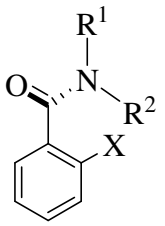
Chapter 2

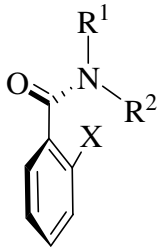
2-(2-Hydroxyaryl)cinnamic amides: a new class of axially chiral molecules

2.1 Non-biaryl classes of atropisomeric molecules

Atropisomers, have received much attention, since they are among the most useful ligands in asymmetric catalysis. In most of the known structures, as specified in Chapter 1, the chiral axis is between two aromatic moieties, but there are also examples of non-biaryl atropisomers. Several reports followed the pioneering work by Curran et al. disclosed in 1994 on atropisomeric anilides.[1] Two classes of compounds emerged afterwards, namely atropisomeric amides **2.1** and anilides **2.2**, and both have been employed in asymmetric catalysis.[2] The rotation along the chiral axis in structures of type **2.1** and **2.2** is hindered by a substituent in the aromatic ortho position of the aryl group. Compounds of class **2.3** with *peri* substitution have also been investigated. The hydrogen atom in the 8-position of the naphthyl moiety causes a rotational barrier of sufficient magnitude to generate optical antipodes, although these compounds readily racemize ($t_{1/2}{}^{25}{}_{rac}$ less than 1 s).[3] There is no reported data on the chiral properties of the corresponding compounds of class **2.4**, in which the nitrogen atom is directly attached to the aromatic ring, such as N,N-disubstituted 1-naphthamides or carbamates.



2.1



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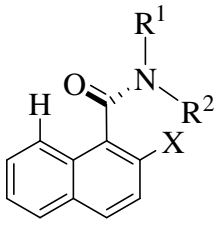

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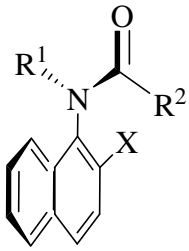
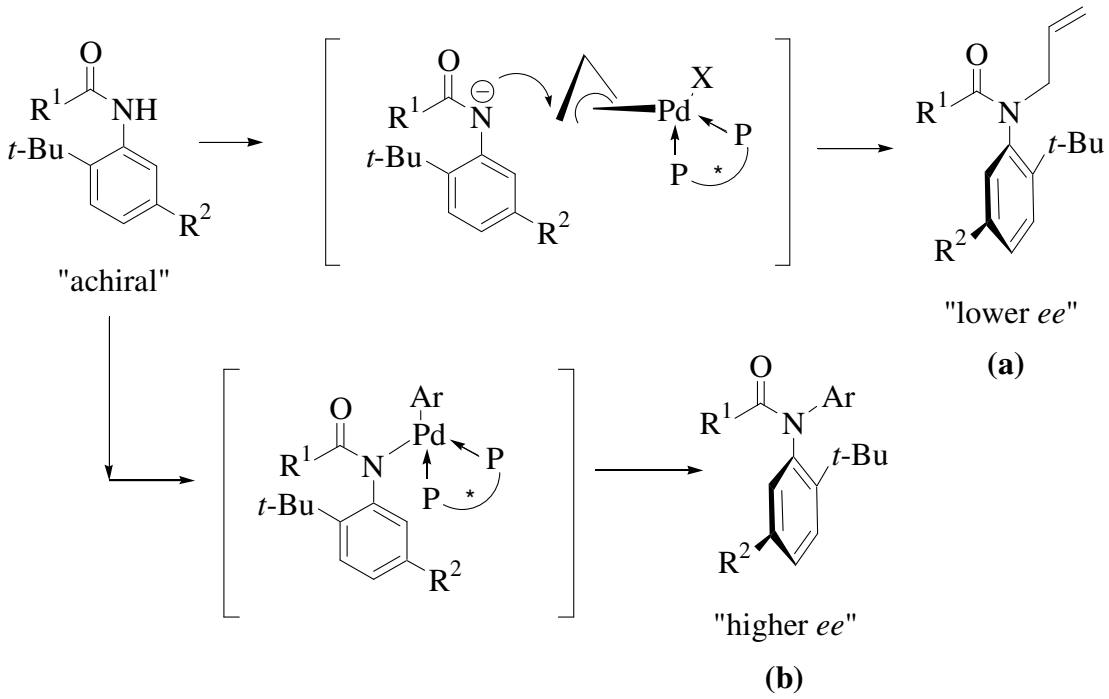


2.4

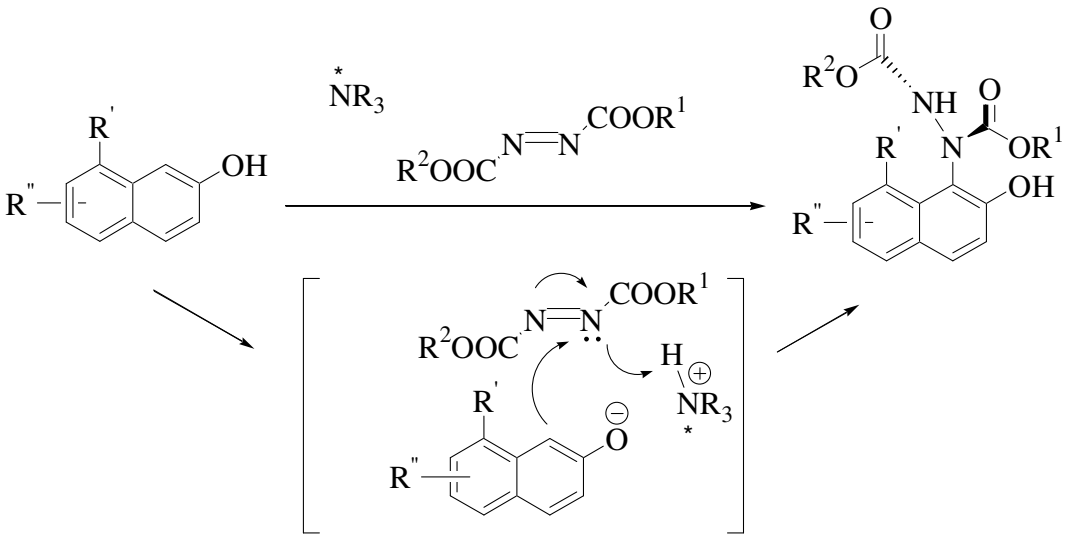
X, R^1, R^2 = Alkyl, Aryl

The preparation of compounds **2.1**–**2.3** is usually a tedious multistep sequence, and in most cases a resolution of the racemate is required to obtain enantiopure material. Only recently Taguchi and co-workers reported a highly enantioselective catalytic synthesis of atropisomeric anilides **2.2**.[4] through enantioselective inter- and intramolecular N-arylation mediated by a chiral Pd catalyst. The present reaction proceeds with high enantioselectivity to give various optically active atropisomeric amides in good yields (see scheme below). Moreover, this study should be also noted as a rare example of catalytic asymmetric N-arylation.



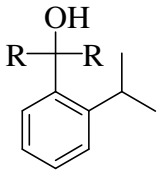
In *N*-allylation with an asymmetric π-allyl Pd catalyst, since a soft nucleophile such as anilide anion attacks the π -allyl carbon from the opposite side of the Pd atom, asymmetric induction at the anilide part by a chiral phosphine ligand may be difficult (eq **a**). Meanwhile, in the Pd-catalyzed asymmetric N-C coupling, it was expected that high enantioselectivity may be achieved through attack of an anilide nucleophile to the Pd atom followed by reductive elimination of the resulting palladium amide complex (II), because in such reaction, N-C bond formation should occur near the chiral ligand (eq **b**).

It is of no doubt that efficient and enantioselective methods to access these compounds can trigger the discovery of new applications. Jørgensen et al. reported the properties and an easy asymmetric organocatalytic synthesis of atropisomers of class **2.4**. The strategy of the formation of this new class of atropisomer is based on the organocatalytic asymmetric amination of 2-naphthols where a tertiary amine is the catalyst:[5]



"Activated naphthoxide
through a chiral ion pair"

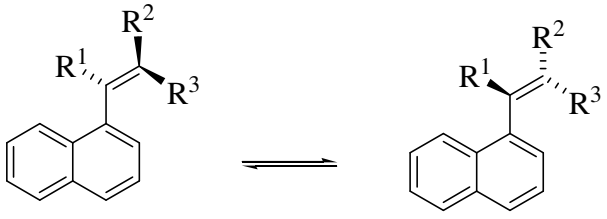
Another class of configurationally stable atropisomers is the family of hindered aryl carbinols studied by the group of Mazzanti.[6] They reported the structural, conformational, and stereodynamic properties of a class of carbinols (compounds **2.5**) having substituents of different dimensions, so that either stereolabile or configurationally stable atropisomers can be obtained:



R = Me, Et, *i*-Pr, *t*-Bu

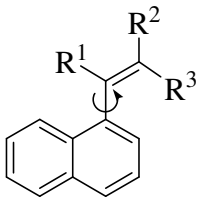
2.5

Reported examples of other classes of atropisomeric molecules include substituted styrenes. Barriers to rotation in 1-alkenyl-naphthalenes, for example, are greatly dependent on both direct and buttressing effects of the substituents on the olefin:[7]



2.6 **2.7**

A dynamic NMR method was used in order to determine the barriers to rotation between **2.6** and **2.7**. Temperature-dependent spectra which allow the determination of these barriers can be expected only when one of the substituents R^1, R^2, or R^3 contains groups which are diastereotopic when rotation **2.6** ↔ **2.7** is slow on the n.m.r. time-scale, so suitable substituents were chosen:



	2.8 R^1 = *i*-Pr	**2.9** R^1 = Et
a; $R^2 = R^3$ = Me	>> 26.0	25.8
b; R^2 = H, R^3 = Me	21.1	12.2
c; R^2 = Me, R^3 = H	16.1	< 7.0
d; $R^2 = R^3$ = H	11.5	< 7.0

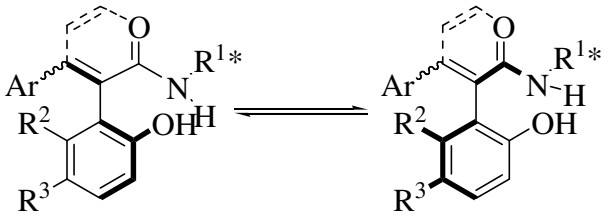
Barriers to rotation in Kcal/mol, barriers are free energies of activation at the following temperatures (°C) for **(2.8a-d)** and **(2.9a-d),** respectively : 200, 165, 48, -61; 195, -48, -151, -156.

