STUDIES TOWARDS THE *N*-ACYLATIVE KINETIC RESOLUTION OF NOBIN

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Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

An investigation into the *N*-acylation of atropisomeric anilines **8** and **2**, which are related to NOBIN (**1**), catalysed by small molecule chiral pyridine-based nucleophilic catalysts is described. The first organocatalytic kinetic resolution (KR) of an atropisomeric aniline is described.

Keywords: Kinetic resolution; Atropisomerism; Asymmetric synthesis; Organocatalysis.

2-Amino-2′-hydroxy-1,1′-binaphthyl [NOBIN (**1**); Fig. 1] was first prepared as a racemate by Kočovský in 1991 *via* oxidative coupling of 2-naphthol and 2-naphthylamine in MeOH using stoichiometric *tert*-butylamine/copper(II) chloride[1–3]. Subsequently, a variant employing aqueous iron(III) chloride was reported[4,5], and (±)-NOBIN has been prepared from (±)-BINOL (**3**; Fig. 1) by a Bucherer reaction[6]. Kočovský has also shown that partial optical resolution concomitant with oxidative coupling can be achieved by inclusion of a stoichiometric amount of various chiral amines in place of *tert*-butylamine during oxidative coupling. This allows for initial precipitation of a complex of NOBIN, the copper salt and the chiral amine in up to 46% *ee* and subsequent fractional crystallisation can yield product with high levels of optical purity[7–11]. Optical resolution of scalemic or (±)-NOBIN by classical crystallisation with camphor sulfonic acid[12,13], by imine exchange of achiral imine derivatives with chiral amines[14] and by inclusion complexation with *N*-benzyl cinchonidinium chloride[15] are alternative methods to obtain enantiomerically highly enriched (*R*)- or (*S*)-NOBIN. Alterna-

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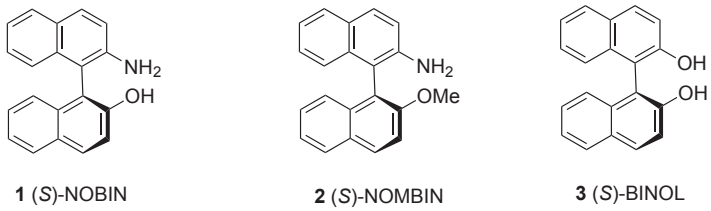
tively, enantiomerically highly enriched NOBIN can be obtained by multi-step Functional Group Interconversion (FGI) from enantiomerically pure BINOL [16,17] or from enantiomerically pure 2′-methoxy-1,1′-binaphthylene-2-carboxylate *via* conversion to its acyl azide, Curtius rearrangement to give NOMBIN [18] (**2**; Fig. 1) then demethylation with BBr_3 [19]. Both enantiomers of BINOL are commercially available whereas enantiomerically pure (*S*)-2′-methoxy-1,1′-binaphthylene-2-carboxylate [which leads to (*S*)-NOBIN] is prepared by a diastereoselective 'Meyers-type'[20] S_NAr reaction of 2-methoxy-1-naphthylmagnesium bromide with (–)-menthyl 1-(–)-menthoxynaphthylene-2-carboxylate then hydrolysis[18,19,21–23]. These synthetic approaches, and the applications of (*S*)- and (*R*)-NOBIN as ligands and auxiliaries for asymmetric catalysis, have been reviewed (Fig. 1)[24–26].



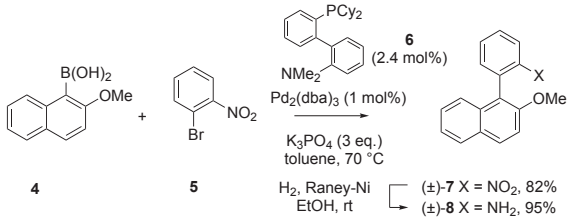
1 (*S*)-NOBIN **2** (*S*)-NOMBIN **3** (*S*)-BINOL

FIG. 1

Interestingly, although the synthesis of enantiomerically enriched BINOL *via* asymmetric catalysis is known [*e.g. via* enzymatic kinetic resolution (KR) of diester derivatives and *via* chiral ligand/metal-complex catalysed oxidative 2-naphthol coupling][27] no direct asymmetric catalysis approach to NOBIN has been reported. Spurred by an interest in non-enzymatic, catalytic acylative KR of alcohols and amines[28], and the knowledge that enzymatic *N*-acylative KR of 2-amino-1,1′-binaphthyls has not yet proved possible[29,30] we became interested in developing the KR of NOBIN and its derivatives *via* chiral nucleophile catalysed non-enzymatic *N*-acylative KR. Efficient procedures for *O*-acylative KR/asymmetric desymmetrisation of alcohols/diols catalysed by small molecule chiral nucleophiles have been developed for many structurally diverse substrate classes, but corresponding *N*-acylative processes for amines are still rather rare[28,31]. This undoubtedly reflects the fact that it is difficult to design catalysts that are substantially more nucleophilic than many potential amine substrates and explains why almost all successful reports of *N*-acylative KR reactions to date have been applied to amine classes of moderate nucleophilicity[32–38]. It was our cognisance of this situation, and the aforementioned substrate limitation of en-

zymatic amine KR processes, that led us to consider that an investigation of atropisomeric anilines such as (±)-NOBIN and congeners as substrates for small molecule chiral nucleophile *N*-acylative KR could be interesting. Herein, we describe our preliminary results towards this end.

