Syntheses and Transformations of α-Aminobenzylnaphthol Derivatives

PhD Thesis

István Szatmári

Institute of Pharmaceutical Chemistry, University of Szeged

Szeged, Hungary

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The test of a first rate intelligence is the ability to hold two opposed ideas in the mind at the same time, and still retain the ability to function. One should, for example, be able to see that things are hopeless and yet be determined to make them otherwise.

(*F. Scott Fitzgerald*)

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Tetrahedron **2003**, *59*, 2877-2884.

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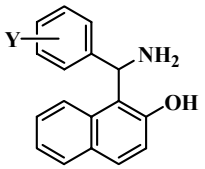
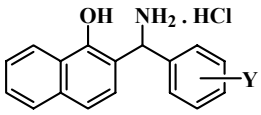
1. INTRODUCTION AND AIMS

One hundred years ago, Betti reported a straightforward synthesis of 1-(α-aminobenzyl)-2-naphthol (the Betti base, **I**: Y = H),[1-5] starting from 2-naphthol, benzaldehyde and ammonia. The Betti procedure can be interpreted as a specification of the Mannich condensation, in which formaldehyde is replaced by an aromatic aldehyde, secondary amine by ammonia and the C-H acid by an electron-rich aromatic compound such as 2-naphthol. The preparation of substituted Betti base derivatives by the modified Mannich reaction has subsequently become of considerable importance because a C-C bond is formed under mild experimental conditions. In the past decade, interest in the chemistry of the Betti base has intensified. Preparation of the enantiomers of the Betti base and its *N*-substituted derivatives is of significance since they can serve as chiral catalysts.



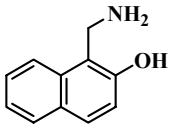
I

Y = NO_2(*m*); Br(*m*); NO_2(*p*); Br(*p*); Cl(*p*); H; F(*p*); Me(*p*); OMe(*p*)



II

Y = NO_2(*m*); Br(*m*); Br(*p*); Cl(*p*); H; Me(*p*); OMe(*p*)



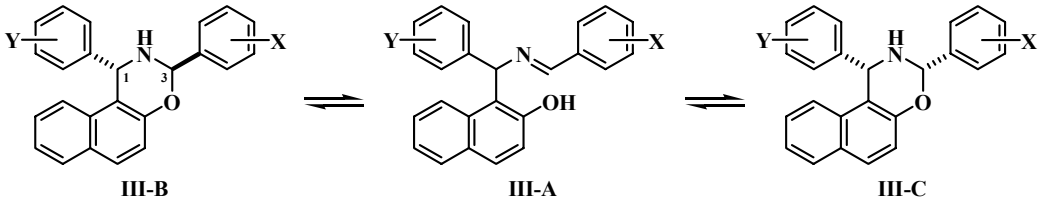
VI

The ring-chain tautomeric interconversion of *N*-unsubstituted 1,3-*O*,*N*-heterocycles and the corresponding hydroxyalkylimines can often be exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry.[6-8] From quantitative studies on such equilibria, it has been concluded that the tautomeric ratios for oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2 can be characterized by an aromatic substituent dependence:[6]

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad \text{(Eq. 1)}$$

where K_X is the [ring]/[chain] ratio and σ^+ is the Hammett-Brown parameter of substituent X on the 2-phenyl group. The scope and limitations of Eq. 1 have been thoroughly studied from the aspects of the applicability of this equation in the case of complex tautomeric mixtures containing several types of open and/or cyclic forms, and the influence of the steric and/or electronic effects of the substituents at positions other than 2 on the parameters in Eq. 1.[8-11] Previous quantitative investigations on the ring-chain tautomeric equilibria of some 1,3-*Y*,*N*-heterocyclic model compounds (Y = *O*, *NR*) did not result in precise mathematical formulae with which to characterize the effects of substituents at positions other than 2, or were restricted to the recording of the substituent-induced changes in the parameters in Eq. 1.[12-14]

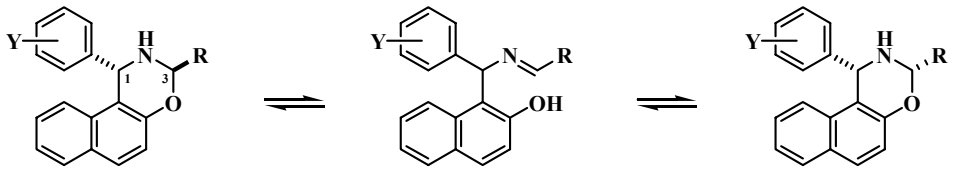
My PhD work focused on the syntheses of α-aminobenzylnaphthol derivatives (**I**, **II** and **VI**) and, by transformation to different substituted 1,3-diaryl- (**III**), 3-alkyl,1-aryl- (**IV**) and 2,4-diarylnaphthoxazines (**V**), study of the double substituent effects on the ring-chain tautomeric equilibria.



III-B **III-A** **III-C**

Y = NO_2(*m*); Br(*m*); NO_2(*p*); Br(*p*); Cl(*p*); H; F(*p*); Me(*p*); OMe(*p*)

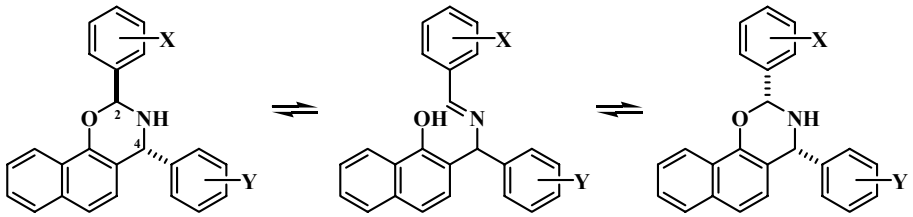
X = NO_2(*p*); Br(*m*); Br(*p*); Cl(*p*); H; Me(*p*); OMe(*p*)



IV-B **IV-A** **IV-C**

Y = NO_2(*m*); Br(*m*); NO_2(*p*); Br(*p*); Cl(*p*); H; F(*p*); Me(*p*); OMe(*p*)

R = Me; Et; Pr; *i*Pr; *t*Bu



V-B **V-A** **V-C**

Y = NO_2(*m*); Br(*m*); Br(*p*); Cl(*p*); H; Me(*p*); OMe(*p*)

X = NO_2(*p*); Br(*m*); Br(*p*); Cl(*p*); H; Me(*p*); OMe(*p*)

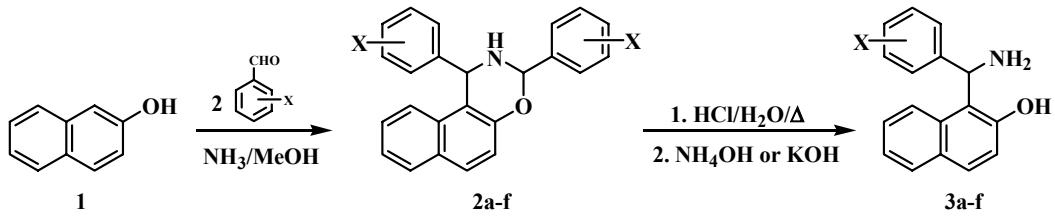
A further aim was to study the synthetic applicability of α-aminobenzylnaphthol derivatives (**I**: Y = H; **II**: Y = H; and **VI**) in some other ring-closure reactions.

2. LITERATURE

2.1. Syntheses of α-aminobenzylnaphthol derivatives

2.1.1. Syntheses of racemic compounds

The chemistry of the Betti bases started at the beginning of the 20th century, when Betti reported the synthesis of 1-(α-aminobenzyl)-2-naphthol. The reaction was performed with 2-naphthol (**1**), benzaldehyde and ammonia (in a ratio of 1:2:1) to obtain 1,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (**2a**). The subsequent acidic hydrolysis and basification with NH_4OH gave the desired aminonaphthol **3a** (Scheme 1).[1-4]



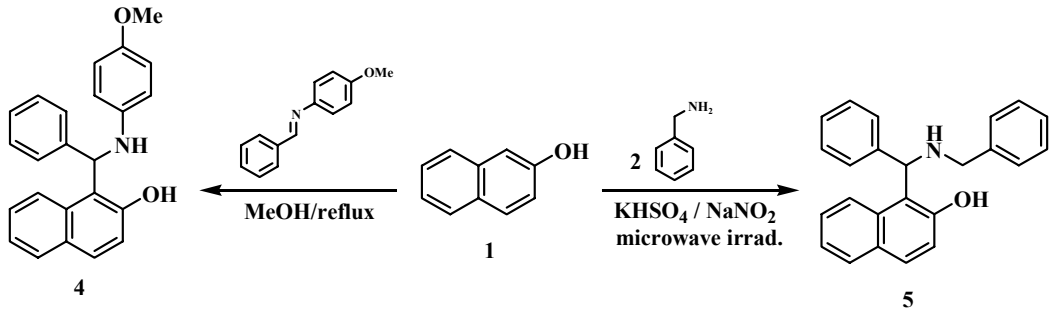
X = H: **a**; Cl(*o*): **b**; Cl(*m*): **c**; Cl(*p*): **d**; Me(*p*): **e**; OMe(*p*): **f**

Scheme 1

The general applicability of the Betti condensation has been tested by using chloro-substituted benzaldehydes. The resulting aminonaphthols **3b**, **3c** and **3d** (Scheme 1) were found to be less stable than **3a**. The sequence of stability was X = H > Cl(*m*) > Cl(*o*) > Cl(*p*).[15] Some further aminonaphthol analogues, **3e** and **3f**, were prepared in order to study the stability of these compounds with respect to acidic hydrolysis.[16] In these early papers, compounds **2a-f** were described as naphthoxazines, but in later publications it was pointed out that in $CDCl_3$ **2a-f** participate in a three-component tautomeric mixture containing two epimeric naphthoxazines besides the Schiff base.[17,18]

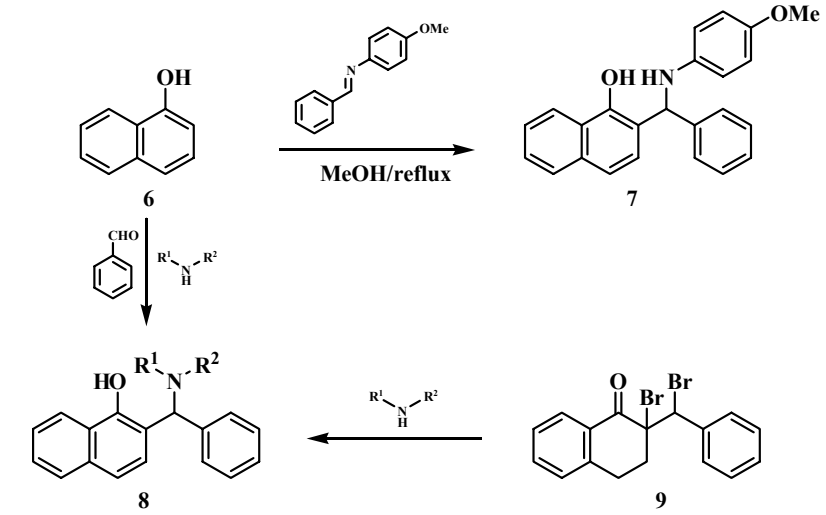
The reaction of 2-naphthol (**1**) with benzylidene(*p*-methoxyaniline) in methanol led to the formation of 1-[α-(*p*-methoxyanilino)benzyl]-2-naphthol (**4**, Scheme 2).[19] The results can be interpreted as an extension of the Betti reaction because benzylidene(*p*-methoxyaniline) serves as an aldehyde source in the reaction, while primary amines were used instead of ammonia.

In a study of the diazotization of 2-naphthol (**1**) with amines, by induction with microwave irradiation in the absence of solvent, replacement of the aromatic amine by benzylamine led to the formation of α-(2-hydroxy-1-naphthyl)dibenzylamine (**5**) instead of the expected benzylazo-2-naphthol (Scheme 2).[20]



Scheme 2

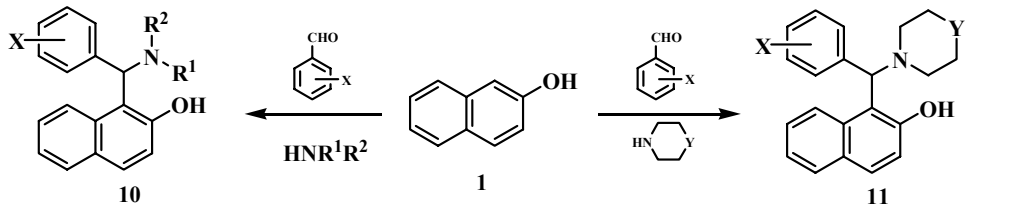
The extension of the Betti reaction, when the electron-rich aromatic compound 2-naphthol (**1**) was replaced by the less reactive 1-naphthol (**6**), was performed by Hanumanthu *et al.* 1-Naphthol (**6**) with benzylidene(*p*-methoxyaniline) in methanol led to the formation of 2-[α-(*p*-methoxyanilino)benzyl]-1-naphthol (**7**) (Scheme 3).[19] Some further secondary and tertiary 2-(α-aminobenzyl)-1-naphthol derivatives **8** were prepared by the reactions of 2-bromo-2-(α-bromobenzyl)-1-tetralone (**9**) with primary or secondary amines (Scheme 3).[21] Compounds **8** were synthesized by the same authors using classical Mannich condensation (*e.g.* 1-naphthol, benzaldehyde and amines) (Scheme 3).[21]



R^1, R^2 = H, C_6H_{11}; Me, C_6H_{11};
$-(CH_2)_5-$; $-(CH_2)_2-O-(CH_2)_2-$

Scheme 3

The Betti condensation was extended by using secondary amines,[22,23] resulting in **10**, or cyclic amines,[22-25] resulting in **11** as the *N*,*N*-disubstituted derivatives of the Betti base (Scheme 4).

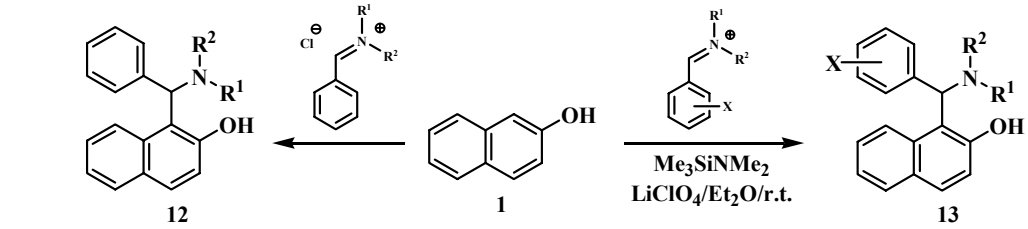


X = H; *p*OMe
R^1 = Me; Et; *n*Pr
R^2 = Me; Et; *n*Pr

X = *p*Cl; H; *p*OMe, Y = -CH_2-
X = H; 3,4-OMe; *p*OMe; *p*NMe_2, Y = O

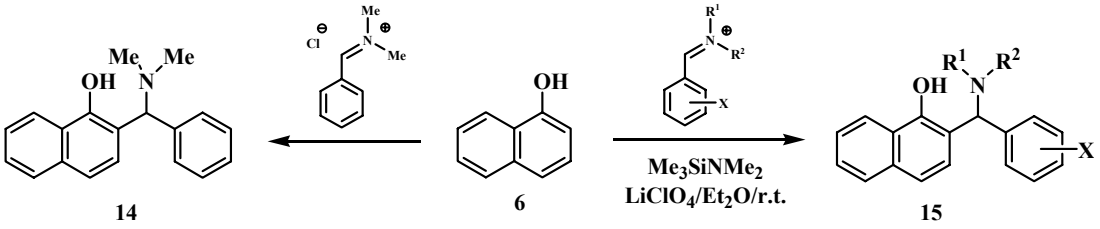
Scheme 4

In contrast with the conventional Mannich procedure, aminomethylations using methylene iminium salts, which function as highly reactive Mannich reagents, furnish basic advantages, because they generally provide superior yields, while the reactions are faster and require milder conditions. This strategy was first applied by Risch *et al.*[26] to prepare **12** and **14** (Scheme 5), and was extended by Saidi *et al.*[27] the iminium salts being prepared *in situ* in 5 M ethereal lithium perchlorate to obtain **13** and **15** (Scheme 5).



