Polymer-Supported Indium Lewis Acid: Highly Versatile Catalyst for Regio- and Stereoselective Ring-Opening of Epoxides

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Abstract: The first example of a polymer-supported indium Lewis acid is presented. This new heterogeneous Amberlyst 15/indium complex effectively catalyses (20 mol % based on indium) the formation of new C–C as well as C–S bonds through the highly regio- and stereoselective ring-opening reaction of enantiomerically pure epoxides. The easily prepared Amberlyst 15/indium Lewis acid does not require inert atmosphere conditions or anhydrous media and can be easily recovered and recycled for several times without loss of activity.

Keywords: asymmetric catalysis; heterogeneous catalysis; immobilization; indium; ring-opening

Introduction

Lewis acid-catalyzed reactions continue to attract increasing attention in the modern organic synthesis scenario.[1] Nowadays, studies focused on the development of highly efficient, selective and safe Lewis acid-based promoting systems are a research topic for numerous chemists. In this context, immobilized *green* Lewis acid catalysts are receiving a great deal of attention due to environmental, practical and economical concerns. Of particular relevance are the resin-supported metal catalysts that, due to the fine tuning of their physico-chemical properties, are emerging as alternative promoting agents for several challenging organic transformations.

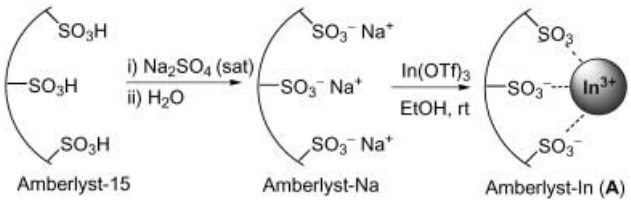
After the pioneering study of Neckers and co-workers on syntheses and applications of organic polymer-supported $AlCl_3$ and BF_3 species,[2] numerous heterogeneously catalyzed organic transformations involving metals anchored to acid ion-exchange resins have been described.[3] In particular, heterogeneous Lewis acids based on metals with high coordination numbers, such as Sc, Yb and Ln, proved to be highly effective in promoting several organic reactions. Among them, Diels–Alder reactions, Friedel–Crafts reactions, allylations of carbonyls, Michael additions and Mukaiyama reactions have been studied in anhydrous as well as aqueous media.[4]

Results and Discussion

In the field of Lewis acid catalysis, indium(III) halides and triflate have emerged as highly effective promoting agents for numerous chemoselective organic reactions.[5] Then, encouraged by the remarkable functional group tolerance showed by indium salts in homogeneous catalysis, we planned to synthesize an unprecedented polymer-supported indium(III) Lewis acid.[6] To this aim, Amberlyst-Na[4c] (2 g) and $In(OTf)_3$ (2 mmol) were shaken at room temperature in EtOH under nitrogen for 16 h to give, after filtration and drying under vacuum, the Amberlyst-In (Amb-In) polymer **A** (Scheme 1).

The present resin-In shows one of the highest contents of metal (estimated 0.92 mmol/g) so far described regarding organic polymer-supported Lewis acids with an exchange percentage (EP) of 59%.[7] On the other hand, previously reported Sc(III)- and lanthanide(III)-supported catalysts are generally characterized by loading levels of less than 0.8 mmol/g.

As a continuation of our recent findings focused on the $InBr_3$-catalyzed ring-opening of epoxides,[8] we started testing the catalytic properties of this novel supported In catalyst in the ring-opening of enantiomerically pure epoxides[9] by using indoles as nucleophiles.[10] In our initial evaluations, we used as the model reaction the addition of *N*-methylindole (**2a**, 1.5 equivs.) to (*R*)-



Scheme 1. Synthesis of the resin-supported indium Lewis acid **A**.

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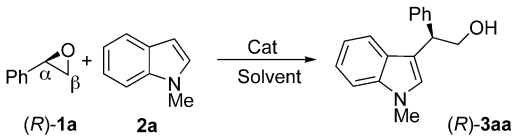
Table 1. Reaction conditions optimization.