It is clear from the results in the table that the height of the barrier greatly depends on the size of R^1 and R^3**,** presumably by virtue of their direct interaction with hydrogens in the 2- and 8- positions of the naphthalene ring, in a way which recalls the substituted binaphthyls. What is less expected is the effect of the substituent R^2, where replacement of a hydrogen atom by a methyl group leads to a barrier which is higher by between 4.6 kcal/mol [(**2.8b**) *vs.* (**2.8a**), (**2.8d**) *vs.* (**2.8c**)] and more than 13 kcal/mol [(**2.9b**) *vs.* (**2.9a**)], The buttressing effect of R^2 is presumably a result of constraint being placed on the conformations adopted by R^1 and R^3 during rotation, which affects the interactions of these groups with the naphthalene ring. The addition of only two methyl groups leads from a molecule (**2.9c**) where rotation is fast on the NMR time-scale even at - 140 °C, to a molecule (**2.8a**) which should be capable of resolution into optical isomers that are stable at room temperature.

Other examples of classes of atropisomeric molecules include 5,6-disubstituted-3,4-dihydro-1*H*-pyridin-2-ones[8] and *o*-substituted *N*-aryl-4-alkyl-thiazoline-2-thiones,[9].

2.2 2-(2-Hydroxyaryl)cinnamic amides: a new class of axially chiral molecules[10]

As part of a project aimed at synthesizing new chiral structures to be used as ligands in catalytic asymmetric applications, we decided to investigate the chiral 2-(2-hydroxyaryl)cinnamic amides **2.10**, obtained from the coupling of the corresponding 2-(2-hydroxyaryl) cinnamic acids and a chiral primary amine. These molecules were chosen since they possess several potential sites of diversity (R^1, R^2, R^3, Ar), which allow for the fine-tuning of their steric, electronic and conformational properties:



2.10 **2.10**

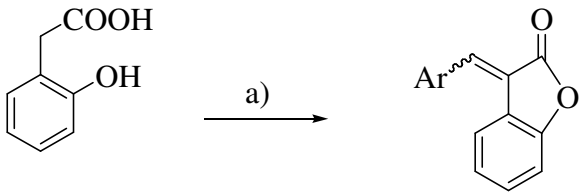
R^1*NH = chiral amine

In addition, we were also intrigued by the fact that they were structurally reminiscent of biaryl compounds and might display restricted rotation about the C_2-C_{aryl} bond and, depending on the energetic barrier to rotation, be resolved into two diastereomeric atropisomeric forms.

Herein we report the synthesis of several differently substituted amides of general type **2.10** derived from 2-(2-hydroxyphenyl)cinnamic and 2-(2-hydroxynaphthyl) cinnamic acid. The barriers to rotation about the C_2-C_{aryl} bond were experimentally determined for both the phenyl and naphthyl derivatives by dynamic ^{1}H-NMR methods.

2.3 Results and Discussion

The synthesis of 2-(2-hydroxyphenyl)cinnamic amides **2.10** was performed using 2-hydroxyphenylacetic acid, as a starting material, which was converted into lactones **2.11(a-c)**, through a Perkin condensation with different aromatic aldehydes:[11]



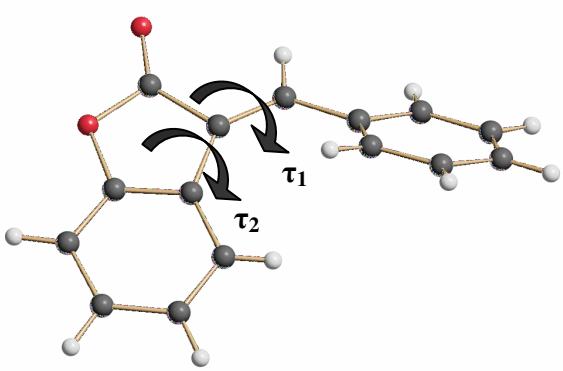
2.11a Ar = C_6H_5 (62%)
2.11b Ar = *o*-MeO-C_6H_4 (86%)
2.11c Ar = *p*-NO_2-C_6H_4 (35%)

a) AcONa (1 equiv), ArCHO (1 equiv), Ac_2O, reflux, 6 h

Lactones **2.11** were obtained as not separable mixtures of *E* and *Z* isomers:

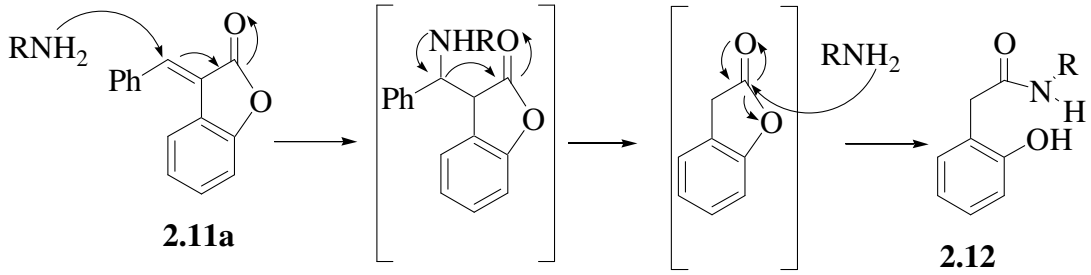
Ar	Lactone	*E/Z*
C_6H_5	2.11a	85/15
o-MeO-C_6H_4	2.11b	100/0
p-NO_2-C_6H_4	2.11c	100/0

Single-crystals of lactone *E*-**2.11a** (Ar = Ph) suitable for an X-ray data collection were obtained from a saturated solution of AcOEt/hexane. In the solid state, the fused rings of lactone *E*-**2.11a** show a very limited deviation from co-planarity, with a τ_1 torsional angle of less than 5°. A more pronounced deviation from planarity is observed at torsion τ_2, reaching a value of about 12°:



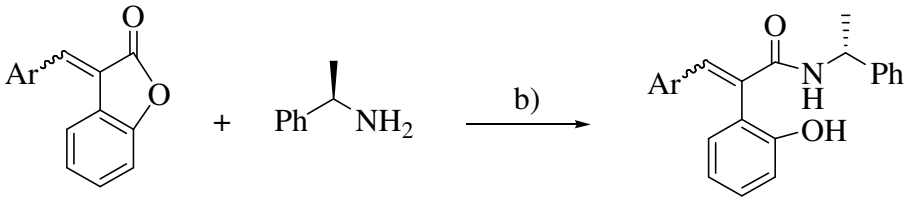
Schakal representation (30% probability level) of the X-ray molecular structure in lactone *E*-**2.11a**. Carbon, grey; hydrogen, light grey; oxygen, red.

The opening of lactones **2.11**, in order to obtain the corresponding amides, was performed using (*R*)-1-phenylethylamine. Simple aminolysis of lactone **2.11a** in several solvents (DCM-toluene, THF) led to the almost exclusive formation of 2-hydroxy phenylacetamide **2.12** [R = (*R*)-1-phenylethylamine], probably through a tandem Michael retro-Mannich sequence:



2.11a **2.12**

In order to favor the opening of lactone **2.11** with respect to the Michael addition, which is the first step of the tandem conjugate addition retro-Mannich sequence, 2-hydroxypyridine was employed as a proton transfer catalyst.[12] Under these conditions, good yields of amides **2.13(a-c)** were obtained as separable mixtures of *E* and *Z* isomers:



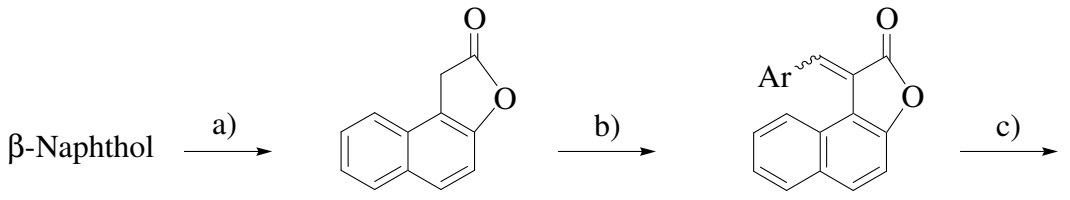
2.11

2.13a Ar = C_6H_5 (84%)
2.13b Ar = *o*-MeO-C_6H_4(41%)
2.13c Ar = *p*-NO_2-C_6H_4 (74%)

b) (*R*)-1-phenylethylamine (2 equiv), 2-hydroxypyridine (0.2 equiv), THF, RT, 72 h.