R^1, R^2 = Me, Me: **a**; -$(CH_2)_5$-: **b**

X = *m*NO_2; 2,4-di-Cl; *p*Cl; *p*CN; H
R^1, R^2 = Me, Me; -$(CH_2)_4$-; -$(CH_2)_5$-;
-$(CH_2)_2$-O-$(CH_2)_2$-



X = 2,4-di-Cl; *p*Cl
R^1, R^2 = -$(CH_2)_4$-; -$(CH_2)_2$-O-$(CH_2)_2$-

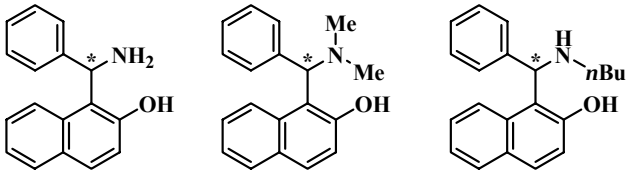
Scheme 5

2.1.2. Syntheses of enantiomeric compounds

2.1.2.1. Resolution of the racemates by separation of the diastereomers

The first resolution of 1-(α-aminobenzyl)-2-naphthol was performed by diastereomeric salt formation with tartaric acid by Betti.[28,29] Naso *et al.* reported the resolution of **3a** through treatment of the racemic compound with an equivalent amount of (2*R*,3*R*)-tartaric acid in a 95%

ethanol-methanol mixture (6:1). Fractional crystallization afforded the less soluble salt (+)-**3a**, and its absolute configuration was found to be (*S*) (determined by X-ray diffraction analysis of its hydrobromide salt, **3a**.HBr).[30] The *N*,*N*-dimethylamino derivative of **3a** was resolved in a similar manner. The diastereomeric salts obtained from the racemate and (2*R*,3*R*)-tartaric acid were separated by fractional crystallization from acetone.[30] The *N*-butyl derivative of **3a** could be resolved by using an equivalent amount of (2*R*,3*R*)-tartaric acid in acetone.[31]

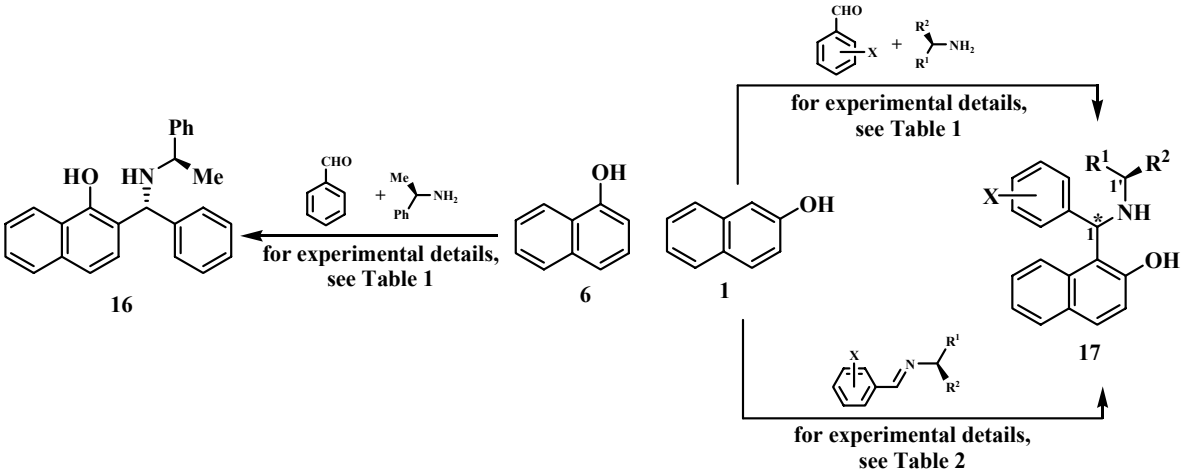


3a

2.1.2.2. Stereoselective syntheses

Palmieri reported an enantioselective synthesis of (1*R*,1'*R*)-**17a** under solvent-free conditions, starting from benzaldehyde, 2-naphthol (**1**) and (*R*)-1-phenylethylamine. Of the two possible diastereomers, the diastereomeric excess (de) of the (*R*,*R*) isomer was found to be 98%.[32] Since **17a** could be obtained in excellent yield and de, the reaction was later extended to substituted benzaldehydes and to obtain (1*R*,1'*R*)-**16**, 2-naphthol being replaced by 1-naphthol (Scheme 6 and Table 1).[33]

A variety of such aminonaphthols were prepared by Palmieri *et al.*, (*R*)-1-phenylethylamine being replaced by other chiral amines. The de values and the reaction conditions are given in Table 1.[34]



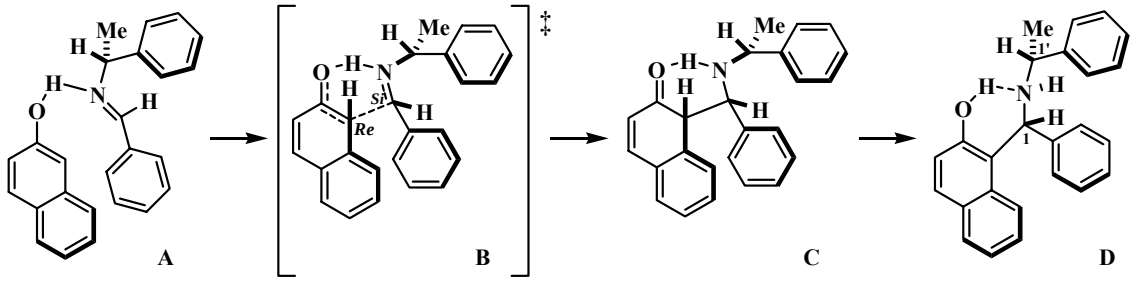
Scheme 6

Table 1. Reaction conditions for the aminoalkylation of 1- or 2-naphthol with enantiopure amines and substituted benzaldehydes

X	R^1	R^2	Main product	Conditions	Yield (%)	de (%)
-	-	-	(1*R*,1'*R*)-**16**	60 °C, 8 h	50	41[a]
H	Ph	Me	(1*R*,1'*R*)-**17a**	60 °C, 8 h	93	98[b]
*p*Me	Ph	Me	(1*R*,1'*R*)-**17b**	60 °C, 8 h	72	92[a]
*p*OMe	Ph	Me	(1*R*,1'*R*)-**17c**	60 °C, 14 h	66	61[a]
*p*Cl	Ph	Me	(1*R*,1'*R*)-**17d**	60 °C, 7 h	72	62[a]
mNO_2	Ph	Me	(1*R*,1'*R*)-**17e**	60 °C, 14 h	86	50[a]
*o*OMe	Ph	Me	(1*S*,1'*R*)-**17f**	60 °C, 9 h	75	50[c]
H	-CH_2-OH	Ph	(1*S*,1'*R*)-**17g**	60 °C, 8 h	66	56[c]
H	1-naphthyl	Me	(1*R*,1'*R*)-**17h**	60 °C, 14 h	80	60[c]

[a] Data from ref. 33. [b] Data from ref. 32. [c] Data from ref. 34

The diastereoselectivity of the reaction was explained by the asymmetric transformation of the second kind induced by the preferential crystallization.[33] The diastereoselectivity of the reaction was interpreted by Palmieri *et al.* as given in Scheme 7. It was assumed that an aldiminium-type complex (**A**) is initially formed through protonation of the C=N nitrogen. In the first step of this Friedel-Crafts reaction, the rate-limiting stage of the whole reaction, the formation of the arenium σ-complex *ul*-(*Re*,*Si*)-(*R*,*R*)-**17a-σ** (**C**) proceeds through a six-membered transition state *ul*-(*Re*,*Si*)-(*R*,*R*)-**17a-*TS*** (**B**), as shown in Scheme 7. The relative stability of the transition state **17a-*TS***, calculated for all four possible combinations, at the semi-empirical PM3 level, accorded with the stereoselectivity observed for this Mannich reaction.[34]



	ΔEatt		
	ul-(*Re*,*Si*)-(*R*,*R*)-**17a-*TS*** 0.00	*ul*-(*Re*,*Si*)-(*R*,*R*)-**17a**-σ 0.00	(*R*,*R*)-**17a** 0.00
80.215 kcal/mol	93.804 kcal/mol	54.109 kcal/mol	42.031 kcal/mol
	ul-(*Si*,*Re*)-(*S*,*R*)-**17a-*TS*** + 0.61	*ul*-(*Si*,*Re*)-(*S*,*R*)-**17a**-σ + 0.17	(1*S*,1'*R*)-**17a** + 0.27
	lk-(*Si*,*Si*)-(*R*,*R*)-**17a-*TS*** + 0.91	*lk*-(*Si*,*Si*)-(*R*,*R*)-**17a**-σ + 1.87	
	lk-(*Re*,*Re*)-(*S*,*R*)-**17a-*TS*** + 1.04	*lk*-(*Re*,*Re*)-(*S*,*R*)-**17a**-σ + 1.82	

Scheme 7

The mechanism and diastereoselectivity of the reactions of 2-naphthol (**1**) and chiral imines, which involve donor-acceptor interactions, were also investigated by Boga *et al*. Table 2 lists the yields, de values and experimental conditions. Those authors assumed the presence of

kinetic control at low temperature, and re-equilibration (by thermodynamic control) at high temperature.[35]

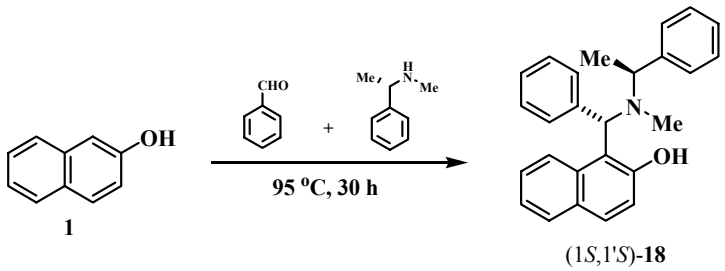
Saidi *et al.* reported a one-pot, three-component Mannich reaction of 2-naphthol (**1**) with imines prepared *in situ* in 5 M ethereal lithium perchlorate at room temperature. Under these conditions, secondary aminonaphthols could be obtained in high yields with high diastereoselectivities (Scheme 6, Table 2).[36]

Table 2. Reaction conditions for the aminoalkylation of 2-naphthol with chiral imines

X	R^1	R^2	Main product	Catalyst	Solvent	Conditions	Yield (%)	de (%)
H	Me	Ph	(1*R*,1'*S*)-**17a**	–	CH_2Cl_2	20 °C, 1 d	75	0[a]
H	Me	Ph	(1*S*,1'*S*)-**17a**	–	CH_2Cl_2	20 °C, 10 d	95	70[a]
H	Me	Ph	(1*R*,1'*S*)-**17a**	Et_3N	CH_2Cl_2	20 °C, 10 d	50	0[a]
H	Me	Ph	(1*S*,1'*S*)-**17a**	CH_3SO_3H	CH_2Cl_2	20 °C, 10 d	87	60[a]
H	Me	Ph	(1*R*,1'*S*)-**17a**	–	CH_2Cl_2	-20 °C, 7 d	50	20[a]
H	Me	Ph	(1*R*,1'*S*)-**17a**	–	THF	20 °C, 3 d	84	20[a]
H	Ph	Me	(1*R*,1'*R*)-**17a**	$LiClO_4$/TMSCl[c]	Et_2O	r.t., 6 h	75	98[b]
*p*Cl	Ph	Me	(1*R*,1'*R*)-**17d**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	78	98[b]
mNO_2	Ph	Me	(1*R*,1'*R*)-**17e**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	70	80[b]
2,4-di-Cl	Ph	Me	(1*R*,1'*R*)-**17i**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	70	90[b]
*p*CN	Ph	Me	(1*R*,1'*R*)-**17j**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	72	90[b]
*p*Br	Ph	Me	(1*R*,1'*R*)-**17k**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	60	86[b]
*p*OMe	Ph	Me	(1*R*,1'*R*)-**17c**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	55	50[b]

[a] Data from ref. 35. [b] Data from ref. 36. [c] Trimethylsilyl chloride

Chan *et al.* reported a new, one-step synthesis of (1*S*,1'*S*)-**18** starting from 2-naphthol (**1**), benzaldehyde and (*S*)-(–)-*N*-α-dimethylbenzylamine. This was the first example of a straightforward asymmetric synthesis of an optically active tertiary aminonaphthol via Mannich aminoalkylation of 2-naphthol (Scheme 8).[37]

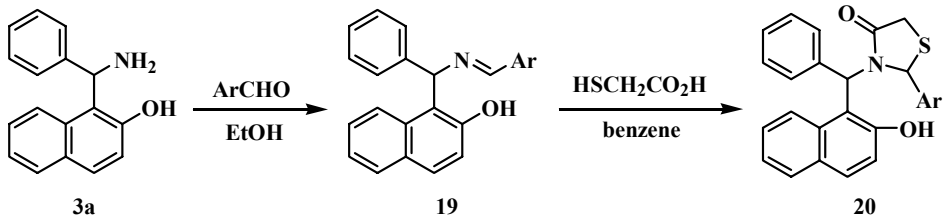


1 (1*S*,1'*S*)-**18**

Scheme 8

2.2. Transformations

In spite of the great reaction possibility resulting from the two functional groups in the Betti base, relatively few publications have appeared on this field. Desai *et al.* used the racemic Betti base for the transformation into 4-thiazolidinones **20**. The first step was the preparation of the Schiff bases **19** with substituted benzaldehydes, but the tautomeric capability of the condensation products was not discussed at all. Compounds **19** were then treated with mercaptoacetic acid to obtain 2-aryl-3-[α-(2-hydroxy-1-naphthyl)benzyl]-4-thiazolidinones (**20**), which exerted antimycobacterial and antibacterial activity (Scheme 9).[38]

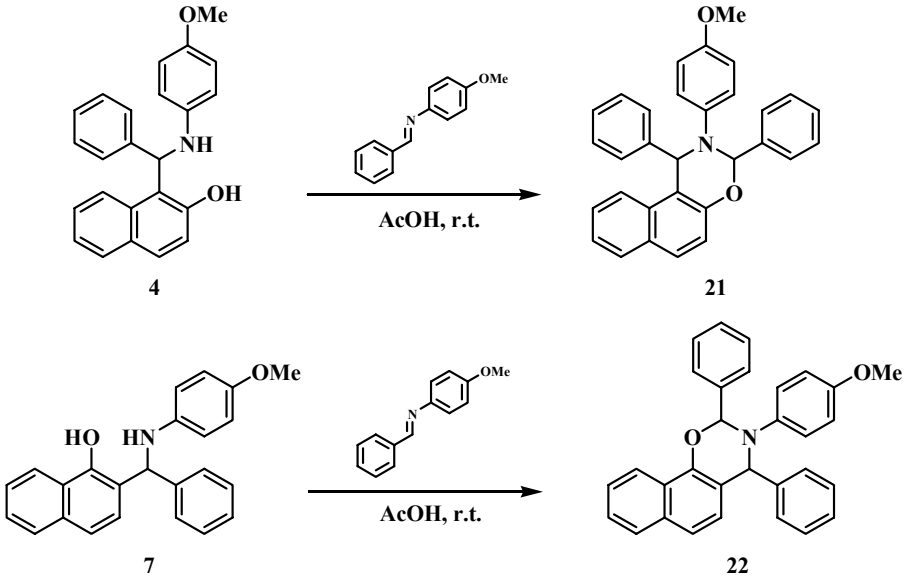


3a **19** **20**

Ar = C_6H_5: **a**; 2-OH-C_6H_4: **b**; 4-OH-C_6H_4: **c**; 4-Cl-C_6H_4: **d**; 4-OMe-C_6H_4: **e**; 5-Br,2-OH-C_6H_3: **f**; 3,5-di-Br,2-OH-C_6H_2: **g**; 3,4-CH_2O_2-C_6H_3: **h**; 4-NO_2-C_6H_4: **i**; 3-NO_2-C_6H_4: **j**; 4-Me-C_6H_4: **k**

Scheme 9

Hanumanthu *et al.* achieved the synthesis of 1,3-diphenyl-2-(*p*-methoxyphenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**21**) and 2,4-diphenyl-3-(*p*-methoxyphenyl)-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines (**22**) by the reactions of 1-[α-(*p*-methoxyanilino)benzyl]-2-naphthol (**4**) and 2-[α-(*p*-methoxyanilino)benzyl]-1-naphthol (**7**) either with benzaldehyde or with benzylidene(*p*-methoxyaniline) in acetic acid (Scheme 10).[19]

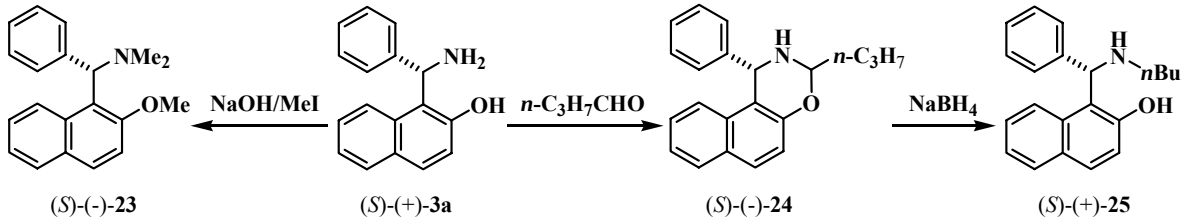


4 **21**

7 **22**

Scheme 10

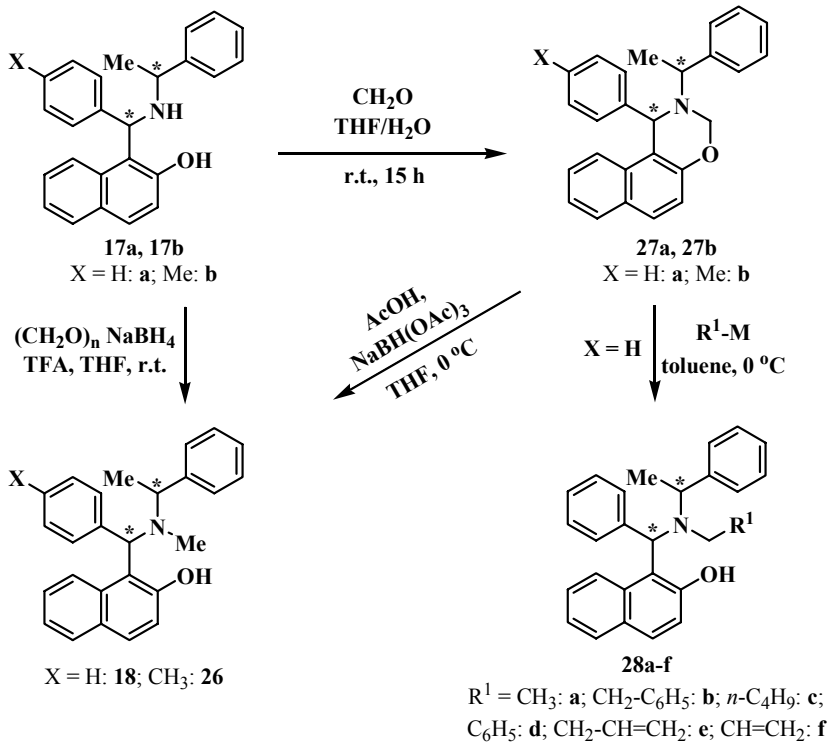
Treatment of (*S*)-(+)-**3a** with NaOH/MeI led to the trimethyl derivative (*S*)-(–)-**23** (Scheme 11).[30] In order to prove the (*S*) configuration of the (+)-**25** produced, Palmieri *et al.* treated (*S*)-(+)-**3a** with *n*-butanal, yielding the oxazine (–)-**24**, which was reduced with $NaBH_4$ to (+)-**25** (Scheme 11).[31]



Scheme 11

The enantiomers of the Betti base derivatives are not only good chiral ligands in asymmetric syntheses, but can also be applied as simple starting materials in the enantioselective syntheses of other chiral inductors.

