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Substituent effects on axial chirality in 1-aryl-3,4-dihydroisoquinolines: controlling the rate of bond rotation.

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SUPPORTING INFORMATION

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General Information

All reactions were performed in flame-dried apparatus under a nitrogen or argon atmosphere unless otherwise stated. All reagents and chemicals were purchased from chemical suppliers and used without further purification. Dry dichloromethane (DCM) was obtained by distillation from calcium hydride under nitrogen. Triethylamine was stored over KOH. All solvents were removed under vacuum using a rotary evaporator. Petrol refers to the fraction of light petroleum ether boiling between 40 °C and 60 °C.

Thin layer chromatography(TLC) was carried out on pre-coated UV₂₅₄ plates (Macherey-Nagel alugram SIL G/UV₂₅₄), with visualisation by UV light at 254 nm or by staining with phosphomolybdic acid (PMA). Flash column chromatography used chromatography grade silica, 60 Å particle size, 40-63 microns from Aldrich.

Capillary melting points were determined on a Stuart Scientific SMP 10 apparatus– melting points uncorrected.

Nuclear Magnetic Resonance (NMR) spectra (¹H NMR and ¹³C NMR) were recorded on either a Varian 400 MHz or a Bruker Ultrashield 300, 400, 500MHz spectrometer. The residual solvent peak for CDCl₃ (δ_H: 7.26 ppm; δ_C:77.16 ppm) was used as internal standard when assigning NMR spectra.¹ NMR data are presented as follows: chemical shifts, δ, are quoted in parts per million (ppm) down-field of tetramethylsilane. Coupling constants, *J*, are reported to the nearest 0.1 Hz and the assignments are based on chemical shift, integration, coupling pattern and 2D-NMR experiments when necessary. The splitting patterns for the spectra assignment are abbreviated to: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), septet (sept.), multiplet (m), broad (br.) and some as a combination of these.

The HPLC traces were carried out on a (*R,R*)-Whelk-01, 25 cm x 4.6 mm ID column at different temperatures, typically eluting with 40% IPA in hexane, flow rate 1 mL/min, 10 µL injection, unless otherwise stated.

Low resolution electrospray mass spectra, ESI, were recorded on a Micromass Platform II mass spectrometer. High resolution mass spectra, HRMS, were recorded on a ThermoFinnigan MAT 95XP mass spectrometer or Waters QTOF, and are accurate to ± 0.001 Da.

Infrared spectra were recorded on a Thermo Scientific iD5 ATR, FT-IR spectrometer and only the most relevant absorptions are reported and quoted as ν in cm⁻¹. The samples were run as solids or evaporated films.

¹ Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, 62, 7512.

¹H and ¹³C NMR spectra

No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height
1	35.20	0.0000	4	126.18	0.0000	7	127.67	0.0000	10	128.72	0.0000	13	130.19	0.0000	16	135.43	0.0000
2	41.21	0.0000	5	126.47	0.0000	8	127.93	0.0000	11	129.04	0.0000	14	130.36	0.0000	17	138.78	0.0000
3	125.46	0.0000	6	126.88	0.0000	9	128.60	0.0000	12	130.15	0.0000	15	134.33	0.0000	18	171.04	0.0000

2 peaks

No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height
1	35.14	0.0000	4	125.40	0.0000	7	128.11	0.0000	10	128.70	0.0000	13	130.72	0.0000	16	135.55	0.0000
2	41.38	0.0000	5	126.52	0.0000	8	128.13	0.0000	11	128.74	0.0000	14	131.68	0.0000	17	135.68	0.0000
3	119.34	0.0000	6	126.58	0.0000	9	128.64	0.0000	12	130.49	0.0000	15	133.33	0.0000	18	138.78	0.0000

No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height
1	35.02	0.0000	4	125.19	0.0000	7	128.34	0.0000	10	129.65	0.0000	13	135.33	0.0000	16	138.76	0.0000
2	41.61	0.0000	5	128.56	0.0000	8	128.65	0.0000	11	130.47	0.0000	14	137.38	0.0000	17	139.66	0.0000
3	91.96	0.0000	6	127.07	0.0000	9	128.77	0.0000	12	131.26	0.0000	15	137.67	0.0000	18	141.88	0.0000
															19	169.82	0.0000

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Eyring plots and HPLC traces

1-(2-chlorophenyl)-3,4-dihydroisoquinoline (4a)