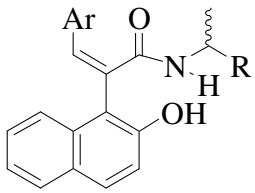
Ar	Amide	E/Z
C_6H_5	2.13a	75/25
o-MeO-C_6H_4	2.13b	100/0
p-NO_2-C_6H_4	2.13c	76/24

2-(2-Hydroxynaphthyl)cinnamic amides **2.16** were prepared starting from β-naphthol (scheme below), which was transformed into lactone **2.14**,[13] and then subjected to Perkin condensation using several aromatic aldehydes. Lactones **2.15** were obtained as mixtures of *E* and *Z* isomers (not separable). Attempts to open lactones **2.15** by reaction with amines in various solvents and in the presence of 2-hydroxypyridine met with limited success and the major isolated products were the 2-hydroxynaphthylacetamides derived from the conjugate addition retro-Mannich mechanism described above. To overcome this problem, we reasoned that the hardness of the amine nucleophile had to be increased, in order to favor the attack to the lactone carbonyl versus the Michael addition. This was achieved by first deprotonating the amines, (*R*)-1-phenylethylamine or (*S*)-1-ethylcyclohexylamine, with *n*-BuLi and then adding the lithium amide solution to a cold solution of the lactone. In this way, no 2-hydroxynaphthylacetamide was detected, and good yields of amides **2.16(a-c)** were obtained as separable mixtures of one *Z* isomer and two atropisomeric *E* isomers:



2.14 (64%)

2.15a Ar = C_6H_5 (62%)
2.15b Ar = *o*-MeO-C_6H_4 (45%)



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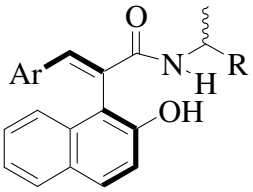

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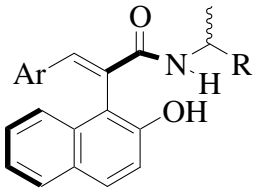


Z-**2.16a** Ar = C_6H_5, R = Ph (47%)
Z-**2.16b** Ar = C_6H_5, R = Chx (54%)
Z-**2.16c** Ar = *o*-MeO-C_6H, R = Ph (68%)

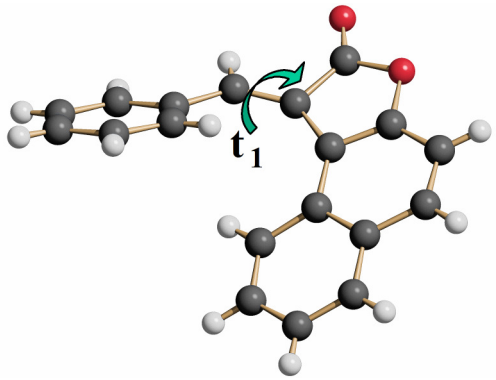
(a*S*)-*E*-**2.16a** Ar = C_6H_5, R = Ph (13%)
(a*S*)-*E*-**2.16b** Ar = C_6H_5, R = Chx (12%)

(a*R*)-*E*-**2.16a** Ar = C_6H_5, R = Ph (11%)
(a*R*)-*E*-**2.16b** Ar = C_6H_5, R = Chx (19%)

a) glyoxal (7 equiv), KOH (1 equiv), H_2O, 30 °C, 4.5 h; b) AcONa (1 equiv), RCHO (1 equiv), Ac_2O, reflux, 6 h; c) *n*-BuLi (3 equiv), $RCH(CH_3)NH_2$ (2.5 equiv), THF, RT 1 h, then, -40 °C, **6** (1 equiv), 2 h.

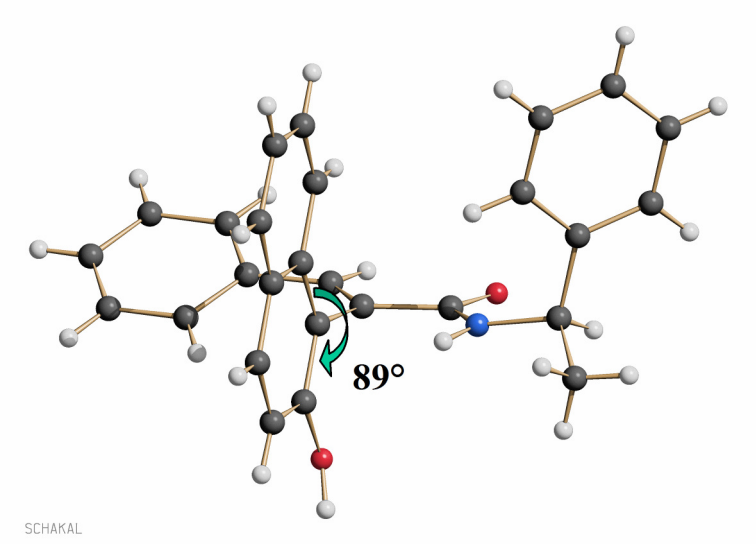
Ar	Lactone	E/Z	R	*R/S*	Amide	E/Z	aS/aR
C_6H_5	2.15a	25/75	Ph	*R*	2.16a	34/66	1.2/1
C_6H_5	2.15a	25/75	Chx	*S*	2.16b	39/61	1/1.3
o-MeO-C_6H_4	2.15b	0/100	*Ph*	*R*	2.16c	0/100	-

X-ray quality crystals of lactone *E*-**2.15a** (Ar = Ph) were obtained from a saturated solution of AcOEt/hexane. The solid state molecular structure of lactone *E*-**2.15a** is substantially similar to that of *E*-**2.11a**, with the notable exception of an enhanced deviation from co-planarity, the τ_1 between the naphtholic aromatic ring and the exocyclic double bond being about 26°. At variance, the τ_2 dihedral angle is only marginally lowered to *ca*. 10°:



Schakal representation (30% probability level) of the X-ray molecular structure in lactone *E*-**2.15a**. Carbon, grey; hydrogen, light grey; oxygen, red.

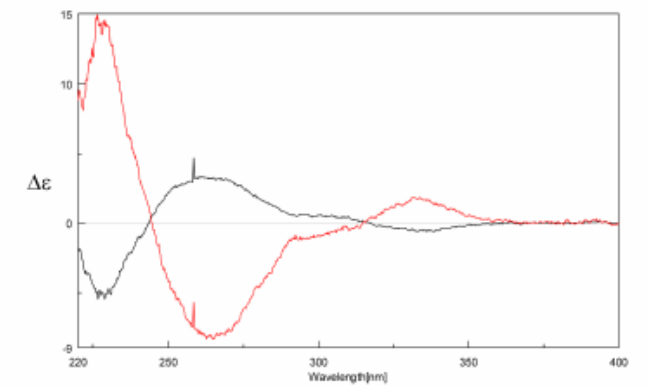
X-ray quality crystals of amide *aR-E*-**2.16a** (Ar = Ph, R = Ph) were obtained from a saturated solution of AcOEt/hexane. The solid state structure of amide *aR-E*-**2.16a** shows that, in the crystal, the molecule adopts a staggered conformation with a dihedral angle of *ca.* 89° between the naphtholic ring and the unsaturated amide plane.



Schakal representation (30% probability level) of the X-ray molecular structure *aR-E*-**2.16a** . Carbon, grey; hydrogen, light grey; oxygen, red.

The absolute configuration of the chiral axis, based on the fixed stereocenter of (*R*)-1-phenylethylamine, resulted to be *aR*.

Circular dicroism (CD) curves were also measured for compounds *aR-E*-**2.16a** and *aS-E*-**2.16b**:



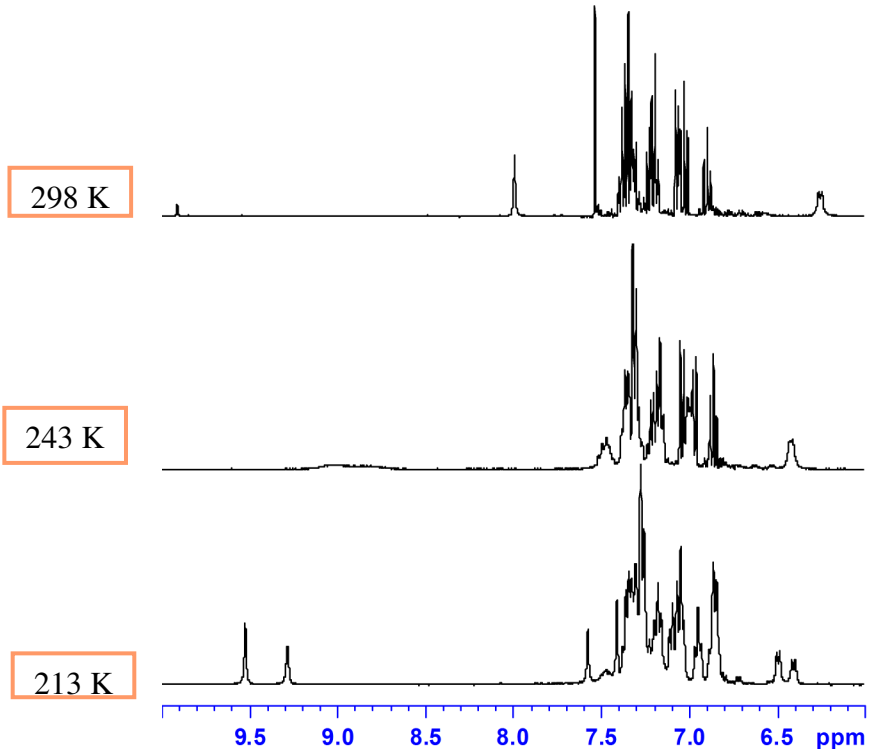
CD spectra of *aR-E*-**2.16a** (red curve) and *aS-E*-**2.16b** (black curve) showing nearly enantiomeric behaviour.

Two nearly mirror image curves were obtained for the two compounds. In the case of *aR-E*-**2.16a,** an intense positive band at 228 nm (Δε +14), a negative band at 264 mn (Δε -8) and a weak positive band at 333 nm (Δε +1.7), were observed**.** In particular the exciton band at about 228 nm has been attributed to the long axis polarized ^1B_b transition of naphthalene,[14] while the band at 264 nm is probably due to the absoption of the cinnamic moiety.[15] These two chromophores are oriented perpendicularly to each other and can be described as two interacting orthogonal dipoles. The strong positive-negative exciton is in agreement with a positive helicity[16] and with the *aR* absolute configuration of the chiral axis, as shown also by the X-ray molecular structure. A negative band at 228 nm (Δε -6), a positive band at 262 mn (Δε +3) and a weak negative band at 335 nm (Δε -0.6), were observed for *aS-E*-**2.16b**. In this case a negative-positive exciton is indicative of a negative helycity and of the *aS* configuration of the chiral axis.