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

Entry	Catalyst [%]	t [h]	Solvent	**3aa** [%][a]	ee [%][b]
1	**A** (20)	24	CH_2Cl_2 (dry)	40	96
2	**A** (5)	24	CH_2Cl_2 (dry)	40	91
3	**A** (20)	24	Toluene (dry)	47	>98
4	**A** (20)	24	Et_2O (dry)	62	>98
5	**A** (20)	24	Et_2O (wet)	64	>98
6	Amb-Na	24	Et_2O (wet)	–	–
7	Amb-15	24	Et_2O (wet)	11[c]	72

[a] After flash chromatography.
[b] Determined by HPLC analysis with a chiral column (Chiralcel-OD).
[c] A mixture of regioisomers was obtained.

(+)-styrene oxide (**1a**, 1 equiv.). The choice of the solvent appeared crucial in order to maximize yield, to minimize side rearrangements and to avoid racemization.[11]

Particularly promising proved to be the use of reagent grade Et_2O that, among the various solvents surveyed and in the presence of 20 mol % of **A** (based on the amount of In^{3+}), led to the desired β-indolyl alcohol (*R*)-(−)-**3aa** in good yield (64%) and >98% enantiomeric excess (entry 5, Table 1). The highest yield obtained by using Et_2O as the solvent can be ascribed to the fruitful swelling of the polymer network of the catalyst in this media, allowing the metal particles located inside the polymer matrix to effect the catalysis.

The key role played by the Lewis acidity of the heterogeneous catalyst **A** was proved by employing the Amberlyst-Na resin (entry 6) and Amberlyst-15 dry (entry 7) as catalysts. In fact, while in the former case no reaction occurred, in the latter, **3** was isolated in low yield (11%) as a mixture of regioisomers with a significant racemization of the benzylic stereocenter (ee = 72%).[12] The leaching of active sites in the organic products is a crucial issue that must be always considered in metallo-supported catalysis. To rule out the presence of concurrent homogeneous catalysis, we ran a probe reaction between **1a** and **2a** in the presence of Amb-In (20 mol %) for 7 h (44% conversion by ^{1}H NMR, ee > 98%). Then the catalyst was removed by filtration and the mixture was allowed to react again. However, after 48 h reaction time **3aa** was obtained as 47% conversion and ee > 99%. This finding suggested that no significant leaching is operating under our reaction conditions.

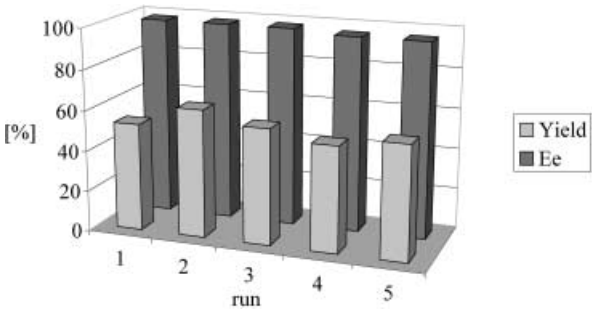


Figure 1. Testing the reusability of the In-supported catalyst.

The catalyst **A** can be easily recovered by filtration after each reaction and reused without further treatments (Figure 1). In particular, the same amount of Amb-In was employed in 5 cycles of the reaction **1a**/**2a** without a remarkable loss of activity.[13]

Then, several indoles were tested in the ring-opening reaction of enantiomerically pure epoxides (**1a, b**, Table 2). All the attempts furnished chemoselectively the alcohol derived from the attack at the benzylic carbon (α position) in moderate to good yields (up to 62%, entry 5) and without detectable racemization (ee > 98%). Only 1*H*-indole gave rise the β-aryl alcohol **3ah** in 90% ee.

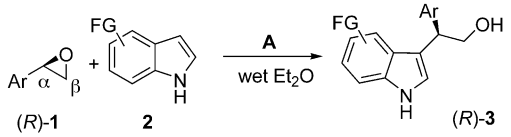
It is noteworthy that while the yields with indole (**2 h**) and alkyl-substituted indoles (**2f**, **2 g**) were only slightly lower than those of homogeneous counterpart,[8] indoles bearing sterically demanding groups such as 2-Ph- and 5-Br-indoles (**2c** and **2e**) furnished the desired alcohols in lower yields (40–42%, entries 2 and 4). This phenomenon can be rationalized by taking into account the poor accessibility of the interior catalytic particles for bulky organic molecules with the consequent drop in activity of the catalytic sites. Interestingly, a different behaviour was recorded for 5-BnO-indole (**2b**) that underwent the reaction with **1a** in good yield (60%) and without racemization (entry 1, Table 2).