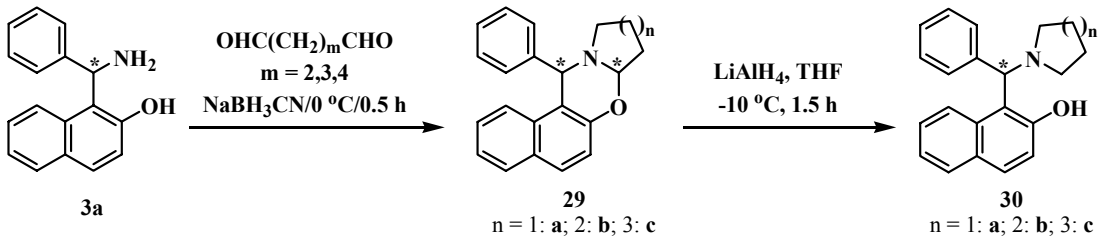
A simple preparation of (1*S*,1'*S*)-**18** starting from (1*S*,1'*S*)-**17a** is its direct *N*-methylation with paraformaldehyde; this was first carried out by Wang *et al.* (Scheme 12).[39] Palmieri *et al.* reported the syntheses of (1*R*,1'*R*)-**18** and a wide group of tertiary aminonaphthols **26** and **28** by reduction or alkylation of **27**[40] with organometallic reagents (Scheme 12).[34]



Scheme 12

The syntheses of (*R*)- and (*S*)-1-[α-(1-azacycloalkyl)benzyl]-2-naphthol **30** were attained by Hu *et al.* via selective *N*-cyclizations of (*R*)-(–) and (*S*)-(+) Betti bases with dials in the

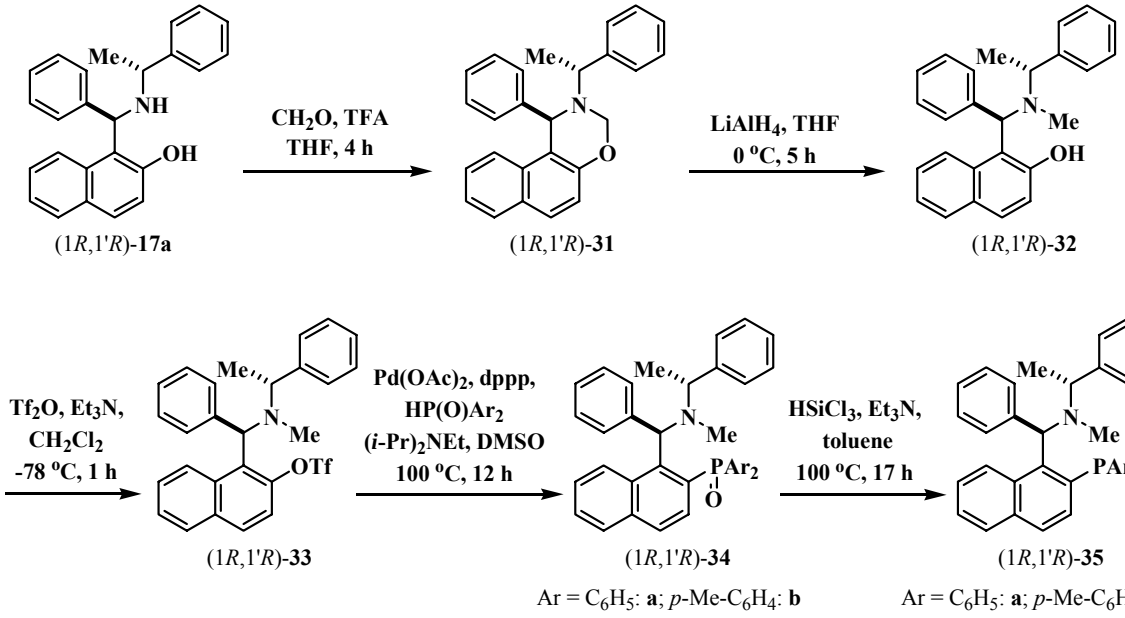
presence of $NaBH_3CN$ to give naphthalene-condensed 1-azacycloalka[2,1-*b*]oxazines **29**, followed by selective cleavage of the C-O bonds with $LiAlH_4$ (Scheme 13).[41,42]



3a **29** n = 1: **a**; 2: **b**; 3: **c** **30** n = 1: **a**; 2: **b**; 3: **c**

Scheme 13

Ding *et al.* described the synthesis of a new type of chiral aminophosphine ligands from (1*R*,1'*R*)-**17a** as starting material, formed by asymmetric 1-aminoalkylation of 2-naphthol (**1**) with (*R*)-1-phenylethylamine and benzaldehyde (Schemes 14 and 15).[43]

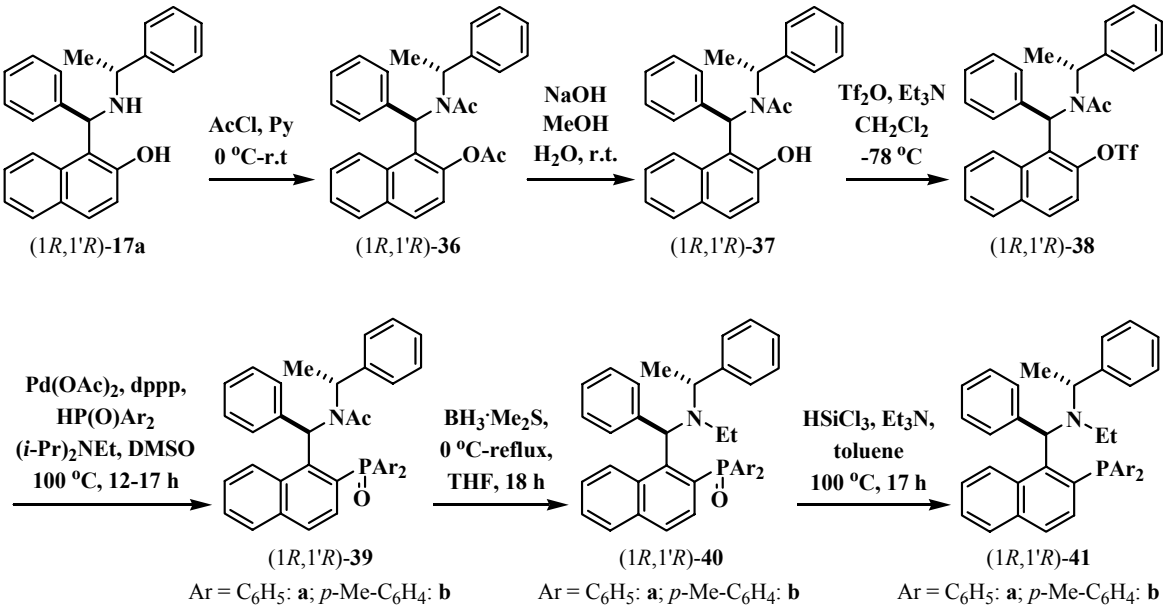


(1*R*,1'*R*)-**17a** (1*R*,1'*R*)-**31** (1*R*,1'*R*)-**32**

(1*R*,1'*R*)-**33** (1*R*,1'*R*)-**34** Ar = C_6H_5: **a**; *p*-Me-C_6H_4: **b** (1*R*,1'*R*)-**35** Ar = C_6H_5: **a**; *p*-Me-C_6H_4: **b**

Tf_2O = trifluoromethanesulfonic anhydride; dppp = 1,3-bis(diphenylphosphino)propane

Scheme 14



(1*R*,1'*R*)-**17a** (1*R*,1'*R*)-**36** (1*R*,1'*R*)-**37** (1*R*,1'*R*)-**38**

(1*R*,1'*R*)-**39** (1*R*,1'*R*)-**40** (1*R*,1'*R*)-**41**

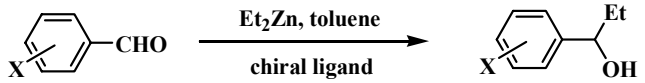
Ar = C_6H_5: **a**; *p*-Me-C_6H_4: **b**

Tf_2O = trifluoromethanesulfonic anhydride; dppp = 1,3-bis(diphenylphosphino)propane

Scheme 15

2.3. Applications

The first resolution of **3a** was reported by Betti. Enantiomers of **3a** were used for the resolution of 2-(*p*-anisyl)propanal[44] and glyceraldehyde[45] and to discriminate between aldohexoses and ketohexoses.[46] However, in spite of the availability and low cost of the Betti base, there was a long silence over this optically active material. This was broken by Naso *et al.*, who described a detailed protocol for resolution of the two isomers,[30] with their application as chiral ligands in the enantioselective addition of diethylzinc to aryl aldehydes (Scheme 16).[31] As indicated in Table 3, depending on the chiral ligand and the aryl aldehyde, the products were obtained in high enantiopurity (up to >99%, Table 3, entries 1-4).[31] Since the dimethyl-substituted Betti base **12a** resulted in higher ee values in the enantioselective alkylation of benzaldehydes, attention focused on the preparation and examination of secondary[32,34,39] (Table 3, entries 5-10) and tertiary[34,39] (Table 3, entries 11-17) amine derivatives of these aminonaphthols. Hu *et al.* tested *N*-cycloalkylaminonaphthols (**30**) as chiral ligands; the best results are listed in Table 3 (entries 18-25).[41]



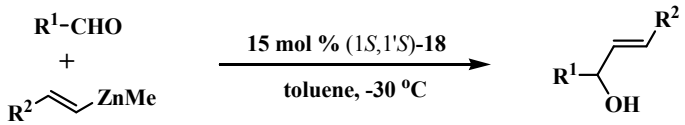
Scheme 16

Table 3. The reaction conditions and results of enantioselective addition of diethylzinc to aromatic aldehydes, using chiral ligands derived from the Betti base

Entry	Ligand	Mol %	X	Conditions	Yield (%)	ee (%)	Config.
1	(*R*)-**3a**	13.3	H	r.t., 24 h	85	35[a]	(*S*)
2	(*S*)-**12a**	13.3	H	r.t., 12 h	93	96 [a]	(*R*)
3	(*S*)-**12a**	13.3	2-Me	r.t., 24 h	75	>99 [a]	(*R*)
4	(*S*)-**12a**	13.3	4-Me	r.t., 24 h	94	96 [a]	(*R*)
5	(1*R*,1'*R*)-**17a**	6	H	r.t., 4 h	89	87[b]	(*S*)
6	(1*S*,1'*S*)-**17a**	15	4-Me	r.t., 24 h	90	92[c]	(*R*)
7	(1*S*,1'*S*)-**17a**	15	4-Cl	r.t., 24 h	88	87 [c]	(*R*)
8	(1*S*,1'*R*)-**17f**	10	H	r.t., 4 h	81	89 [d]	(*S*)
9	(1*R*,1'*R*)-**17g**	10	H	r.t., 24 h	68	15 [d]	(*S*)
10	(1*R*,1'*R*)-**17h**	10	H	r.t., 4 h	84	81 [d]	(*S*)
11	(1*S*,1'*S*)-**18**	15	H	r.t., 24 h	95	99.4 [c]	(*R*)
12	(1*S*,1'*S*)-**18**	15	4-Me	r.t., 24 h	96	99.8 [c]	(*R*)
13	(1*S*,1'*S*)-**18**	15	4-Cl	r.t., 24 h	98	96 [c]	(*R*)
14	(1*S*,1'*S*)-**18**	15	4-NO_2	r.t., 24 h	86	99.8 [c]	(*R*)
15	(1*R*,1'*R*)-**18**	15	H	r.t., 2 h	90	86 [d]	(*S*)
16	(1*R*,1'*R*)-**26**	10	H	r.t., 5 h	97	85 [d]	(*S*)
17	(1*R*,1'*R*)-**28f**	10	H	r.t., 5 h	86	85 [d]	(*S*)
18	(*S*)-**30a**	10	H	0 °C, 8 h	93	99 [d]	(*R*)
19	(*S*)-**30b**	10	H	0 °C, 8 h	95	98 [e]	(*R*)
20	(*S*)-**30b**	10	4-Me	0 °C, 8 h	95	98 [e]	(*R*)
21	(*S*)-**30b**	10	4-F	0 °C, 8 h	96	98 [e]	(*R*)
22	(*S*)-**30c**	10	H	0 °C, 8 h	93	73 [e]	(*R*)
23	(*R*)-**30a**	10	H	0 °C, 8 h	91	98 [e]	(*S*)
24	(*R*)-**30b**	10	H	0 °C, 8 h	91	98 [e]	(*S*)
25	(*R*)-**30c**	10	H	0 °C, 8 h	92	75 [e]	(*S*)

[a] Data from ref. 31. [b] Data from ref. 32. [c] Data from ref. 39.
[d] Data from ref. 34. [e] Data from ref. 41

The applicability of the tertiary aminonaphthols was extended by utilizing the addition of alkenylzinc to aldehydes (Scheme 17).[37] The best results are given in Table 4.

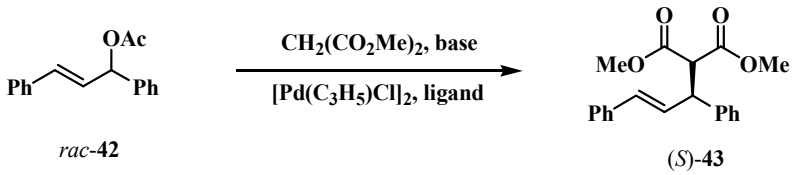


Scheme 17

Table 4. Results of the enantioselective addition of alkenylzinc to aldehydes, using chiral ligands derived from the Betti base

R^1	R^2	Yield (%)	ee (%)	Config.
$Ph(CH_2)_2$	*c*-C_6H_{11}	93	95	(*S*)
n-C_4H_9	*o*-NO_2-C_6H_4	77	98	(*R*)
n-C_4H_9	*o*-Cl-C_6H_4	90	>99	(*R*)
n-C_4H_9	*o*-Br-C_6H_4	87	98	(*R*)
n-C_4H_9	*m*-Br-C_6H_4	92	94	(*R*)

Ding *et al.* tested the asymmetric induction properties of aminophosphine ligands derived from the Betti bases **35** and **41** in the Pd(0)-catalysed allylic substitution of 1,3-diphenylprop-2-en-1-yl acetate with dimethyl malonate (Scheme 18).[43] The main results are listed in Table 5.



rac-**42** (*S*)-**43**

Scheme 18

Table 5. The reaction conditions and the results of the Pd(0)-catalysed asymmetric substitution of (±)-**42**, using chiral aminophosphine ligands derived from the Betti base

Ligand	Solvent	Time (h)	Yield (%)	ee (%)
35a	CH_2Cl_2	24	99	71.2
35a	$ClCH_2CH_2Cl$	24	99	72.2
35b	CH_2Cl_2	24	96	61.5
41a	$ClCH_2CH_2Cl$	24	67	70.2
41b	CH_2Cl_2	24	83	59.7

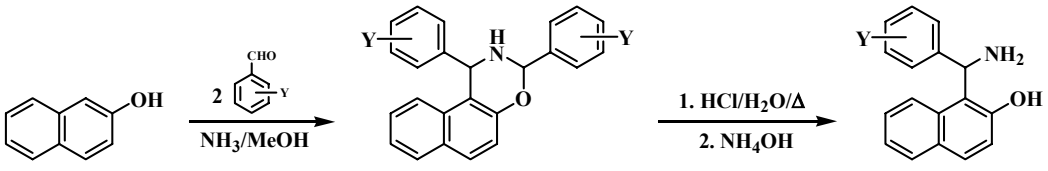
2.4. Biological effects

Little attention has been paid to the discussed compounds as concerns their biological activity. Desai *et al.* examined the *in vitro* antimycobacterial activity of **19** and **20** (Scheme 9) against the $H_{37}R_V$ strain of *Mycobacterium tuberculosis* in Lowenstein-Jensen egg medium at 0.02 mg/mL. The antibacterial activities of **19** and **20** were also tested, and they proved to be active against *E. coli* and *S. aureus*.[38] It was found that **19** does not possess significant antimycobacterial activity; the presence of a thiazolidine nucleus (**20**) is necessary for good antituberculotic activity, and the presence of halogen atoms enhances the activity.

3. RESULTS AND DISCUSSION

3.1. Syntheses and ring-chain tautomerism of 1,3-diarylnaphth[1,2-e][1,3]oxazines

Betti's classical procedure,[5] a Mannich-type aminoalkylation reaction of 2-naphthol, was applied to prepare the starting materials for the synthesis of the target compounds. Condensation of 2-naphthol (**1**) and benzaldehyde or substituted benzaldehydes in the presence of ammonia, and subsequent acidic hydrolysis, gave aminonaphthols **45a-i** in good yields (Scheme 19).

