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Syntheses, transformations and applications of aminonaphthol derivatives prepared via modified Mannich reactions

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Enantioselective transformations

Contents

1. Introduction

The Mannich reaction is one of the most frequently applied multicomponent reactions in organic chemistry.[1,2] In the original form of the reaction, the Mannich product is formed through the reaction of a C–H acid, formaldehyde and a secondary amine.

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A special alteration is the three-component modified Mannich reaction (mMR), in which formaldehyde is replaced by an aromatic aldehyde, the secondary amine by ammonia, and the C–H acid by an electron-rich aromatic compound such as 1- or 2-naphthol, quinolinol or isoquinolinol. Based on this, it can be interpreted as a formal Mannich reaction. Starting from ammonia, benzaldehyde, and 2-naphthol in this mMR, 100 years ago, Mario Betti reported the straightforward synthesis of 1,3-diphenylnaphthoxazine in methanol. Acidic hydrolysis of the ring compound produced led to 1-aminobenzyl-2-naphthol. The aminonaphthol product became known in the literature as a Betti base, and the protocol as the Betti reaction.[3–5] This reaction has subsequently been extended by using different *N* sources, the order and character of which (ammonia, amine or amide) greatly determine the reaction conditions and the method of isolation of the Mannich product.[6] On the other hand, the use of non-racemic amines has opened up a new area of application of enantiopure aminonaphthols as chiral catalysts in enantioselective transformations.[6]

The syntheses of a wide-ranging library of racemic and non-racemic Betti base derivatives were recently reviewed,[7] with special attention to their use as versatile *N*,*O* and *N*,*P* ligands for organometallic processes, and to the possibilities of their application as building blocks. With regard to the synthetic potential of this reaction, we consider that some additional aspects should now be surveyed. One of these is the application of amides or their derivatives as *N* sources in mMRs.[8–10] This can be interpreted as a further extension of this reaction, with a large number of publications. On the other hand, in consequence of the relatively low reactivity of the *N*-containing naphthol analogues, there are comparatively few examples of their transformations in mMRs.[11–13] Some relevant publications did appear earlier, but it seems that their promising biological activity has led to the chemistry of these compounds again becoming a hot topic.[14–16]

2. Modified Mannich reactions

This section will deal with the different variants of the mMR. The subsections are divided according to the amine source applied. Since the possible variations of the aldehyde component greatly increase the diversity of the topic, these modifications will be treated in the following sections and will not be discussed separately.

2.1. Syntheses with ammonia as N source

A new approach was published by the present authors, who successfully applied ammonium acetate and formate (as solid ammonia sources that are greener than methanolic ammonia solution) to prepare **3a**–**d** (Scheme 1) and **6a**–**h** (Scheme 2). The reaction mixtures contained 2-naphthol (**1**), 1-naphthol (**4a**) or their *N*-containing analogues (**4b**,**c**), an aromatic, heteroaromatic or aliphatic aldehyde and a solid ammonia source. Use of ammonium acetate or formate led to **2a**–**d** or **5a**–**h**, but their isolation required an aqueous work-up, which meant that the rapidity and one-pot handling of the reaction were lost. Similar results were obtained with several equivalents of ammonium carbamate (NH_4OOCNH_2), which yielded **3a**–**d** or **6a**–**h**.[17]

Through the use of salicylaldehyde, functionalized aminonaphthol analogue **3e** was prepared. The reaction was achieved through acidic hydrolysis of intermediate **2e** with TFA.[18]

Turgut et al. extended the series of aminonaphthols by using different aromatic aldehydes, but it should be noted that hydrolysis of the intermediate naphthoxazines (**2b**,**f**–**l**) was performed only in some cases (**3f**–**h**, Scheme 1).[19]

On the application of 1- or 2-naphthaldehyde in the mMR, aminonaphthols **3m** and **3n** were prepared by the acidic hydrolysis of the intermediates **2m** and **2n** (Scheme 1).[20] The reaction was extended to 1-naphthol, yielding **6i** and **6j** via **5i** and **5j** (Scheme 2).[20]

The present authors first applied aliphatic aldehydes in the mMR to obtain **3d**,**o**–**r**. In those experiments, naphthoxazines **2d**,**o**–**r** were formed by the condensation of 2-naphthol and the corresponding aliphatic aldehyde in the presence of methanolic ammonia at 60 °C. The acidic hydrolysis of **2d**,**o**–**r** led to the desired aminonaphthols **3d**,**o**–**r** in low yields in a two-step process. The overall yield was improved considerably when the residue of **2d**,**o**–**r** was directly hydrolysed with hydrochloric acid (Scheme 1).[21]