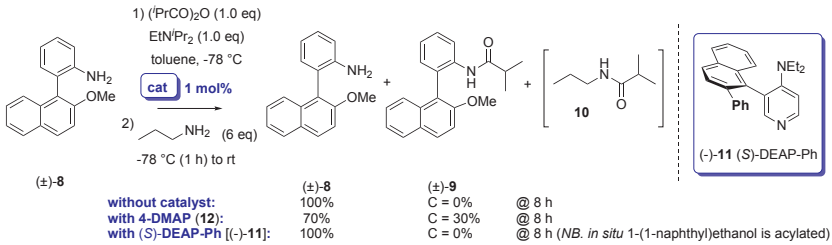
The starting point for our investigation was our previous successful *O*-acylative KR of various classes of alcohols using the atropisomeric chiral 4-(dialkylamino)pyridine derivative (*S*)-DEAP-Ph (–)-**11** (Scheme 2, below)[39] Specifically, we planned initially to investigate this catalyst as a chiral nucleophilic catalyst for effecting the *N*-acylative KR of atropisomeric aniline **8**. This substrate was selected as it could be readily prepared from 2-methoxynaphthalene-1-boronic acid (**4**) using a Suzuki cross-coupling[40] with 2-nitro-1-bromobenzene (**5**) to give nitro biaryl **7**, followed by nitro to amine reduction using Raney nickel (→ **8**; Scheme 1).



SCHEME 1

Gratifyingly, aniline **8** proved unreactive towards isobutyric anhydride (1.0 equiv.) and Hünig's base (1.0 equiv.) at –78 °C in toluene in the absence of a catalyst but showed ~30% conversion to its isobutyramide **9** after 8 h at this temperature in the presence of 1 mole % of 4-(dimethylamino)-pyridine (4-DMAP; **12**) as catalyst. Moreover, aniline **8** and its isobutyramide **9** were verified as being sufficiently atropisomerically stable to allow for analysis without racemisation by chiral stationary phase (CSP) high performance liquid chromatography (HPLC)[41]. We also developed a quenching protocol in which an excess of *n*-propylamine (6 equiv.) was added to the reaction mixture at –78 °C to react with any unreacted isobutyric anhydride (→ **10**) prior to warming to room temperature for work-up and analysis by CSP-HPLC. The use of a Chiralpak AD column allowed for baseline separation of both enantiomers of aniline **8** and isobutyramide **9** in a single injection (see Experimental). The stage was therefore set to attempt the KR of aniline **8**. To our surprise, however, no *N*-isobutyrylation occurred when

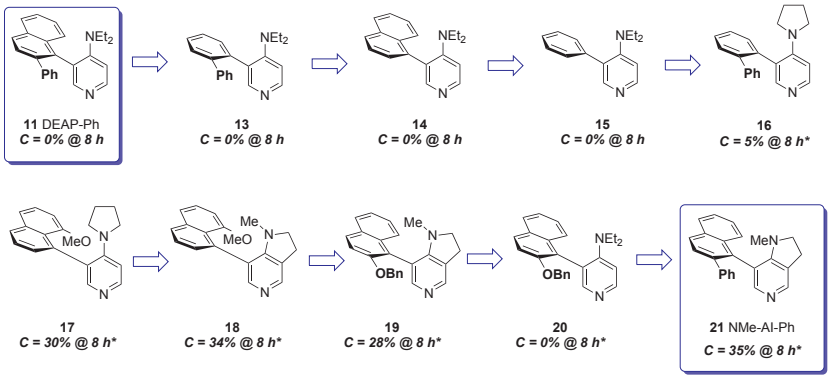
chiral 4-(dialkylamino)pyridine (*S*)-DEAP-Ph (–)-**11** (1 mole %) was used as a catalyst in place of 4-DMAP (**12**) for the attempted KR of aniline **8** (Scheme 2).



SCHEME 2

Clearly our atropisomeric chiral 4-(dialkylamino)pyridine **11** was insufficiently active to catalyse *N*-acylation under conditions that 4-DMAP (**12**) itself could. In order to determine whether this reflected lack of formation of the required acyl pyridinium salt under the reaction conditions or whether the salt itself was less reactive than that formed from 4-DMAP (**12**), a competition reaction in which both aniline **8** and 1-(1-naphthyl)ethanol were present as potential substrates was carried out. The alcohol was *O*-acylated cleanly and the aniline remained unreacted proving that the requisite acyl pyridinium salt was formed[42] and implicating an intrinsic lack of reactivity towards aniline **8** of the acylpyridinium salt derived from (*S*)-DEAP-Ph (–)-**11** relative to that derived from 4-DMAP (**12**). We formulated two hypotheses for this – either steric hindrance was precluding attack by the aniline on the salt or partial conjugation across the biaryl axis was electronically deactivating the salt towards attack. We therefore undertook a survey of the effect of catalyst structure on the ability to catalyse isobutyrylation of aniline **8** using a panel of racemic 4-(dialkylamino)pyridines (**13**–**17** and **20**) and *N*-methyl-5-azaindolines (**18**, **19** and **21**) that we had prepared previously during our development of alcohol KR (Fig. 1)[43–45].

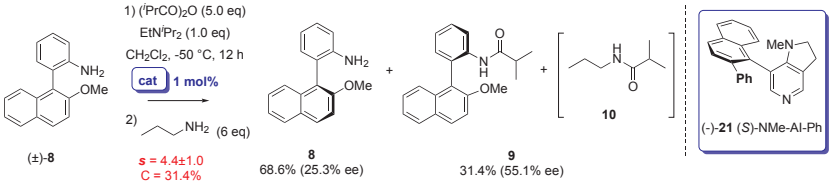
Catalysts **11**, **13**, **14** and **15**, which form a series displaying successively reduced levels of steric bulk around their biaryl axes, all failed to catalyse the *N*-isobutyrylation reaction and so steric hindrance was concluded not to account for the lack of reactivity. However, the nature of the catalyst core was more decisive: those catalysts based on 4-PPY (**16** and **17**) and particularly those based on *N*-methyl-5-azaindoline (**18**, **19** and **21**) gave levels of catalysis comparable to that of 4-DMAP (**12**) itself. Both of these cores are known to exhibit greater nucleophilicity at the pyridyl nitrogen as the



C = conversion (**8** -> **9**) under the conditions shown in Scheme 3. An asterix denotes the use of 5 eq of $(^{i}PrCO)_2O$ in CH_2Cl_2.