2.4 Barriers to rotation

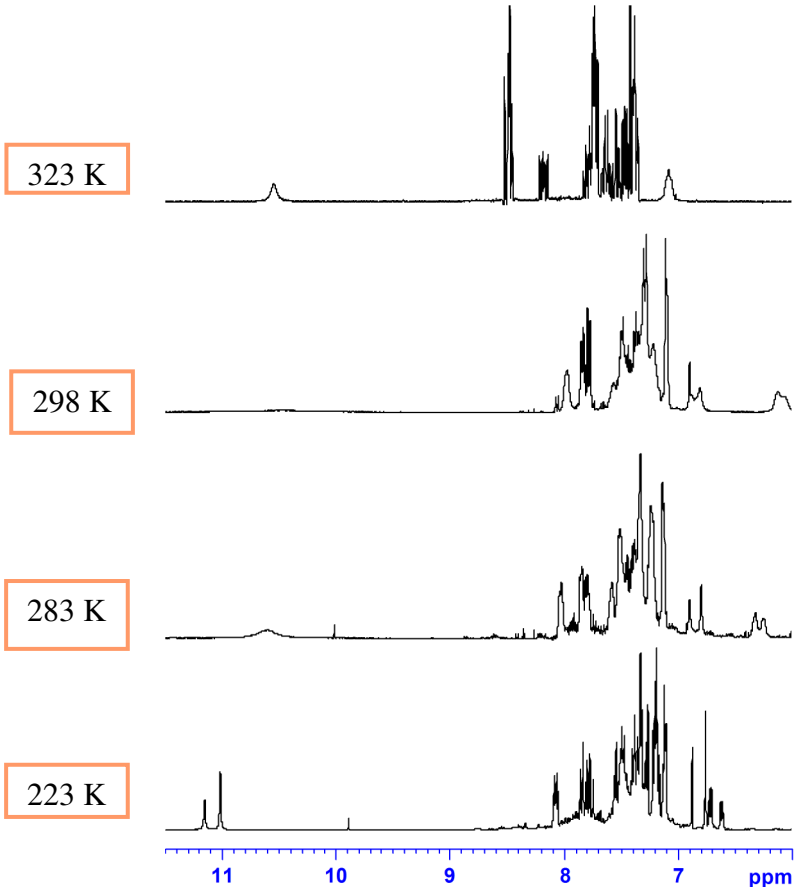
A study of the barrier to rotation about the C_2-C_{aryl} bond was then undertaken for all the amides synthesised. Kinetic data and energy barriers of interconversion of configurationally labile compounds have been conveniently investigated, among others, by means of dynamic NMR.[19] The free energy barriers to internal rotation in the phenol-substituted amides **2.13(a-c)** and *Z*-**2.16(a-c)** were estimated from their variable temperature ^{1}H-NMR spectra by measuring the coalescence temperature of the N-H signal. The rate constants k_c were calculated from the relationship $k_c = \pi\Delta\nu/\sqrt{2}$, and the free energies of activation ($\Delta G_c^{\ddagger}$) were derived by substituting k_c into the Eyring equation.[17]

For example for amide **2.13a** the signals broaden at the coalescence temperature which is at 243 K, while the signals split at 213 K:



For amides *Z*-**2.16(a-c)**, the NMR experiments were performed in $CDCl_3$ and the coalescence is observed near RT, with a single set of well resolved signals above 313 K and two completely resolved sets of signals below 243 K (Figure 4).

For example, for the amide ***Z*-2.16a** the coalescence was reached at 298 K (room temperature):

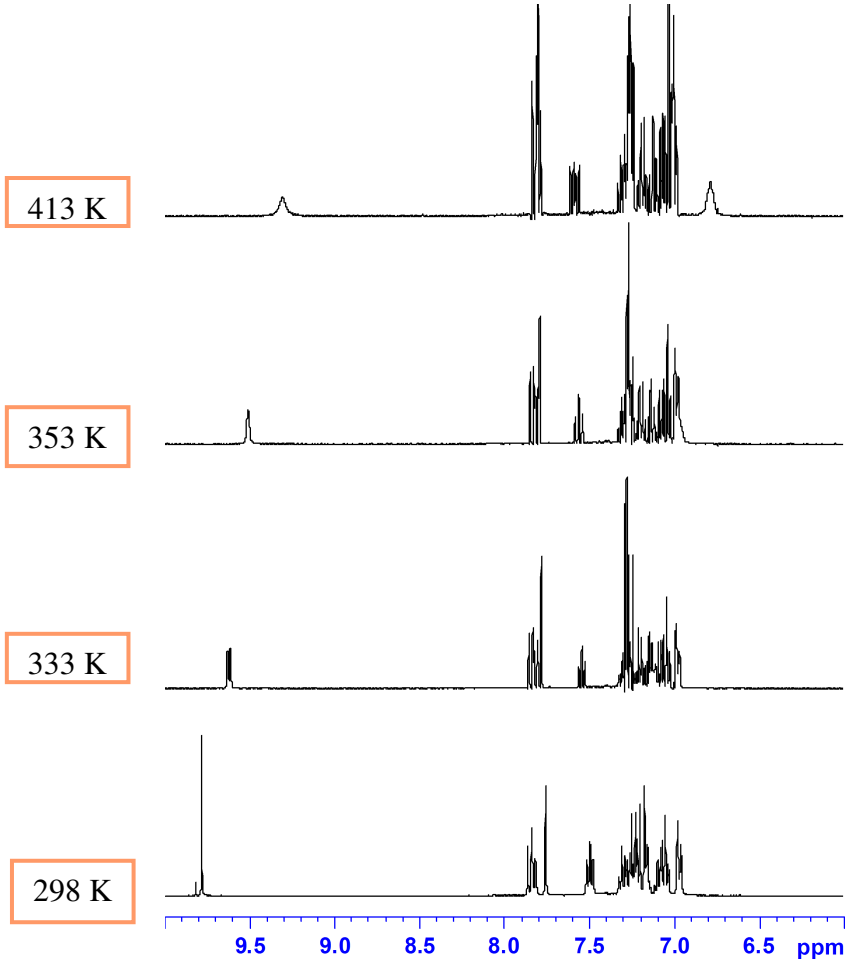


The calculated values of $\Delta G_c^{\ddagger}$ for both families of amides **2.13(a-c)** and Z-**2.16(a-c)** are reported in the table below:

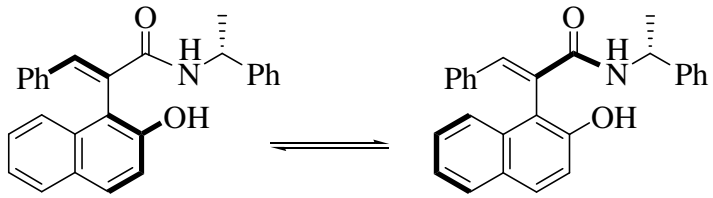
Entry	Amide	T_c (K)	k_c (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1	**2.13a**	243	120.6	11.8
2	**2.13b**	245	72.5	12.2
3	**2.13c**	248	96.7	12.2
4	*Z*-**2.16a**	298	88.4	14.8
5	*Z*-**2.16b**	303	48.3	15.3
6	*Z*-**2.16c**	303	193.6	14.6

The values for $\Delta G_c^{\ddagger}$ are in the range between 11.8 and than 15.3 kcal mol^{-1} and are in agreement with the free rotation about the chiral axis at RT.

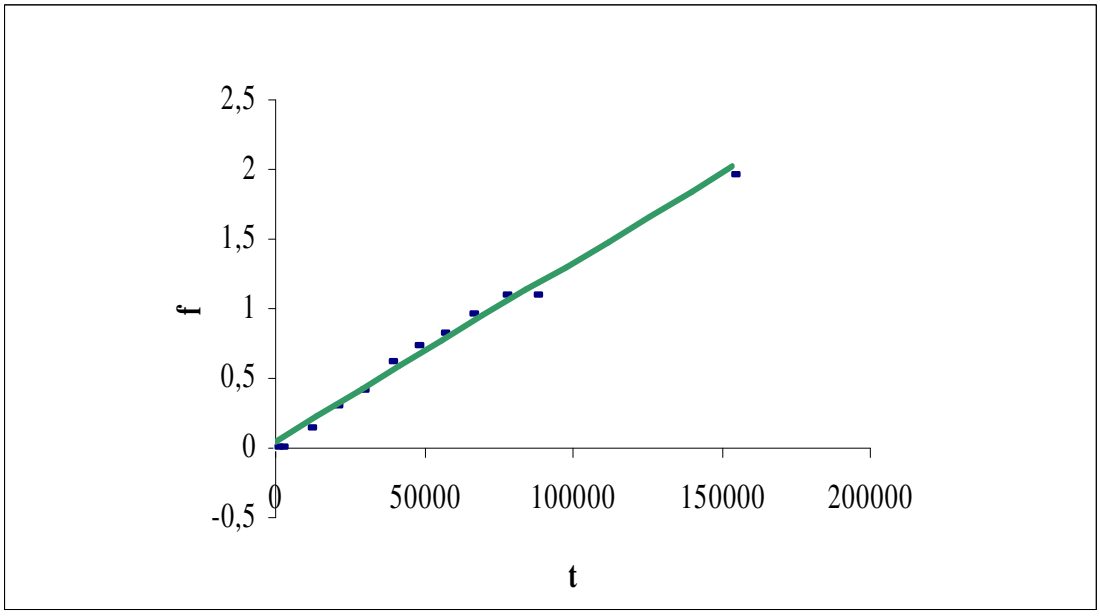
The barriers to rotation for amides *E*-**2.16(a-b)** were also investigated. In this case, in variable temperature ^{1}H-NMR studies, the coalescence temperature was not reached even upon heating a d_6-DMSO sample to 413 K.