Interestingly, while the homogeneous indium(III) bromide-catalyzed ring-opening of epoxides by indoles needed strictly anhydrous conditions to isolate the products in high chemical as well as optical yields,[8] the present indium-supported protocol did not show this requirement. The water-tolerance enhancement of the heterogeneous catalyst may be ascribed to the different and more lipophilic microenvironment of the metal particles in the resin-supported catalyst in comparison to the bulk liquid phase.[14]

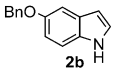
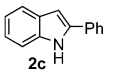
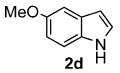
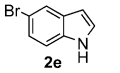
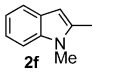
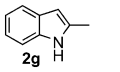
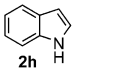
The thiolysis of epoxides is a powerful route to the synthesis of β-hydroxy sulfides that are widely employed for the synthesis of biologically and pharmacologically active compounds.[15] Numerous catalytic strategies have been effectively applied to the ring-opening of aryl and alkyl-epoxides with thiols by using acidic as well as basic conditions.[16] Among them, indium-based Lewis acids also proved to be remarkably active in aqueous media.[17] However, to the best of our knowledge no examples of the catalytic regio- and stereoselective thiolysis of enantiomerically pure epoxides have been described.[18]

To probe the effectiveness of **A** in this process we reacted enantiomerically pure **1a** with 2-naphthalenethiol

Table 2. Screening of various indoles in the Amb-In catalyzed ring-opening of enantiomerically pure epoxides.[a]

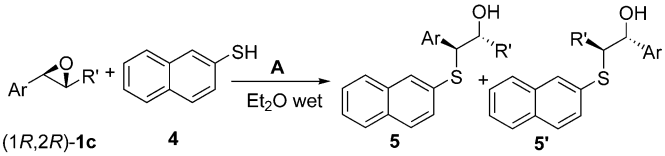


1a: Ar = Ph
1b: Ar = *m*-ClC$_6$H$_4$

Entry	Epoxide	Indole	Product Yield [%][b]	ee [%][c]
1	**1a**	 **2b**	**3ab** (60)	>98
2	**1a**	 **2c**	**3ac** (40)	>98
3	**1a**	 **2d**	**3ad** (54)	97
4	**1a**	 **2e**	**3ae** (42)	>98
5	**1a**	 **2f**	**3af** (62)	>98
6	**1a**	 **2g**	**3ag** (58)	>98[d]
7	**1a**	 **2h**	**3ah** (54)	90
8	**1b**	**2 g**	**3bg** (58)	>98
9	**1b**	**2 h**	**3ch** (57)	>98

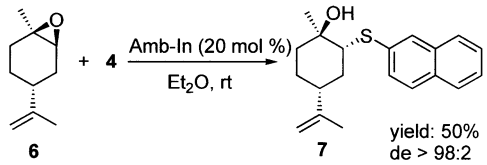
[a] All the reactions were carried out at room temperature for 24 h reaction time, in the presence of 20 mol % of catalyst **A**.
[b] After flash chromatography. Only one regioisomer was obtained.
[c] Determined by HPLC analysis with a chiral column (Chiralcel-OD).
[d] Determined by ^{1}H NMR with Eu(hfc)$_3$ shift reagent.

Table 3. Thiolysis of enantiomerically pure epoxides mediated by Amb-In.



Entry[a]	Epoxide	Yield [%][b]	**5**:**5**′[c]	ee of **5** [%][d]
1	**1a**	(**5a**) <10	–	75[e]
2	**1a**	(**5a**) 13[f]	1:1	–
3	**1a**	(**5a**) 54[g]	>49:1	60
4	**1a**	(**5a**) 50[h]	>49:1	50
5	**1a**	(**5a**) 63	>49:1	81
6	**1b**	(**5b**) 65	>11:1	82
7	**1c**	(**5c**) 67	>49:1	90

[a] All the reactions were carried out at room temperature in Et$_2$O for 24 h reaction time, in the presence of 20 mol % of catalyst **A** unless otherwise specified.
[b] After flash chromatography.
[c] Determined by ^{1}H NMR of the crude mixtures.
[d] Determined by HPLC analysis with a chiral column (Chiralcel-OD).
[e] Reaction in the absence of catalyst.
[f] In the presence of Amb-Na (20 mol %).
[g] Toluene was used as the solvent.
[h] Anhydrous CH_2Cl_2 was used as the solvent.