FIG. 2

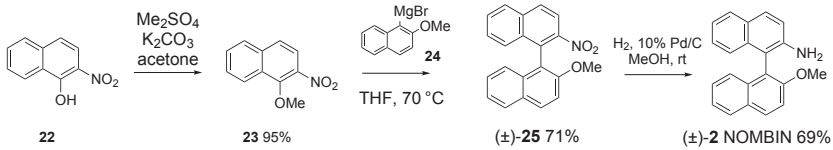
result of superior conjugation of the non-pyridyl nitrogen lone pair and the pyridine ring π-system and this presumably compensates for the deactivation resulting from partial conjugation across the biaryl axis[46,47]. Armed with these findings we returned to the KR of the atropisomeric aniline substrate **8** and were pleased to find that we could achieve KR of atropisomeric aniline (±)-**8** using *N*-methyl-5-azaindoline (*S*)-NMe-Al-Ph (–)-**21** (1 mole %)[39,45], Hünig's base (1 equiv.) and isobutyric anhydride (5.0 equiv.) in CH_2Cl_2 at –50 °C for 12 h with a selectivity factor[48] s = 4.4 ± 1.0 at 31.4% conversion (Scheme 3).



SCHEME 3

The absolute stereochemistry of neither the substrate **8** nor the isobutyramide product **9** were determined and so the sense of stereoinduction in this KR process was not ascertained; the enantiomers depicted in Scheme 3 are therefore arbitrary. Encouraged by these results, and hoping that increased levels of selectivity would be displayed by the 1,1-binaphthyl congener, NOMBIN (**2**), we prepared this compound as a racemate *via* 'Meyers-type' S_NAr coupling between 1-methoxy-2-nitronaphthalene (**23**) and the

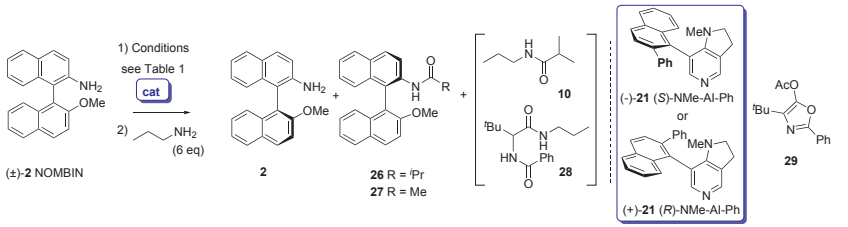
Grignard reagent derived from 2-methoxy-1-bromonaphthalene (**24**) according to the method of Miyano[49] (Scheme 4).



SCHEME 4

Attempted KR of 1,1′-binaphthyl aniline (±)-**2** (NOMBIN) under identical conditions to those that had proved successful for its 1-phenylnaphthyl congener (±)-**8** (*cf.* Scheme 3) resulted in just 14.0% conversion after 43 h at –50 °C in CH_2Cl_2. Moreover, the reaction displayed a selectivity factor of just $s = 1.4 \pm 0.2$. As previously, there was no background reaction in the absence of catalyst and the reaction could be conveniently monitored and the selectivity analysed by CSP-HPLC following a single injection onto

TABLE I



Entry	Conditions	Additives	*t*, h	*T*, °C	Yields, % (ee, %)[a]	
1	(–)-**21** (1.2 mol %) $(i\text{-PrCO})_2O$ (4.3 eq) EtN*i*-Pr_2 (1 eq) CH_2Cl_2 (0.4 ml)	–	43	–50	(*S*)-**2** 86.0 (2.8 ± 0.5)	(*R*)-**26** 14.0 (17.0 ± 0.5)
2	(+)-**21** (5 mol %) **29** (0.5 eq) tol (0.7 ml)	LiBr (1.5 eq); 18-c-6 (0.75 eq)	44	–10	**2** 94.0 (0.0 ± 0.5)	**27** 6.0 (0.0 ± 0.5)
3	(+)-**21** (20 mol %) **29** (3.0 eq) tol/CH_2Cl_2 (1:1, 0.5 ml)	–	54	–10	**2** 23.0 (0.0 ± 0.5)	**27** 72.0 (0.0 ± 0.5)

[a] In all cases control reactions were conducted under identical conditions but in the absence of catalyst and no reaction was observed (*e.g.* see Fig. 3, below).

a chiralpak AD column. The absolute configuration of both the substrate **2** and the isobutyramide product **26** were assigned by reference to correlations established by Hattori[49] (Table I, entry 1).

Pursuing further the hypothesis that the efficiency of catalysis is critically dependent upon the structure and reactivity of the acyl pyridinium salt derived from the *N*-methyl-5-azaindoline catalyst **21** we explored alternative

