2a). Prepared by general procedure A: flash chromatography (20% Et$_2$O in hexanes as eluent) yielded an orange oil; 1.58 g (62%); $[\alpha]^{25}_{D}$ -37.9° (*c* 0.8, CHCl$_3$); IR (neat) 3200–3500 cm^{-1} (NH, OH); ^{1}H NMR (CDCl$_3$) δ 7.17–7.30 (m, 10 H), 3.82 (dd, 1 H, *J* = 7.0, 4.6 Hz), 3.73 (dd, 1 H, *J* = 10.7, 4.6 Hz), 3.47–3.54 (m, 2 H), 1.86 (m, 1 H), 1.67 (m, 1 H), 0.76 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR (CDCl$_3$) δ 143.9, 141.3, 128.5, 128.4, 127.4, 127.2, 127.1, 65.5, 61.6, 61.2, 29.4, 10.4; MS (CI) [*m/e* (% RA)] 256 [(M + 1)$^+$, 100]; HRMS (CI) calcd for (M + 1)$^+$ $C_{17}H_{22}NO$ 256.1701, found 256.1709.

Prepared by general procedure B: flash chromatography (20% Et$_2$O in hexanes as eluent); 2.16 g (85%) as a colorless oil.

(2*R*,1′*R*)-2-[(1′-Phenylpentyl)amino]-2-phenylethanol (2b). Prepared by general procedure A: flash chromatography (20% Et$_2$O in hexanes as eluent) yielded an orange oil; 3.3 g (47%); $[\alpha]^{25}_{D}$ -48.2° (*c* 0.6, CHCl$_3$); IR (neat) 3200–3500 cm^{-1} (NH, OH); ^{1}H NMR (CDCl$_3$) δ 7.16–7.30 (m, 10 H), 3.81 (dd, 1 H, *J* = 6.8, 4.7 Hz), 3.58 (dd, 1 H, *J* = 8.4, 5.3 Hz), 3.50 (dd, 1 H, *J* = 10.6, 6.9 Hz), 1.82 (m, 1 H), 1.64 (m, 1 H), 1.02–1.32 (m, 4 H), 0.82 (t, 3 H, *J* = 7.0 Hz); MS (CI) [*m/e* (% RA) 284 [(M + 1)$^+$, 100]. Anal. Calcd for HCl salt $C_{19}H_{26}ClNO$: C, 71.34; H, 8.19; N, 4.38. Found: C, 71.30; H, 8.01; N, 4.46.

(2*R*,1′*R*)-2-[[1′-(4-Methoxyphenyl)ethyl]amino]-2-phenylethanol (2f). Prepared by general procedure A: flash chromatography (50% Et$_2$O in hexanes as eluent) yielded 1.22 g (45%) of a yellow oil; $[\alpha]^{25}_{D}$ -25.5° (*c* 0.3, CHCl$_3$); IR (neat) 3400 cm^{-1} (broad, NH, OH); ^{1}H NMR (CDCl$_3$) δ 7.20–7.31 (m, 5 H), 7.14 (d, 2 H, *J* = 8.6 Hz), 6.80 (d, 2 H, *J* = 8.6 Hz), 3.84 (dd, 1 H, *J* = 7.6, 4.5 Hz), 3.74 (s, 3 H), 3.67–3.70 (m, 2 H), 3.48 (dd, 1 H, *J* = 10.4, 7.8 Hz), 1.32 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR (CDCl$_3$) δ 158.6, 141.1, 137.8, 128.5, 127.8, 127.4, 127.2, 113.9, 66.1, 61.4, 55.2, 53.8, 22.2; MS (CI) [*m/e* (% RA)] 272 [(M + 1)$^+$, 1.65], 135 [(CH$_3$O(C$_6$H$_4$)CHCH$_2$ + 1)$^+$, 100]; HRMS (CI) calcd for (M + 1)$^+$ $C_{17}H_{22}NO_2$ 272.1651, found 272.1642.

