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$InBr_3$-Catalyzed Friedel−Crafts Addition of Indoles to Chiral Aromatic Epoxides: A Facile Route to Enantiopure Indolyl Derivatives

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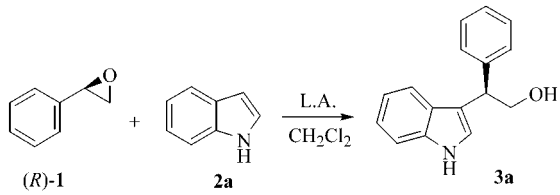
Abstract: Aromatic optically active epoxides can be opened in a regioselective and clean way with indoles in the presence of catalytic amount of $InBr_3$ (1 mol %). The reaction takes place with a S_N2 pathway affording the 2-aryl-2-(3′-indolyl)-ethan-1-ols with excellent enantioselectivity (ee up to 99%).

The preparation of enantiopure chiral compounds for searching biologically active molecules is becoming an important issue for pharmaceutical industries.[1] Diversity,[2] exploited in synthesizing arrays of compounds and coupled with highthroughput screening methodologies,[3] is helping for the fast discovery of new active compounds. In this context, simply synthetic methodologies focused toward the preparation of chiral optically active compounds can be beneficial to the discovery of new leads.[4] Indole is a key motif in many pharmacologically and biologically active compounds[5] as well as in many natural products it belongs to the class of the alkaloids[6] and a direct synthesis of optically active indolyl derivatives is desired. Normally, Friedel−Crafts (F−C) reactions[7] are performed in a non-enantioselective way, via the use of catalytic or stoichiometric amount of Lewis acids.[8] Recently, however, an interesting preparation of optically active compounds bearing aromatic systems was reported in the literature.[9] Focusing on indole-type frameworks, an elegant catalytic asymmetric Lewis acid mediated F−C protocol was introduced by Jørgensen et al.[10] However, the F−C reaction is particularly critical with indoles. In fact, their tendency to react with carbonyls producing diindolyl compounds,[11] significantly limited their use in catalytic strategies. On the other hand, indole can be added to optically active aromatic epoxides.[12] Aromatic epoxides are an ideal source for diversity, because they can be easily opened with nucleophiles[13] furnishing functionally diverse compounds. However, in the Friedel−Crafts reaction conditions, aromatic optically active epoxides could rearrange to isomeric carbonyl compounds or racemize.[14] Herein, we report on a straightforward $InBr_3$-catalyzed approach toward the preparation of optically active indolyl derivatives in good yield and high enantioselectivity (ee up to 99%, Scheme 1).

SCHEME 1. Regio- and Stereoselective Ring Opening of Optically Active Styrene Oxide by Indole



(*R*)-**1** **2a** **3a**

Procedures for the indole ring-opening reaction of aromatic epoxides are reported in the literature and can be catalyzed by high pressure (10 kbar) or by the use of SiO_2.[12] While the employment of high pressure requires the use of special equipment, for the latter method, although simple, several days were necessary in order

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TABLE 1. Lewis Acid Mediated Addition of Indole to Styrene Oxide

entry[a]	Lewis acid (mol %)	yield[b] (%)	ee[c] (%)
1	$Cu(OTf)_2$ (10)	33[d]	*e*
2	$Zn(OTf)_2$ (10)	29	69
3	$Sc(OTf)_3$ (10)	54	99
4	$Sc(OTf)_3$ (1)	52	99
5	ZnI_2 (10)	57	90
6	$BF_3{\cdot}OEt_2$ (1)	54	99
7	$InCl_3$ (10)	55	99
8	$InBr_3$ (10)	60	75
9	$InBr_3$ (5)	64	99
10	$InBr_3$ (1)	70[f]	99
11	$InBr_3$ (1)	20[g]	*e*

