Catalytic Enantioselective Synthesis of a 3-Aryl-3-benzyloxindole (= 3-Aryl-3-benzyl-1,3-dihydro-2*H*-indol-2-one) Exhibiting Antitumor Activity

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Dedicated to Prof. *Dieter Seebach* on the occasion of his 75th birthday

A palladium-catalyzed intramolecular α-arylation of an amide in the presence of a bulky chiral N-heterocyclic carbene ligand is the key step in the first catalytic synthesis of (3*R*)-6-chloro-3-(3-chlorobenzyl)-1,3-dihydro-3-(3-methoxyphenyl)-2*H*-indol-2-one ((*R*)-**5**). This oxindole, in racemic form, had been shown previously to be an anticancer agent. (*R*)-**5** was obtained with an overall yield of 45% and with 96% enantioselectivity.

Introduction. – Oxindoles (= 1,3-dihydro-2*H*-indol-2-ones) containing a quaternary stereogenic center at the C(3) position are found in a growing number of natural and synthetic products presenting biological activities of interest [1]. Spiro[oxindole-3,3′-pyrrolidines], in particular, constitute a large family of natural products. Examples are the spirooxindole alkaloids **1**–**4** (*Fig. 1*) [2]. Spirocyclic compounds apart, oxindoles having a quaternary stereogenic center at the C(3) position have also shown pharmaceutical activity. Examples include a large range of compounds that were contained in a patent by *F. Hoffmann–La Roche AG* as anticancer agents with *rac*-**5** showing particularly high activity [3]. We also note that SSR-149415 (**6**) [4] is in clinical trials for treatment of anxiety and depression, and SM-130686 (**7**) [5], containing a 3-aryl-3-hydroxyoxindole skeleton, is a highly potent and orally active nonpeptidic growth hormone secretagogue.

Not surprisingly, a large number of synthesis methods has been developed to provide access to oxindoles [1d][1e][6]. Increasingly, attention has also focused on asymmetric catalytic methods. One powerful route is the palladium-catalyzed intramolecular α-arylation of amides developed by *Hartwig* and co-workers in 2001 as a simple and useful method for the synthesis of 3,3-disubstituted oxindoles. Bulky chiral N-heterocyclic carbene (NHC) ligands worked best for the asymmetric transformation, but enantioselectivities were modest (50–70% ee) [7].

We, and subsequently others, have developed bulky NHC ligands that brought largely improved asymmetric inductions in this reaction [8][9]. With the chiral ligands reported from our laboratory[1]), highly enantiomer-enriched 3,3-disubstituted oxindoles are now accessible in excellent yields (*Scheme 1*). X-Ray crystal structures of borane adducts of these ligands and applications of [Pd(**L1**)] and [Pd(**L4**)] in

[1]) (*S,S*)-[**L1**H]I and (*S,S*)-[**L4**H]I will be available commercially shortly (*Aldrich*).

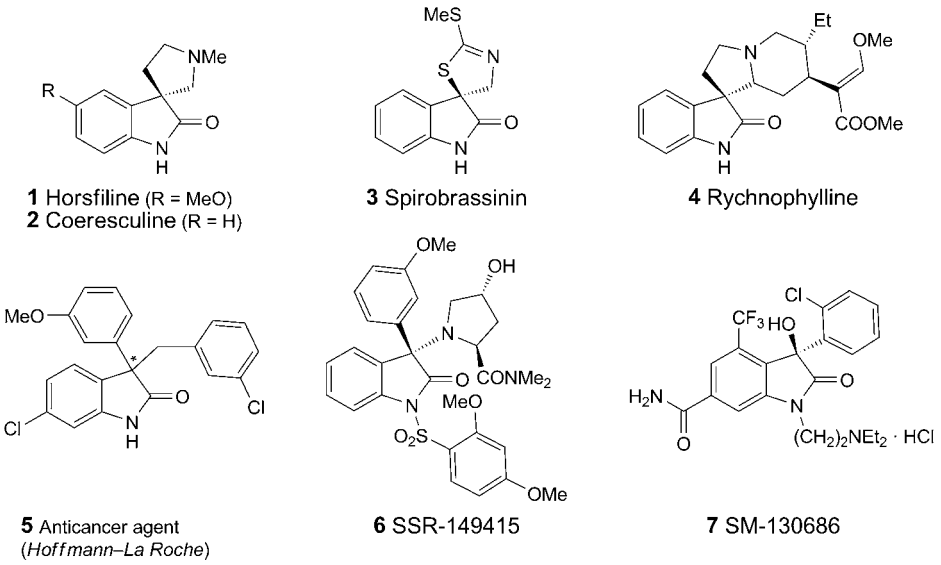
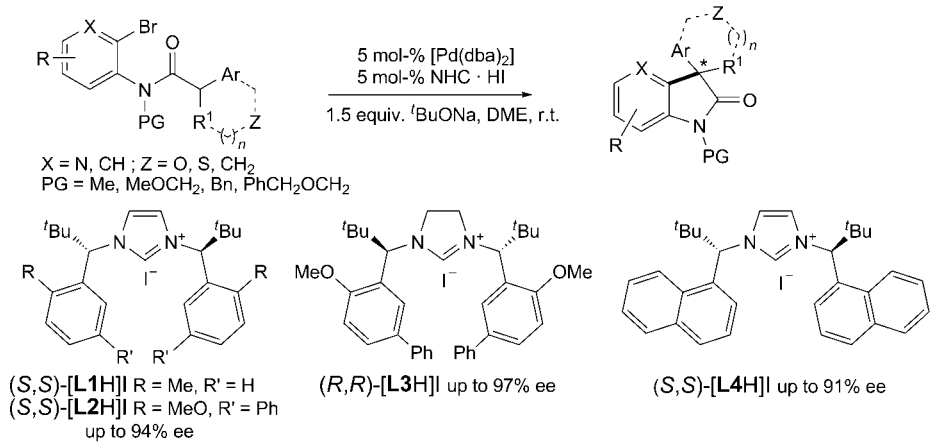