(2*R*,1′*R*)-2-[[1′-(4-Bromophenyl)ethyl]amino]-2-phenylethanol (2e). Prepared by general procedure A: flash chromatography (50% Et$_2$O in hexanes as eluent) yielded 2.18 g (60%) of an orange oil; $[\alpha]^{25}_{D}$ +12.5° (*c* 1.6, CHCl$_3$); IR (neat) 3350 cm^{-1} (broad, NH, OH); ^{1}H NMR (CDCl$_3$) δ 7.11–7.40 (m, 9 H), 3.85 (dd, 1 H, *J* = 7.8, 4.5 Hz), 3.72 (m, 2 H), 3.52 (dd, 1 H, *J* = 10.8, 7.8 Hz), 1.59 (br s, 2 H), 1.33 (d, 3 H, *J*, = 6.5 Hz); MS (CI) [*m/e* (% RA)] 320 [(M + 1)$^+$, 100], 322 [(M + 3)$^+$, 94.7]; HRMS (CI) calcd for (M + 1)$^+$ $C_{16}H_{19}BrNO$ 320.0650, found 320.0632.

(2*R*,1′*R*)-2-[(1′,2′-Diphenylethyl)amino]-2-phenylethanol (2d). Prepared from general procedure A: flash chromatography (50% Et$_2$O in hexanes as eluent) yielded 2.77 g (87%) of a white solid; mp 62–64 °C (from EtOAc/Hexanes); $[\alpha]^{25}_{D}$ -6.3° (*c* 1.6, CHCl$_3$); IR (KBr) 3350 cm^{-1} (broad, NH, OH); ^{1}H NMR (CDCl$_3$) δ 6.99–7.29 (m, 15 H), 3.86 (t, 1 H, *J* = 6.8 Hz), 3.79 (dd, 1 H, *J* = 6.6, 4.5 Hz), 3.68 (dd, 1 H, *J* = 10.8, 4.5 Hz), 3.46 (dd, 1 H, *J* = 10.8, 6.8 Hz), 3.06 (dd, 1 H, *J* = 13.4, 6.8 Hz), 2.94 (dd, 1 H, *J* = 13.4, 6.9 Hz); ^{13}C NMR (CDCl$_3$) δ 143.5, 141.2, 138.7, 129.3, 128.4, 128.2, 128.1, 127.3, 127.2, 126.1, 65.4, 62.0, 61.5, 43.8; MS (CI) [*m/e* (% RA)] 318 [(M + 1)$^+$, 100]; HRMS (CI) calcd for (M + 1)$^+$ $C_{22}H_{24}NO$ 318.1858, found 318.1843.

Prepared by general procedure B: flash chromatography yielded 2.47 g (78%) of a white solid.

(1*R*,2*S*,1′*S*)-2-[[1′-(4-Bromophenyl)ethyl]amino]-1-phenylpropanol (2g). Prepared from general procedure A: flash chromatography (50% Et$_2$O in hexanes as eluent) yielded 1.71 g(51%) of a light yellow solid; $[\alpha]^{25}_{D}$ -27.7° (*c* 1.0, CHCl$_3$); IR (KBr) 3350 cm^{-1} (broad, NH, OH); ^{1}H NMR (CDCl$_3$) δ 7.47 (d, 2 H, *J* = 3.5 Hz), 7.17–7.44 (m, 7 H), 4.81 (d, 1 H, *J* = 3.5 Hz), 3.95 (q, 1 H, *J* = 6.7 Hz), 2.78 (m, 3 H), 1.37 (d, 3 H, *J* = 6.6 Hz), 0.72 (d, 3 H, *J* = 6.6 Hz); MS (CI) [*m/e* (% RA)] 334 [(M + 1)$^+$, 69.67], 336 [(M + 3)$^+$, 66.46]. Anal. Calcd for HCl salt $C_{17}H_{21}BrClNO$: C, 55.08; H, 5.71; N, 3.78. Found: C, 55.78; H, 5.85; N, 3.80.