The atropisomers are stable enough to be isolated at RT, although it was noticed that both diastereomerically pure atropisomers slowly equilibrated to a 1/1 mixture of the *aR* and *aS* atropisomers, upon standing in solution (24 h in $CDCl_3$) at RT. The transformation rates of (*aR*)-*E*-**2.16a** and (*aR*)-*E*-**2.16b** were followed at 298 K, by monitoring the time-dependent first-order variation of the relative intensities of the ^{1}H-NMR spectra in $CDCl_3$. The Eyring equation was used to derive the $\Delta G_c^{\ddagger}$ values from the rate constants k_c:



(a*S*)-*E*-**2.16a** (a*R*)-*E*-**2.16a**



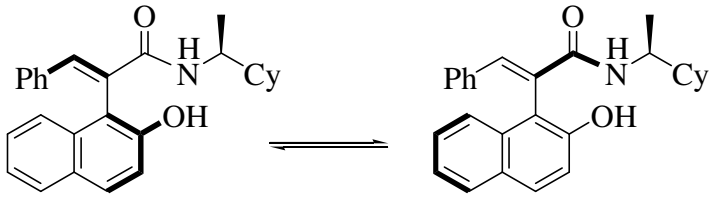
$\mathbf{k_C}$ were calculated following this equation:

$\ln(\mathbf{a_0} / (2\mathbf{a_t} - \mathbf{a_0})) = 2\mathbf{k_C}t$

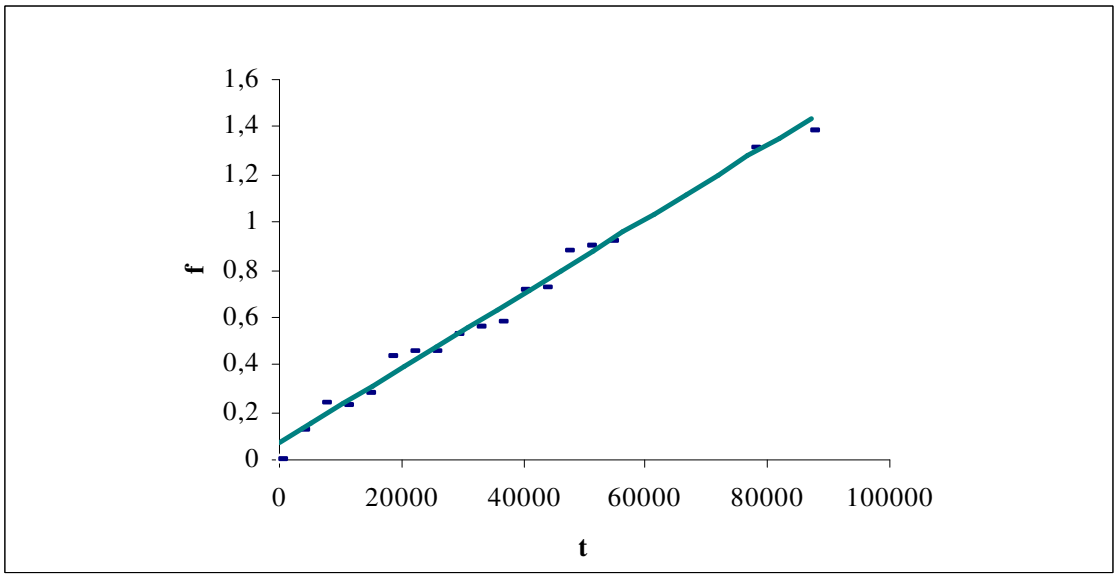
$\mathbf{a_0}$ = integral intensity when t = 0

$\mathbf{a_t}$ = integral intensity at time t

$\mathbf{k_C}$ = 6.40·10-6 sec^{-1}



(a*S*)-*E*-**2.16b** (a*R*)-*E*-**2.16b**



$\mathbf{k_C}$ was calculated in the same way:
$\mathbf{k_C}$ = 7.85·10-6 sec-1

In the table below are reported the found values for $\Delta G_c^{\ddagger}$:

Entry	Compound	k_c (s^{-1})	$\Delta G^{\ddagger}$(kcal mol^{-1})
1	(*aR*)-*E*-**2.16a**	6.40×10^6	24.4
2	(*aR*)-*E*-**2.16b**	7.85×10^6	24.5

When comparing the values of the barrier to rotation for compounds **2.13(a-c)** and *Z*-**2.16(a-c)** to those observed for 2,2',6 trisubstituted biphenyls[18] and 1,1',10 trisubstituted-2,2'-binaphthyls[19] (actually, both amides **2.13a-c** and *Z*-**2.16a-c** are reminiscent of a trisubstituted biaryl chiral axis, it can be noted that the former are

significantly lower. A similar behaviour is found in amides *E*-**2.16(a-b)** with respect to tetrasubstituted biaryl moieties. In fact, slowly interconverting atropisomeric biaryls have been observed, particularly, when associated to 2,2',6 trisubstituted biphenyls, and 1,1',10 trisubstituted-2,2'-binaphthyls, depending on the size of the substituents, but in general tetrasubstituted biarlys are configurationally stable compounds. In the case of our 2-(2-hydroxyaryl)cinnamic amides, the rather low barrier to rotation and the relatively fast atropisomerization process can be explained assuming that, in the lower energy transition state for rotation, the carboxamide moiety is not coplanar with the double bond, thus facilitating the rotation about the C_2-C_{aryl} bond. The atropisomerization process was in fact simulated by molecular mechanics (SPARTAN '02, Wavefunction, Inc., Irvine, CA.) in the case of amide *aR*-*E*-**7a**. The computed barrier (only a few kcal mol^{-1} higher than the experimental value), clearly indicated the assistance of the slight rotation of the amide residue (with concomitant partial loss of conjugation) during the interconversion process, lowering the expected barrier well below that of binol (see previous table).

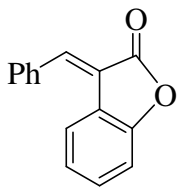
2.5. Conclusions

The synthesis of several differently substituted chiral amides formally derived from a chiral amine and either *E*-2-(2-hydroxyphenyl)cinnamic acid (**2.13a**-**c**) or both *E*- and *Z*-2-(2-hydroxynaphthyl)cinnamic acid (**2.16a**-**c**) is reported. These molecules display a restricted rotation about the C_2-C_{aryl} bond and, depending on their barrier to rotation, can be isolated in two atropisomeric forms. The barriers to rotation about the C_2-C_{aryl} were measured by dynamic ^{1}H-NMR and were found to to vary between 11.8 and 24.5 kcal mol^{-1}, depending on the substitution. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides **2.16** displayed a high barrier to rotation ($\Delta G_c^{\ddagger} > 24.4$ Kcal/mol) and could be isolated as both diastereomerically pure forms at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, (*aR*)-*E*-**2.16a**, was resolved, allowing the determination of the absolute configuration of the chiral axis. The application of these new chiral structures as chiral organic catalysts and ligands for enantioselective metal catalyzed reactions are now actively being investigated in our laboratories.

2.6. **Experimental section**

All manipulations requiring anhydrous conditions were carried out in flame-dried glassware, with magnetic stirring, and under an atmosphere of purified nitrogen. All aldehydes were distilled before use. All other commercially available reagents were used as received. Anhydrous solvents were purchased from commercial sources and withdrawn from the container by syringe, under a slightly positive pressure of nitrogen. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a permanganate solution. Flash column chromatography was performed using silica gel 60 A, particle size 40-64 μm, following the procedure by Still and co-workers. Melting point are uncorrected. Proton NMR spectra were recorded on a 400 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ 7.26 ppm). Carbon NMR spectra were recorded on a 400 spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) with the solvent reference relative to (TMS) employed as the internal standard ($CDCl_3$ δ 77.0 ppm). Infrared spectra were recorded on a standard Infrared spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter with 1 dm cell at the sodium D line. CHN-Analyses were performed using a Perkin Elmer 2400 Series II CHNS/O Analyzer. CD spectra were recorded at 298 K on a Jasco J-500C spectropolarimeter, in acetonitrile, in a 0.01 cm cell in the range 220-400 nm.

2.11a 3-[1-Phenyl-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one.

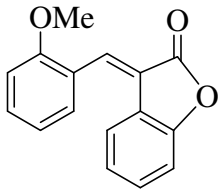


$NaHCO_3$ (1 eq, 32.9 mmol, 2.80 g) was dissolved in 50 mL of water. 2-hydroxyphenylacetic acid (1 eq, 32.9 mmol, 5 g) was added to the mixture obtaining a yellow solution. The system was stirred vigorously and warmed at 50 °C for 2 h. The solvent was evaporated under reduced pressure affording a white solid and the last

traces of water were azeotropically removed by evaporation with toluene (2 × 30 mL) and drying under vacuum. Sodium 2-hydroxyphenylacetate (32.0 mmol, 5.60 g) was treated with benzaldehyde (3.4 mL, 33.6 mmol) and acetic anhydride (13 mL) at reflux temperature for 6 h. The hot mixture was then added to water and stirred vigorously overnight. HCl concentrated was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and successively precipitated with petroleum ether at –15 °C affording the lactone **2.11a** as an orange solid (2.14 g, 62% yield), m.p. = 88 °C. IR (nujol): ν_{max} = 1782, 1769, 1629, 1607, 1293, 1240, 1148, 1121, 1082, 1080, 1022, 967, 932, 877, 757, 754, 732, 703; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H, C**H**), 7.75 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.69-7.72 (m, 2H, Ar**H**), 7.48-7.54 (m, 3H, Ar**H**), 7.37 (dddd, J_1 = 8.1 Hz, J_2 = 7.3 Hz, J_3 = 1.2 Hz, J_4 = 1.2 Hz, 1H, Ar**H**), 7.16 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.06 (dd, J_1 = 7.8 Hz, J_2 = 7.5 Hz, 1H, Ar**H**); ^{13}C-NMR (400 MHz, $CDCl_3$): δ =169.2, 154.9, 141.3, 134.4, 131.4, 131.0, 129.8, 129.3, 124.1, 123.2, 122.6, 122.2, 111.6; $C_{15}H_{10}O_2$ calcd. C 81.07, H 4.54; found: C 79.96, H 4.46.