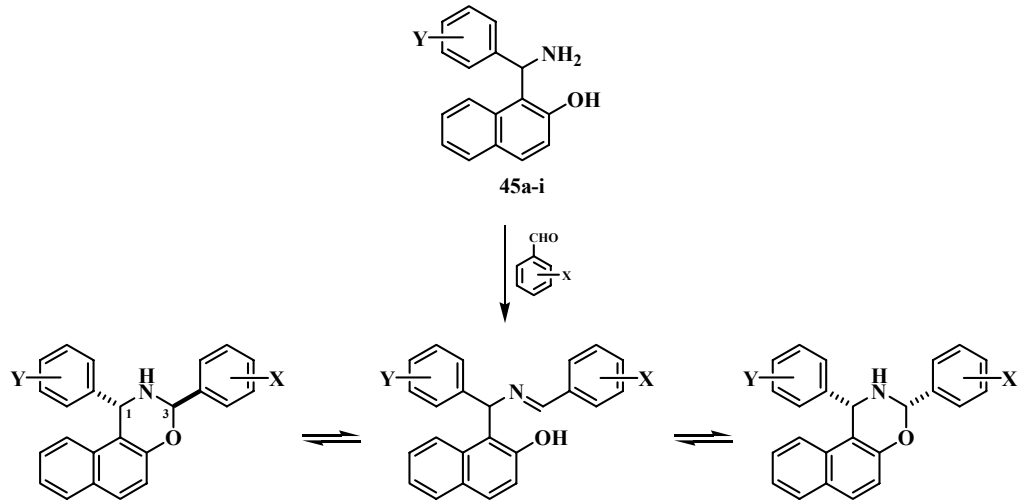


1 **44a-i** **45a-i**

Y = NO_2(*m*): **a**; Br(*m*): **b**; NO_2(*p*): **c**; Br(*p*): **d**; Cl(*p*): **e**; H: **f**; F(*p*): **g**; Me(*p*): **h**; OMe(*p*): **i**

Scheme 19

Condensations of aminonaphthols **45a-i** with equivalent amounts of aromatic aldehydes resulted in naphthoxazine model compounds **46-54** as crystalline products (Scheme 20). The ^{1}H NMR spectra of **46-54** revealed that, in $CDCl_3$ solution at 300 K, the members **a-g** of each set of compounds **46-54** participated in three-component ring-chain tautomeric equilibria involving C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**).



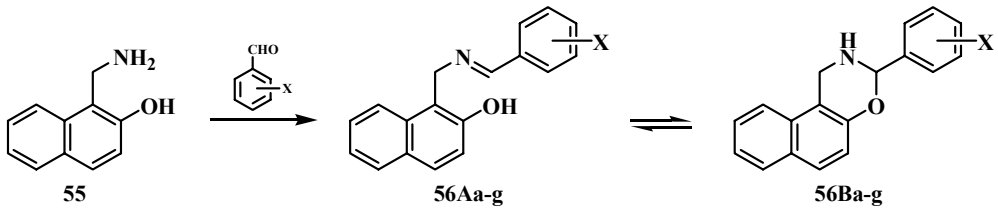
Y = NO_2(*m*):	**46Ba-g**	**46Aa-g**	**46Ca-g**
Y = Br(*m*):	**47Ba-g**	**47Aa-g**	**47Ca-g**
Y = NO_2(*p*):	**48Ba-g**	**48Aa-g**	**48Ca-g**
Y = Br(*p*):	**49Ba-g**	**49Aa-g**	**49Ca-g**
Y = Cl(*p*):	**50Ba-g**	**50Aa-g**	**50Ca-g**
Y = H:	**51Ba-g**	**51Aa-g**	**51Ca-g**
Y = F(*p*):	**52Ba-g**	**52Aa-g**	**52Ca-g**
Y = Me(*p*):	**53Ba-g**	**53Aa-g**	**53Ca-g**
Y = OMe(*p*):	**54Ba-g**	**54Aa-g**	**54Ca-g**

X = NO_2(*p*): **a**; Br(*m*): **b**; Br(*p*): **c**; Cl(*p*): **d**; H: **e**; Me(*p*): **f**; OMe(*p*): **g**

Scheme 20

The intermediate of the Betti reaction was earlier presumed to have a ring-chain tautomeric character.[17,18] By condensation of the Betti base with aromatic aldehydes, Smith and Cooper prepared 1-phenyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines, and studied their ring-chain tautomeric equilibria by means of 60 MHz ^{1}H NMR.[17] They made the assumption that 1,3-diaryl groups prefer pseudo-equatorial and therefore a *cis* arrangement in the *major* ring-closed tautomer. In contrast with this assumption, the NOESY measurements of **50a** unequivocally showed that the *major* ring forms in all tautomeric equilibria (**46-54**) contain the 1,3-diaryl substituents in the *trans* position (**B**). In consequence of the very similar NMR spectroscopic characters of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **46-54**, determination of the relative configurations of the *major* and *minor* ring-closed tautomers was performed only for **50a**.

To characterize the effects of the aryl substituent at position 1 on the tautomeric character of this ring system, 1-unsubstituted 3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**56**) were prepared from the readily available[47] 1-aminomethyl-2-naphthol (**55**, synthesized by acidic hydrolysis of the product of 2-naphthol and hexamethylenetetramine) and aromatic aldehydes. In $CDCl_3$ at 300 K, **56a-g** proved to participate in ring-chain tautomeric equilibria (Scheme 21).



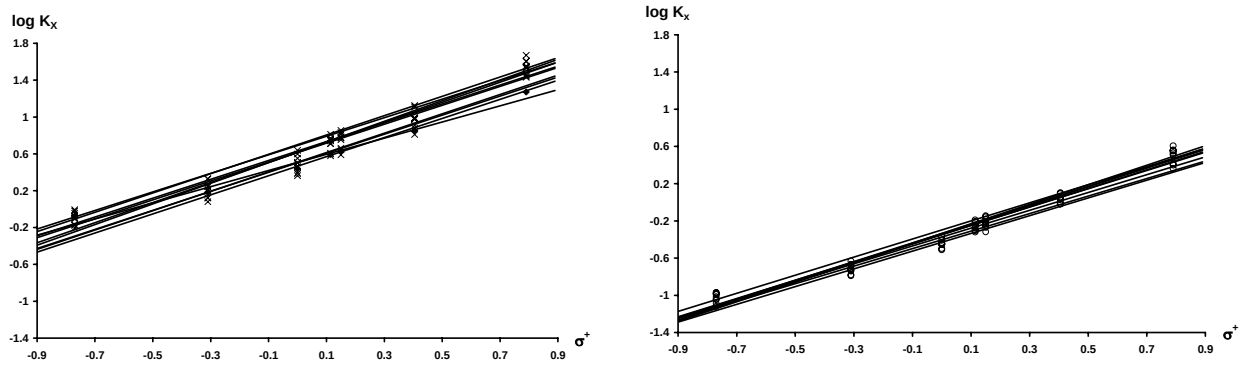
55 **56Aa-g** **56Ba-g**

X = NO_2(*p*): **a**; Br(*m*): **b**; Br(*p*): **c**; Cl(*p*): **d**; H: **e**; Me(*p*): **f**; OMe(*p*): **g**

Scheme 21

The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equilibria of **46-54** and **56** (K_X) were determined by integration of the well-separated O-C*H*Ar-N (ring) and N=C*H*Ar (chain) proton singlets or doublets in the ^{1}H NMR spectra.

When Eq. 1 was applied to the log K_X values, good linear correlations were obtained *vs* the Hammett-Brown parameter σ^+ of the substituent X on the 3-phenyl group for **46-54** and **56** (Figure 1 and Table 6).



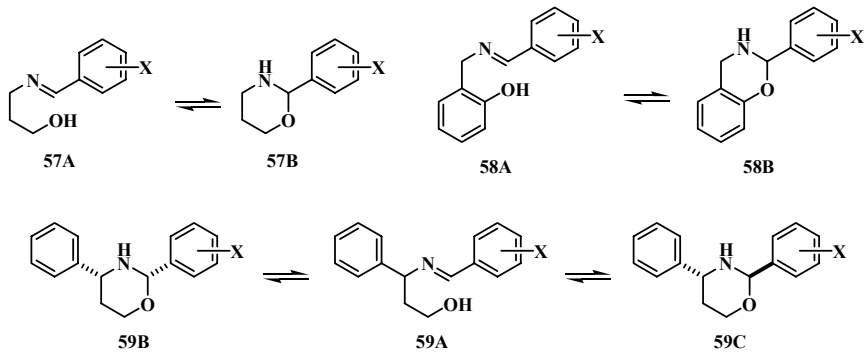
a *b*

Figure 1. *a*: Plots of log K_X for **46-54B** (x) and **56B** (♦) *vs* Hammett-Brown parameter σ^+. *b*: Plots of log K_X for **46-54C** (○) *vs* Hammett-Brown parameter σ^+

The linear regression analysis data in Table 6 show that, as is customary among 2-aryl-1,3-*O*,*N* heterocycles, the value of ρ is positive in each case, *i.e.* electron-withdrawing (EW) substituents on the 3-phenyl ring favour the ring-closed tautomer. While the value of ρ for 1-unsubstituted 3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**56**: 0.88) is the same (within experimental error) as that for the parent 2-arylperhydro-1,3-oxazines (**57**: 0.74), the values of ρ for 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**46-54**: 0.94-1.05) are somewhat higher. The *cis* or *trans* arrangement of the 1,3-diaryl substituents in the ring forms of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines does not seem to influence the value of ρ; the plots for the equilibria containing C-3 epimeric ring forms of **46-54** (**B**-**A** and **C**-**A**) are practically parallel.

To characterize the effects of the substituents and the presence of an annelated ring on the stability of the ring forms, a substitution effect parameter (c_s) was calculated as the difference in the intercepts for the given naphthoxazine derivative (**46-54**, **56**) and the parent 2-arylperhydro-1,3-oxazine (**57**: log K_0 = -0.15): c_s = log $K_{X=H}$ – log K_0. This kind of relative ring stability constant was introduced earlier for the saturated 2-aryl-1,3-*O*,*N*-heterocycles bearing substituents at positions 4-6.[8,9] A positive value of c_s means a more stable ring form relative to the corresponding parent 2-arylperhydro-1,3-*O*,*N*-heterocycle.

Table 6. Linear regression data on compounds **46-54**, **56**, 2-aryl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**57**), 2-aryl-3,4-dihydro-2*H*-1,3-benzoxazines (**58**) and 2-aryl-4-phenyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**59**)



X = NO_2(*p*); NO_2(*m*); Cl(*m*); Cl(*p*); H; Me(*p*); OMe(*p*); NMe_2(*p*)

Equilibrium	No. of points	Slope (ρ)	Intercept	Correlation coefficient	c_s [a]
46A ⇌ **46B**	7	1.01	0.68	0.993	0.83
46A ⇌ **46C**	7	1.05	-0.34	0.997	-0.19
47A ⇌ **47B**	7	1.12	0.62	0.977	0.77
47A ⇌ **47C**	7	1.00	-0.34	0.984	-0.19
48A ⇌ **48B**	7	1.05	0.70	0.994	0.85
48A ⇌ **48C**	7	0.97	-0.29	0.992	-0.14
49A ⇌ **49B**	7	1.02	0.63	0.987	0.78
49A ⇌ **49C**	7	1.03	-0.34	0.991	-0.19
50A ⇌ **50B**	7	1.03	0.61	0.988	0.76
50A ⇌ **50C**	7	0.96	-0.37	0.994	-0.22
51A ⇌ **51B**	7	1.05	0.51	0.986	0.66
51A ⇌ **51C**	7	0.98	-0.35	0.983	-0.20
52A ⇌ **52B**	7	1.09	0.62	0.985	0.57
52A ⇌ **52C**	7	1.00	-0.35	0.978	-0.20
53A ⇌ **53B**	7	1.04	0.47	0.982	0.62
53A ⇌ **53C**	7	0.95	-0.43	0.993	-0.28
54A ⇌ **54B**	7	1.03	0.50	0.985	0.65
54A ⇌ **54C**	7	0.94	-0.40	0.986	-0.25
56A ⇌ **56B**	7	0.88	0.51	0.991	0.66
57A ⇌ **57B**[b]	7	0.74	-0.15	0.984	–
58A ⇌ **58B**[b]	7	0.82	-0.66	0.995	-0.51
59A ⇌ **59B**[c]	6	0.72	0.42	0.997	0.57
59A ⇌ **59C**[c]	6	0.99	-1.12	0.996	-0.97

[a] Relative ring stability constant: see the text. [b] Data from ref. 9. [c] For compounds **59** (ref. 13), the tautomeric ratios were remeasured and the linear regression analysis was performed separately for the equilibria involving C-2 epimeric ring forms.

While an annelated benzene ring considerably decreased the stability of the ring form of 2-arylperhydro-1,3-oxazine (**58**: c_s = -0.51),[9] an annelated naphthalene ring caused a dramatic increase in ring stability (**56**: c_s = 0.66). This increased stability of the ring form was observed

for all naphthoxazines having *trans* diaryl substituents (**46-54 B**: c_s = 0.57 – 0.85), while the negative c_s values for the *cis* isomers of these compounds (**46-54 C**: c_s = -0.14 – -0.28) indicate that the stabilizing effect of the naphthalene ring is diminished by the unfavourable steric arrangement of the aryl substituents.

Hansch analysis of equilibrium constants

The influence of the 3-aryl group on the tautomeric equilibria of 1,3-naphthoxazines **46-54** could be described by using Eq. 1. The Hammett-Brown parameter σ^+ was found to be inadequate to describe the influence of aryl substituents at position 1. The effect of substituent Y was therefore divided into two parts: σ_F (inductive effect) and σ_R (resonance effect). Since the Hammett-Brown parameter σ^+ has proved to be a convenient substituent parameter with which to characterize the influence of substituent X on tautomeric equilibria, it was used to set up the following Hansch quantitative structure-properties relationship (QSPR) model (Eq. 2):

$$DV = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho^X \sigma^{+X} \qquad \text{(Eq. 2)}$$

where DV is the dependent variable (log K or donation energies). However, analogously with that of substituent Y, the influence of substituent X can also be divided into two parts (σ_F and σ_R), as represented by Eq. 3. Multiple linear regression analysis of Eqs 2 and 3 was performed by using the SPSS statistical software. A value of 0.05 was chosen as the significance level.[48]

$$DV = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho_F^X \sigma_F^X + \rho_R^X \sigma_R^X \qquad \text{(Eq. 3)}$$

Multiple linear regression analysis of Eqs 2 and 3 with DV as log K values led to the results listed in Table 7. As regards substituent X, both inductive and resonance effects seem to be significant for equilibria **B**⇌**A** and **C**⇌**A**. On the other hand, substituent Y does not affect the equilibrium **C**⇌**A** at all, and only inductive effects are significant for the equilibrium **B**⇌**A**. The present results can be interpreted as an extension of the Hammett equation (Eq. 1) and it means that for *trans*⇌chain (**B**⇌**A**) equilibria the equilibrium constants can be described by using a double substituent parameter treatment and a plane can be fitted to the data points with data error r = 0.980 (Figure 2).

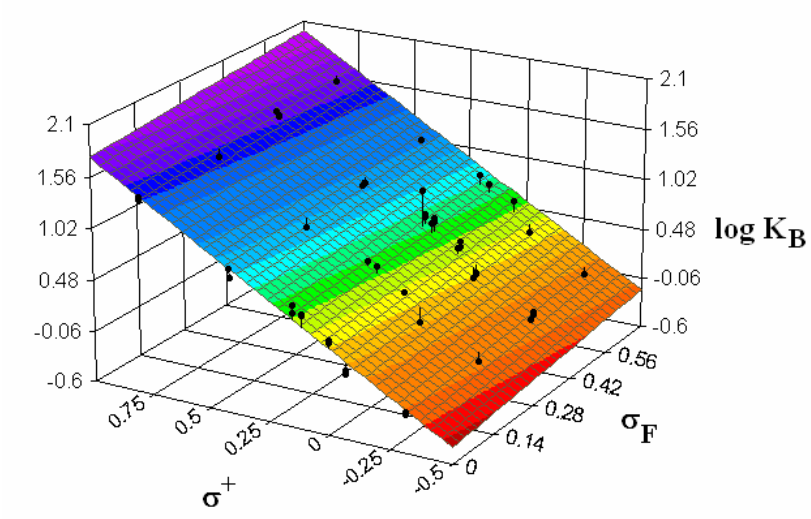


Figure 2. Plots of log K_B for **48-54B** (●) *vs* Hammett parameters σ^+ and σ_F

The observed values of both ρ_F^X (inductive) and ρ_R^X (resonance) are positive. Positive values mean that EW substituents increase the relative proportion of the ring form both inductively and by resonance. Interestingly, somewhat more positive ρ values are observed for the equilibrium **B**⇌**A**, indicating that the sensitivity of the equilibrium in question to substituent X depends on the orientation of the phenyl ring at position 1 (a disubstitution effect). The positive values for all of the observed ρ's indicate that EW substituents on both phenyl rings increase the relative proportion of the ring form for both equilibria studied. Good correlations of log K with σ^+ show that both inductive and resonance effects are usually significant. For excellent reasons, this can be stated to be *the normal behaviour of the substituent dependence of the ring-chain equilibria*. The origin of this effect is now understood.[49] As regards substituents X, the present results are in harmony with the above concept. In contrast with the above behaviour, in the case of a phenyl substituent on C-1, the sensitivities of the K values for the *cis* and *trans* isomers differ. For the equilibrium **C**⇌**A**, no significant dependence on substituent Y was observed. For the equilibrium **B**⇌**A**, a positive value of ρ_F^Y (0.32) was found, but there was no significant dependence on resonance parameter ρ_R. Accordingly, the present results show for the first time that aromatic ring substituents which are not attached to a phenyl ring situated between two heteroatoms can have a systematic effect on the relative proportions of the ring tautomers. The diminished inductive sensitivity, as compared with that of substituent X, reflects the fact that the substituent in question is situated farther away from the reaction centre. In summary, the equilibrium **B**⇌**A** seems to be somewhat more sensitive to both substituent X and substituent Y than the equilibrium **C**⇌**A**. The origins of these substituent effects and their connections with stereoelectronic effects caused by the electron donation of the nitrogen lone

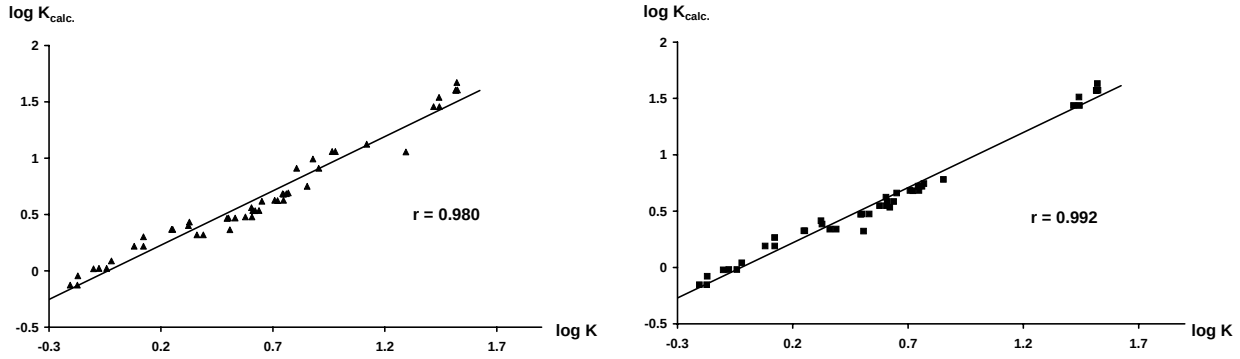
pair (potential anomeric effects)[50] are discussed below with the aid of the donation energies calculated for the minimum energy conformations.