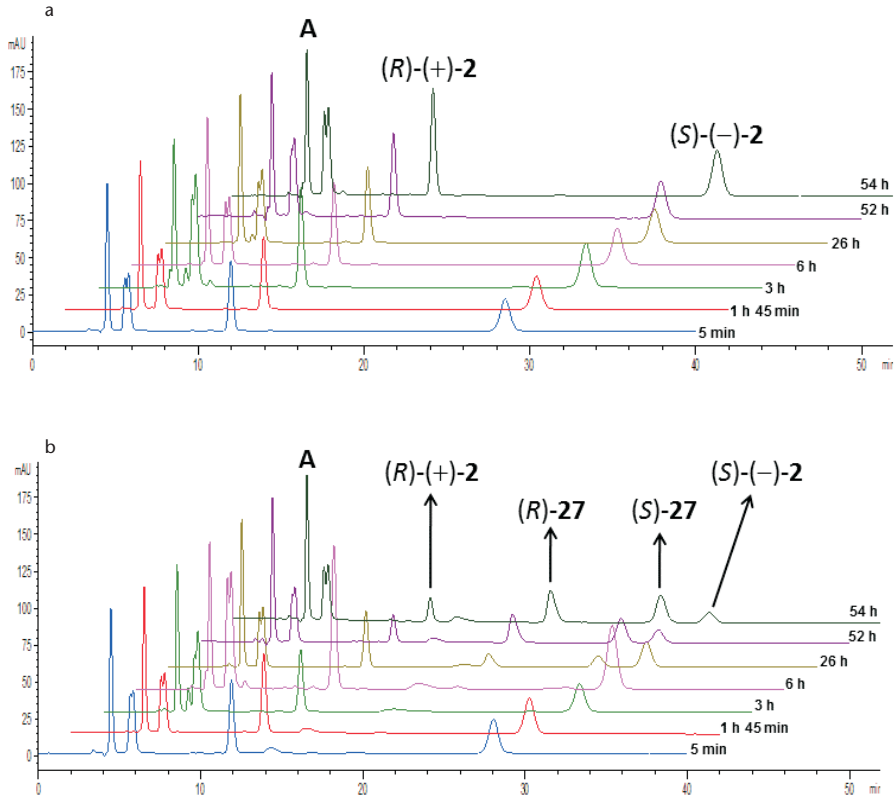


FIG. 3

a CSP-HPLC time-course for the *uncatalysed* background reaction corresponding to Table I, entry 3. A – 9-methylanthracene (internal standard), B – first enantiomer of **2** (unreacted NOMBIN), B′ – second enantiomer of **2** (unreacted NOMBIN); analytical Chiralpak AD-H column (0.46 cm × 25 cm), mobile phase: *n*-hexane/2-propanol (9:1), flow rate: 1 ml/min @ 25 °C, UV: λ = 250 nm (ref. = 360 nm), injection: 2 µl solution in 2-propanol (25 µl of the reaction mixture was quenched with *n*-propyl amine overnight). b CSP-HPLC time-course for the *catalysed* reaction corresponding to Table I, entry 3. A – 9-methylanthracene (internal standard), B – first enantiomer of **2** (unreacted NOMBIN), B′ – second enantiomer of **2** (unreacted NOMBIN), C – first enantiomer of amide **27**, C′ – second enantiomer of amide **27**; same conditions as above

acylating reagents in place of isobutyric anhydride. After considerable experimentation we found that use of conditions closely similar to those disclosed by Fu et al. for the acylative KR of indolines[34] allowed for *N*-acetylation even at –10 °C without the intervention of a background reaction (Table I, entry 2). These conditions feature *O*-acetylazlactone derivative **29** as acylating agent in conjunction with LiBr and 18-crown-6 as additives in toluene. However, even when employing 5 mole % catalyst (*cf*. 1.2 mole % in entry 1), conversion remained just 6.0% after 44 h and no enantioselectivity was measurable. Good levels of conversion could be achieved under modified conditions in which 20 mole % catalyst was employed in a toluene/CH_2Cl_2 mixed solvent system at –10 °C with an excess of the acylating agent **29** (3 equiv. *cf*. 0.5 equiv. in entry 2) and no additives (Table I, entry 3). This allowed for 72% conversion after 54 h but again no enantioselectivity was discernable. HPLC time-courses for the uncatalysed and catalysed reactions corresponding to this experiment are shown below (Fig. 3).

In conclusion, we have described an investigation into the *N*-acylation of atropisomeric anilines **8** and **2**, which are related to NOBIN (**1**), catalysed by small molecule chiral pyridine-based nucleophilic catalyst **21**. Although conditions for the *N*-acylation of 1,1′-binaphthyl aniline (±)-**2** (NOMBIN) catalysed by 20 mole % *N*-methyl-5-azaindoline catalyst (*S*)-NMe-AI-Ph (–)-**21** have been established, the reaction proceeds without enantioselectivity. By contrast, conditions for the *N*-acylative KR of its 1-phenylnaphthyl congener (±)-**8** ($s = 4.4 \pm 1.0$ @ C = 31.7%) using just 1 mole % of the same catalyst has been achieved; this is the first example of an organocatalytic acylative KR of an atropisomeric substrate. Clearly, there is a significant difference in reactivity and propensity for chiral recognition between these topologically related substrates. We are currently exploring the role of the nature of the ether group in NOMBIN-type substrates and further structural variants of the nucleophilic catalyst and acylating agent in order to discover conditions for an efficient KR protocol leading to NOBIN itself and these studies will be reported in due course.

EXPERIMENTAL

General Directions

Solvents and reagents: Solvents were dried as follows – CH_2Cl_2 (CaH_2), benzene (CaH_2), toluene (Na), Et_2O (Na/benzophenone ketyl), MeOH [$Mg(OMe)_2$] and EtOH [$Mg(OEt)_2$]. Reagents were used as commercially supplied unless otherwise stated and handled in accordance with COSHH regulations[50]. *Chromatography*: Flash chromatography was performed on

silica gel (60 F_{254}, 230–400 mesh) according to the method of W. C. Still[51]. Thin layer chromatography (TLC) was performed on aluminium plates pre-coated with silica (60 F_{254}, 0.2 mm) which were developed using standard visualising agents: ultraviolet fluorescence (254 nm), $KMnO_4/\Delta$ or vanillin/Δ. Chiral stationary phase (CSP)-high performance liquid chromatography (HPLC) – An Agilent 1100 instrument was employed with elution with commercial HPLC grade, degassed solvents. *Spectra*: ^{1}H NMR spectra were recorded at 250 and 400 MHz. Chemical shifts (δ_H) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak, with the abbreviations s, d, t and m denoting singlet, doublet, triplet and multiplet, respectively. ^{13}C NMR spectra were recorded at 62.5 and 100 MHz. Chemical shifts (δ_C) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak, with the abbreviations s, d, t and q denoting C, CH, CH_2 and CH_3, respectively. Coupling constants *J* are given in Hz. Infra red (IR) spectra were recorded as thin films or as solids. Only selected absorbencies (ν_{max}, cm^{-1}) are reported. Mass spectra (MS) – Molecular ions and major peaks only are reported for low resolution spectra. Intensities are given as percentages of the base peak. HRMS values are valid to 5 ppm. *Melting points*: Analyses were carried out using a hot stage and are uncorrected.