Scheme 2. Regioselective ring-opening of *cis*-limonene 1,2-epoxide mediated by Amb-In with **4**.

4 in the presence of Amb-In (20 mol %) in a series of reagent grade solvents.

From the data of Table 3 we see that also for the thiolysis the use of Amb-In in Et$_2$O provided the highest chemical and optical yield. In particular, (*R*)-(+)-styrene oxide (**1a**) smoothly reacted with **4** yielding regioselectively (α attack >98%) the (*S*)-β-hydroxy sulfide **5a** in optimal 63% yield and 81% ee.[19]

Although a partial racemization of the starting epoxides was observed, the present protocol represents the first example of regiolective thiolysis of enantiomerically pure epoxides in the presence of heterogeneous catalysts. Again the role of indium in the regio- and stereoselectivity was demonstrated by running the model reaction both in the absence of catalyst (entry 1: product in traces) and in the presence of 20 mol % of Amb-Na (entry 2, 1:1 regioselectivity, 13% yield). Comparable results in terms of stereoselection were also obtained with (*R*)-(+)-3-chlorostyrene oxide (**1b**) (entry 6, ee = 82%) although the **5**:**5**′ ratio slightly decreased to 11:1.

Interestingly, also more hindered 1,2-disubstituted and 1,2-trisubstituted aryl- as well as alkyloxiranes, namely (1*R*,2*R*)-(+)-1-phenylpropylene oxide (**1c**) and (+)-*cis*-limonene-1,2-epoxide[20] (**6**, Scheme 2), smoothly reacted with 2-naphthalenethiol. Thus, under not strictly anhydrous conditions, a catalytic amount of Amb-In (20 mol %) did afford the corresponding hydroxy thiols **5c** and **7** in good optical (ee = 90%, de > 98:2, respectively) and chemical yields (67%, 50%).

Conclusion

In summary, a new green indium-supported Lewis acid is presented. Its effectiveness in promoting regio- and

stereoselective ring-opening reactions of internal as well as terminal epoxides is discussed. In particular, optically active β-indolyl alcohols and β-hydroxy sulfides can be isolated in good yields after the reaction in the presence of 20 mol % of catalyst without a strict nitrogen atmosphere. This new heterogeneous catalyst, due to the mild operating conditions and to the possible reusability without reactivation, could represent a valuable candidate for environmentally benign stereoselective flow processes.

Experimental Section

General Remarks

^{1}H NMR spectra were recorded on Varian 200 (200 MHz) or Varian 300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (*J*, Hz). ^{13}C NMR spectra were recorded on Varian 200 (50 MHz) or Varian 300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ = 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240–400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a cross-linked 5% PH ME siloxane (30 m) column or a Megadex-5 chiral (25 m) column (flow rate 15 mL/min, method: 50 °C for 2 min, ramp at 10 °C/min to 250 °C for 15 min). Analytical high performance liquid chromatography (HPLC) was performed on an HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190–600 nm) and using a Daicel Chiralcel™ OD column (0.46 cm I. D. × 25 cm) (Daicel Inc.). HPLC grade isopropyl alcohol and *n*-hexane were used as the eluting solvents. Elemental analyses were carried out using an EACE 1110 CHNOS analyzer. All the commercially available reagents were used without further purification. Compounds **3aa**, **3ad**, **3ae**, **3ag**, **3bg** and **3bh** have already been reported and analytically characterized.[8]

Preparation of the Amb-In Catalyst (A)

A flamed two-necked flask was charged with 25 mL of EtOH, 2 g of Amb-Na and 1.12 g (2 mmol) of $In(OTf)_3$ under a nitrogen atmosphere and the resulting mixture was shaken overnight (16 h). Then, the resin was collected by filtration, washed with 50 mL of EtOH and dried under vacuum overnight.