Fig. 1. *Some examples of natural products and bioactive compounds containing the 3,3-disubstituted oxindole scaffold*

Scheme 1. *Application of the Developed N-Heterocyclic Carbene* (NHC) *Ligands to the Synthesis of 3,3-Disubstituted Oxindoles.* Ligand dba = dibenzylideneacetone = 1,5-diphenylpenta-1,4-dien-3-one; DME = 1,2-dimethoxyethane.

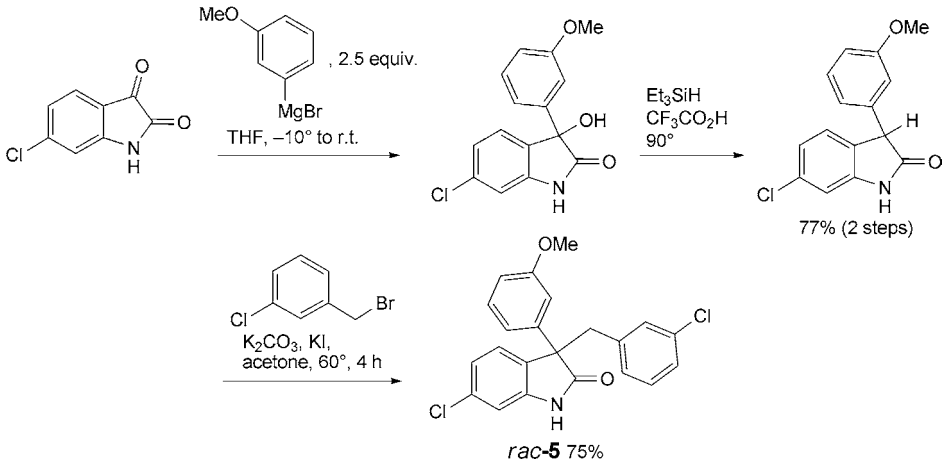


unprecedented asymmetric alkyl chain C–H activation shed light on the mechanism of action and of the potential of these monodentate ligands [10].

Enantiomer-enriched oxindoles synthesized to date have always been model compounds. They have provided information on scope and limitations of the reaction but they were neither natural products nor synthetic bioactive agents. In most cases, *N*-

methyloxindoles were prepared whereas biologically active compounds contain an unsubstituted NH moitey. Reactions with *N*-benzyl protection usually delivered products with lower enantioselectivity [8]. In this paper, we single out 6-chloro-3-(3-chlorobenzyl)-1,3-dihydro-3-(3-methoxyphenyl)-2*H*-indol-2-one (**5**), one of the most active compounds contained in the *Roche* 2006 patent [3] to test the asymmetric catalytic method developed in our laboratory. The patent reports that 3,3-disubstituted oxindoles are MDM2 antagonists and disrupt nefarious MDM2-p53 interactions. Since p53 is a tumor-suppressor protein, MDM2 antagonists can offer a novel approach to cancer therapy. Oxindole **5** is also mentioned in a recent patent dealing with a method for improving the production of influenza viruses and vaccine seeds [11]. The reported synthesis of *rac*-**5** is shown in *Scheme 2*. To the best of our knowledge, no report of an enantiomer-enriched oxindole **5** is literature-known.

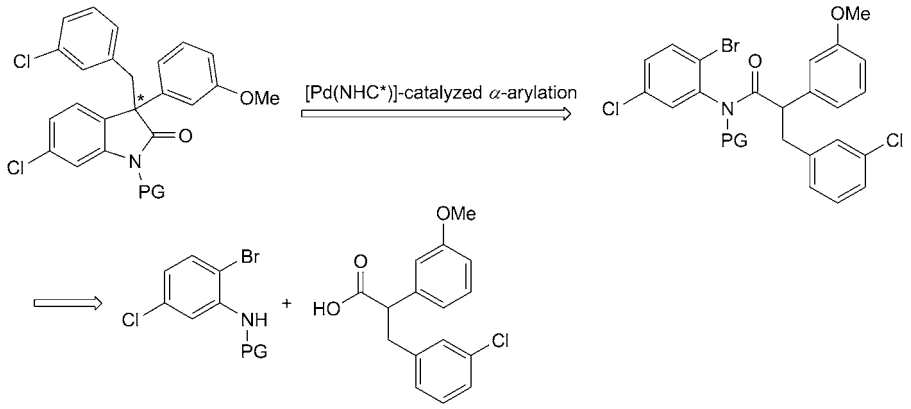
Scheme 2. F. Hoffmann–LaRoche *Synthesis of* rac-**5** [3]