(±)-2-Methoxy-1-(2′-nitrophenyl)naphthalene (**7**)[40,52]

A mixture of 2-methoxynaphthalene-1-boronic acid[53] (**4**; 750.5 mg, 3.72 mmol), 2-nitro-1-bromobenzene (**5**; 500 mg, 2.48 mmol), $Pd_2(dba)_3$ (22.6 mg, 0.02 mmol, 1 mole %), 2-dicyclohexylphosphino-2′-(*N*,*N*′-dimethylamino)biphenyl[54] (**6**; 23.4 mg, 0.06 mmol, 2.4 mole %) and K_3PO_4 (1.05 mg, 4.46 mmol) in dry toluene (10 ml) was stirred under nitrogen at 70 °C for 1 h 30 min. The mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ (aq.), water, brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash chromatography eluting with CH_2Cl_2 then hexane/EtOAc (20:1) gave nitroaryl compound **7** as brown needles (570 mg, 82%). M.p. 133–134 °C (hexane/EtOAc) [lit.[52] 133–134 °C]; R_F 0.42 (hexane/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): 3.83 (3 H, s, OCH_3), 7.35 (1 H, d, *J* = 8.9, ArH), 7.36–7.42 (3 H, m, ArH), 7.45 (1 H, dd, *J* = 7.5, 1.4, ArH), 7.60 (1 H, ddd, *J* = 7.8, 7.7, 1.4, ArH), 7.73 (1 H, ddd, *J* = 7.7, 7.5, 1.3, ArH), 7.84–7.90 (1 H, m, ArH), 7.95 (1 H, d, *J* = 8.9, ArH), 8.14 (1 H, dd, *J* = 7.8, 1.3, ArH). IR (neat): 3064, 2941, 2840, 1622, 1594, 1524, 1512, 1464, 1353, 1340, 1276, 1262, 1251, 1149, 1126, 1067, 1022, 909, 857, 810, 787, 750. MS (EI) *m/z* (rel. int., %): 279 (100, $M^{\bullet+}$), 220 (52), 189 (48), 165 (23), 109 (18), 95 (21), 77 (7). HRMS (EI) *m/z*: found: (M^+) 279.0904, $C_{17}H_{13}NO_3$ requires 279.0895 (Δ = +3.2 ppm).

(±)-2-(2′-Methoxynaphthalene-1-yl)phenylamine (**8**)[52]

To a suspension of 2-methoxy-1-(2-nitrophenyl)naphthalene (**7**; 2.41 mg, 8.6 mmol) in ethanol (120 ml) was added Raney Nickel as a 50% slurry in water (1 g). The reaction flask was evacuated and backfilled with H_2 (3×) and the reaction mixture allowed to stir under 1 atmosphere of H_2 at room temperature for 16 h. The catalyst was removed by filtration through Celite®, washed through repeatedly with ethanol. The solvent was removed under reduced pressure to give yellow oil. Purification by flash chromatography eluting with CH_2Cl_2 then hexane/EtOAc (5:1) gave aniline **8** as pale yellow needles (2.04 g, 95%). M.p. 81.5–82.5 °C (hexane/EtOAc) [lit.[52] 83–84 °C]; R_F 0.27 (petrol ether/EtOAc, 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): 3.78 (3 H, s), 6.83 (2 H, m), 7.03 (1 H, dd, *J* = 7.0, 1.5), 7.19 (1 H, m), 7.25–7.29 (3 H, m), 7.36 (1 H, m), 7.82 (1 H, d, *J* = 9.0). IR (neat): 3457, 3375, 3053, 2938, 2837, 1614, 1592, 1507, 1496, 1453, 1382, 1332, 1298, 1262, 1250, 1179, 1147, 1120, 1067,

1020, 905, 812, 749. MS (EI) *m/z* (rel. int., %): 249 (97, $M^{\bullet+}$), 218 (100), 217 (89), 204 (22), 189 (12), 178 (10), 165 (4), 125 (6), 117 (7), 109 (9), 102 (11), 93 (4), 77 (4). HRMS (EI) *m/z*: found: (M^+) 249.1161, $C_{17}H_{15}NO$ requires 249.1154 (Δ = +2.8 ppm).

Kinetic Resolution of Biaryl Aniline (±)-**8** (Scheme 3)

A solution of the atropisomeric aniline (±)-**8** (80 mg, 0.32 mmol), Hünig's base (55 µl, 0.32 mmol) and catalyst (–)-(*S*)-NMe-AI-Ph **21** [39,45] (1.1 mg, 0.0032 mmol, 1 mole %) in CH_2Cl_2 (0.65 ml) was cooled to –50 °C using a cryostat. During vigorous stirring, isobutyric anhydride (270 µl, 1.6 mmol) was then added dropwise over 2 min and the resulting mixture stirred at –50 °C for 12 h. *n*-Propylamine (0.16 ml, 1.92 mmol) was then added dropwise with rapid stirring and the mixture was stirred for a further 1 h at –50 °C before allowing the reaction mixture to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed sequentially with sat. $NaHCO_3$ (aq.) (2 × 50 ml) and brine (50 ml). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude mixture of products **8**, **9** and **10** was analysed by ^1H NMR spectroscopy and by CSP-HPLC: Chiralpak AD (4.6 mm × 25 cm); hexane/EtOH (99:1); 0.6 ml/min; 40 °C; UV detection at 230 nm, reference at 360 nm. Retention times: aniline **8**: 25.5 min (minor) and 31.8 min (major); isobutyramide **9**: 19.3 min (major) and 20.5 min minor). *NB*. The absolute stereochemistry of the enantiomers were not assigned; by product **10** is not detected at this wavelength.