Table 7. Multiple linear regression analysis of log K values for **48-54** and for **60-66**

		k	ρ_F^Y	ρ_R^Y	ρ^X, ρ_F^X and ρ_R^X, ρ^R		r
Acc. to Eq. 2	**48-54B≒48-54A**	0.32	0.33	–[a]	1.44		0.980
	48-54C≒48-54A	-0.53	–[a]	–[a]	1.30		0.971
Acc. to Eq. 3	**48-54B≒48-54A**	0.34	0.30	–[a]	1.17	1.87	0.992
	48-54C≒48-54A	-0.53	–[a]	–[a]	1.08	1.66	0.981
Acc. to Eq. 6	**60-66B≒60-66C**	0.48	0.22	–[a]	7.97		0.919

[a] Insignificant (significance value > 0.05)

In order to prove the validity of Eqs 2 and 3, linear regression analysis was carried out by plotting log $K_{calc.}$ (calculated by applying the parameters of Eq. 2 or 3) against log K determined experimentally (Figure 3).

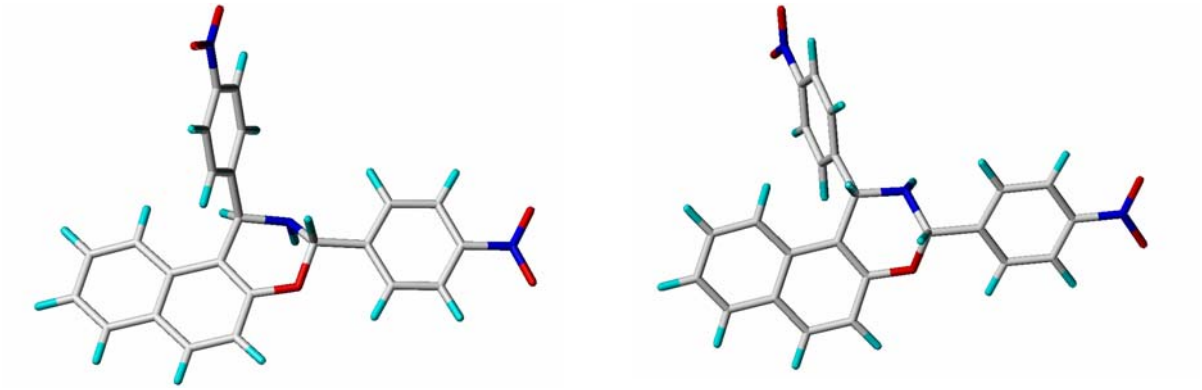


a *b*

Figure 3. *a*: Plots of log $K_{calc.}$ (calc. via Eq. 2) *vs* log K (experimental) for **48-54B**. *b*: Plots of log $K_{calc.}$ (calc. via Eq. 3) *vs* log K (experimental) for **48-54B**

Hansch analysis of the donation energies for the rigid model structures

Donation energy calculations were performed with conformationally rigid models in order to clarify the potential connections between the anomeric effect and the relative stabilities of the *cis* and *trans* isomers. The conformational search protocol involved PM3 geometry minimization, followed by optimization at the *ab initio* level, using the HF/6-31G* base set for all of the compounds. The final conformations, with **48aB** and **48aC** as examples, are shown in Figure 4. *Ab initio* calculations were performed by second-order perturbative analysis of the Fock matrix in the NBO base,[51-54] where the energy of donation (kcal/mol) of a lone pair to a given antibonding orbital could be calculated. We considered that, by comparison with the experimental findings, the factors governing the relative stability of the *cis* and *trans* isomers, and the substituent sensitivity of the ^{13}C NMR chemical shifts, could be evaluated more reliably.



48aB **48aC**

Figure 4. Final predominant minimum energy molecular structures for **48aB** and **48aC**, obtained by using *ab initio* HF/6-31G* calculations.

In the present calculated model conformations, the nitrogen lone pair can overlap with six different vicinal antibonding orbitals associated with C1 ($\sigma^*_{C1\text{-}H}$, $\sigma^*_{C1\text{-}C1'}$ and $\sigma^*_{C1\text{-}C10b}$) or with C3 ($\sigma^*_{C3\text{-}H}$, $\sigma^*_{C3\text{-}C1''}$ and $\sigma^*_{C3\text{-}O4}$). The results of Hansch analysis of the energy values as DV according to Eq. 2 are given in Table 8.

Table 8. Multiple linear regression analysis of overlapping energy values according to Eq. 2 for **48-54**

	Overlapping	k	ρ_F^Y	ρ_R^Y	ρ^X	r
B	$n_N \rightarrow \sigma^*_{C1\text{-}C1'}$	3.13	0.34	0.37	-0.13	0.983
	$n_N \rightarrow \sigma^*_{C1\text{-}C10b}$	8.94	–[a]	–[a]	-0.25	0.915
	$n_N \rightarrow \sigma^*_{C3\text{-}O4}$	20.31	-0.36	-0.24	-0.16	0.956
	$n_N \rightarrow \sigma^*_{C3\text{-}C1''}$	1.10	-0.11	-0.07	0.12	0.909
	$n_N \rightarrow \sigma^*_{C3\text{-}H}$	1.42	0.09	0.09	-0.05	0.865
C	$n_N \rightarrow \sigma^*_{C1\text{-}H}$	4.49	–[a]	–[a]	-0.13	0.799
	$n_N \rightarrow \sigma^*_{C1\text{-}C10b}$	8.70	0.09	0.15	-0.25	0.942
	$n_N \rightarrow \sigma^*_{C3\text{-}O4}$	20.82	-0.72	-0.61	-0.10	0.984
	$n_N \rightarrow \sigma^*_{C3\text{-}C1''}$	1.07	–[a]	–[a]	-0.08	0.819
	$n_N \rightarrow \sigma^*_{C3\text{-}H}$	1.62	-0.08	–[a]	–[a]	0.642

[a] Insignificant (significance value > 0.05)

Significant overlapping of the nitrogen lone pair was observed in the *trans* forms **B** (to $\sigma^*_{C1\text{-}C1'}$, $\sigma^*_{C1\text{-}C10b}$ and $\sigma^*_{C3\text{-}O4}$) and in the *cis* forms **C** (to $\sigma^*_{C1\text{-}H}$, $\sigma^*_{C1\text{-}C10b}$ and $\sigma^*_{C3\text{-}O4}$). As concerns the donation energies, the clearest difference between the *cis* and *trans* forms is that, for the *trans* form, there is no significant $n_N \rightarrow \sigma^*_{C1\text{-}H}$ donation, but there is a significant $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation. On the other hand, for the *cis* form there is no $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation, but there is a significant $n_N \rightarrow \sigma^*_{C1\text{-}H}$ donation. Further, while the $n_N \rightarrow \sigma^*_{C1\text{-}H}$ donation energy detected for the *cis* form does not depend on the substituent Y, the $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation energy

detected for the *trans* form exhibits a clear substituent dependence on Y, both inductive and resonance effects being important. As for the $n_N \rightarrow \sigma^*_{C1\text{-}C10b}$ donation, for the *cis* form there is a slight dependence on substituent Y, but for the *trans* isomer no analogous dependence was observed. However, the sums of the different significant donation energies listed above are relatively close to each other: for X = Y = H, they are 34.98 and 36.80 (in other words, the sums of the k values in Table 3) for the *trans* and *cis* isomers, respectively. It should be noted that the *cis* isomers exhibit somewhat larger donation energy sums. This is contrary to the idea that *an anomeric effect controls* the marked stability difference between the *cis* and *trans* series.

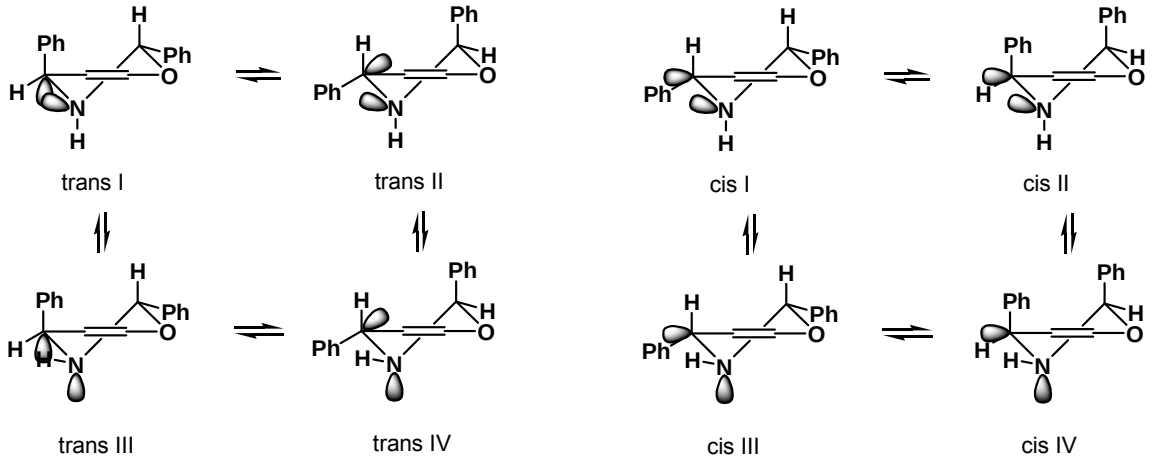
For the *trans* forms (**B**), the overlapping energy for $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ was clearly dependent on substituent Y ($\rho_F^Y = 0.34$ and $\rho_R^Y = 0.37$; Table 8). On the other hand, for the *cis* forms (**C**), the overlapping energy for $n_N \rightarrow \sigma^*_{C1\text{-}C10b}$ was substituent-dependent, but to an essentially smaller extent ($\rho_F^Y = 0.09$ and $\rho_R^Y = 0.15$; Table 8). Thus, the extent of the effect of substituent Y on the donation energies seems to depend on the configuration. In both cases, electron donation/withdrawal by both inductive and resonance mechanisms is important, but the sensitivity to the resonance effect is slightly higher. The positive values of both ρ_F^Y and ρ_R^Y mean that EW substituents increase the value of the DV. It is generally thought that the mechanism of the anomeric effect is the overlapping between an occupied lone pair orbital and an antibonding orbital of an adjacent polar bond. According to this interpretation, electron density is transferred from N-2 to the C1 –C1' antibonding orbital. This can be explained as follows. In the case of $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ overlapping, the positive ρ_F^Y and ρ_R^Y values can be understood in terms of the contribution of the corresponding double bond – no-bond resonance structure ***e*** (Scheme 23). EW substituents stabilize structure ***e*** both inductively and by direct resonance. The stabilization of resonance structure ***e*** results in an increase in the donation energy in question as compared with that of the parent compound, and consequently positive ρ values are observed.

Both **B** and **C** possess a half-chair structure. Scheme 22 gives the relevant conformations due to nitrogen/ring inversions. It is generally thought that in 1,3-oxazine systems the equatorial orientation of the substituent attached to the O-*C*-N carbon is favoured.[55,56] The 1,3-axial-pseudo-axial orientations (*cis* II and IV) of the *cis* forms are highly unfavoured due to the severe steric interaction, and their presence can be neglected. Hence, the equatorial–pseudo-equatorial orientations (*cis* I and III) preponderate in the *cis* forms. As a result of the equatorial preponderance of 3-phenyl substituents (*trans* I and III), the *trans* forms exhibit 1-phenyl pseudo-axial orientations.[55,56] Thus, the minimum energy conformations used in the NBO

analysis (*trans* I and *cis* I, *cf.* Figure 4) are relevant model structures. In the orientation *trans* I (see Scheme 22), overlap between the nitrogen lone pair and the sigma antibonding orbital of the C1-C1' bond is possible, even if it is not as favoured as it could be in the orientation *trans* III. In *cis* I, the spatial orientations of the nitrogen lone pair and the C1-C1' antibonding orbital do not allow overlap. Accordingly, the calculations did not indicate any significant $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation for the *cis* isomers. Interestingly, for *trans* I the dependence of the overlapping energy of $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ on substituent Y is clearly significant ($\rho_F^Y = 0.34$ and $\rho_R^Y = 0.37$; Table 8), the overlapping increasing with EW substituents. As concerns the $\sigma^*_{C1\text{-}C10b}$ orbital, the favourable overlapping of the nitrogen lone pair is possible in orientations I, which possess an equatorial nitrogen lone pair orientation for both the *cis* and the *trans* isomers. The calculated donation energies are about three times greater than those for $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation in the case of the *trans* isomers. However, in contrast with the above, the dependence on substituent Y is small for the *cis* isomers and insignificant for the *trans* isomers. The differences between the calculated substituent-dependent stereoelectronic effects (anomeric effects) at C-1 can therefore be understood on a conformational basis.

The largest values of the overlapping energies observed for our compounds are connected with the $n_N \rightarrow \sigma^*_{C3\text{-}O4}$ transmission. However, the donation energies in question for both the *cis* and the *trans* series are very close to each other. Hence, this anomeric effect can not explain the stability differences between the isomers. For both the *trans* (**B**) and the *cis* forms (**C**), the overlapping energy for $n_N \rightarrow \sigma^*_{C3\text{-}O4}$ was clearly dependent on substituent Y (**B**: $\rho_F^Y = -0.36$ and $\rho_R^Y = -0.24$; **C**: $\rho_F^Y = -0.72$ and $\rho_R^Y = -0.61$, Table 8). Reverse behaviour (values of $\rho < 0$) means that the sensitivity of the process in question is diminished by an electron-donating (ED) substituent. Since both the inductive and resonance sensitivities in question exhibit a reverse substituent dependence, the value of the donation energy is decreased on ED substitution. It can be assumed that the deviations in the half-chair structure itself between the *cis* and *trans* isomers are small. Thus, the different magnitudes of the ρ values indicate that the substituent dependence of the donation energy in question is dependent on the orientation of the substituted phenyl ring at C-1, the eq'-Ph–N–C–O pathway being able to transmit the effect of substituent Y more efficiently than the ax'-Ph–N–C–O pathway. The variation in the substituent dependence of the $n_N \rightarrow \sigma^*_{C3\text{-}O4}$ donation energy can be explained by comparison with $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ transfer (**B**: $\rho_F^Y = 0.34$ and $\rho_R^Y = 0.37$; **C**: ρ_F^Y and ρ_R^Y, not significant), if we neglect the contributions of the $n_N \rightarrow \sigma^*_{C3\text{-}C1''}$ and $n_N \rightarrow \sigma^*_{C3\text{-}H}$ transformations for which the donation energy values are small and for which the ρ_F^Y and ρ_R^Y values are in most cases significant, but relatively small. The

donation ability of one nitrogen lone pair is limited as regards the number and extent of different donations. The routes giving the maximum stabilization of the molecular structure prevail. For the donation $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ observed for the *trans* isomer, both the ρ_F^Y and ρ_R^Y values are positive. This means that EW substituents increase the value of the donation energy. In contrast, for $n_N \rightarrow \sigma^*_{C3\text{-}O4}$ both ρ_F^Y and $\rho_R^Y < 0$. This means that EW substituents decrease the value of the donation energy. This decrease compensates the increase in $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$. These two effects compete. As a consequence, the absolute values of ρ_F^Y and ρ_R^Y for $n_N \rightarrow \sigma^*_{C3\text{-}O4}$ donation for the *trans* isomer are only about half those observed for the *cis* isomer. The $n_N \rightarrow \sigma^*_{C3\text{-}O4}$ transmission also seems to be sensitive to substituent X, but to an essentially smaller extent than above. It has been shown by Neuvonen *et al.* that an increase in the contribution of $n_N \rightarrow \sigma^*_{C3\text{-}O4}$ donation facilitates the ring opening in ring-chain tautomerism.[49]



Scheme 22

Influences of the substituents on the ^{13}C NMR chemical shifts of compounds 48-54

The ^{13}C NMR chemical shift changes induced by phenyl substituents (SCS) on C-2 have been analysed by several different dual substituent parameter approaches.[49,57-63] The best correlation was obtained with the equation $SCS = \rho_F \sigma_F + \rho_R \sigma_R$.[54] For all the studied 1,3-heterocyclic systems, negative ρ_F values were observed, indicating reverse behaviour of the electron density on C-2.[49]

To check the previous hypothesis, the chemical shifts of C-1 and C-3 were measured in $CDCl_3$. Chemical shift changes induced by an aryl substituent (SCS) for a given compound were calculated as the differences in ^{13}C chemical shift for the substituted relative to the unsubstituted (X = H, Y = H) compound.

$$SCS = \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho_F^X \sigma_F^X + \rho_R^X \sigma_R^X \qquad \text{(Eq. 4)}$$

The multiple regression analysis data obtained via Eq. 4 for C-1 and C-3 are presented in Table 9.