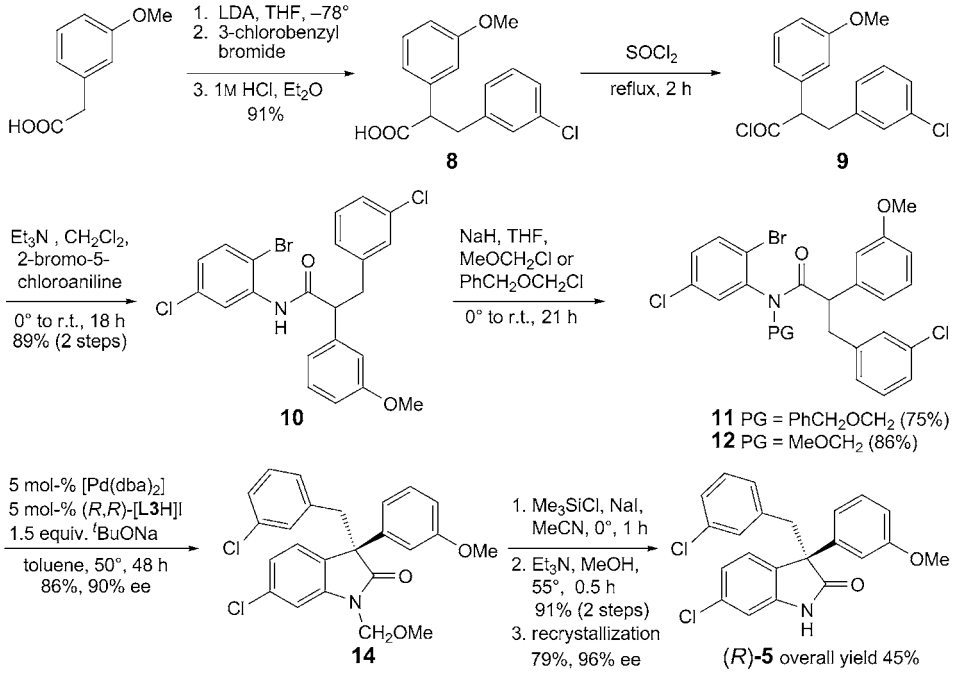
Results and Discussion. – The target molecule (*R*)-**5** contains a quaternary stereogenic center at the benzylic position and also two chloroaryl groups making the key step of the intramolecular arylation of the precursor amide to give an oxindole more challenging due to the potential of competition in the transition-metal oxidative addition process. Our approach to the synthesis of (*R*)-**5** is depicted in *Scheme 3*. We envisaged that the requisite amide can easily be prepared from the dihaloaniline and the carboxylic acid shown in *Scheme 3*. An asymmetric intramolecular Pd-catalyzed α-arylation would then generate the sought-after oxindole.

Thus commercially available 3-methoxybenzeneacetic acid was converted to acid **8** by alkylation with 3-chlorobenzyl bromide in the presence of freshly prepared lithium diisopropylamide (LDA) (*Scheme 4*). Then 2-bromo-5-chloroaniline (=2-bromo-5-chlorobenzenamine) was coupled with acyl chloride **9** producing amide **10** in high yield (89% over the two steps). Amides **11** and **12** were synthesized by treating **10** with the corresponding alkoxy chlorides $MeOCH_2Cl$ or $PhCH_2OCH_2Cl$ in the presence of NaH in THF.

Scheme 3. *Our Retrosynthetic Analysis of* **5**



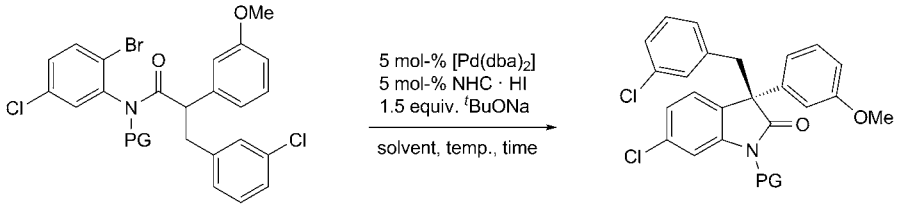
Scheme 4. *Catalytic Enantioselective Synthesis of (*R*)-***5***



Earlier data had shown that the choice of the chiral NHC ligand, the solvent, as well as the *N*-protecting group influence both yield and asymmetric induction of the α-arylation [8]. As shown in the *Table*, both (benzyloxy)methyl ($PhCH_2OCH_2$) and methoxymethyl ($MeOCH_2$) groups were suitable for the transformation to oxindole: **13** and **14**, respectively, the best yields being obtained with **12** and toluene as solvent at 50°.