The content of indium in the resin (0.92 mmol/g) was determined by titration of the remaining amount of In^{3+} in the solution following the known procedure (EDTA 0.01 M, xylenol orange as the indicator, buffer: 20% hexamethylenetetraamine).[4c]

General Procedure for the Ring-Opening of Epoxides

A sample vial containing 2 mL of reagent grade Et_2O was charged with 0.2 mmol of epoxide, 0.3 mmol of nucleophile and 44 mg (20 mol % based on indium content) of Amb-In. The mixture was shaken for 24 h with a basic orbital mixer and then the catalyst was recovered by filtration. Evaporation of the solvent and subsequent purification by flash chromatography furnished the desired indolyl alcohols **3** or β-hydroxy sulfide **5**.

(*R*)-2-(5-Phenylmethoxy-1*H*-indol-3-yl)-2-phenylethan-1-ol (3ab)

Colourless oil; yield: 60%; M. W. = 343.43 g/mol; R_f = 0.2 (cyclohexane/AcOEt, 7:3); $[\alpha]_D^{25}$: +64.9 (*c* 1.3, $CHCl_3$); ee 98% by HPLC: OD, isocratic 85:15 *n*-hexane/*i*-PrOH, flow 0.5 mL/min, acquisition wavelength 225 nm, t_R = 41.0 min, t_S = 47.1 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (1H, br), 7.47–7.14 (13H, m), 7.00–6.94 (1H, m), 5.03 (2H, s), 4.46 (1H, t, *J* = 6.6 Hz), 4.44–4.22 (2H, m), 1.30 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1, 141.5, 137.5, 131.8, 128.6, 128.5, 128.2, 127.8, 127.6, 127.4, 126.7, 122.7, 115.7, 113.1, 111.8, 102.9, 70.9, 66.3, 45.6; IR (nujol): ν = 3552, 3272, 1618, 1582, 1184, 1046, 1012, 934, 819, 798, 711 cm^{-1}; anal. calcd. for $C_{23}H_{21}NO_2$: C 80.44, H 6.16, N 4.08; found: C 80.39, H 6.11, N 4.06.

(*R*)-2-(2-Phenyl-1*H*-indol-3-yl)-2-phenylethan-1-ol (3ac)

Yellow oil; yield: 40%; M. W. = 313.40 g/mol; R_f = 0.25 (cyclohexane/AcOEt, 8:2); $[\alpha]_D^{25}$: +31.7 (*c* 0.78, $CHCl_3$); ee 98% by HPLC: OD, isocratic 85:15 *n*-hexane/*i*-PrOH, flow 0.5 mL/min, acquisition wavelength 225 nm, t_S = 21.5 min, t_R = 30.9 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (1H, br), 7.65–7.09 (14H, m), 4.72 (1H, t, *J* = 8.4 Hz), 4.39 (2H, m), 1.30 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 137.7, 136.2, 132.6, 128.8, 128.5, 128.2, 128.1, 127.6, 127.4, 126.5, 126.4, 122.3, 120.8, 120.1, 111.2, 65.5, 45.2; IR (nujol): ν = 34547, 3404, 1600, 1027, 907, 737, 697 cm^{-1}; anal. calcd. for $C_{22}H_{19}$NO: C 84.31, H 6.11, N 4.47; found: C 84.25, H 6.06, N 4.46.

(*R*)-2-(1,2-Dimethyl-indol-3-yl)-2-phenylethan-1-ol (3af)

Yellow oil; yield: 62%; M. W. = 265.15 g/mol; R_f = 0.3 (cyclohexane/AcOEt, 8:2); $[\alpha]_D^{25}$: −44.9 (*c* 1.6, $CHCl_3$); ee 98% by HPLC: OD, isocratic 85:15 *n*-hexane/*i*-PrOH, flow 0.5 mL/min, acquisition wavelength 225 nm, t_S = 22.7 min, t_R = 28.1 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.06 (9H, m), 4.56 (1H, t, *J* = 7.8 Hz), 4.38 (2H, dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 3.73 (3H, s), 2.43 (3H, s), 1,30 (1H, br); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.8, 136.9, 135.2, 128.4, 127.9, 126.6, 126.2, 120.7, 119.3, 119.1, 109.2, 108.9, 65.1, 45.4, 29.7, 10.7; GC-MS: *m/z* (relative intensity) = 265 (11), 247 (2), 234 (100), 218 (11), 204 (3), 176 (2), 158 (6), 144 (2), 115 (4), 109 (3), 77 (3), 56 (4); IR (nujol): ν = 3398, 3050, 3026, 1407, 1368, 1333, 1030, 738, 700 cm^{-1}; anal. calcd. for $C_{18}H_{19}$NO: C 81.47, H 7.22, N 5.28; found: C 81.50, H 7.16, N 5.26.