Table 9. Multiple linear regression analysis of chemical shifts for **48-54** according to Eq. 4

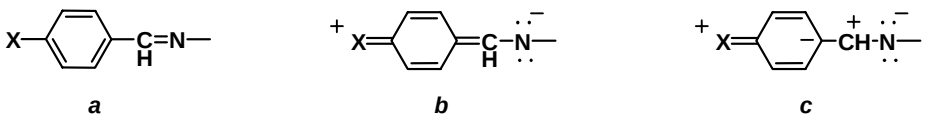
		ρ_F^Y	ρ_R^Y	ρ_F^X	ρ_R^X	r
For C-1	**A**	-1.81	–[a]	–[a]	0.45	0.967
	B	-1.12	0.75	–[a]	–[a]	0.982
	C	-1.51	0.60	-0.49	–[a]	0.983
For C-3	**A**	1.74	2.31	-2.96	–[a]	0.977
	B	–[a]	0.44	-1.56	-0.56	0.968
	C	-0.53	-0.30	-1.88	-0.44	0.987

[a] Insignificant (significance value > 0.05)

The *trans* isomers **B** exhibit low-field (*i.e.* high-frequency) C-1 ^{13}C NMR chemical shifts as compared with those of the *cis* isomers **C**, ΔSCS being about 3 ppm. The values of ρ_F^Y and ρ_R^Y for C-1 seem to depend on the configuration. The *trans* isomers exhibit somewhat less negative ρ_F^Y values, but slightly more positive ρ_R^Y values. Thus, the sensitivity to the inductive effect is somewhat stronger within the *cis* series. It was shown above that the sensitivity to the anomeric effect was larger in the *trans* series.

The anomeric effect can explain the differences in sensitivity of the ^{13}C NMR chemical shifts of C-1 to substituent Y between the *trans* and the *cis* series. A significant $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation was observed in the *trans* series, but not in the *cis* series. The valence bond representation of the anomeric effect is the double bond – no-bond resonance structure (Scheme 23). For the *trans* isomers, the resonance structure ***e*** and therefore the sp^2 character of C-1 are more prominent as compared with those for the *cis* isomers. Typically, the sp^2 hybridized carbons exhibit lower-field ^{13}C NMR chemical shifts than those of the sp^3 hybridized carbons. Therefore, the *trans* series exhibit low-field C-1 shifts. If a substituent-dependent stereoelectronic effect $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ is present in the *trans* form, the absolute value of ρ_F^Y has to be decreased because the phenyl substituents cause an opposite dependence in the carbon chemical shifts. Since EW substituents stabilize resonance form ***e***, the sp^2 character of C-1 is increased. As a consequence, a less negative ρ_F^Y value is observed. Unexpectedly, both the *trans* and *cis* isomers exhibit positive ρ_R^Y values. Instead, they give negative ρ_R^X values, analogously as observed earlier for 1,3-*O*,*N*-heterocycles. ρ_R values are measures of prevailing resonance interactions. In principle, there are two possible mechanisms for the resonance interaction of a side-chain-substituted benzene derivative (a C=N double bond as an example). Direct (normal)

resonance is based on an interaction of type ***b***. A resonance-induced polar effect, which is indirect resonance, is based on an interaction of type ***c***.



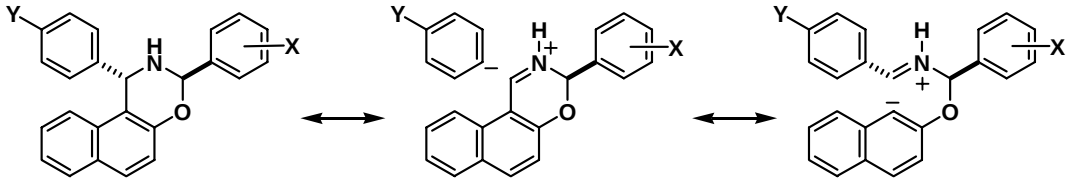
a ***b*** ***c***

mechanism of direct resonance

mechanism of resonance-induced polar effect

In direct resonance, ED substituents increase the electron density at the probe site (C-1) resulting in upfield ^{13}C NMR chemical shifts (*i.e.* smaller shift values) and consequently in $\rho_R > 0$. In contrast, in resonance-induced polar effects, ED substituents decrease the electron density at the probe site (C-1), resulting in $\rho_R < 0$. The observed positive ρ_R^Y values indicate the operation of direct resonance. This can be understood by the appearance of the double bond – no-bond structure ***f***, which is sensitive to resonance interaction and corresponding to $n_N \rightarrow \sigma^*_{C1\text{-}C10b'}$ donation (see above). In summary, the behaviour of the ^{13}C NMR chemical shifts of C-1 can be nicely explained on the basis of the anomeric effect directed on C-1.

The values of ρ_F^X and ρ_R^X for C-3 also seem to depend on the configuration. The *trans* isomers exhibit somewhat less negative ρ_F^X values but slightly more negative ρ_R^X values. Accordingly, the sensitivity to the inductive effect is again somewhat stronger for the *cis* series. For C-1, positive ρ_R^Y values were observed for both the *trans* and the *cis* forms (Table 9), whereas for C-3, negative ρ_R^X values were found for both series.



d ***e*** ***f***

Scheme 23

Table 9 reveals a reverse trend of the inductive substituent effects (*i.e.* ρ_F^Y for C-1 and ρ_F^X for C-3 < 0) for both the *cis* and the *trans* series. This behaviour means that the EW substituents induce upfield ^{13}C NMR chemical shifts as compared with those of the corresponding non-substituted derivative. This behaviour is contrary to the well-established idea of a generalized inductive effect, but its appearance is nowadays well documented for many different series of unsaturated side-chain derivatives of substituted benzene. The origin of the reverse trend of the substituent effect is qualitatively satisfactorily understood. On the other hand, the appearance of

the analogous effect with saturated carbon centres such as those situated between the two heteroatoms in 1,3-*O*,*N*-heterocycles has been much less well studied.[49] The *trans* and *cis* series of the present model compounds offer an interesting opportunity to study this type of reversed trend of substituent effect. The negative ρ_F values have been explained by Neuvonen *et al.* by the concept of the substituent-sensitive polarization of the N–C–O system.[49] The substituent interaction with the polar C–O and/or C–N bond results in dipolar induction, as depicted in Figure 5. In consequence, with EW substituents the electron density at the carbon joined to a heteroatom is increased, whereas with ED substituents it is decreased. The idea of substituent interaction with the polar bond (PSI = polar substituent interaction) is, like that of π-polarization, in conflict with the concept of the generalized inductive effect. Interestingly, the concept of PSI now seems to hold in connection with the polar (C-1)–N bonds in the title compounds.

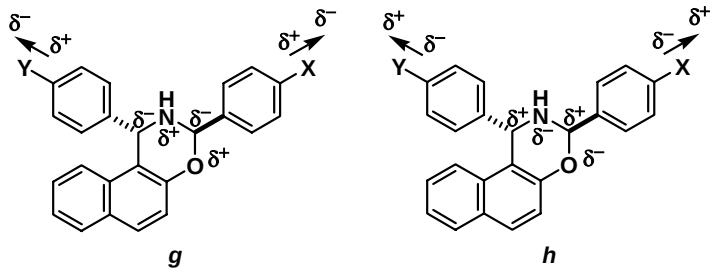
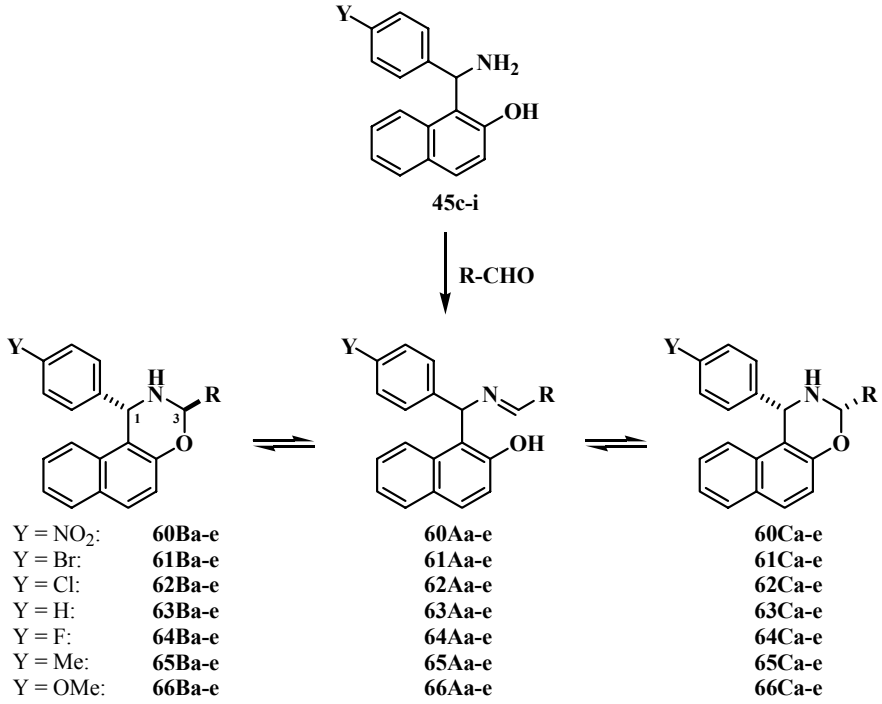


Figure 5. Polar substituent interactions in the *trans* form

Both the *cis* and the *trans* isomers exhibit negative ρ_R^X values, in harmony with the operation of a resonance-induced polar mechanism (***c***).[49]

3.2. Syntheses and ring-chain tautomerism of 3-alkyl-1-arylnaphth[1,2-e][1,3]oxazines

The ring-chain tautomeric ratio is determined by the free energy difference between the tautomeric forms. Therefore, the observed systematic change in log K can not be simply related to the energetic changes either in the ring form or in the chain form. To find evidence of the substituent effect in the ring form, the tautomeric system of 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **60-66** was analysed. Condensations of aminonaphthols **45c-i** with equivalent amounts of aliphatic aldehydes resulted in the naphthoxazine model compounds **60-66** (Scheme 24).



Y = NO_2:	**60Ba-e**	**60Aa-e**	**60Ca-e**
Y = Br:	**61Ba-e**	**61Aa-e**	**61Ca-e**
Y = Cl:	**62Ba-e**	**62Aa-e**	**62Ca-e**
Y = H:	**63Ba-e**	**63Aa-e**	**63Ca-e**
Y = F:	**64Ba-e**	**64Aa-e**	**64Ca-e**
Y = Me:	**65Ba-e**	**65Aa-e**	**65Ca-e**
Y = OMe:	**66Ba-e**	**66Aa-e**	**66Ca-e**

R = Me: **a**; Et: **b**; Pr: **c**; *i*Pr: **d**; *t*Bu: **e**

Scheme 24

The ^{1}H NMR spectra of **60-66** showed that, in $CDCl_3$ solution at 300 K, the members **a-e** of each set of compounds **60-66** participated in two-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** and **C**). The relative configurations of **B** and **C** were proved by using NOE measurements. In any set of compounds, chain forms (**A**) could not be detected. This is in accordance with the results of earlier studies on the condensation products of 2- or 3-aminoalkanols and aliphatic carbonyl compounds, in which branching of the chain in 2-alkyl substituents proved to stabilize the cyclic tautomers.[64]

The epimerization constants were calculated from the ratio of the ring forms (K_R = [**B**]/[**C**]). To find a linear equation to describe the influence of the alkyl substituents on log K_R, three different alkyl substituent parameters were studied: E_s (calculated from the hydrolysis or aminolysis[65] of esters) and two other steric parameters independent of any kinetic data: ν (derived from the van der Waals radii[66,67]) and V^a (the volume of the portion of the substituent that is within 0.3 nm of the reaction centre[68]). Good correlations were found with all three alkyl substituent parameters. The linear regression analysis data for series **60-66** are given in Table 10. As the best correlations were observed *vs* the Meyer parameters (V^a, Eq. 5), this was used for the further examinations (Figure 6).

Table 10. Linear regression analysis data with different alkyl substituent parameters for series **60-66**

Substituent parameter	Series	Intercept	Slope	Correlation coefficient
V^a	**60a-e**	0.63	8.62	0.922
	61a-e	0.40	9.82	0.963
	62a-e	0.62	7.58	0.957
	63a-e	0.54	6.36	0.966
	64a-e	0.51	8.39	0.987
	65a-e	0.51	7.42	0.904
	66a-e	0.53	7.61	0.898
E_s	**60a-e**	0.65	-0.24	-0.975
	61a-e	0.48	-0.24	-0.899
	62a-e	0.66	-0.19	-0.955
	63a-e	0.48	-0.24	-0.899
	64a-e	0.59	-0.19	-0.876
	65a-e	0.52	-0.20	-0.951
	66a-e	0.57	-0.19	-0.882
ν	**60a-e**	0.67	0.51	0.982
	61a-e	0.49	0.52	0.914
	62a-e	0.68	0.42	0.965
	63a-e	0.59	0.35	0.959
	64a-e	0.61	0.42	0.889
	65a-e	0.54	0.44	0.961
	66a-e	0.59	0.42	0.898

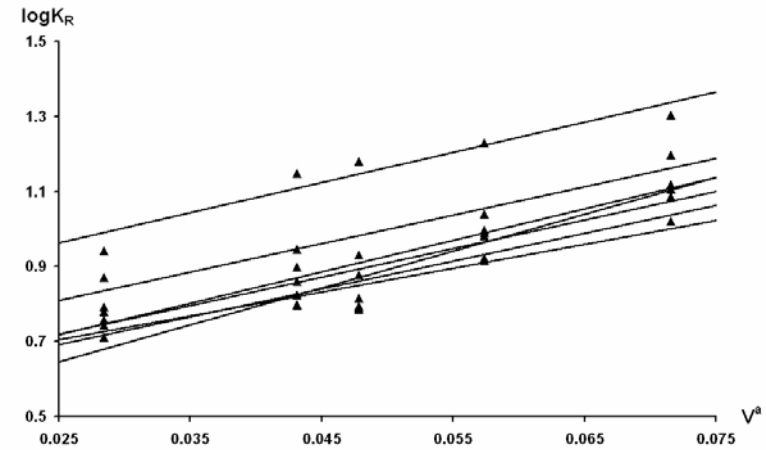


Figure 6. Plots of log K_R (in $CDCl_3$) for **60-66a-e** (▲) *vs* Meyer parameter V^a

$$\log K_R = 0.55 + 7.88V^a \qquad \text{(Eq. 5)}$$

To study the common influence of the aryl substituents at position 1 and the alkyl substituents at position 3, multiple linear regression analysis of log K_R as dependent variable was performed according to Eq. 6. The analysis results are listed in Table 7.

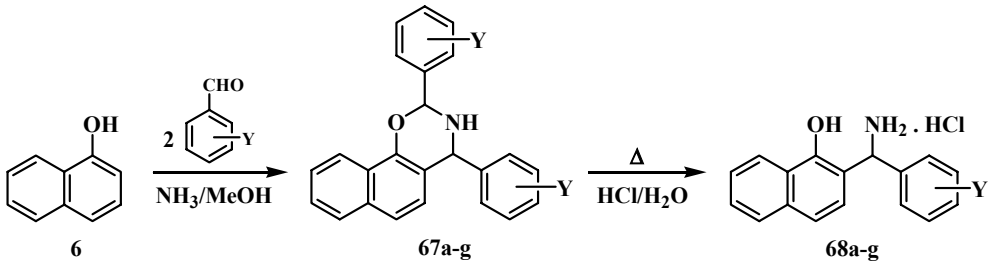
$$\log K_R = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho^R V^a \qquad \text{(Eq. 6)}$$

The significant dependence of log K_R on the inductive effect (σ_F) of substituent Y for **60-66**, together with the σ_F dependence of log K for **48-54**, led us to conclude that only the free energy of the *trans* forms is influenced by the inductive effect of substituent Y, which can be explained by the anomeric effect influenced quantitatively by Y. The ρ_F^Y value obtained via Eq. 6 is relatively close to that obtained according to Eq. 3 for the equilibrium *trans*⇌chain (**B**⇌**A**). This supports the validity of the ρ_F^Y values, indicating that these parameters reflect the pure contribution of Y.

3.3. Syntheses and ring-chain tautomerism of 2,4-diarylnaphth[2,1-e][1,3]oxazines

A further aim was to examine the applicability of Eq. 2 in the case of a new model system, the 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines, which are regioisomers of the previously studied model compounds **46-54**.