Conditions used previously with success (5 mol-% of **L1** · HI or **L4** · HI, 5 mol-% of [Pd(dba)$_2$], and 1.5 equiv. of ^{t}BuONa in 1,2-dimethoxyethane (DME) at r.t.) afforded **13** and **14** with good enantioselectivities but in low yields (*Table*, *Entries 1–3*). The reaction was accompanied by decomposition of starting material. Fortunately, changing the solvent to toluene and increasing the temperature to 50° improved the situation as shown in *Entries 5–8*. While all four chiral ligands **L1**–**L4** performed very well, ligand (*R*,*R*)-**L3** proved best giving the oxindole **14** in 86% yield and 90% ee. The high yield shows that the Pd-catalyzed cyclization takes place selectively and without interference of the chloroaryl moieties present. This procedure was then incorporated into the synthesis protocol for (*R*)-**5**. The MeOCH$_2$ protecting group was chosen for its high yield of incorporation into **10** and its ready removal from **14**. The latter was carried out with the *Fukuyama* procedure [12] that consisted of treating **14** with Me$_3$SiCl in the presence of NaI. The *N*-(hydroxymethyl) derivative produced, upon heating with Et$_3$N in MeOH at 55°, furnished (*R*)-**5** in 91% yield. Recrystallization from hexane/CH$_2$Cl$_2$ increased the enantiomer purity of (*R*)-**5** to 96% *ee* (yield 79%). The absolute configuration of **5** was assigned as (*R*) by comparison of its circular-dichroism (CD) spectrum with that of similar oxindole structures described in the literature [8].

Table. *Palladium Catalyzed α-Arylation of Substrates* **11**[a]) *and* **12**[a])



11 PG = $PhCH_2OCH_2$
12 PG = $MeOCH_2$

13[b]) PG = $PhCH_2OCH_2$
14[b]) PG = $MeOCH_2$

Entry	Substrate	NHC · HI	Solvent	Temp. [°]	Time [h]	Yield [%][c])	ee [%][b])[d])
1	**11**	(*S*,*S*)-[**L1**H][I]	DME	r.t.	24	28	– 84
2	**11**	(*S*,*S*)-[**L4**H][I]	DME	r.t.	24	31	– 86
3	**12**	(*S*,*S*)-[**L4**H][I]	DME	r.t.	24	30	– 89
4	**12**	(*S*,*S*)-[**L4**H][I]	toluene	r.t.	48	25	– 89
5	**12**	(*S*,*S*)-[**L4**H][I]	toluene	50	48	85	– 87
6	**12**	(*S*,*S*)-[**L1**H][I]	toluene	50	48	86	– 85
7[e])	**12**	(*R*,*R*)-[**L3**H][I]	toluene	50	48	86	90
8	**12**	(*S*,*S*)-[**L2**H][I]	toluene	50	48	85	– 87

[a]) Substrate **11** or **12** (0.2 mmol) with NHC · HI (0.01 mmol) and [Pd(dba)$_2$] (0.01 mmol). [b]) Absolute configurations are assigned by analogy [8] and are tentative. [c]) Yield isolated of product. [d]) The enantiomer excess (*ee*) ratio was determined by HPLC with a chiral stationary phase (*Chiracel-AD-H* column). [e]) 1 mmol scale.

In conclusion, we have successfully applied the [Pd(NHC)*]-catalyzed asymmetric α-arylation of amides to the total synthesis of highly enantiomer-enriched (*R*)-**5**. The sequence involves 6 steps with an overall yield of 45%. These studies demonstrate that

the [Pd(NHC)*] catalysis can be used in an asymmetric C–C bond formation at a late stage in the synthesis of complex structures.

Experimental Part

General. Chemicals were purchased from *Aldrich*, *Acros*, or *Alfa Aesar* and used without further purification. Solvents were purified by filtration through drying columns by means of a *Solvtec*© system or by distillation over Na/benzophenone. Reactions and manipulations involving organometallic or moisture sensitive compounds were carried out under N_2, and glassware was further dried by heating under vacuum as necessary. ^{t}BuONa was sublimed and stored in a glove box. Flash chromatography (FC): silica gel *60* (SiO_2, 40 μm). HPLC: *Agilent-1100* chromatograph and detection system, *Jasco-PU-980* pump; t_R in min. M.p.: *Büchi-M-560* apparatus; uncorrected. Optical rotations: *Perkin–Elmer-241* polarimeter, with a quartz cell ($l = 10$ cm) and a Na high-pressure lamp (λ 589 nm); at 20°. IR Spectra: *Perkin–Elmer-Spectrum-One* photometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AMX-500*, *AMX-400* or *AMX-300* spectrometer; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-MS: *VG-7070E* analytical instrument; in m/z.