(*S*)-2-(2-Thionaphthalenyl)-2-phenylethan-1-ol (5a)

White solid; mp 99–103 °C; yield: 60%; M. W. = 280.39 g/mol, R_f = 0.25 (cyclohexane/AcOEt, 85:15); $[\alpha]_D^{25}$: +223.8 (*c* 0.9, $CHCl_3$); ee 81% by HPLC: OD, isocratic 85:15 *n*-hexane/*i*-PrOH, flow 0.5 mL/min, acquisition wavelength 229 nm, t_S = 18.0 min, t_R = 23.5 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.72 (4H, m), 7.49–7.30 (8H, m), 4.45 (1H, t, *J* = 7.3 Hz), 3.98 (2H, m), 2.06 (1H, br); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.8, 133.5, 132.4, 131.3, 131.0, 129.6, 128.8, 128.5, 128.1, 127.9, 127.6, 127.4, 126.5, 126.3, 65.3, 55.9; GC-MS: *m/z* (relative intensity) = 280 (22), 249 (15), 215 (6), 171 (11), 160 (100), 128 (15), 121 (30), 115 (38), 103 (35), 91 (12), 77 (22), 65 (8), 51 (7); IR (nujol): ν = 3473, 3057, 1584, 1490, 1132, 1045, 859, 820, 738, 697 cm^{-1}; anal. calcd. for $C_{18}H_{16}OS$: C 77.11, H 5.75; found: C 77.07, H, 5.71.

(*S*)-2-(2-Thionaphthalenyl)-2-(3-chlorophenyl)-ethan-1-ol (5b)

Yellow oil; yield (total of the two regioisomers): 65%; M. W. = 314.84; **5b**:**5′b** ratio = 91:9; R_f = 0.3 (cyclohexane/AcOEt, 85:15); $[\alpha]_D^{25}$: +154.1 (*c* 1.4, $CHCl_3$); ee 82% by HPLC: OD, isocratic 85:15 *n*-hexane/*i*-PrOH, flow 0.5 mL/min, acquisition wavelength 229 nm, t_S = 17.9 min, t_R = 25.7 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.77 (4H, m), 7.52–7.23 (7H, m), 4.42 (1H, t, *J* = 6.9 Hz), 3.98 (2H, m), 1.56 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 134.5, 133.5, 132.5, 131.7, 130.5, 129.9, 129.7, 128.6, 128.2, 128.0, 127.7, 127.4, 126.6, 126.5, 126.3, 65.0, 55.6; GC-MS: *m/z* (relative intensity) = 314 (16), 283 (14), 207 (22), 191 (8), 160 (100), 138 (63), 128 (44), 115 (23), 103 (61), 91 (40), 77 (34), 65 (12), 51 (22); IR (nujol): ν = 3388, 3169, 3057, 2726, 2660, 1594, 1568, 1303, 1170, 1058, 943, 892, 850, 813, 722 cm^{-1}; anal. calcd. for $C_{18}H_{15}ClOS$: C 68.67, H 4.80; found: C 68.61, H 4.76.

(1*S*,2*R*)-1-(2-Thionaphthalenyl)-1-phenylpropan-2-ol (5c)