2-(α-Aminobenzyl)-1-naphthols, the starting materials for the synthesis of the target naphth[2,1-*e*][1,3]oxazine model compounds, were prepared in a manner similar to that for their regioisomeric 1-(α-aminobenzyl)-2-naphthol derivatives, by Betti aminoalkylation of 1-naphthol.[5] The condensation of 1-naphthol (**6**) and benzaldehyde or substituted benzaldehydes in the presence of ammonia, and subsequent acidic hydrolysis, furnished aminonaphthol hydrochlorides **68a-g** in moderate yields (Scheme 25). In consequence of the close analogy to 1-(α-aminobenzyl)-2-naphthols, which are known as "Betti bases", the regioisomeric compounds **68a-g** can be referred as to "reverse Betti bases".



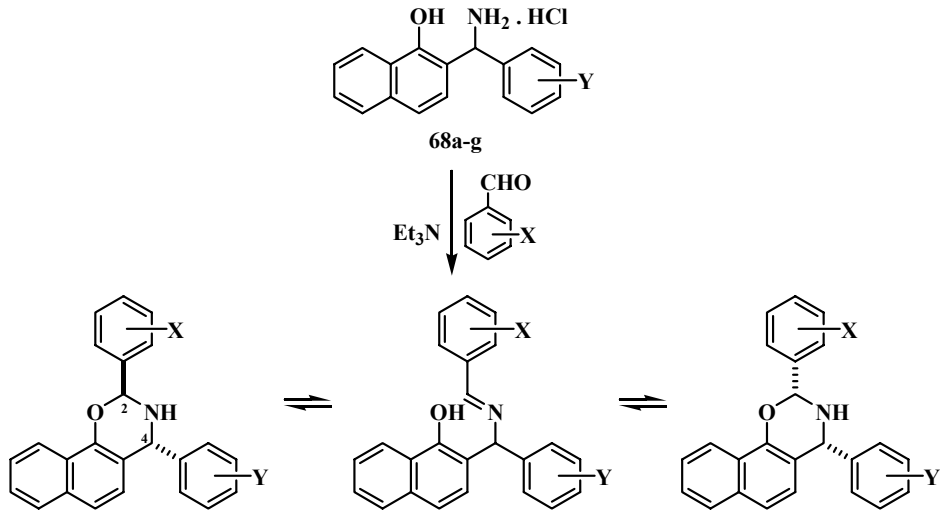
6 **67a-g** **68a-g**

Y = NO_2(*m*): **a**; Br(*m*): **b**; Br(*p*): **c**; Cl(*p*): **d**; H: **e**; Me(*p*): **f**; OMe(*p*): **g**

Scheme 25

In contrast with the regioisomeric 1-(α-aminobenzyl)-2-naphthols, which are relatively stable crystalline substances, the bases of **68a-g** proved to be quite unstable comnpounds, which were therefore liberated *in situ* in the further transformations. The naphthoxazine model compounds **69-75** were prepared by condensations of aminonaphthol hydrochlorides **68a-g** with equivalent amounts of aromatic aldehydes in the presence of Et_3N (Scheme 26). The ^1H NMR spectra of **69-75** proved that, in $CDCl_3$ solution at 300 K, the members **a-g** of each set of

compounds **69-75** formed three-component tautomeric mixtures, containing C-2 epimeric oxazines (**B** and **C**) besides the open-chain tautomer (**A**). Because of the very similar NMR spectroscopic characters of 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines **69-75**, the relative configurations of the *major* (**B**) and *minor* (**C**) ring-closed tautomers were determined and conformational analysis was performed only for compounds **70a** and **69g**. The NOESY spectra of compound **70a** proved that, similarly to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines, the *major* ring-closed tautomer contains the 2,4-diaryl substituents in the *trans* position (**B**). 2D spectroscopic analysis of **69g** revealed that the configuration of the azomethine double bond is *E*.

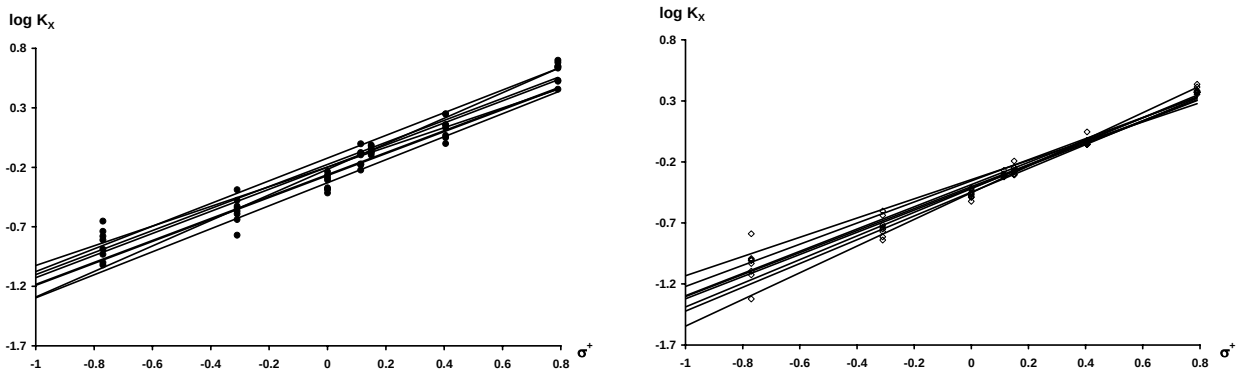


Y = NO_2(*m*):	**69Ba-g**	**69Aa-g**	**69Ca-g**
Y = Br(*m*):	**70Ba-g**	**70Aa-g**	**70Ca-g**
Y = Br(*p*):	**71Ba-g**	**71Aa-g**	**71Ca-g**
Y = Cl(*p*):	**72Ba-g**	**72Aa-g**	**72Ca-g**
Y = H:	**73Ba-g**	**73Aa-g**	**73Ca-g**
Y = Me(*p*):	**74Ba-g**	**74Aa-g**	**74Ca-g**
Y = OMe(*p*):	**75Ba-g**	**75Aa-g**	**75Ca-g**

X = NO_2(*p*): **a**; Br(*m*): **b**; Br(*p*): **c**; Cl(*p*): **d**; H: **e**; Me(*p*): **f**; OMe(*p*): **g**

Scheme 26

The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) in the tautomeric equilibria of **69-75** (K_X) were determined by integration of the well-separated O-C*H*Ar-N (ring) and N=C*H*Ar (chain) proton singlets from the ^{1}H NMR spectra. When Eq. 1 was applied to the log K_X values, good linear correlations were obtained *vs* the Hammett-Brown parameter σ^+ of the substituent X on the 2-phenyl group for compounds **69-75** (Figure 7, Table 11).



a *b*

Figure 7. *a*: Plots of log K_X for **69-75B** (●) *vs* Hammett-Brown parameter σ^+.
b: Plots of log K_X for **69-75C** (□) *vs* Hammett-Brown parameter σ^+

For each series, the value of ρ was found to be positive, as is customary among 2-aryl-1,3-*O*,*N* heterocycles. The plots for the equilibria containing C-2 epimeric ring forms of **69-75** (**B-A** and **C-A**) proved to be practically parallel, which points to the fact that 2,4-diaryl substituents in the ring forms of 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines do not influence the value of ρ (Table 11).

Table 11. Linear regression data on compounds **69-75** and the oxazines **51**, **57** and **58**

Equilibrium	No. of points	Slope (ρ)	Intercept	Correlation coefficient	c_s [b]
69A ⇌ 69B	7	0.95	-0.12	0.992	0.03
69A ⇌ 69C	7	0.97	-0.45	0.994	-0.30
70A ⇌ 70B	7	1.07	-0.22	0.997	-0.07
70A ⇌ 70C	7	1.09	-0.45	0.998	-0.30
71A ⇌ 71B	7	0.93	-0.18	0.977	-0.03
71A ⇌ 71C	7	0.91	-0.41	0.988	-0.26
72A ⇌ 72B	7	0.93	-0.20	0.981	-0.05
72A ⇌ 72C	7	0.91	-0.39	0.991	-0.24
73A ⇌ 73B	7	0.92	-0.27	0.981	-0.12
73A ⇌ 73C	7	0.90	-0.40	0.994	-0.25
74A ⇌ 74B	7	0.97	-0.33	0.984	-0.18
74A ⇌ 74C	7	0.97	-0.42	0.994	-0.27
75A ⇌ 75B	7	0.92	-0.26	0.991	-0.11
75A ⇌ 75C	7	0.86	-0.36	0.994	-0.21
57A ⇌ 57B[b]	7	0.74	-0.15	0.984	–
58A ⇌ 58B[b]	7	0.82	-0.66	0.995	-0.51
51A ⇌ 51B	7	1.05	0.51	0.986	0.66
51A ⇌ 51C	6	0.98	-0.35	0.983	-0.20

[a]Relative ring stability constant: see the text. [b]Data from ref. 9

Table 11 shows that an annelated naphthalene ring decreases the stability of the ring form; this was observed for all naphthoxazines having *trans* (**69-75B**: c_s = -0.18 – 0.03) or *cis* (**69-75C**: c_s = -0.30 – -0.21) diaryl substituents. The differences between the c_s values for the *trans* and *cis* series are smaller than that found for regioisomeric naphthoxazines (**51B**: c_s = 0.66, **51C**: c_s = -0.20), which can be explained by the less unfavourable steric arrangement of the diaryl substituents in **69-75**.

While the inductive effect of substituent Y (characterized by substituent parameter σ_F) was found to be significant as concerns the tautomeric equilibrium constant according to Eq. 2 for the 1,3-diaryl-substituted naphthoxazines **48-54**, our aim was to study the applicability of Eq. 2 for the present model compounds **71-75**. The significance level was taken as 0.05. The linear regression analysis of Eq. 2 in Table 12 shows that the *trans*⇌chain (**B**⇌**A**) equilibrium constants are significantly influenced by the inductive effect (σ_F) of substituent Y on the 4-phenyl ring. This means that for the *trans*⇌chain (**B**⇌**A**) equilibria the equilibrium constant can be described by applying a double substituent parameter treatment, and a plane can be fitted to the data points with data error r = 0.971 (Figure 8).

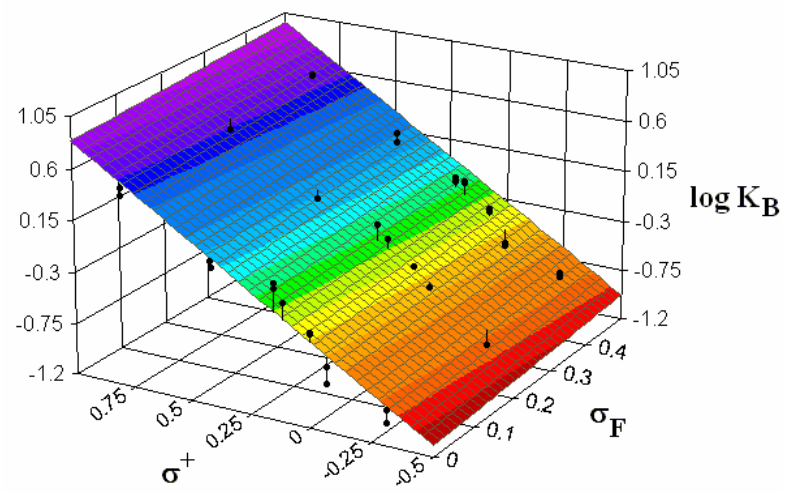


Figure 8. Plots of log K_B for **71-75B** (●) *vs* Hammett parameters σ^+ and σ_F

The double substituent dependence of log K for the *trans*-chain equilibria is related to the relative configurations of C-2 and C-4 and thereby the spatiality of the model compound. This observation is in accordance with the concept of the stereoelectronically mediated substituent effect.[50] The present results are in harmony with those found for the ring-chain tautomerism of 1,3-diarylnaphth[1,2-*e*][1,3]oxazines **48-54**. The positive value of ρ_F^Y (0.28) shows that aromatic ring substituents not attached to a phenyl ring situated between two heteroatoms can also have a systematic effect on the relative proportions of the ring tautomers. It can be concluded that equilibrium **B**⇌**A** seems to be somewhat more sensitive to both substituent X and substituent Y

than is equilibrium **C**⇌**A**. These substituent effects can be explained in terms of a stereoelectronic effect related to the relative configuration of C-4.

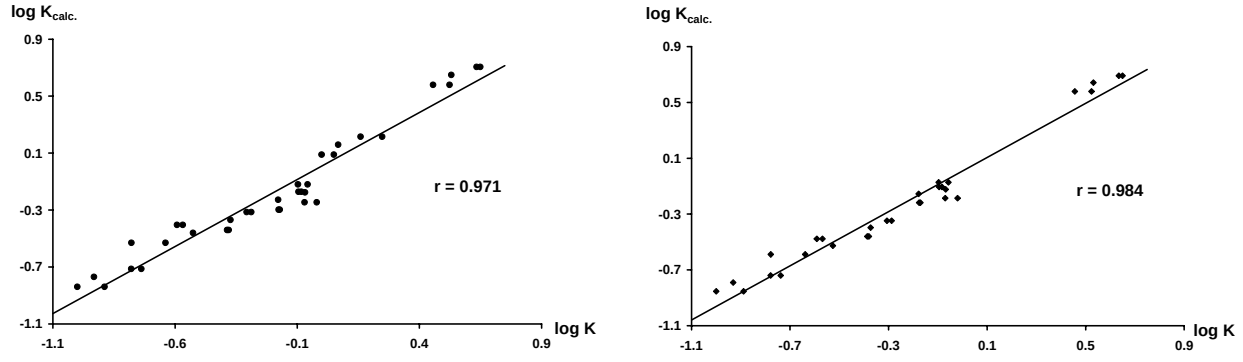
For a better understanding of the ring-chain tautomeric process, multiple linear regression analysis of Eq. 3 was performed (Table 12). Both ρ_F^X (inductive) and ρ_R^X (resonance) are positive, *i.e.* both the inductive and resonance effects of EW substituents increase the proportion of the ring form (*the normal behaviour of the substituent dependence of the ring-chain equilibria*).

Table 12. Multiple linear regression analysis of log K values for **71-75**

		k	ρ_F^Y	ρ_R^Y	ρ^X or ρ_F^X	ρ_R^X	r
Acc. to Eq. 2	**71-75A** ⇌ **71-75B**	-0.44	0.28	–[a]	1.29		0.971
	71-75A ⇌ **71-75C**	-0.58	–[a]	–[a]	1.27		0.965
Acc. to Eq. 3	**71-75A** ⇌ **71-75B**	-0.46	0.25	–[a]	1.15	1.62	0.984
	71-75A ⇌ **71-75C**	-0.58	–[a]	–[a]	1.05	1.66	0.976

[a] Insignificant (significance value > 0.05)

The validity of the parameters of Eqs 2 and 3 was checked by means of regression analysis of the log $K_{calc.}$ values (calculated by applying the parameters of Eq. 2 or 3) against log K determined from the ^{1}H NMR spectra (Figure 9).



a *b*

Figure 9. *a*: Plots of log $K_{calc.}$ (calculated by applying Eq. 2) *vs* log K (experimental) for **71-75B**. *b*: Plots of log $K_{calc.}$ (calculated by applying Eq. 3) *vs* log K (experimental) for **71-75B**

3.4. Transformations of α-aminobenzylnaphthol derivatives

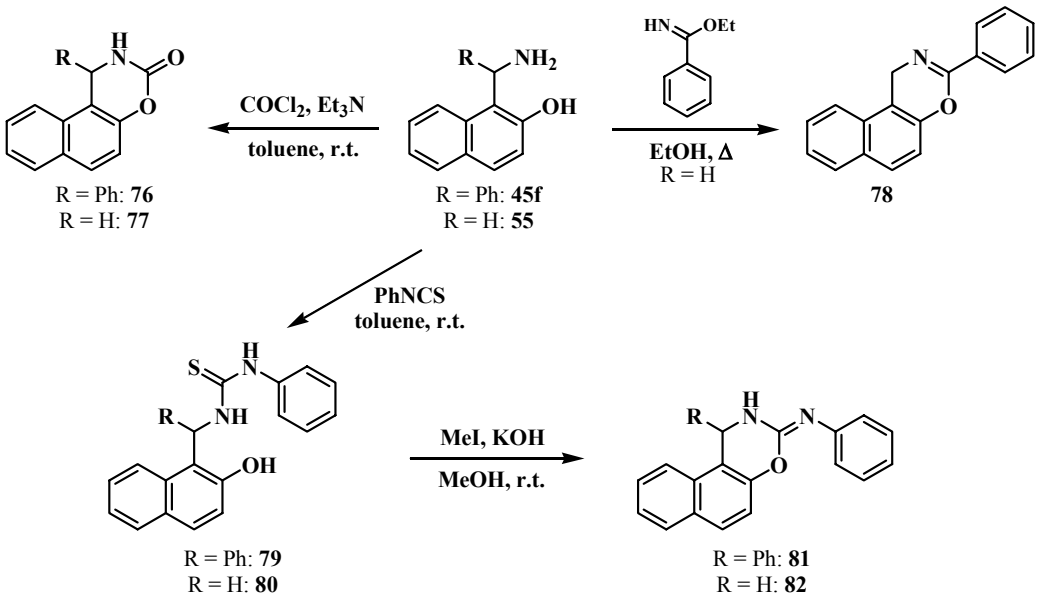
Application of the Betti base (**45f**) in the ring-closure reactions toward naphthalene-condensed heterocyclic derivatives has not been thoroughly investigated. The few publications that have appeared on this field focus on the reactions of **45f** with aldehydes.

In the first stage of the transformations of compounds **45f**, **55** and **68e** toward heterocyclic derivatives a one-carbon segment with sp^2 configuration was inserted between the hydroxy and amino groups.