3-(3-Chlorophenyl)-2-(3-methoxyphenyl)propanoic Acid (= *3-Chloro-α-(3-methoxyphenyl)benzenepropanoic Acid*; **8**). Lithium diisopropylamide (LDA) was prepared by adding 1.7M BuLi in pentane (2 equiv., 14 ml, 24.0 mmol) into freshly distilled diisopropylamine (2 equiv., 3.4 ml, 24.0 mmol) in THF (10 ml) and stirring for 30 min. Then 3-methoxybenzeneacetic acid (1 equiv., 2.0 g, 12.0 mmol) was added to the magnetically stirred soln. at −78°, followed by the introduction of 3-chloro benzyl bromide (= 1-(bromomethyl)-3-chlorobenzene; 1 equiv., 2.46 g, 12 mmol). The mixture was warmed to r.t. and stirred for 16 h before quenching with 2M aq. HCl (50 ml) followed by extraction with AcOEt (3 × 20 ml). The org. layer was dried ($MgSO_4$), and the solvents were evaporated: crude **8** (3.17 g, 91%), which was used in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.03 (*dd*, $J = 6.9$, 13.8, 1 H); 3.39 (*dd*, $J = 6.9$,13.8, 1 H); 3.82 (*s*, 3 H); 3.87 (*m*, 1 H); 6.86 (*d*, $J = 7.5$, 1 H); 6.88 (*s*, 1 H); 6.92 (*d*, $J = 7.5$, 1 H); 7.03 (*m*, 1 H); 7.18 (*m*, 3 H); 7.28 (*d*, $J = 7.5$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 38.71; 53.11; 55.24; 113.17; 113.85; 120.44; 126.70; 127.10; 129.00; 129.65; 129.81; 134.11; 138.96; 140.64; 159.87.

N-*(2-Bromo-5-chlorophenyl)-3-(3-chlorophenyl)-2-(3-methoxyphenyl)propanamide* (= N-*(2-Bromo-5-chlorophenyl)-3-chloro-α-(3-methoxyphenyl)benzenepropanamide*; **10**). A mixture of **8** (1 equiv., 2.0 g, 6.88 mmol) and $SOCl_2$ (3 equiv., 2.45 g, 20.6 mmol) was refluxed for 2 h. The excess of $SOCl_2$ was removed under vacuum. To the crude acyl chloride **9**, Et_3N (1.5 equiv., 1.04 g, 10.3 mmol) in CH_2Cl_2 (20 ml) was added at 0° followed by 2-bromo-5-chloroaniline (1 equiv., 1.4 g, 6.88 mmol). The resulting mixture was stirred for 18 h at r.t. before quenching by the addition of aq. NH_4Cl soln. (10 ml). Extraction with CH_2Cl_2 (3 × 40 ml), drying ($MgSO_4$), and evaporation of the volatiles afforded **10** (2.93 g, 89%), which was used in the next step without purification. Colorless oil. IR (neat): 3287*m*, 3075*w*, 2933*w*, 2836*w*, 1723*w*, 1655*s*, 1600*s*, 1574*s*, 1519*s*, 1494*s*, 1402*s*, 1355*m*, 1304*m*, 1260*s*, 1233*s*, 1202*s*, 1187*m*, 1156*m*, 1089*s*, 1032*s*, 996*m*, 872*m*, 858*s*, 807*s*, 787*s*, 777*s*, 695*s*, 653*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.07 (*dd*, $J = 7.9$, 13.8, 1 H); 3.61 (*dd*, $J = 7.9$, 13.8, 1 H); 3.79 (*m*, 1 H); 3.81 (*s*, 3 H); 6.84 (*m*, 2 H); 6.92 (*m*, 1 H); 7.01 (*m*, 1 H); 7.14 (*d*, $J = 3.4$, 3 H); 7.29 (*m*, 1 H); 7.34 (*d*, $J = 8.5$, 1 H), 7.59 (br. *s*, 1 H); 8.42 (*d*, $J = 1.7$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 38.30; 55.36; 56.25; 110.83; 113.58; 113.92; 118.63; 118.71; 120.61; 121.38; 125.12; 126.69; 127.28; 129.09; 129.68; 130.42; 132.71; 134.14; 134.25; 136.33; 139.37; 141.19; 160.24; 170.66.

N-*[(Benzyloxy)methyl]*-N-*(2-bromo-5-chlorophenyl)-3-(3-chlorophenyl)-2-(3-methoxyphenyl)propanamide* (= N-*(2-Bromo-5-chlorophenyl)-3-chloro-α-(3-methoxyphenyl)*-N-*[(phenylmethoxy)methyl]-benzenepropanamine*; **11**). A suspension of NaH (1.5 equiv., 0.075 g, 3.13 mmol) in THF (10 ml) at 0° was treated with **10** (1 equiv., 1.0 g, 2.087 mmol), and the mixture was stirred for 1 h at r.t. Cooling to 0° was followed by slow addition of $PhCH_2OCH_2Cl$ ((benzyloxy)methyl chloride; 1.5 equiv., 0.49 g, 3.13 mmol). The mixture was allowed to warm to r.t. and stirred for 20 h. After the addition of aq. NH_4Cl soln. (30 ml), the mixture was extracted with AcOEt (3 × 40 ml), the extract dried ($MgSO_4$) and concentrated, and the residue purified by FC (pentane/AcOEt 7:1): **11** (0.937 g, 75%). Colorless oil. IR (neat): 2938*w*, 1674*s*, 1596*m*, 1578*m*, 1464*m*, 1402*m*, 1257*s*, 1147*w*, 1116*w*, 1090*s*, 1049*s*, 875*m*, 812*m*,