X-ray crystallographic data of **2.11a**. Orthorhombic, space group *Pcab*, *a* = 9.855(1), *b* = 12.208(2), *c* = 18.268(3) Å, *V* = 2197.8(6) Å^3, Z = 8, $\rho_{.}$ = 1.343 g/cm^3, μ(Mo-Kα) = 0.09 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final *R* and *wR* values of 0.047 for 1171 reflections with I > 2σI, and 0.111 for 1928 reflections, respectively.

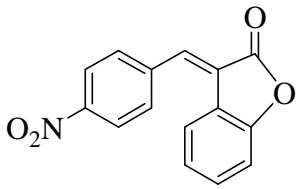
2.11b 3-[1-(2-Methoxy-phenyl)-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one.



2-hydroxyphenylacetic acid (1 eq, 9.85 mmol, 1.50 g) was treated with sodium acetate (1 eq, 9.85 mmol, 1.35 g), 2-methoxy-benzaldehyde (1 eq, 9.85 mmol, 1.35 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. Water (70 mL) was then added to the hot mixture followed by vigorous stirring overnight. Concentrated HCl (10 mL) was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted

with toluene and the organic phase was successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product which was then purified by flash chromatography on silica gel (CH_2Cl_2/Hexane = 75/25) affording the desired product as a yellow solid (2.13 g, 86% yield), m.p. = 123 °C. IR (nujol): ν_{max} = 1782, 1723, 1634, 1594, 1316, 1295, 1255, 1165, 1126, 1075, 1021, 967, 876, 773, 745; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1H, C**H**), 7.76 (d, *J* = 7.6 Hz, 1H, Ar**H**), 7.65 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.49 (dd, J_1 = 7.8 Hz, J_2 = 7.9 Hz, 1H, Ar**H**), 7.33 (dd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, 1H, Ar**H**), 7.13 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.01-7.09 (m, 3H, Ar**H**), 3.91 (s, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 169.4, 158.7, 154.7, 137.8, 132.9, 130.9, 130.0, 123.9, 123.5, 123.1, 122.7, 122.1, 120.6, 111.5, 111.4, 56.0; $C_{16}H_{12}O_3$ calcd. C 76.19, H 4.76; found: C 76.07, H 4.57.

2.11c 3-[1-(4-Nitro-phenyl)-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one.

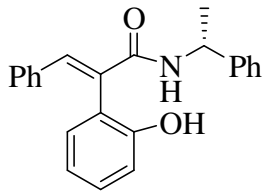


2-hydroxyphenylacetic acid (1 eq, 9.85 mmol, 1.5 g) was treated with sodium acetate (1 eq, 9.85 mmol, 1.35 g), 4-nitro-benzaldehyde (1 eq, 9.85 mmol, 1,50 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. The hot mixture was then poured into water (70 mL) and stirred vigorously overnight. Concentrated HCl (10 mL) was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and the organic phase was successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product which was then purified by flash chromatography on silica gel (Hexane/AcOEt = 70/30) affording the desired product as a yellow solid (0.92 g, 35% yield), m.p. = 189 °C. IR (nujol): ν_{max} = 1780, 1613, 1588, 1524, 1515, 1343, 1319, 1239, 1145, 1123, 1079, 880, 774, 751, 698; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.86 (s, 1H, C**H**), 7.85 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.57 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.43 (dd, J_1 = 8.0 Hz, J_2 = 7.7 Hz, 1H, Ar**H**), 7.19 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.08 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 1H, Ar**H**); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.3, 155.5, 148.8, 140.9, 137.2, 132.6, 131.8, 130.4, 124.6, 124.4, 123.3, 121.4, 112.1; $C_{15}H_9NO_4$ calcd. C 67.41, H 3.37, N 5.24; found: C 67.23, H 3.25, N 5.14.

General procedure for the synthesis of 2-(2-hydroxyphenyl)cinnamic amides.

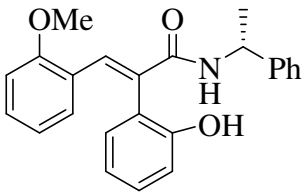
A solution of lactone (1 eq, 1.35 mmol), (R)-1-phenylethylamine (2 eq, 2.70 mmol, 350 μL) and 2-hydroxypyridine (0.2 equiv, 0.27 mmol, 28 mg) in THF (24 mL) was stirred at room temperature for 3 d. The reaction mixture was then hydrolyzed with HCl 1M and extracted with AcOEt (12 × 3 mL). The combined organic layers were washed with brine and then dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography on silica gel:

2.13a (*E*)-2-(2-Hydroxy-phenyl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide.



pale orange solid (0.29 g, 63% yield). IR (nujol): ν_{max} = 3397, 1644, 1612, 1595, 1514, 1293, 1247, 1234, 1015, 937, 750, 702; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 (s, 1H, C**H**), 7.31-7.35 (m, 3H, Ar**H**), 7.24-7.27 (m, 3H, Ar**H**), 7.13-7.21 (m, 3H, Ar**H**), 7.03-7.10 (m, 4H, Ar**H**), 6.90-6.95 (m, 1H, Ar**H**), 6.20 (d, *J* = 7.9 Hz, 1H, N**H**), 5.18 (m, 1H, C**H**), 1.44 (d, *J*= 6.9 Hz, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ =168.2, 154.9, 143.2, 139.0, 134.7, 131.3, 131.1, 130.5, 129.4, 129.1, 128,7, 127.9, 127.8, 126.3, 122.3, 121.6, 117.9, 49.8, 22.3; $[\alpha]_D$ = -25.6 (c 0.50, $CHCl_3$); $C_{23}H_{21}NO_2$ calcd. C 80.19, H 7.01, N 3.90; found: C 79.80, H 6.87, N 3.96.

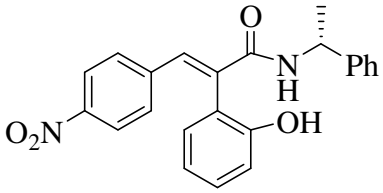
2.13b (*E*)-2-(2-Hydroxy-phenyl)-3-(2-methoxy-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide.



yellow solid (0.06 g, 41% yield), m.p. = 125 °C. IR (nujol): ν_{max} = 3410, 3402, 3125, 1653, 1600, 1522, 1292, 1252, 1163, 1105, 1024, 759, 750, 698; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H, C**H**), 7.23-7.37 (m, 6H, Ar**H**), 7.18 (dd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, 1H, Ar**H**), 7.02 (d, *J* = 8.2 Hz, 1H, Ar**H**), 6.96 (d, *J* = 7.6 Hz, 1H, Ar**H**), 6.84-6.75

(m, 3H, Ar**H**), 6.62 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H, Ar**H**), 6.28 (d, J = 7.8 Hz, 1H, N**H**), 5.26-5.19 (m, 1H, C**H**), 1.51 (d, J = 6.9 Hz, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 169.3, 158.2, 155.2, 143.2, 133.7, 132.8, 131.2, 130.8, 130.5, 130.3, 129.1, 127.8, 126.5, 123.8, 122.7, 121.0, 120.7, 117.9, 110.8, 55.8, 49.8, 22.2; $[\alpha]_D$ = -10.1 (c 0.11, $CHCl_3$); $C_{24}H_{23}NO_3$ calcd. C 77.21, H 6.17, N 3.75; found: C 76.87, H 6.16, N 3.65.

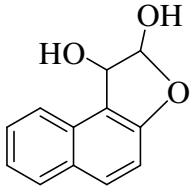
2.13c (*E*)-2-(2-Hydroxy-phenyl)-3-(4-nitro-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide.



yellow solid (0.07 g, 56% yield), m.p. = 70 °C. IR (nujol): ν_{max} = 3404, 3240, 1651, 1614, 1599, 1518, 1343, 1289, 1109, 1043, 1014, 852, 833, 758, 700; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (bs, 1H, O**H**), 7.96 (d, J = 8.4 Hz, 2H, Ar**H**), 7.65 (s, 1H, C**H**), 7.25-7.35 (m, 6H, Ar**H**), 7.14 (d, J = 8.3 Hz, 2H, Ar**H**), 7.06 (d, J = 8.1 Hz, 1H, Ar**H**), 6.86-6.94 (m, 2H, Ar**H**), 6.28 (d, J = 7.9 Hz, 1H, N**H**), 5.14-5.21 (m, 1H, C**H**), 1.46 (d, J = 6.8 Hz, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 167.8, 155.0, 147.6, 142.8, 141.6, 136.3, 135.6, 131.7, 130.9, 130.8, 130.0, 129.2, 127.9, 126.3, 123.8, 121.7, 121.4, 118.2, 50.0, 22.1; $[\alpha]_D$ = - 15.5 (c 0.15, $CHCl_3$); $C_{23}H_{20}N_2O_4$ calcd. C 71.13, H 5.15, N 7.22; found: C 70.84, H 5.06, N 7.03.

4.3 1*H*-Naphtho[2,1-*b*]furan-2-one (**5**). This compound was prepared following a literature procedure.[13]

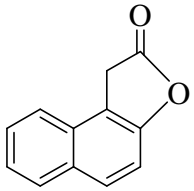
1,2-Dihydronaphthol[2,1-*b*]furan-1,2-diol



In a flask equipped with a mechanical stirrer was placed 40% aqueous glyoxal (7 eq, 96 mmol, 14g). A solution of 2-naphthol (1 eq, 14 mmol, 2g) in 30 mL of H_2O containing

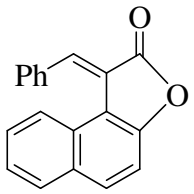
KOH (1 eq, 14 mmol, 0.78g) was added dropwise at 30° C over 1.5 h. The mixture was stirred at 30° C for 3 h. The precipitate formed during the reaction was collected on a filter, washed successively with $CHCl_3$ and H_2O and dried in vacuum to afford the product as a pale yellow solid (2.5 g, 85% yield), m.p. = 60 °C. IR (KBr, cm^{-1}): ν_{max} = 3400 (with a shoulder at 3500, broad and strong ν_{OH}), 1140, 800, 740; ^{1}H-NMR (DMSO-d_6): δ = 7.1-7.9 (m, 7H, Ar**H** + ArCH(OH)CH(O**H**)O-), 5.7-5.9 (m, 2H, ArCH(OH)C**H**(OH)O- + 1O**H**), 5.25 (d, 1H, *J* = 6.3 Hz, 3H, ArC**H**(OH)-); ^{13}C-NMR (DMSO-d_6): δ = 156.9, 131.1, 130.8, 129.0, 128.7, 127.0, 123.1, 122.7, 119.7, 112.6, 108.9, 76.9; $C_{12}H_{10}O_3\,H_2O$ calcd. C 65.44, H 5.49; found: C 65.32, H 5.39.