[a] All the reactions were carried out in anhydrous CH_2Cl_2 at 0 °C for 4 h unless otherwise specified. [b] The chemical yields are given on the isolated product after chromatographic purification. [c] The enantiomeric excess of the indolyl alcohol was determined by chiral HPLC analysis (column: Chiralcel OD). Racemic **3a** was obtained starting from (±)-**1a**. [d] A 1:1 mixture of regioisomers was observed. [e] Not determined. [f] The reaction was performed at room temperature. [g] The reaction was carried out in THF (isolated yield after 5 days).

to obtain good conversions. In fact, it was reported that indole **2a** adsorbed with styrene oxide **1** on silica gel allowed to react in *1 week* affording the 2-(1*H*-indol-3-yl)-2-phenylethanol (**3a**) in 88% yield. Most importantly, the reported methodologies gave the desired (*R*)-(−)-**3a** in 92 and 88% ee, respectively. In such conditions, a slight racemization of the product was observed due to the partial formation of benzylic carbocations.

In the course of our investigations toward the development of new reactions promoted by indium salts,[15] we were pleased to discovered that anhydrous $InBr_3$ was able to promote the addition of indole[16] **2a** to (*R*)-(+)-styrene oxide in mild experimental conditions (cat. 1 mol %, room temperature, 8−18 h). Although other Lewis acids were able to perform the attack of indole to styrene oxide (Scheme 1), indium tribromide was the unique Lewis acids that allowed low loading of catalyst (1 mol %), furnishing clean reactions and the highest chemical yields (entries 9 and 10, Table 1).[17] For instance, the use of $Zn(OTf)_2$ as the Lewis acid furnished the product in low chemical and optical yields (yield 29%, ee 70%). The partial racemization must be ascribed to an S_N1-type mechanism. Only $Sc(OTf)_3$-catalyzed the ring-opening reaction with comparable stereoselection to indium tribromide (entries 3, 4 and 9, 10, Table 1). However, in terms of activity, functional group tolerance and regio/stereoselectivity, $InBr_3$ was significantly superior and the catalytic system was investigated further.

The loading of the catalyst (optimal 1 mol %) appeared to be crucial for the effectiveness of the protocol. In fact, initial attempts to carry out the indium-mediated process in the presence of 10 mol % catalyst furnished the compound **3a** in 75% ee (Table 1, entry 8). The lower enantiomeric excess could be ascribed to the attack of indole via an S_N1-type mechanism. For general interest, it should be noted that BF_3 was an effective promoter even in low catalytic amount (1 mol %, entry 6, Table 1). However, in this case the reaction suffered of scarce regioselectivity. In fact, after chromatographic separation, the regioisomer 1-(1*H*-indol-3-yl)-2-phenylethanol, derived from the nucleophilic attack of indole to the less substituted carbon, was isolated in 12% yield.

In general, aliphatic epoxides were not suitable substrates for our reaction conditions, giving indolyl alcohols in low isolated yields and with negligible regiocontrol. For example, when the reaction of **2a** with (*S*)-(−)-propylene oxide in the presence of 10 mol % $InBr_3$ was performed, two regioisomers were isolated in 1:1 ratio and in 35% yield.

The absolute configuration of the product obtained by the attack of **2a** to (*R*)-(+)-styrene oxide was assigned by comparison with the chiral HPLC analysis previously reported in the literature for the compound **3a**.[18] The generality and the scope of this Lewis acid catalyzed reaction is summarized by the data reported in Table 2. Substituted indoles were reacted with a few representative optically active aromatic epoxides (Scheme 2).[19] In general, indoles bearing electron-donating groups furnished higher reaction rates, affording the corresponding alcohols in moderate to good yields (entries 4 and 6, Table 2). On the other hand, electron-withdrawing groups significantly decreased the reactivity of indoles in this Friedel−Crafts process. In fact, when 5-nitro- and 5-cyanoindole were used as nucleophiles, low yields (24−41%) and partial racemization (ee = 70%) were observed (entries 2 and 5, Table 2). The dropped ee of the compound **3b** can be imputable to the extremely slow reaction rate (96 h). With different aromatic optically active epoxides such as (*R*)-(+)-3-chlorostyrene oxide **4** and (1*R*,2*S*)-1,2-dihydronaphthalene oxide **5**,[20] remarkable enantioselectivity was always recorded (ee up to 99%, entries 9 and 10, Table 2) showing the effectiveness of $InBr_3$ in the synthesis of indolyl derivatives in enantiomerically pure form. It is worthy to note that the presence of strongly coordinating groups in this Lewis acid catalyzed reaction is well tolerated. Indium salts and in particular Lewis acid catalyzed reactions promoted by $InBr_3$ shown this interesting feature.[16] This properties can be understood taking into account the low heterophilcity exhibited by indium species.[14]