777*s*, 731*s*, 693*s*. ^{1}H-NMR (400 MHz, $CDCl_3$) 2.83 (*dd*, *J* = 3.9, 13.5, 1 H); 2.87 (*dd*, *J* = 6.7, 13.6, 2 H); 3.34 (*t*, *J* = 7.2, 2 H); 3.50 (*m*, 3 H); 3.58 (*dd*, *J* = 3.8, 11.0, 1 H); 3.72 (*s*, 5 H); 3.78 (*s*, 3 H); 4.39 (*d*, *J* = 6.4, 1 H); 4.50 (*d*, *J* = 10.6, 2 H); 4.59 (*d*, *J* = 4.7, 3 H); 5.64 (*d*, *J* = 10.6, 2 H); 5.72 (*d*, *J* = 10.7, 1 H); 6.42 (*m*, 6 H); 6.70 (*m*, 2 H); 6.80 (*td*, *J* = 2.1, 7.3, 7.9, 3 H); 6.90 (*m*, 2 H); 7.15 (*m*, 12 H); 7.35 (*m*, 22 H); 7.50 (*d*, *J* = 8.6, 1 H); 7.60 (*d*, *J* = 8.6, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 40.44; 41.45; 52.07; 53.53; 55.24; 69.93; 70.94; 71.22; 75.82; 76.45; 88.66; 91.62; 113.20; 113.41; 113.78; 120.24; 120.84; 121.85; 122.18; 126.47; 127.09; 127.63; 127.81; 127.95; 128.47; 128.52; 129.45; 129.47; 129.54; 129.81; 129.92; 130.21; 130.41; 132.60; 133.33; 133.52; 133.88; 133.96; 134.35; 134.53; 137.65; 137.67; 139.48; 139.93; 140.01; 140.20; 141.49; 159.68; 159.99; 172.55; 172.79.

N-*(2-Bromo-5-chlorophenyl)-3-(3-chlorophenyl)*-N-*(methoxymethyl)-2-(3-methoxyphenyl)propanamide* (= N-*(2-Bromo-5-chlorophenyl)-3-chloro*-N-*(methoxmethyl)-α-(3-methoxyphenyl)benzenepropanamine*; **12**). As described for **11**, with **10** (4.17 mmol) and $MeOCH_2Cl$ (methoxymethyl chloride; 1.5 equiv., 0.5 g, 6.26 mmol): **12** (1.87 g, 86%). Colorless oil. IR (neat): 2937*w*, 2833*w*, 1674*s*, 1596*m*, 1577*m*, 1465*s*, 1436*m*, 1400*m*, 1362*m*, 1257*s*, 1113*s*, 1079*s*, 1029*s*, 1003*m*, 913*m*, 875*m*, 814*m*, 776*s*, 727*m*, 693*s*, 523*m*. ^{1}H-NMR (400 MHz, $CDCl_3$, mixture of rotamers): 2.82 (*m*, 1.4 H); 3.22 (*s*, 1.4 H); 3.29 (*t*, *J* = 6.7, 1 H); 3.35 (*s*, 3 H); 3.45 (*m*, 2 H); 3.71 (*s*, 3 H); 3.77 (*s*, 1.4 H); 4.28 (*d*, *J* = 10.5, 0.4 H); 4.34 (*d*, *J* = 10.4, 1 H); 5.52 (*d*, *J* = 10.4, 1 H); 5.56 (*d*, *J* = 10.5, 0.4 H); 6.30 (*d*, *J* = 2.3, 0.4 H); 6.36 (*s*, 1 H); 6.41 (*m*, 2 H); 6.67 (*d*, *J* = 7.6, 0.4 H); 6.73 (*s*, 0.4 H); 6.78 (*d*, *J* = 8.1, 1.4 H); 6.91 (*t*, *J* = 3.8, 1 H); 7.04 (*s*, 1.4 H); 7.19 (*m*, 6 H); 7.50 (*d*, *J* = 8.6, 0.4 H); 7.58 (*d*, *J* = 8.5, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 40.43; 41.44; 52.10; 53.49; 55.22; 56.85; 56.99; 77.64; 78.02; 113.05; 113.19; 113.36; 113.71; 120.16; 126.40; 127.76; 129.39; 129.40; 130.19; 133.27; 133.92; 139.51; 139.94; 139.96; 140.20; 141.40; 141.44; 159.61; 159.91; 172.57; 172.71. HR-EI-MS: 522.0223 ($[M+H]^+$, $C_{24}H_{23}BrCl_2NO_3^+$; calc. 522.0232).