2.14 1*H*-Naphtho[2,1-*b*]furan-2-one.



A mixture of $CHCl_3$ (40 mL), 1,2-Dihydronaphthol[2,1-*b*]furan-1,2-diol (1 eq, 12 mmol, 2.4 g) and aqueous HCl(3N, 57 mL) was stirred at 50 °C for 1 h. The $CHCl_3$ layer was separated. Evaporation of the solvent afforded the product as a pale yellow solid (1.6 g, 72% yield); m.p. = 103 °C. IR (KBr, cm^{-1}): ν_{max} = 1800, 860, 805, 760, 750; ^{1}H-NMR ($CDCl_3$): δ = 7.7-6.9 (m, 6H, Ar**H**), 3.45 (s, 2H, ArC$\mathbf{H}_2$-CO-); ^{13}C-NMR ($CDCl_3$): δ = 174.3, 152.0, 130.3, 129.5, 129.0, 127.5, 124.8, 122,8, 116.5, 111.3, 31.9; $C_{12}H_8O_2$ calcd. C 78.25, H 4.38; found: C 78.12, H 4.38.

2.15a 1-[1-Phenyl-meth-(*E*)-ylidene]-1*H*-naphtho[2,1-*b*]furan-2-one + 1-[1-Phenyl-meth-(*Z*)-ylidene]-1*H*-naphtho[2,1-*b*]furan-2-one.

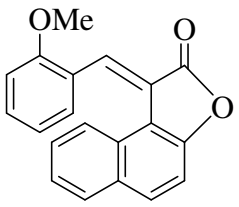


1*H*-Naphtho[2,1-*b*]furan-2-one (1 eq, 10.15 mmol, 1.87 g) was treated with sodium acetate (1 eq, 10.15 mmol, 1.38 g), benzaldehyde (1 eq, 10.15 mmol, 1.03 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. The hot mixture was added to water (120 mL) and stirred vigorously overnight. The mixture was then acidified with

concentrated HCl (15 mL) keeping the system under magnetic stirring at 60 °C for 5 h. The reaction mixture was cooled and the product was extracted in toluene, drying the organic phase over Na_2SO_4. Evaporation of toluene gave the crude product which was purified by flash chromatography on silica gel (Hexane/AcOEt = 8/2) affording the desired product as a yellow solid (1.68 g, 62% yield) and as a 1:3 mixture of *E* and *Z* diastereomers. IR (nujol): ν_{max} = 1771, 1610, 1573, 1523, 1262, 1139, 1106, 987, 889, 853, 801, 765, 740, 688; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.6 Hz, 1H, Ar**H**), 8.30 (s, 1H, C**H**), 8.09 (s, 1H, C**H**), 8.04-8.07 (m, 2H, Ar**H**), 7.95 (d, *J* = 8.7 Hz, 2H, Ar**H**), 7.89 (d, *J* = 8.8 Hz, 1H, Ar**H**), 7.86 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.69 (ddd, J_1 = 7.6 Hz, J_2 = 7.1 Hz, J_3 = 1.3 Hz, 1H, Ar**H**), 7.35-7.53 (m, 12H, Ar**H**), 7.16 (ddd, J_1 = 7.8 Hz, J_2 = 7.7 Hz, J_3 = 1.1 Hz, 1H, Ar**H**), 6.99 (d, *J* = 8.5 Hz, 1H, Ar**H**); ^{13}C-NMR (400 MHz, $CDCl_3$): 170.2, 155.0, 153.1, 143.1, 140.7, 135.7, 134.0, 133.6, 132.4, 131.9, 131.6, 131.5, 131.1, 130.7, 130.6, 129.8, 129.1, 128.7, 127.5, 127.2, 125.2, 125.1, 123.7, 123.1, 122.5, 112.1, 112.0; $C_{19}H_{12}O_2$ calcd. C 83.82, H 4.41; found: C 83.46, H 4.34.

X-ray crystallographic data of **2.15a**. Orthorhombic, space group *Pcab*, *a* = 7.932(4), *b* = 13.908(10), *c* = 24.500(17) Å, *V* = 2703(3) Å^3, Z = 8, $\rho_{.}$ = 1.338 g/cm^3, (Mo-Kα) = 0.09 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final *R* and *wR* values of 0.068 for 971 reflections with I > 2σI, and 0.145 for 2458 reflections, respectively. CCDC No. 602857.

2.15b 1-[1-(2-Methoxy-phenyl)-meth-(*E*)-ylidene]-1*H*-naphtho [2,1-*b*]furan-2-one.



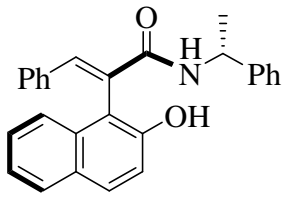
1*H*-Naphtho[2,1-*b*]furan-2-one (1 eq, 4.54 mmol, 0.83 g) was treated with sodium acetate (1 eq, 4.54 mmol, 0.37 g), 2-methoxy-benzaldehyde (1 eq, 4.54 mmol, 0.62 g) and acetic anhydride (6 mL) at reflux temperature for 6 h. The hot mixture was added to water (120 mL) and stirred vigorously overnight. The mixture was then acidified with HCl (15 mL) keeping the system under magnetic stirring at 60 °C for 5 h. A brown precipitate was formed. The reaction mixture was cooled and the product was extracted

in toluene, drying the organic phase over Na_2SO_4. Evaporation of toluene gave the crude product which was purified by flash chromatography on silica gel (Hexane/AcOEt = 75/25) affording the desired product as an orange solid (1.47 g, 45% yield) m.p. = 157 °C. IR (nujol): ν_{max} = 1775, 1599, 1524, 1292, 1254, 1112, 1001, 1020, 973, 807, 780, 744; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H, Ar**H**), 8.38 (d, *J* = 8.5 Hz, 1H, Ar**H**), 8.19 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.92 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.86 (d, *J* = 8.7 Hz, 1H, Ar**H**), 7.67 (dd, J_1 = 7.4 Hz, J_2 = 7.9 Hz, 1H, Ar**H**), 7.52-7.45 (m, 2H, Ar**H**), 7.34 (d, *J* = 8.7 Hz, 1H, Ar**H**), 7.08 (dd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, 1H, Ar**H**), 6.99 (d, *J* = 8.3 Hz, 1H, Ar**H**), 3.96 (s, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 166.7, 158.6, 152.8, 141.5, 138.7, 132.9, 132.4, 131.9, 131.5, 130.5, 128.9, 128.7, 125.1, 123.0, 122.8, 120.5, 117.4, 112.0, 110.8, 56.1; $C_{20}H_{14}O_3$ calcd. C 79.47, H 4.63; found: C 79.44, H 4.50.

2.16a 2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide.

*n*BuLi (1.6 M in hexanes 4.31 mL, 6.90 mmol) was slowly added to a solution of (R)-1-phenylethylamine (0.742 mL, 5.75 mmol) in anhydrous tetrahydrofuran (14 mL), in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to –40 °C and lactone **2.15a** (626 mg, 2.30 mmol) was added. The reaction mixture was stirred at –40 °C for 2 h, quenched with 1M HCl (42 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography giving 3 pale yellow solids.

[(*aR*)-E-**2.16a**] **(*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide.**

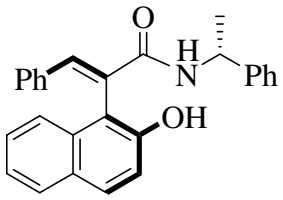


(0.10 g, 11% yield) m.p. = 180 °C. IR (nujol): ν_{max} = 3403, 3397, 3115, 1650, 1600, 1582, 1342, 1276, 1247, 1211, 1158, 1079, 992, 955, 821, 775, 751, 699, 692; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1H, C**H**), 7.90 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.85-7.88 (m, 1H, Ar**H**), 7.60-7.63 (m, 1H, Ar**H**), 7.39-7.41 (m, 2H, Ar**H**), 7.29 (d, *J* = 8.4 Hz, 1H, Ar**H**), 7.16-7.21 (m, 4H, Ar**H**), 6.97-7.10 (m, 6H, Ar**H**), 5.82 (d, *J* = 7.8 Hz, 1H, N**H**),

5.15-5.20 (m, 1H, C**H**), 1.31 (d, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 166.5, 151.8, 143.3, 142.4, 134.4, 132.8, 131.6, 130.2, 130.0, 129.6, 129.0, 128.9, 128.8, 128.0, 127.5, 126.8, 126.1, 124.6, 124.4, 118.6, 114.0, 49.6, 22.3; $[\alpha]_D$ = -200.4 (c 0.15, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd. C 82.44, H 5.85, N 3.56; found: C 80.71, H 6.17, N 3.32.

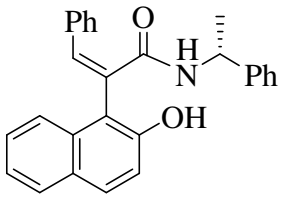
*X-ray crystallographic data of (aR)-E-***2.16a**. Monoclinic, space group $P2_1$, *a* = 10.014(6), *b* = 10.129(3), *c* = 21.348(15) Å, *β* = 99.30(6)°, *V* = 2137(2) Å^3, Z = 4, ρ = 1.223 g/cm^3, *μ*(Mo-Kα) = 0.08 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final *R* and *wR* values of 0.063 for 2160 reflections with I > 2σI, and 0.117 for 4114 reflections, respectively. CCDC No. 602858.