$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger_{298}$	$t_{1/2}$ (T = 298 K)
56.6 kJ mol ⁻¹	-9 J mol ⁻¹	59.2 kJ mol ⁻¹	≈ 0.001 s

1-(2-bromophenyl)-3,4-dihydroisoquinoline (4b)

$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger_{298}$	$t_{1/2}$ (T = 298 K)
50.7 kJ mol ⁻¹	-26 J mol ⁻¹	58.4 kJ mol ⁻¹	<0.001 s

1-(2-iodophenyl)-3,4-dihydroisoquinoline (4c)

$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger_{298}$	$t_{1/2} (T = 298 \text{ K})$
64.0 kJ mol^{-1}	-20 J mol^{-1}	57.9 kJ mol^{-1}	<0.001 s

1-(naphthalen-1-yl)-3,4-dihydroisoquinoline (4d)

$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger_{298}$	$t_{1/2} (T = 298 \text{ K})$
55.1 kJ mol^{-1}	1 J mol^{-1}	54.7 kJ mol^{-1}	$\approx 0.0001 \text{ s}$

1-(2-chloronaphthalen-1-yl)-3,4-dihydroisoquinoline (4e)

HPLC trace of **4e**: (*R,R*)-Whelk-O1 column; n-Hex:IPA 60:40, flow = 1 mL/min; λ = 254 nm; T = 25 °C. t_R = 8.1 min.

1-(2-bromonaphthalen-1-yl)-3,4-dihydroisoquinoline (4f)

DHPLC
(*R,R*)-Whelk-O1 column
n-Hex:IPA 60:40,
flow = 1 mL/min, λ = 254 nm

$\Delta H^\ddagger$ $\Delta S^\ddagger$ $\Delta G^\ddagger_{298}$ $t_{1/2}$ (T = 298 K)

34.6 kJ mol⁻¹ -195 J mol⁻¹ 92.6 kJ mol⁻¹ 926 s

1-(2-iodonaphthalen-1-yl)-3,4-dihydroisoquinoline (4g)

DHPLC
(*R,R*)-Whelk-O1 column
n-Hex:IPA 60:40,
flow = 1 mL/min, λ = 254 nm

$\Delta G^\ddagger_{273}$ $t_{1/2}$ (T = 273 K)

81.9 kJ mol⁻¹ 275 s

T (°C)	HPLC trace	k (s ⁻¹)
0		0.0025
5		-

1-(3,4-dihydroisoquinolin-1-yl)naphthalen-2-yl trifluoromethanesulfonate (4h)

HPLC trace

Chiralpak® AD-H column
n-Hex:IPA 80:20, T = 25 °C
flow = 1 mL/min, λ = 254 nm
 $t_{R,A}$ = 4.8 min, $t_{R,B}$ = 8.2 min

$\Delta H^\ddagger$

$\Delta S^\ddagger$

$\Delta G^\ddagger_{298}$

$\Delta G^\ddagger_{323}$

$t_{1/2}$ (T = 323 K)

10.7 kJ mol⁻¹ 14.5 J mol⁻¹ 103.1 kJ mol⁻¹ 102.7 kJ mol⁻¹ 66 min

Decay in ee for compound **4h** in IPA at 3 different temperatures

Time [s]	58 °C	Time [s]	50 °C	Time [s]	43 °C
0	100	0	96	0	99
300	88	300	89	1800	90
600	78	600	84	3000	83
1200	61	1200	75	3600	81
1800	47	1800	67	6000	70
2400	35	2400	60	7380	64
3000	27	3000	53	9000	56
3600	21	3600	48	11100	49
4260	15	5340	35	21900	25
7680	4	8160	21		

Plots of $\ln(\text{ee})$ v T to obtain the rate of racemisation for compound **4h** in IPA at three different temperatures.

(1-(3,4-dihydroisoquinolin-1-yl)naphthalen-2-yl)diphenylphosphine oxide (4i)

HPLC trace of **4i**: (*R,R*)-Whelk-O1 column; n-Hex:IPA 60:40, flow = 1 mL/min; $\lambda = 254$ nm; $T = 50$ °C. $t_R(A) = 6.8$ min; $t_R(B) = 10.2$ min.

$$\Delta G^\ddagger_{323}$$

$$t_{1/2} (T = 323 \text{ K})$$

$$>102.2 \text{ kJ mol}^{-1} \qquad >30 \text{ min}$$