*(3*S*)-1-[(Benzyloxy)methyl]-6-chloro-3-(3-chlorobenzyl)-1,3-dihydro-3-(3-methoxyphenyl)-2*H-*indol-2-one* (=*(3*S*)-6-Chloro-3-[(3-chlorophenyl)methyl]-1,3-dihydro-3-(3-methoxyphenyl)-1-[(phenylmethoxy)methyl]-2*H-*indol-2-one*; (*S*)-**13**). Under N_2, a dried *Schlenk* tube was charged with $[Pd(dba)_2]$ (5 mol-%, 5.7 mg, 0.01 mmol), (*S*,*S*)-[**L4**H]I (5 mol-%, 5.8 mg, 0.01 mmol), and ^{t}BuONa (1.5 equiv., 28.8 mg, 0.3 mmol). DME (1 ml) was added, and the mixture was stirred for 10 min at r.t. Then a soln. of **11** (1 equiv., 0.119 g, 0.2 mmol) in DME (3 ml) was added and the mixture stirred at r.t for 48 h. After addition of sat. aq. NH_4Cl soln. (10 ml), the mixture was extracted with AcOEt (3 × 10 ml), the combined org. phase washed with H_2O (20 ml) and brine (20 ml), dried ($MgSO_4$), and concentrated, and the crude product purified by FC (pentane/AcOEt 10 : 1): (*S*)-**13** (0.032 mg, 31%). Yellow oil. $[\alpha]_D^{20} = -1.89$ (*c* = 1.0, CH_2Cl_2). HPLC (*Chiralcel AD-H*, hexane/^{i}PrOH 95 : 5, 1.0 ml/min, 254 nm): t_R 17.80 (minor) and 39.38 (major); 86% ee. IR (neat): 2921*w*, 2852*m*, 1725*s*, 1606*m*, 1488*m*, 1458*m*, 1290*m*, 1259*s*, 1083*s*, 1021*s*, 800*s*, 744*m*, 696*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.49 (*d*, *J* = 13.1, 1 H); 3.76 (*d*, *J* = 13.0, 1 H); 3.85 (*s*, 3 H); 3.98 (*d*, *J* = 11.6, 1 H); 4.18 (*d*, *J* = 11.6, 1 H); 5.02 (*d*, *J* = 11.2, 1 H); 5.12 (*d*, *J* = 11.2, 1 H); 6.81 (*d*, *J* = 6.8, 1 H); 6.90 (*m*, 2 H); 7.01 (*m*, 8 H); 7.28 (*m*, 11 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 43.07; 55.33; 58.17; 69.81; 70.12; 110.83; 112.61; 113.62; 119.30; 123.01; 126.42; 127.28; 127.95; 128.13; 128.39; 128.72; 129.14; 129.85; 130.36; 133.73; 134.55; 136.92; 137.38; 140.63; 143.29; 159.85; 177.62. HR-EI-MS: 540.1103 ($[M+Na]^+$, $C_{30}H_{25}Cl_2NaNO_3^+$; calc. 540.1127).

*(3*R*)-6-Chloro-3-(3-chlorobenzyl)-1,3-dihydro-1-(methoxymethyl)-3-(3-methoxyphenyl)-2*H-*indol-2-one* (=*(3*R*)-6-Chloro-3-[(3-chlorophenyl)methyl]-1,3-dihydro-1-(methoxymethyl)-3-(3-methoxyphenyl)-2*H-*indol-2-one*; **14**). Under N_2, a dried *Schlenk* tube was charged with $[Pd(dba)_2]$ (5 mol-%, 5.7 mg, 0.01 mmol), (*R*,*R*)-[**L3**H]I (5 mol-%, 7.02 mg, 0.01 mmol), and ^{t}BuONa (1.5 equiv., 28.8 mg, 0.3 mmol). Toluene (1 ml) was added, and the mixture was stirred for 30 min at r.t. Then a soln. of **12** (1 equiv., 104.6 mg, 0.2 mmol) in toluene (3 ml) was added, and the mixture was stirred at 50° for 48 h. After addition of sat. aq. NH_4Cl soln. (10 ml), the mixture was extracted with AcOEt (3 × 10 ml), the combined org. phase washed with H_2O (10 ml) and brine (10 ml), dried ($MgSO_4$), and concenrated, and the crude product purified by FC (pentane/AcOEt 10 : 1): (*R*)-**14** (76.0 mg, 86%). Yellow oil. $[\alpha]_{r.t.}^{D} = +1.71$ (*c* = 1.0, CH_2Cl_2). HPLC (*Chiracel AD-H*, hexane/^{i}PrOH 99 : 1, 1.0 ml/min, 254 nm): t_R 39.22 (major) and 65.18 (minor)); 90% ee. CD: *Fig. 2*. IR (neat): 2933*w*, 2834*w*, 1720*s*, 1604*s*, 1487*s*, 1432*s*, 1394*w*, 1340*s*, 1290*m*, 1240*s*, 1179*m*, 1129*m*, 1081*s*, 1049*s*, 971*m*, 915*m*, 875*m*, 781*s*, 746*m*, 686*s*, 658*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.95 (*s*, 3 H); 3.42 (*d*, *J* = 13.0, 1 H); 3.71 (*d*, *J* = 13.0, 1 H); 3.79 (*s*, 3 H); 4.88 (*d*, *J* = 11.0, 1 H); 4.92 (*d*, *J* = 11.0, 1 H); 6.72 (*d*, *J* = 7.6, 1 H); 6.84 (*dd*, *J* = 2.4, 8.2, 1 H); 6.98 (*m*,