An improved method for the enantioseparation of racemic **3a** involved the in situ reaction of **2a** with L-(+)-tartaric acid in a ratio of 1:1. The products of this reaction were (*S*)-**3a** tartrate, the acetal of benzaldehyde and tartaric acid, and (+)-**2a**, which were easily separated by crystallization (Scheme 1).[22]

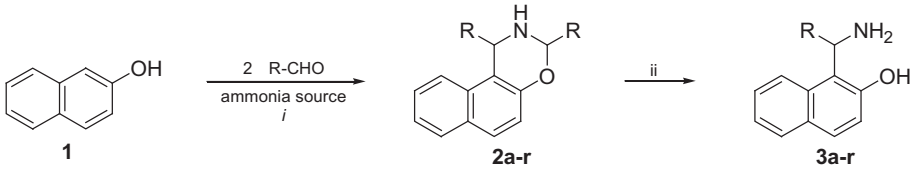
Harrison et al. recently reported the syntheses of 6-bromo-substituted aminonaphthol derivatives (**9a**–**n**) from 6-bromo-2-naphthol (**7**), methanolic ammonia and the corresponding aromatic aldehyde. The naphthoxazine intermediates **8a**–**n** were hydrolysed with hydrochloric acid to yield the desired aminonaphthol derivatives **9a**–**n** (Scheme 3).[23]

The one-pot procedure reported by Foroughifar et al. for the preparation of 4,9-dihydroxy-1,3-diaryl-2,3-dihydro-2-azaphenalenes **11a**–**m** from aromatic aldehydes, 2,7-naphthalenediol (**10**) and ammonia or two ammonium salts was optimized through the use of ammonium hydrogenphosphate in a mixture of ethanol–water under reflux conditions (Scheme 4).[24]

2.2. Syntheses with amines as N source

2.2.1. Syntheses from 2- or 1-naphthol derivatives. A simple microwave-assisted one-pot synthesis of **12** or **13** (Scheme 5) from 2-naphthol, the corresponding aldehydes and amines was carried out by Jha et al. under solvent-free conditions in the presence of *p*-TSA.[25] The yields were improved by the application of a non-ionic surfactant (Triton X-100) in water,[26] or by using basic nanocrystalline MgO as catalyst in an aqueous medium.[27]

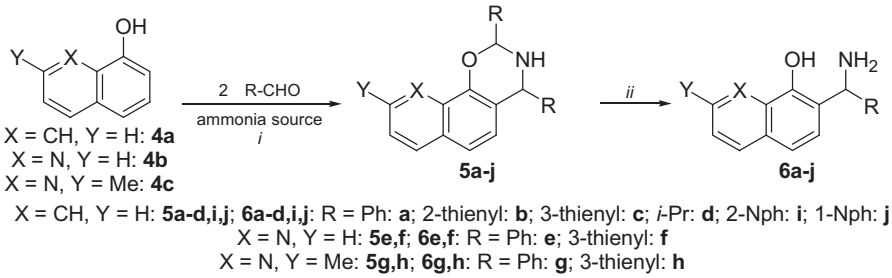
1-((2-Hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ol derivatives (**14a**–**j**) as novel selective oestrogen receptor modulators