Colourless oil; yield: 67%; M. W. = 294.42 g/mol; R_f = 0.3 (cyclohexane/AcOEt, 9:1); $[\alpha]_D^{25}$: +231.2 (*c* 1.3, $CHCl_3$); ee 90% by HPLC: OD, isocratic 85:15 *n*-hexane/*i*-PrOH, flow 0.5 mL/min, acquisition wavelength 229 nm, $t_{(1R,2S)}$ = 13.5 min, $t_{(1S,2R)}$ = 16.4 min; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.86–7.65 (4H, m), 7.52–7.23 (8H, m), 4.52 (1H, d, *J* = 5.5 Hz), 4.14 (1H, m), 1.98 (1H, br), 1.26 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.2, 133.5, 132.3, 131.7, 130.9, 129.4, 128.9, 128.5, 128.5, 127.7, 127.6, 127.3, 126.5, 126.2, 69.4, 61.4, 20.3; IR (nujol): ν = 3457, 3421, 3051, 1719, 1623, 1583, 1489, 1267, 1123, 1066, 943, 907, 815, 735, 699 cm^{-1}; anal. calcd. for $C_{19}H_{18}OS$: C 77.51, H 6.16; found: C 77.45, H 6.11.

(1*R*,2*R*,4*S*)-1-Hydroxy-2-(2-thionaphthalenyl)-limonene (7)

Colourless oil; yield: 50%, M. W. = 312.48 g/mol; R_f = 0.3 (cyclohexane/AcOEt, 9:1); $[\alpha]_D^{25}$: +88.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (1H, s), 7.87–7.77 (3H, m), 7.57–7.51 (3H, m), 4.77 (2H, d, *J* = 7.8 Hz), 3.89 (1H, br), 2.38 (2H, dd, J_1 = 8.4, J_2 = 4.8 Hz), 1.89–1.65 (8H, m), 1.29 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2, 137.4, 134.2, 133.3, 133.1, 128.5, 127.9, 127.8, 127.6, 126.8, 126.4, 109.2, 76.0; 53.3, 38.0, 33.7, 32.8, 26.6, 25.4, 21.1; GC-MS: *m/z* (relative intensity) = 312 (5), 207 (6), 160 (100), 128 (13), 115 (21), 109 (9), 79 (8), 67 (9), 55 (6); IR (neat): ν = 3423, 3054, 2928, 2853, 1645, 1450, 1374, 1261, 1184, 1132, 1018, 957, 890, 858, 816, 745 cm^{-1}; anal. calcd. for $C_{20}H_{24}OS$: C 78.88, H 7.74; found: C 77.82, H 7.78.

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References and Notes

[1] *Lewis Acids in Organic Synthesis*, (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2002**.

[2] a) E. C. Blossey, L. M. Turner, D. C. Neckers, *Tetrahedron Lett.* **1973**, 1823–1826; b) E. C. Blossey, L. M. Turner, D. C. Neckers, *J. Org. Chem.* **1975**, *40*, 959–960.

[3] a) K. Wilson, J. H. Clark, *Pure Appl. Chem.* **2000**, *72*, 1313–1319; b) J. H. Clark, *Acc. Chem. Res.* **2002**, *35*, 791–7; c) A. Corma, H. García, *Chem. Rev.* **2002**, *102*, 3837–3892; d) A. Corma, H. García *Chem. Rev.* **2003**, *103*, 4307–4366.

[4] a) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1996**, *118*, 8977–8978; b) S. Kobayashi, S. Nagayama, *J. Org. Chem.* **1996**, *61*, 2256–2257; c) L. Yu, D. Chen, J. Li, P. G. Wang, *J. Org. Chem.* **1997**, *62*, 3575–3581; d) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1998**, *120*, 2985–2986.

[5] a) B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347–2356; b) K. K. Chauhan, C. G. Frost, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3015–3019; c) G. Babu, P. T. Perumal, *Aldrichimica Acta* **2000**, *33*, 16–22.

[6] For the use of $InCl_3$-impregnated zeolite catalysts in radical acylation of aromatics, see: a) V. R. Choudhary, S. K. Jana, N. S. Patil, *Tetrahedron Lett.* **2002**, *43*, 1105–1107; b) V. R. Choudhary, S. K. Jana, N. S. Patil, S. K. Bhargava, *Micropor. Mesopor. Mater.* **2003**, *57*, 21–35.

[7] EP was calculated as: (In content × 3)/proton exchange capacity (≅4.7 mmol/g).

[8] M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *J. Org. Chem.* **2002**, *67*, 5386–5389.