[(*aS*)-E-**2.16a**] **(*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide.**



(0.12 g, 13% yield) m.p. = 181 °C. IR (nujol): ν_{max} = 3399, 3150, 1651, 1593, 1576, 1537, 1516, 1504, 1342, 1285, 1246, 1209, 1141, 1080, 923, 955, 822, 766, 754, 692; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1H, C**H**), 7.90 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.88 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.69 (d, *J* = 8.2 Hz, 1H Ar**H**), 7.39-7.48 (m, 2H, Ar**H**), 7.00-7.29 (m, 11H, Ar**H**), 5.84 (d, *J* = 7.8 Hz, 1H, N**H**), 5.13-5.21 (m, 1H, C**H**), 1.24 (d, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 166.3, 151.8, 143.3, 142.5, 134.4, 132.8, 131.6, 130.3, 130.0, 129.7, 129.0, 128.9, 128.0, 127.6, 126.7, 126.2, 124.6, 124.2, 118.6, 114.0, 49.6, 22.1; $[\alpha]_D$ = +93.2 (c 0.19, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd. C 82.44, H 5.85, N 3.56; found: C 80.71, H 6.17, N 3.32.

(*Z*-**2.16a**) **(*Z*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide**.

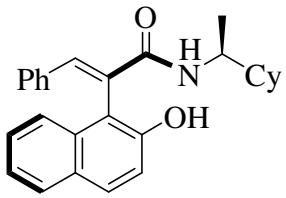


(0.43 g, 47% yield), m.p. = 81 °C. IR (nujol): ν_{max} = 3320, 3056, 1618, 1512, 1510, 1260, 1232, 1225, 975, 950, 819, 751, 698; ^{1}H-NMR (400 MHz, $CDCl_3$, 313 K): δ = 7.99 (d, *J* = 8.5 Hz, 1H, Ar**H**), 7.84 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.78 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.25-7.51 (m, 11H, Ar**H**), 7.09-7.11 (m, 2H, Ar**H**), 6.85 (s, 1H, C**H**), 6.05 (d, *J* = 7.3 Hz, 1H, N**H**), 5.13-5.20 (m, 1H, C**H**), 1.39 (d, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$, 313 K): δ = 171.2, 153.9, 141.9, 138.1, 135.2, 133.4, 130.7, 129.8, 129.2, 129.1, 129.0, 128.9, 128.7, 128.0, 127.0, 123.7, 123.3, 120.4, 118.1, 50.0, 21.1; $[\alpha]_D$ = -26.1 (c 0.15, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd. C 82.44, H 5.85, N 3.56; found: C 80.99, H 5.88, N 3.34.

2.16b *N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide

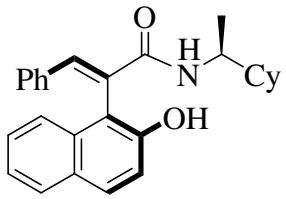
*n*BuLi (1.6 M in hexanes 3.80 mL, 5.94 mmol) was slowly added to a solution of (*S*)-1-cyclohexyl-ethylamine (0.74 mL, 4.95 mmol) in anhydrous tetrahydrofuran, in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to –40 °C and lactone **2.15a** (540 mg, 1.98 mmol) was added. The reaction mixture was stirred at -40 °C for 2 h, quenched with HCl 1 M (42 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The product obtained was purified by flash chromatography giving 3 different pale yellow solids.

[(*aR*)-E-**2.16b**] **(*E*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide**.



(0.09 g, 15% yield), m.p. = 70 °C. IR (nujol): ν_{max} = 3410, 3171, 1652, 1600, 1506, 1344, 1282, 1206, 958, 820, 749, 690, 668; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1H, C**H**), 7.90 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.86 (d, *J* = 7.6 Hz, 1H, Ar**H**), 7.64 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.37-7.43 (m, 2H, Ar**H**), 7.29 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.02-7.15 (m, 5H, Ar**H**), 5.44 (d, *J* = 8.9 Hz, 1H, N**H**), 3.85-3.95 (m, 1H, C**H**), 1.47-1.65 (m, 5H, Cy**H**), 1.01-1.16 (m, 4H, Cy**H**), 0.85-0.89 (m, 4H, C$\mathbf{H}_3$), 0.62-0.71 (m, 1H, C$\mathbf{H}_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 166.5, 151.8, 141.9, 134.6, 132.8, 131.5, 130.2, 129.8, 129.6, 128.9, 128.8, 128.0, 127.1, 124.5, 124.2, 118.5, 114.3, 50.5, 43.1, 29.5, 28.9, 26.7, 26.4, 18.0; $[\alpha]_D$ = -57.9 (c 0.39, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd. C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

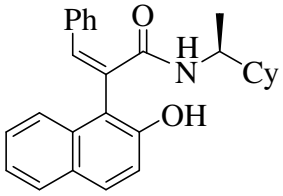
[(*aS*)-E-**2.16b**] **(*E*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide**.



(0.07 g, 19% yield), m.p. = 179 °C. IR (nujol): ν_{max} = 3399, 3227, 1652, 1605, 1595, 1511, 1351, 1246, 1205, 1143, 827, 749, 690; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1H, C**H**), 7.90 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.86 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.67 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.37-7.46 (m, 2H, Ar**H**) 7.27 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.16-7.21 (m, 1H, Ar**H**), 7.05-7.12 (m, 4H, Ar**H**), 6.04 (bs, 1H, O**H**), 5.36 (d, *J* = 9.0 Hz, 1H, N**H**), 3.88-3.97 (m, 1H, C**H**), 1.48-1.60 (m, 3H, Cy**H**), 1.23-1.38 (m, 3H, Cy**H**), 0.68-1.10 (m, 7H, Cy**H**), 0.33-0.42 (m, 1H, Cy**H**); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 166.3, 151.5, 141.9, 134.5, 132.8, 131.5, 130.2, 129.9, 129.6, 129.0, 128.8, 127.9, 127.1,

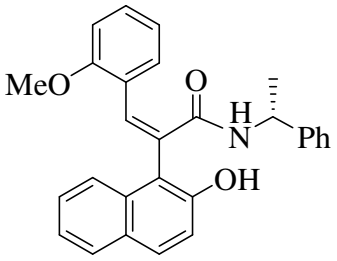
124.6, 118.4, 114.2, 50.2, 43.3, 29.4, 28.3, 26.6, 26.4, 26.3, 18.2; $[\alpha]_D$ = +154.8 (c 0.12, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd. C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

(*Z*-**2.16b**) **(*Z*)-*N*-((S)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide**.



(0.41 g, 54% yield), m.p. = 168 °C. IR (nujol): ν_{max} = 3333, 3150, 1602, 1555, 1305, 1258, 1218, 1204, 1169, 1146, 1107, 1000, 919, 885, 819, 818, 753, 699, 639, 635; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.62 (bs, 1H, O**H**), 7.97 (d, *J* = 8.4 Hz, 1H, Ar**H**), 7.84 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.78 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.50-7.56 (m, 3H, Ar**H**), 7.35-7.45 (m, 4H, Ar**H**), 7.29 (d, *J* = 8.9 Hz, 1H, Ar**H**), 6.84 (s, 1H, C**H**), 5.60 (bs, 1H, N**H**) 3.78-3.90 (m, 1H, C**H**), 1.60-0.73 (m, 11H, Cy**H**), 0.93 (d, *J* = 6.5 Hz, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 171.6, 153.9, 137.7, 133.2, 130.3, 129.7, 129.2, 129.0, 128.9, 127.1, 125.0, 123.6, 123.3, 120.5, 117.5, 50.9, 43.0, 29.3, 29.2, 26.6, 26.4, 16.8; $[\alpha]_D$ = +36.5 (c 0.20, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd. C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

(*Z*-**2.16c**) **(*Z*)-2-(2-Hydroxy-naphthalen-1-yl)-3-(2-methoxy-phenyl)-*N*-((R)-1-phenyl-ethyl)-acrylamide**.



*n*BuLi (1.6 M in hexanes 0.62 mL, 0.99 mmol) was slowly added to a solution of ((R)-1-phenylethylamine (0.107 mL, 0.83 mmol) in anhydrous tetrahydrofuran, in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to –40 °C and lactone **6b** (100 mg, 0.33 mmol) was added. The reaction mixture was stirred at –40 °C for 2 h, quenched with HCl 1 M (7 mL) and extracted with AcOEt. The organic phase

was washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography giving a greenish-yellow solid (0.10 g, 68% yield), m.p. = 65 °C. IR (nujol): ν_{max} = 3406, 3292, 3061, 3031, 2974, 2931, 1665, 1617, 1602, 11538, 1510, 1463, 1336, 1250, 1114, 1026, 821, 753, 700, 623; ^{1}H-NMR (400 MHz, $CDCl_3$, 313 K): δ = 10.50 (bs, 1H, O**H**), 8.18 (d, *J* = 8.4 Hz, 1H, Ar**H**), 7.81 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.77 (d, *J* = 8.9 Hz, 1H, Ar**H**), 6.85-7.61 (m, 13H, Ar**H**), 6.18 (bs, 1H, N**H**), 5.00-5.07 (m, 1H, C**H**), 3.83-3.90 (m, 3H, C**H**$_3$), 1.35-1.27 (m, 3H, C**H**$_3$); ^{13}C-NMR (400 MHz, $CDCl_3$, 313 K): δ = 171.1, 157.3, 153.9, 135.2, 133.6, 130.2, 130.0, 129.7, 129.0, 128.7, 127.7, 126.8, 126.5, 124.2, 123.1, 121.5, 120.4, 111.2; $[\alpha]_D$ = -31.7 (c 0.28, $CHCl_3$); $C_{28}H_{25}NO_3$ calcd. C 79.43, H 5.91, N 3.31; found: C 78.51, H 5.95, N 3.16.

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