(±)-*N*-[2-(2-Methoxynaphthalen-1-yl)phenyl]isobutyramide (**9**)

A colourless viscous oil. R_F 0.38 (petrol/EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$): 0.81 (3 H, d, *J* = 7.0), 0.90 (3 H, d, *J* = 7.0), 2.10 (1 H, m), 3.90 (3 H, s), 6.96 (1 H, br s), 7.27–7.52 (7 H), 7.87 (1 H, m), 8.01 (1 H, d, *J* = 9.0), 8.43 (1 H, d, *J* = 8.0). ^{13}C NMR (100 MHz, $CDCl_3$): 19.1 (2 × q), 36.5 (d), 56.6 (q), 113.3 (d), 119.6 (s), 121.1 (d), 123.8 (d), 124.1 (d), 124.9 (d), 126.0 (s), 127.2 (d), 128.0 (d), 128.6 (d), 129.1 (s), 130.5 (d), 131.5 (d), 133.3 (s), 136.5 (s), 154.1 (s), 174.7 (s). IR (neat): 3414, 2966, 1690, 1511. MS (EI^+) *m/z* (rel. int., %): 319 (30, $M^{\bullet+}$), 217 (100). HRMS (EI^+) *m/z*: found: (M^+) 319.1569, $C_{20}H_{21}NO_2$ requires 319.1572 (Δ = –0.9 ppm).

n-Propylisobutyramide (**10**)[55]

A low-melting white solid, m.p. 36 °C. ^1H NMR (400 MHz, $CDCl_3$): 0.93 (3 H, t, *J* = 7.4, CH_2CH_3), 1.16 (6 H, d, *J* = 6.9, 2 × CH_3), 1.53 (2 H, tq, *J* = 7.0, 7.4, CH_2CH_3), 2.35 (1 H, sep, *J* = 6.9, CH), 3.21 (2 H, app q, *J* = 7.0, NCH_2), 5.63 (1 H, broad s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 11.3 (q), 19.7 (2 × q), 22.9 (t), 35.7 (d), 41.0 (t), 177.0 (s). IR (neat): 3293, 3092, 2966, 2933, 2875, 1644, 1547, 1465, 1376, 1242, 1151, 1094, 942, 778. MS (EI^+) *m/z* (rel. int., %): 129 (33, $M^{\bullet+}$), 114 (9), 100 (7), 86 (17), 72 (21), 71 (35), 55 (5), 43 (100). HRMS (EI^+) *m/z*: found: (M^+) 129.1158, $C_7H_{15}NO$ requires 129.1154 (Δ = +3.1 ppm).

1-Methoxy-2-nitronaphthalene (**23**)[56]

To a solution of 2-nitro-1-naphthol (**22**; 2.79 g, 14.7 mmol) in acetone (20 ml) were added K_2CO_3 (3.8 g, 27.5 mmol) and dimethylsulfate (2.0 ml, 21.1 mmol). The resulting reaction mixture was stirred at reflux for 20 h before being cooled to room temperature, concen-

trated *in vacuo* and the residue partitioned between CH_2Cl_2 (20 ml) and sat. $NaHCO_3$ (aq.) (40 ml). The phases were separated, the organic phase washed with brine (30 ml), dried over Na_2SO_4 and then concentrated *in vacuo* to give a brown solid. Recrystallisation of this solid from hexane/EtOAc (3:1) yielded methyl ether **23** as bright yellow needles (2.85 g, 95%). M.p. 78–79 °C (hexane/EtOAc) [lit.[56] 80 °C]; R_F 0.36 (hexane/EtOAc, 19:1). ^{1}H NMR (400 MHz, $CDCl_3$): 4.17 (3 H, s, OCH_3), 7.62–7.73 (3 H, m, ArH), 7.88–7.95 (2 H, m, ArH), 8.30–8.37 (1 H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 63.7 (q), 121.0 (d), 124.2 (d), 124.3 (d), 127.6 (d), 128.2 (d), 128.6 (s), 129.5 (d), 136.5 (s), 139.1 (s), 151.7 (s). IR (neat): 3102, 2990, 2947, 2861, 1620, 1584, 1521, 1498, 1460, 1439, 1427, 1375, 1340, 1321, 1262, 1214, 1144, 1086, 1027, 976, 913, 859, 874, 816. MS (EI^+) *m/z* (rel. int., %): 203 (100, $M^{\bullet+}$), 156 (76), 142 (20), 129 (33), 128 (43), 127 (92), 114 (53), 102 (20), 88 (14), 77 (12), 63 (12), 51 (7). HRMS (EI^+) *m/z*: found: (M^+) 203.0587, $C_{11}H_9NO_3$ requires 203.0582 (Δ = +2.5 ppm).

(±)-2-Methoxy-2′-nitro-1,1′-binaphthyl (**25**)[57]

To a solution of 2-methoxy-1-bromonaphthalene (**24**; 1.40 g, 5.91 mmol) in diethyl ether (40 ml) were added magnesium turnings (0.57 g, 23.6 mmol), dibromomethane (0.62 g, 0.30 ml, 0.30 mmol) and a small crystal of iodine. The reaction mixture was sonicated for 3 h after which time a white slurry had formed; this was dissolved by addition of benzene (40 ml). An aliquot of the resulting solution containing the Grignard reagent (55 ml) was added *via* cannula to a solution of 1-methoxy-2-nitronaphthalene (**23**; 800 mg, 3.94 mmol) in benzene (55 ml). A red colouration appeared and the reaction mixture was allowed to stir for 1 h at room temperature before the remaining solution of Grignard reagent (25 ml) was added dropwise. The reaction mixture was stirred for further 30 min then the solution was cooled to 0 °C and water (10 ml) added dropwise. The phases were separated and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure. Column chromatography eluting with CH_2Cl_2 then hexane/EtOAc (20:1) gave nitroaryl compound **25** as yellow crystals (923 mg, 71%). M.p. 169–171 °C (hexane/EtOAc) [lit.[57] 170–171 °C]; R_F 0.15 (hexane/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): 3.79 (3 H, s), 6.93–8.14 (12 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): 56.6 (q), 113.3 (d), 117.6 (s), 120.6 (d), 123.9 (d), 124.4 (d), 127.1 (d), 127.9 (d), 128.0 (s), 128.26 (2 × d), 128.30 (d), 128.7 (d), 129.0 (s), 129.3 (d), 130.6 (d), 132.8 (s), 133.4 (s), 135.1 (s), 147.5 (s), 154.4 (s). IR (neat): 3056, 3006, 2939, 2839, 1621, 1593, 1524, 1506, 1464, 1345, 1273, 1263, 1179, 1132, 1083, 1021, 810, 759, 750. MS (EI^+) *m/z* (rel. int., %): 329 (97, $M^{\bullet+}$), 314 (21), 299 (13), 270 (100), 241 (49), 239 (50), 226 (18), 215(16), 188 (12), 158 (10), 155 (9), 134 (18), 120 (26), 113 (12), 102 (9), 89 (10), 43 (27). HRMS (EI^+) *m/z*: found: (M^+) 329.1058, $C_{21}H_{15}NO_3$ requires 329.1052 (Δ = +1.8 ppm).