[9] Enantiomerically pure epoxides are valuable electrophiles for the synthesis of key synthetic building blocks, see: a) A. B. Smith III, S. M. Pitram, A. M. Boldi, M. J. Gaunt, C. Sfouggatakis, W. H. Moser, *J. Am. Chem. Soc.* **2003**, *125*, 14435–14445; b) M. Pastó, B. Rodríguez, A. Riera, M. A. Pericàs, *Tetrahedron Lett.* **2003**, *44*, 8369–8372.

[10] The ring-opening of functionalized epoxides by *N*-Me-indole in the presence of a stoichiometric amount of $SnCl_4$ has been recently used as the key step in the synthesis of tripeptides, see: R. Reddy. J. B. Jaquith, V. R. Neelagiri, S. Saleh-Hanna, T. Durst, *Org. Lett.* **2002**, *4*, 695–697.
[11] For a comprehensive discussion on the morphology of polymer supports in solution, see: D. C. Sherringhton, *Chem. Commun.* **1998**, 2275–2286.
[12] A comparative ring opening reaction between (*R*)-**1a** and **2a** in the presence of 10 mol % of $In(OTf)_3$ (wet Et_2O, rt, 24 h) was carried out. Under these optimal conditions the desired β-indolyl alcohol **3aa** was isolated only in traces, 1,1-bisindolyl-2-phenylethane being the major reaction product (yield: 85%), derived from the double addition of **2a** to phenylacetaldehyde (rearrangement of **1a**).
[13] 1st cycle: yield = 53%, ee = 98%; 2nd cycle: yield = 67%, ee = 98%; 3rd cycle: yield = 57%, ee = 98%; 4th cycle: yield = 52%, ee = 96%; 5th cycle: yield = 56%, ee = 96%.
[14] A. Biffis, R. Ricoveri, S. Campestrini, M. Kralik, K. Jeřàbek, B. Corani, *Chem. Eur. J.* **2003**, *9*, 2962–2967.
[15] a) J. R. Luly, N. Yi, J. Soderquist, H. Stein, J. Cohen, T. J. Perun, J. J. Plattner, *J. Med. Chem.* **1987**, *30*, 1609–1616; b) P. Wipf, P. Jeger, Y. Kim, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351–356.
[16] Lewis acid catalysis: F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaio, *J. Org. Chem.* **2003**, *68*, 8248–8251 and references cited therein; basic catalysis: R.-H. Fan, X.-L. Hou, *J. Org. Chem.* **2003**, *68*, 726–730; stereoselective: J. Wu, X.-L. Hou, L.-X. Dai, L.-J. Xia, M.-H. Tang, *Tetrahedron: Asymmetry* **1998**, *9*, 3431–3436; M. H. Wu, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 5252–5254; T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784.
[17] a) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, *Adv. Synth. Cat.* **2002**, *344*, 379–384; b) J. S. Yadav, B. V. S. Reddy, G. Baishya, *Chem. Lett.* **2002**, 906–907; c) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, *Tetrahedron Lett.* **2003**, *44*, 6785–6787.
[18] A survey based on the SciFinder database revealed that the ring opening of enantiomerically pure epoxides with sulfur nucleophiles was published only by Tang et al. in the presence of chiral titanium catalysts and a partial racemization of the starting styrene oxide was observed: Z. Li, Z. Zhou, K. Li, L. Wang, Q. Zhou, C. Tang, *Tetrahedron Lett.* **2002**, *43*, 7609–7611.
[19] The absolute configuration of hydroxyl sulfides **5** was assigned considering that the reaction proceeded with an S_N2 mechanism. As support to this statement the ring opening of (*R*)-**1a** with thiophenol was carried out using 20 mol % of Amb-In and the optical rotation value of the corresponding (*S*)-hydroxy sulfide {ee = 68%, $[\alpha]_D$: 184 (*c*, 0.9, EtOH)} was compared with the known compound {ee > 98%, $[\alpha]_D$: 268 (*c*, 0.9, EtOH)}, see: A. Toshimitsu, C. Hirosawa. K. Tamao, *Tetrahedron* **1994**, *50*, 8997–9008.
[20] For a discussion on the stereochemistry of the nucleophilic addition of sulfur reagents to limonene oxides, see: V. A. Morgunova, L. E. Nikitina, V. V. Plemenkov, V. V. Klochkov, R. A. Shaikhutdinov, *Russ. J. Org. Chem.* **1999**, *35*, 44–47.