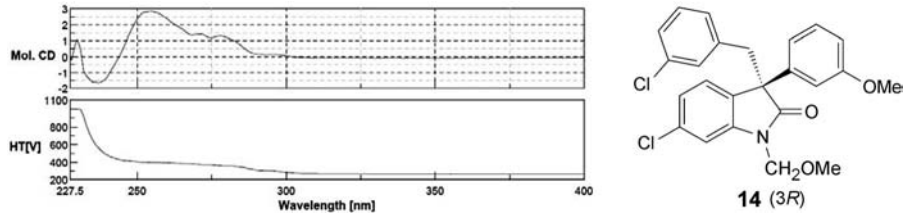


Fig. 2. *CD Spectrum of* **14** ($c = 0.0001$M, in CH_2Cl_2)

5 H); 7.06 (*dd*, $J = 1.7$, 7.9, 1 H); 7.13 (*dd*, $J = 1.8$, 7.9, 1 H); 7.20 (*d*, $J = 8.0$, 1 H); 7.27 (*t*, $J = 7.8$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 43.06; 55.31; 55.96; 58.18; 71.71; 110.68; 112.60; 113.59; 119.27; 122.92; 126.41; 127.15; 128.43; 128.65; 129.09; 129.82; 130.28; 133.71; 134.47; 137.40; 140.67; 143.21; 159.83; 177.70. HR-EI-MS: 464.0791 (M^+, $C_{24}H_{21}Cl_2NaNO_3^+$; calc. 464.0790).

*(3*R*)-6-Chloro-3-(3-chlorobenzyl)-1,3-dihydro-3-(3-methoxyphenyl)-2*H*-indol-2-one* (=*(3*R*)-6-Chloro-3-[(3-chlorophenyl)methyl]-1,3-dihydro-3-(3-methoxyphenyl)-2*H*-indol-2-one*; (*R*)-**5**). To a soln. of **14** (1 equiv., 76 mg, 0.17 mmol) in MeCN (6 ml) at 0° were added trimethylsilyl chloride (4.5 equiv., 83 mg, 0.76 mmol) and NaI (4.5 equiv., 114 mg, 0.76 mmol), and the resulting mixture was stirred at 0° for 1 h. After addition of sat. $NaHCO_3$ soln. (6 ml), the mixture was extracted with AcOEt (2×15 ml) and the combined org. layer washed with brine (20 ml), dried (Na_2SO_4), and concentrated. MeOH (40 ml) at r.t. was added to the residue, followed by Et_3N (3 equiv., 52.0 mg, 0.51 mmol). This mixture was stirred at 60° for 30 min. After cooling to r.t., the reaction was quenched with sat. aq. NH_4Cl soln. (20 ml), and hexane/AcOEt 1:1 (100 ml) was added. The aq. layer was extracted with hexane ($2 \times$ 30 ml), the combined org. phase, washed with brine (100 ml), dried (Na_2SO_4), and concentrated, and the residue purified by FC (hexane/AcOEt 5:1) (*R*)-**5** (61.6 mg, 91%). Recrystallization from CH_2Cl_2/hexane gave (*R*)-**5** (53.0 mg, 79%). White solid. M.p. 164.5–166.5°. $[\alpha]_D^{20} = +8.7$ ($c = 1.0$, CH_2Cl_2). HPLC (*Chiracel OD-H*, hexane/^{i}PrOH 7:3, 1.0 ml/min, 254 nm): t_R 6.98 (minor) and 23.91 (major); 96% ee. CD: *Fig. 3*. IR (neat): 3222*m*, 2930*w*, 2835*w*, 1711*s*, 1612*s*, 1596*s*, 1485*s*, 1454*s*, 1431*s*, 1322*m*, 1255*s*, 1221*m*, 1174*m*, 1069*m*, 1037*m*, 859*m*, 786*s*, 691*s*, 635*m*, 590*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.53 (*d*, $J =$ 12.8, 1 H); 3.64 (*d*, $J = 12.8$, 1 H); 3.78 (*s*, 3 H); 6.74 (*d*, $J = 1.8$, 1 H); 6.87 (*m*, 2 H); 7.05 (*m*, 6 H); 7.28 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 41.71; 54.29; 58.46; 109.89; 112.28; 112.79; 118.78; 121.67; 126.43; 126.48; 128.27; 128.71; 129.34; 129.77; 130.76; 133.07; 133.61; 137.91; 141.06; 142.93; 159.97; 180.30. HR-EI-MS: 398.0709 (M^+, $C_{22}H_{17}Cl_2NO_2^+$; calc. 398.0706).

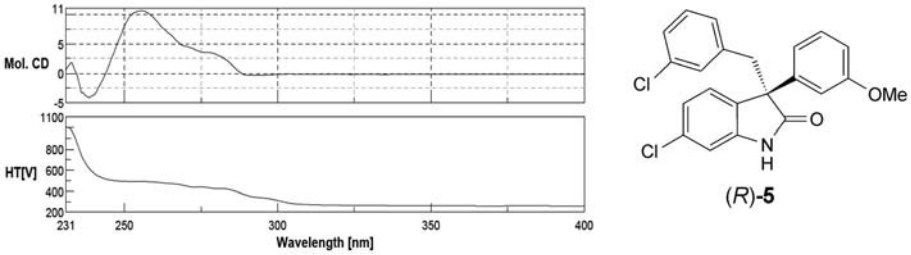


Fig. 3. *CD Spectrum of* (*R*)-**5** ($c = 0.0001$M, in CH_2Cl_2)

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