When aminonaphthols **45f**, **55** and **68e** were treated with phosgene in the presence of Et_3N, the corresponding naphthalene-condensed 1,3-oxazin-2ones (**76**, **77** and **90**) were formed in each case (Schemes 27 and 30). The similar ring closures of the analogous 2-(aminomethyl)phenol were investigated recently.[69] The reactions of **45f**, **55** and **68e** with ethyl benzimidate in boiling EtOH gave the desired 1,3-oxazine derivative (**78**) only with the unsubstituted aminophenol **55**; for the phenyl-substituted regioisomers **45f** and **68e**, only decomposition of the starting aminonaphthols could be observed (Scheme 27). While the preparation of dihydro-1,3-oxazine derivatives by the ring closure of amino alcohols with imidates is well known in the literature,[70] compound **78** was the first aminophenol, for which this transformation was successfully accomplished.

For the preparation of 2-phenylimino-substituted 1,3-oxazines, aminonaphthols **45f**, **55** and **68e** were reacted with phenyl isothiocyanate. In the cases of 1-substituted 2-naphthols **45f** and **55**, the corresponding thiourea derivatives **79** and **80** were formed in good yields. Thioureas **79** and **80** were converted with methyl iodide to the corresponding *S*-methyl isothiourea derivatives, treatment of which with methanolic KOH gave the corresponding 2-arylimino-substituted 1,3-oxazines **81** and **82** via methyl mercaptan elimination (Scheme 27). While this type of ring closure is well known among *N*-thiocarbamoyl-substituted aminoalcohols,[71] as far as we are aware, compounds **81** and **82** are the first 2-arylimino-substituted 1,3-oxazine derivatives formed from *N*-thiocarbamoyl-substituted aminophenols in this way. Endocyclic-exocyclic tautomerism of the C=N bond was not investigated.

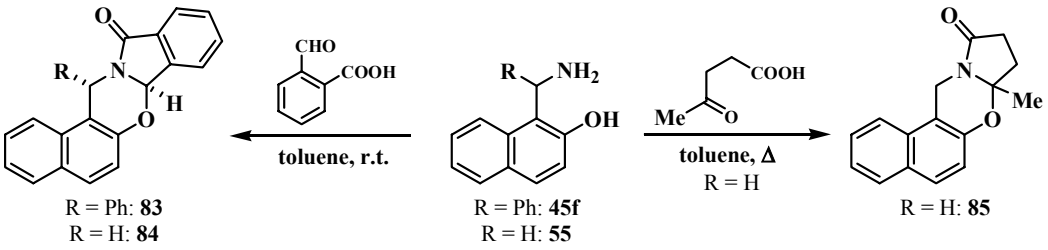
The ring closures of *N*-unsubstituted aminonaphthols **45f**, **55** and **68e** with oxo compounds (*i.e.* the insertion of a one-carbon segment with sp^3 configuration) result in naphthalene-condensed 1,3-oxazines with a ring-chain tautomeric character. If the oxo compound used in this reaction contains another functional group capable of reacting with the amino group of the naphthoxazine formed, the tautomeric equilibrium can be shifted completely toward the ring-closed form by this second ring closure, resulting in nitrogen-bridged heterocycles. This principle was successfully applied earlier in the domino ring-closure reactions of *N*-unsubstituted aminoalcohols or aminophenols with γ- or δ-oxoacids.[72,73]



Scheme 27

The reactions of aminonaphthols **45f**, **55** and **68e** with 2-carboxybenzaldehyde, performed under mild conditions (r.t.), gave the corresponding isoindole-condensed naphthoxazines **83**, **84** and **91** (Schemes 28 and 30). According to the NMR measurements, pentacycles **83** and **91** were formed with practically complete stereoselectivity, with the relative configuration depicted in the Schemes; no minor diastereomers could be detected even in the crude products. Similarly high diastereoselectivities are often observed in analogous ring closures of aminoalcohols and are explained as a result of the kinetic control governing the second ring closures of the cyclic tautomeric intermediates.[6,74]

The analogous reactions of compounds **45f**, **55** and **68e** with levulinic acid could not be accomplished under mild conditions; only the corresponding pyrrolonaphthoxazine (**85**) could be obtained in the case of the unsubstituted aminonaphthol **55** (Scheme 28). Elevated temperature again caused decomposition of aminonaphthols **45f** and **68e** instead of cyclization.

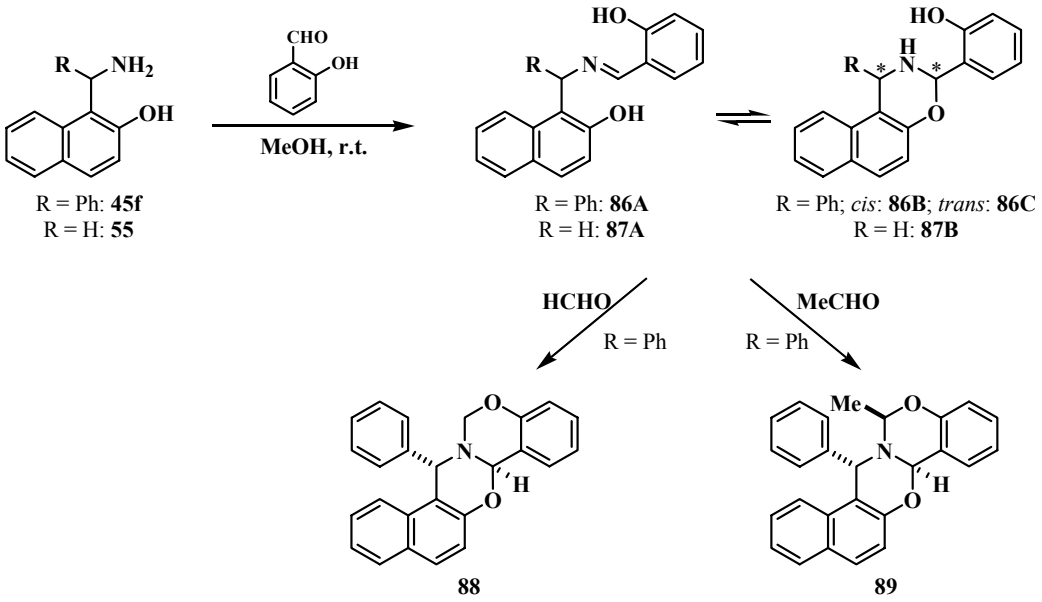


Scheme 28

A complete shift of the ring-chain tautomeric equilibrium of 1,3-*O*,*N*-heterocycles can be achieved by another transformation. If the oxo compound contains another functional group (*e.g.* OH) capable of coupling with the amino group of the ring-closed tautomers via an appropriate agent, this reaction can also be a second ring closure with another aldehyde. This type of

transformation was exploited earlier in the preparation of 1,3-*O*,*N*-heterocycle-condensed 1,3-oxazines by subsequent cyclization of aminoalcohols with salicylaldehyde and another aldehyde.[75-77]

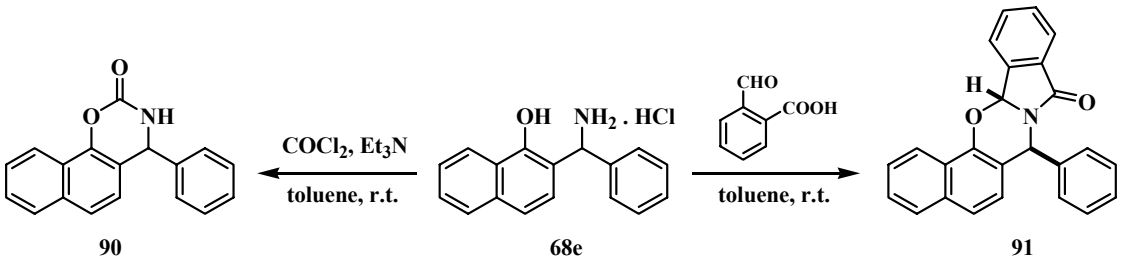
When aminonaphthols **45f** and **55** were reacted with salicylaldehyde, crystalline condensation products (**86**, **87**) were formed. The NMR measurements showed that the tautomeric equilibrium of **87** in $CDCl_3$ at 300 K was practically totally shifted toward the open form (**87A**), while the phenyl-substituted compound **86** was found to participate under similar conditions in a three-component tautomeric equilibrium involving the *trans* (**86B**: 56.7%) and the *cis* (**86C**: 8.5%) cyclic diastereomers besides the Schiff base (**86A**: 34.8%). These data are in accordance with earlier observations on the predominance of the open form in the tautomeric equilibria of the condensation products of 1,2- and 1,3-aminoalcohols and salicylaldehyde, which is explained by the stabilization due to the strong intramolecular hydrogen bonds.[75,76]



Scheme 29

Treatment of compound **86** with 40% formalin or ethanolic acetaldehyde solution resulted in the formation of phenyl-substituted naphthoxazinobenzoxazines **88** and **89** as crystalline products, whereas the similar transformations of **87** failed. The difference in cyclization behaviour between **86** and **87** can be explained on the basis of the better crystallization ability of the pentacyclic products (**88** and **89**) formed from **86**, which caused a continuous shift of the tautomeric equilibrium toward the predominant cyclic tautomer (**86B**).[75,76] In contrast, Stankevich *et al.* related the successful formation of oxazolobenzoxazines in analogous reactions to the increased proportion of the cyclic form in the tautomeric equilibria of the 2-(*o*-hydroxyphenyl)oxazolidine intermediates.[77] According to the NMR data, pentacycles **88** and **89**

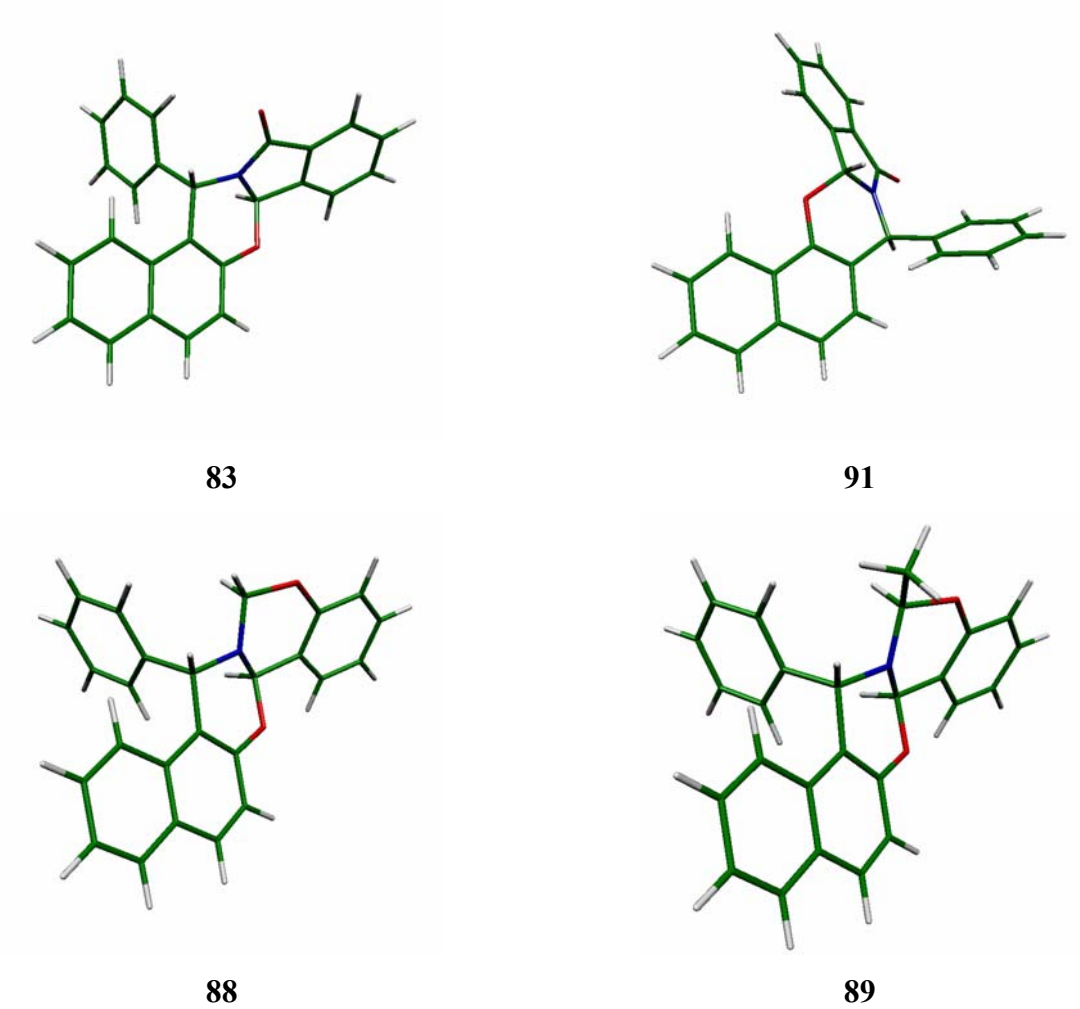
were formed with high stereoselectivity (de ~100%) with the relative configuration depicted in Scheme 29.



Scheme 30

The relative configurations of the diastereomer for **83**, **86**, **88**, **89** and **91** were deduced from the NOESY spectra, in which the cross-peak for the protons of the chiral C-atoms proves their *trans* arrangement for all the compounds.

The structures were also confirmed by molecular modelling. The conformational protocol comprised a stochastic search using the Merck Molecular Force Field (MMFF94) and a subsequent minimization of the resulting low-energy conformations at the *ab initio* level, using the HF/3-21G* basis set for all the compounds **83**, **86**, **88**, **89** and **91**. The resulting structures proved to be rigid, since no minor conformation was found within the 6 kcal/mol energy window. The final conformations for **83**, **88**, **89** and **91** are shown in Figure 10.



83 **91**

88 **89**

Figure 10. Final predominant minimum energy molecular structures for **83**, **88**, **89** and **91**, obtained by using *ab initio* HF/3-21G* calculations.

3.5. Methods

Details of the syntheses, physical and analytical data on the new compounds described in the thesis, and descriptions of the NMR spectroscopic analyses of the tautomeric equilibria can be found in the experimental sections of the enclosed publications.

4. SUMMARY

1. By using Betti's classical procedure (starting from 2-naphthol), 1-[α-amino(Y-substituted-benzyl)]-2-naphthols (**45a-i**) were prepared. The analogous transformation of 1-naphthol led to 2-[α-amino(Y-substituted-benzyl)]-1-naphthols (**68a-g**), which were isolated as hydrochloride salts.

2. The reactions of 1-[α-amino(Y-substituted-benzyl)]-2-naphthols (**45a-i**) and substituted benzaldehydes led to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**46-54**) which at 300 K in $CDCl_3$ proved to be three-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** > **C**) besides the open tautomer (**A**). The influence of aryl substituents at position 3 on the ring-chain tautomeric equilibria could be described by the Hammett equation.

3. In order to examine the influence of aryl substituents at positions 1 and 3 on the ring-chain equilibria of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**48-54**), multiple linear regression analysis of Eqs 2 and 3 was performed. The significant dependence of log K *vs* the inductive parameter σ_F^Y of substituent Y for the *trans*⇌chain (**B**⇌**A**) tautomeric equilibria was explained with the aid of the anomeric effect in the *trans* ring form. The multiple linear regression analysis of the chemical shifts of C-1 and C-3 for the *cis* and *trans* diastereomers revealed a significant dependence on σ_F^Y. The differences between the intercepts could be explained nicely in terms of the anomeric effect in the *trans* ring form. For a deeper examination of this phenomenon, the donation energies of the nitrogen lone pairs to vicinal antibonding orbitals were calculated by using NBO molecular modelling calculations. The calculations showed that the donation energy values are strongly influenced by the relative configuration of C-1 and C-3.

4. To find evidence of the substituent effect in the ring form, the tautomeric system of 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **60-66** was analysed. Condensations of aminonaphthols **45a-i** with equivalent amounts of aliphatic aldehydes resulted in the naphthoxazine model compounds **60-66**, which at 300 K in $CDCl_3$ proved to be two-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** > **C**). The

epimerization constant was calculated from the ratio of the diastereomers (K_R = [**B**]/[**C**]). The influence of alkyl substituents on log K_R could be described in terms of their Meyer parameters V[a]. The results of multiple linear regression analysis of the log K_R values reveal a significant dependence on the inductive effect of substituent Y (σ_F), which can improve the anomeric effect in the *trans* ring form.

5. The ring-closure reactions of aminonaphthols **68a-g** with equivalent amounts of aromatic aldehydes resulted in 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines (**69-75**), which in $CDCl_3$ at 300 K formed three-component tautomeric mixtures containing major (**B**) and minor (**C**) ring-closured epimeric forms beside the open chain form (**A**), and they proved to be good model compounds for study of the double substituent influence on the tautomeric eqilibria. Systematic quantitative investigations on the ring-chain tautomeric equilibria of 2,4-diarylnaphth[2,1-*e*][1,3]oxazines demonstrated an analogous inductive influence on the *trans*⇌chain (**B**⇌**A**) tautomeric equilibria.

6. By simple or domino ring-closure reactions of 1-(α-aminobenzyl)-2-naphthol (**45f**), 1-aminomethyl-2-naphthol (**55**) and 2-(α-aminobenzyl)-1-naphthol (**68e**) with phosgene, ethyl benzimidate, 2-carboxybenzaldehyde, levulinic acid, salicylaldehyde/formalin or salicylaldehyde/acetaldehyde, naphth[1,2-e][1,3]oxazine and naphth[2,1-e][1,3]oxazine derivatives were prepared. All of the nitrogen-bridged polycyclic derivatives of **45f** and **68e** with several centres of asymmetry were formed with nearly total diastereoselectivity. Considerable differences were found in the ring-closing abilities of the unsubstituted and phenyl-substituted aminonaphthols **45f** and **55** and the regioisomeric compounds **45f** and **68e**.

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ANNEX