Enantiomeric excesses were established by chiral HPLC analysis (Chiralcel OD column), and the absolute configuration of the indolyl compounds **3b**−**j** was assigned by analogy considering the correlation of elution order made for **3a**.

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(16) Several aromatic compounds were considered as nucleophiles for the F−C reaction such as pyrroles, thiophenes, and furans. However, due to the instability of the F−C products (pyrroles) and due to the decomposition of the aromatic epoxides (thiophenes and furans), unclear reaction mixtures were always observed.

(17) No appreciable formation of *β*-bromohydrines was observed on the crude reaction mixtures.

(18) Carrying out the ring-opening reaction of **1a** with **2a** in the presence of SiO_2 (500 mg, mesh 270 nm), the indolyl alcohol **3a** was isolated in 86% ee (see ref 12). However, although the elution order (chiral HPLC) of (*R*)-**3a** and (*S*)-**3a** was in agreement with the literature, the measured optical rotation value shown opposite sign: +13.6 (*c* 1.3, $CHCl_3$) [lit. −0.435 (*c* 0.46, $CHCl_3$)].

(19) Aromatic optically active epoxides can be easily obtained by [Co(Salen)] mediated hydrolytic kinetic resolution of the corresponding racemic epoxides; see: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

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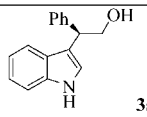
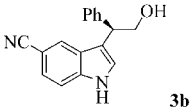
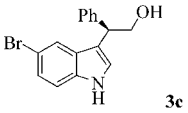
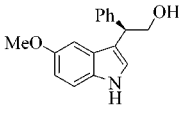
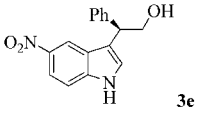
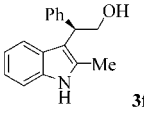
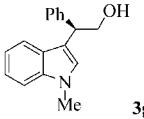
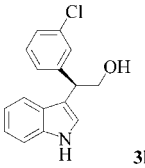
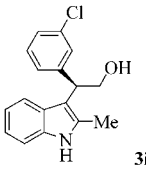
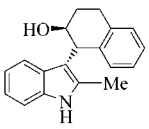
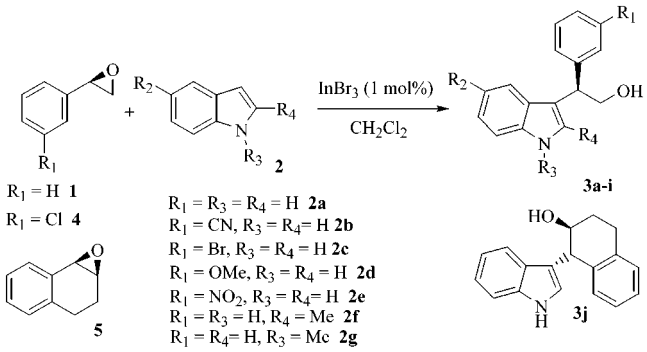
TABLE 2. Addition of Indoles to Aromatic Epoxides Catalyzed by $InBr_3$[a]