(±)-2-Amino-2′-methoxy-1,1′-binaphthyl (NOMBIN; **2**)[49]

A solution of 2-methoxy-2′-nitro-1,1′-binaphthyl (**25**; 688 mg, 2.09 mmol) in methanol (30 ml) and CH_2Cl_2 (10 ml) was sonicated for 2 min and then 10% Pd/C (206.4 mg) was added. The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 3 h. The reaction mixture was filtered through Celite® and the solvent was evaporated under reduced pressure. Flash chromatography eluting with CH_2Cl_2 then hexane/EtOAc (10:1) gave the aminobinaphthyl **2** as a violet solid (609 mg, 69%). M.p. 138–139 °C (hexane/EtOAc) [lit.[49] 139–141°C]; R_F 0.19 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): 3.14 (br,

2 H), 3.76 (s, 3 H), 6.95–8.01 (m, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): 56.9 (q), 114.0 (s), 114.4 (d), 118.3 (d), 118.9 (s), 122.2 (d), 124.0 (d), 124.3 (d), 125.1 (d), 126.3 (d), 127.0 (d), 128.05 (d), 128.10 (d), 128.3 (s), 129.0 (d), 129.6 (s), 130.0 (d), 133.7 (s), 134.2 (s), 141.9 (s), 155.5 (s). IR (neat): 3466, 3377, 3200, 3054, 3007, 2936, 2837, 1617, 1590, 1505, 1476, 1463, 1430, 1380, 1351, 1329, 1259, 1245, 1178, 1146, 1075, 1048, 1019, 904, 809, 747, 735. MS (EI^+) *m/z* (rel. int., %): 299 (100, $M^{\bullet+}$), 284 (10), 267 (27), 254 (11), 239 (10), 226 (6), 156 (14), 143 (4), 134 (12), 127 (6), 120 (5), 113 (4), 101 (3), 91 (2), 57 (2). HRMS (EI^+) *m/z*: found: (M^+) 299.1319, $C_{21}H_{17}NO$ requires 299.1310 (Δ = +3.0 ppm).

Kinetic Resolution of NOMBIN (±)-**2** (Table I)

Entry 1: A solution of NOMBIN (±)-**2** (25.7 mg, 0.086 mmol), Hunig's base (15.0 µl, 0.087 mmol) and catalyst (–)-(*S*)-NMe-AI-Ph **21** [39,45] (0.29 mg, 0.8 µmol, 1.2 mole %) in CH_2Cl_2 (0.4 ml) was cooled to –50 °C using a cryostat. During vigorous stirring, isobutyric anhydride (70 µl, 0.42 mmol) was then added dropwise over 2 min and the resulting mixture stirred at –50 °C for 12 h. *n*-Propylamine (42 ml, 0.52 mmol) was then added dropwise with rapid stirring and the mixture was stirred for a further hour at –50 °C before allowing the reaction mixture to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed sequentially with sat. $NaHCO_3$ (aq.) (2 × 50 ml) and brine (50 ml). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue containing compounds **2**, **26** and **10** was analysed by ^{1}H NMR spectroscopy and by CSP-HPLC: Chiralpak AD (4.6 mm × 25 cm); hexane/*i*-PrOH (80:20); 1.0 ml/min; 20 °C; UV detection at 250 nm, reference at 525 nm. Retention times: NOMBIN (**2**): 7.1 min [(*R*)-(+)-minor] and 12.9 min [(*S*)-(–)-major]; NOMBIN isobutyramide **26**: 5.5 min [(*R*)-major] and 9.4 min [(*S*)-minor]. *NB*. The absolute stereochemistry of the enantiomers of NOMBIN (**2**) were assigned by reference to those determined by Hattori et al.[49] using identical CSP-HPLC conditions; by product **10** is not detected at this wavelength.

N-[2-Amino-2′-methoxy-1,1′-binaphthyl]isobutyramide (**26**)

A pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): 0.80 (3 H, d, *J* = 6.9, CH_3), 0.88 (3 H, d, *J* = 6.9, CH_3), 2.12 (1 H, tt, *J* = 6.9, 6.9, CH), 6.97 (1 H, broad s, NH), 7.11 (1 H, app d, *J* = 8.5, ArH), 7.14 (1 H, app d, *J* = 8.5, ArH), 7.22–7.31 (2 H, m, ArH), 7.35–7.44 (2 H, m, ArH), 7.52 (1 H, d, *J* = 9.0, ArH), 7.89–7.96 (2 H, m, ArH), 8.01 (1 H, d, *J* = 9.0, ArH), 8.10 (1 H, d, *J* = 9.0, ArH), 8.63 (1 H, app d, *J* = 9.0, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 19.1 (2 × q), 36.4 (d), 56.6 (q), 113.5 (d), 117.1 (s), 120.8 (d), 121.3 (s), 124.2 (d), 124.6 (d), 124.8 (d), 125.7 (d), 126.2 (d), 127.5 (d), 128.10 (d), 128.14 (d), 128.7 (d), 129.3 (s), 130.9 (d), 132.9 (s), 133.5 (s), 134.5 (s), 155.1 (s), 174.9 (s). MS (CI) *m/z* (rel. int., %) 387 (10, M + NH_4^+), 370 (100, M + H^+), 299 (5). HRMS (CI) *m/z*: found: (M + H^+) 370.1819, $C_{25}H_{23}NO_2$ requires 370.1807 (Δ = +3.3 ppm).