(1*R*,2*S*,1′*S*)-2-[*N*-Methyl-*N*-[1′-(4-bromophenyl)ethyl]amino]-1-phenylpropanol (2h). Prepared by general procedure A as a 60:40 ratio of isomers: flash chromatography (20% Et$_2$O in hexanes as eluent) yielded 0.8 g (77%) of a light yellow oil; IR (neat) 3440 cm^{-1} (OH); ^{1}H NMR (CDCl$_3$) δ 7.22–7.45 (m, 6 H), 7.10, 6.98 (2 d, 2 H, *J* = 8.4 Hz each), 4.80, 4.68 (2 d, 1 H, *J* = 5.1 Hz and *J* = 5.7 Hz), 3.84, 3.78 (2 q, 1 H, *J* = 6.7 Hz each), 3.07, 2.76 (2 p, 1 H, *J* = 6.7 Hz each), 2.11, 2.07 (2 s, 3 H), 1.29, 1.27 (2 d, 3 H, *J* = 6.7 Hz each), 0.92 (d, 3 H, *J* = 6.7 Hz); MS (CI) [*m/e* (% RA)] 348 [(M + 1)$^+$, 46.64], 350 [(M + 3)$^+$, 42.88]. Anal. Calcd for $C_{18}H_{22}BrNO$: C, 62.07; H, 6.37; N, 4.02. Found: C, 61.76; H, 6.29; N, 3.88.

General Procedure C. Oxidative Cleavage of Amino Alcohol and Hydrolysis to Phenethylamine. To a solution of the amino alcohol (0.02–0.05 M) in CH$_2$CL$_2$/MeOH (2/1) at 0 °C was added, in one portion, 1 equiv of lead tetraacetate. The reaction mixture was stirred for 2–20 min, whereupon 5 mL of 15% NaOH was added. The phases were separated, and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic extracts were evaporated in vacuo. The crude product was then dissolved in ether and stirred for 4–16 h with an equal volume of 3 N aqueous HCl solution. The aqueous phase was made basic by the addition of Na$_2$CO$_3$ and extracted with ether. The organic extract was dried (MgSO$_4$) and evaporated in vacuo. The crude amine was purified by Kugelrohr distillation or flash column chromatography.

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Supplementary Material Available: General experimental procedures for the synthesis of oxazolidines **1a–c** (including spectral data); spectral data for phenethylamines **3a–f**; and ^1H 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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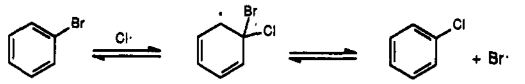
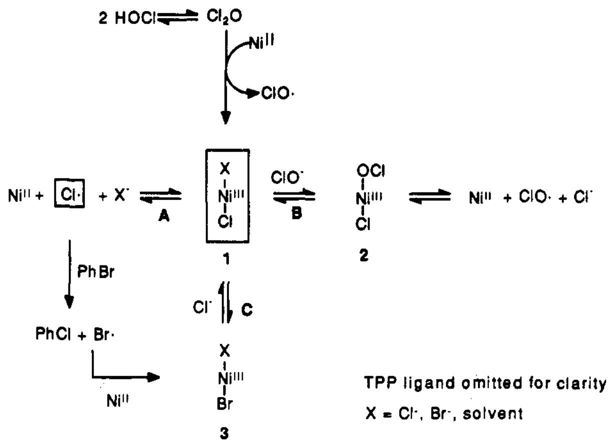
Due to the ease with which aryl–halogen bonds are activated by transition metals, aryl halides have become important precursors to a wide variety of synthetically useful compounds.[1] One successful method for the synthesis of haloarenes is the halogen exchange reaction. Although Ni^0, Ni^{II}, and Cu^I 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)

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]

Scheme I



TPP ligand omitted for clarity

X = Cl·, Br·, solvent

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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(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.

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