Entry	Epoxide	Indole	Product	Yield (%)[b]	ee (%)[c]
1	**1**	**2a**	 **3a**	70	99
2	**1**	**2b**	 **3b**	41[d]	70
3	**1**	**2c**	 **3c**	54	99
4	**1**	**2d**	 **3d**	54	99
5	**1**	**2e**	 **3e**	24[e]	-[f]
6	**1**	**2f**	 **3f**	79	99
7	**1**	**2g**	 **3g**	68	99
8	**4**	**2a**	 **3h**	65	99
9	**4**	**2f**	 **3i**	82	99
10	**5**	**2f**	 **3j**	84[g]	83

[a] All the reactions were carried out in anhydrous CH_2Cl_2 at room temperature, employing 1 mol % of $InBr_3$ for 8−16 h unless otherwise specified. [b] The chemical yields are given on the isolated product after chromatographic purification. [c] The enatiomeric excesses were determined by HPLC analysis with chiral column (Chiralcel OD). Racemic products were obtained performing the reaction on racemic epoxides with $InBr_3$. [d] The reaction was performed using 10 mol % of $InBr_3$ at room temperature for 16 h. [e] The reaction was performed using 10 mol % of $InBr_3$ at room temperature for 96 h. [f] The enantiomeric excess was not evaluated. [g] The optically active epoxide (1*R*,2*S*)-**5** was prepared using the asymmetric Jacobsen epoxidation in 83% ee.[20]

SCHEME 2. Reaction of Substituted Indoles with Aromatic Epoxides Catalyzed by $InBr_3$



In summary, we have described a new direct protocol for the preparation of enantiomerically pure indolyl derivatives via a Friedel−Crafts-catalyzed ring opening of optically active aromatic epoxides. The use of the $InBr_3$ as catalyst besides to guarantee a general tolerance toward the presence of different functional groups on the indole motif, allows the isolation of the indolyl alcohols in excellent ees and good chemical yields via a rigorous S_N2 pathway. Although Lewis acids are normally responsible for the rearrangement of aromatic epoxides to the corresponding carbonyls, the mild Lewis acid character exploited by $InBr_3$ allowed the isolation of the desired compounds in high yields and without significant racemization.

Experimental Section

General Methods. Chemical shifts of the ^1H NMR spectra are reported in δ (ppm) with respect to TMS, and coupling constants *J* were measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = douplet, t = triplet, q = quartet, br = broad, m = multiplet). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform, δ = 77.0 ppm; deuteriodimethyl sulfoxide, δ = 39.0 ppm). GC−MS spectra were taken by EI ionization at 70 eV with GC injection. They are reported as *m*/*z* (relative intensity). Column flash chromatographies were run over 270−400 mesh silica gel. Elemental analyses were carried out by using a CHNOS analyzer. IR analyses were performed with an FT-IR spectrophotometer. IR spectra of neat compounds are expressed by wavenumber (cm^{-1}). Analytical high-performance liquid chromatograph (HPLC) was performed on a liquid chromatograph equipped with a variable-wavelength UV detector (deuterium lamp 190−600 nm), using a Daicel Chiralcel OD column (0.46 cm i.d. × 25 cm) (Daicel Inc.). HPLC-grade 2-propanol and hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (Na_D line). The melting points were uncorrected. All the commercially available epoxides and indoles were utilized as received.

Typical Experimental Procedure for $InBr_3$-Mediated Ring-Opening of Epoxides. A flamed two-necked flask was charged, under a nitrogen atmosphere, with 3 mL of anhydrous CH_2Cl_2, $InBr_3$ (5.5 mg, 0.015 mmol), and 2.25 mmol of indole. The mixture was stirred for a few minutes, and then 1.5 mmol of epoxide was added. This clear solution was then stirred at room temperature until the disappearance of the epoxide (8−16 h, checked by GC). Then the reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with Et_2O. The organic portions were dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product mixture was purified by flash chromatography.

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Supporting Information Available: Analytical and spectral characterization data for the indole derivatives **3a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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