Entry 2: An oven-dried 0.5 ml microwave glass vial (0.7 cm ID × 7.5 cm, Biotage Ltd.) equipped with a Teflon® magnetic stirring bar was charged with catalyst (+)-(*R*)-NMe-AI-Ph **21** [39,45] (0.8 mg, 5 mole %), NOMBIN (**2**; 0.015 g, 0.05 mmol), 18-crown-6 (0.010 g, 0.0375 mmol), anhydrous LiBr (0.0065 g, 0.075 mmol), and the vial was sealed with an air-tight aluminium/rubber septum using a crimper. The contents in the vial was dried *in vacuo* and purged with argon gas (3×). Toluene (0.4 ml) was added and the reaction mixture was stirred vigorously for 0.5 h at room temperature with occasional sonication to afford a heterogeneous mixture containing a white precipitate in a clear pale brown solution. It was

then cooled to –10 °C using a cold isopropanol bath and stirred for 30 min. A solution of the acylating reagent **29** [34] (0.0065 g, 0.025 mmol) in dry toluene (0.3 ml) at –10 °C was added to the reaction mixture under an argon atmosphere. The contents were stirred at –10 °C for stipulated reaction time, after which the reaction mixture was quenched with excess *n*-propylamine (25 µl, 0.3 mmol) and stirred at –10 °C for 1 h and slowly warmed to room temperature overnight. The reaction mixture was then extracted with EtOAc (50 ml) and washed sequentially with sat. $NaHCO_3$ solution (2 × 25 ml) and brine (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue containing compounds **2**, **27** and **28** was analysed by ^{1}H NMR spectroscopy and by CSP-HPLC: Chiralpak AD-H (4.6 mm × 25 cm); hexane/*i*-PrOH (90:10); 1.0 ml/min; 25 °C; UV detection at 250 nm, reference at 360 nm. Retention times: NOMBIN (**2**): 11.6 min [(*R*)-(+)] and 28.2 min [(*S*)-(–)]; NOMBIN acetamide **27**: 19.0 min (*R*) and 25.3 min (*S*). *NB*. The absolute stereochemistry of the enantiomers of NOMBIN (**2**) were assigned by analogy with those from entry 1; by product **28** is not detected at this wavelength.

2-Amino-2′-methoxy-1,1′-binaphthyl acetamide (**27**)

A brown solid; m.p. 178–180 °C (CH_2Cl_2); R_F 0.53 (*n*-hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (3 H, s, $COCH_3$), 3.81 (3 H, s, OCH_3), 6.92 (1 H, broad s, NH), 7.01–7.11 (2 H, m, ArH), 7.20–7.31 (2 H, m, ArH), 7.35–7.45 (2 H, m, ArH), 7.52 (1 H, app d, J = 9.0, ArH), 7.89–7.96 (2 H, m, ArH), 8.00 (1 H, d, J = 9.0, ArH), 8.09 (1 H, d, J = 9.0, ArH), 8.58 (1 H, d, J = 9.0, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 24.6 (q), 56.7 (q), 113.7 (d), 117.1 (s), 120.8 (d), 124.2 (d), 124.7 (d), 124.9 (d), 125.7 (d), 126.3 (d), 127.4 (d), 128.1 (d), 128.2 (d), 128.7 (d), 129.3 (s), 130.9 (d), 131.7 (s), 132.9 (s), 133.5 (s), 134.4 (s), 155.2 (s), 168.3 (s), (1 × s absent). IR (neat): 3408, 3263, 3057, 2935, 1677, 1619, 1593, 1495, 1425, 1353, 1263, 1249, 1147, 1083, 1055, 1018, 864, 811, 746. MS (EI) *m/z* (rel. int., %) 341 (100, $M^{\bullet+}$), 299 (79), 267 (49), 239 (12), 198 (21), 156 (21), 105 (20). HRMS (EI^+) *m/z*: found: (M^+) 341.1419, $C_{23}H_{19}NO_2$ requires 341.1416 (Δ = +0.9 ppm).

N-Benzoyl-*tert*-butylglycine propylamide (**28**)[34]

Colourless needles (EtOAc/*n*-hexane, 1:1); m.p. 186.5–187.5 °C; R_F 0.39 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): 0.92 (3 H, t, J = 7.4, CH_2CH_3), 1.09 (9 H, s, 3 × CH_3), 1.54 (2 H, q, J = 7.4, CH_2CH_3), 3.14 (1 H, m, NCH_2), 3.34 (1 H, m, NCH_2), 4.66 (1 H, d, J = 9.2, CH), 6.84 (1 H, broad s, NH), 7.05 (1 H, d, J = 9.2, NH), 7.42–7.45 (2 H, m, ArH), 7.50–7.55 (1 H, m, ArH), 7.80–7.85 (2 H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 11.5 (q), 22.7 (t), 26.8 (3 × q), 35.3 (s), 41.3 (t), 60.8 (d), 127.1 (d), 128.6 (d), 131.7 (d), 134.3 (s); 167.2 (s), 170.5 (s). IR (neat): 3308, 2962, 2935, 2872, 1670, 1629, 1578, 1529, 1491, 1481, 1389, 1367, 1335, 1278, 1241, 1188, 1149, 802, 751. MS (ESI) *m/z* (rel. int., %): 299 (19, M + Na^+), 277 (100, M + H^+), 218 (20), 190 (7). MS (EI) *m/z* (rel. int., %): 276 (11, $M^{\bullet+}$), 261 [22, $(M\text{-}CH_3)^+$], 220 [16, $(M\text{-}t\text{Bu})^+$], 202 (5), 190 (72), 176 (16), 161 (10), 115 (14), 105 (100), 77 (41), 60 (23), 51 (7). HRMS (ESI+ve) *m/z*: found: (M + H^+) 277.1917, $C_{16}H_{25}N_2O_2$ requires 277.1916 (Δ = +0.4 ppm).

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