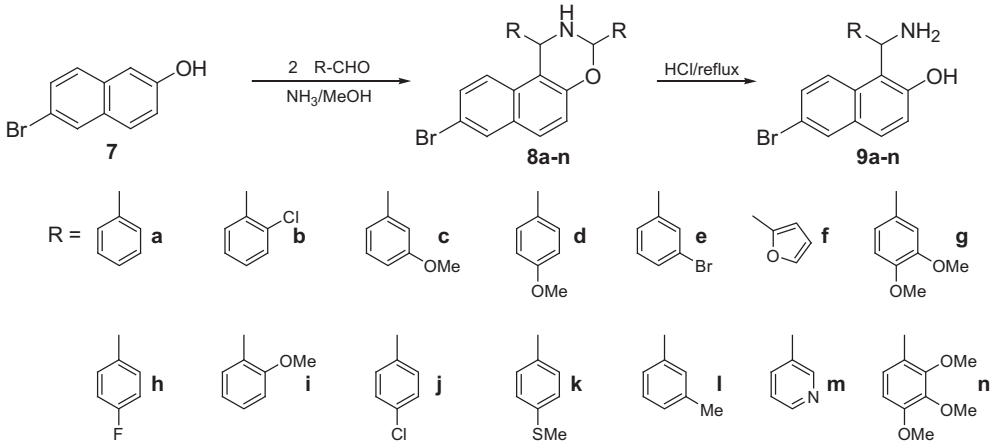
1 **2a-r** **3a-r**

R = Ph: **a**; 2-thienyl: **b**; 3-thienyl: **c**; *i*-Pr: **d**; 2-OH-C_6H_4: **e**; 3-OPh-C_6H_4: **f**; 3,4-di-OMe-C_6H_3: **g**; 3,4,5-tri-OMe-C_6H_2: **h**; 3-OH-C_6H_4: **i**; 3,4-di-Me-C_6H_3: **j**; 2-OH,5-Br-C_6H_3: **k**; 2-py: **l**; 1-Nph: **m**; 2-Nph: **n**; Me: **o**; Et: **p**; Pr: **q**; *t*-Bu: **r**

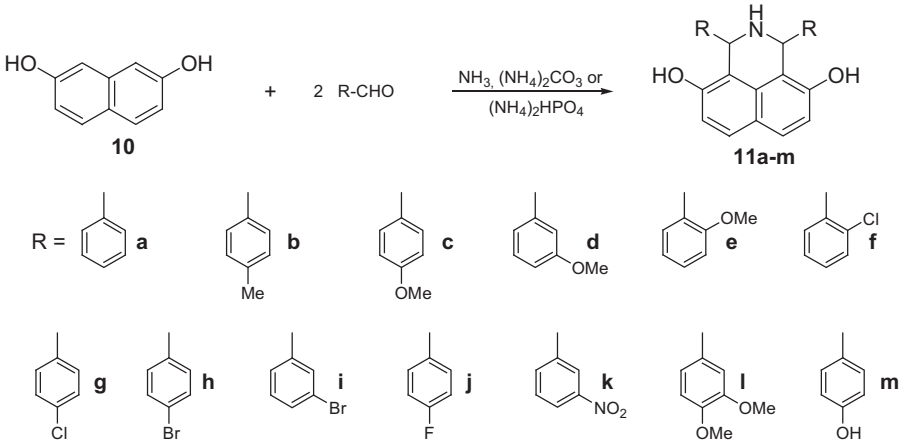
Scheme 1. Syntheses of 1-aminomethyl-2-naphthol derivatives **3**.



Scheme 2. Syntheses of 2-aminomethyl-1-naphthol or 7-aminomethyl-8-quinolinol derivatives **6**.



Scheme 3. Syntheses of 6-bromo-substituted aminonaphthol derivatives **9**.

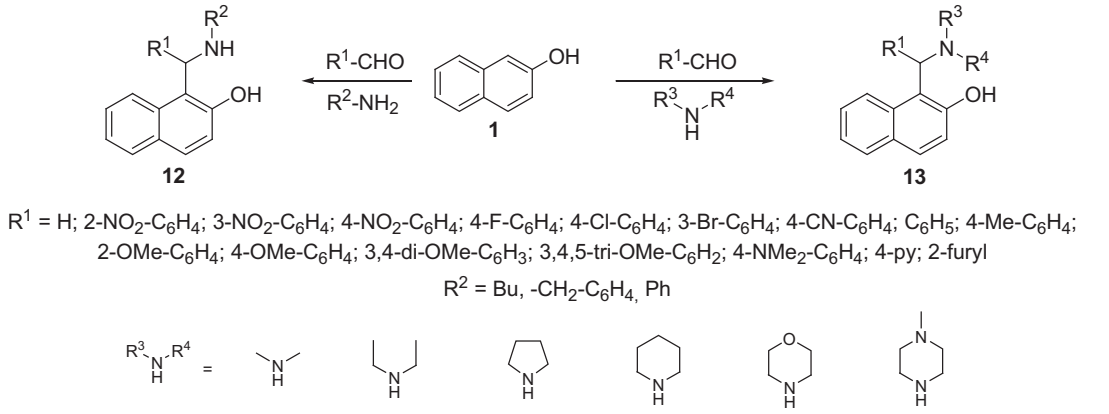


Scheme 4. Symmetric aminoalkylation of 2,7-naphthalenediol.

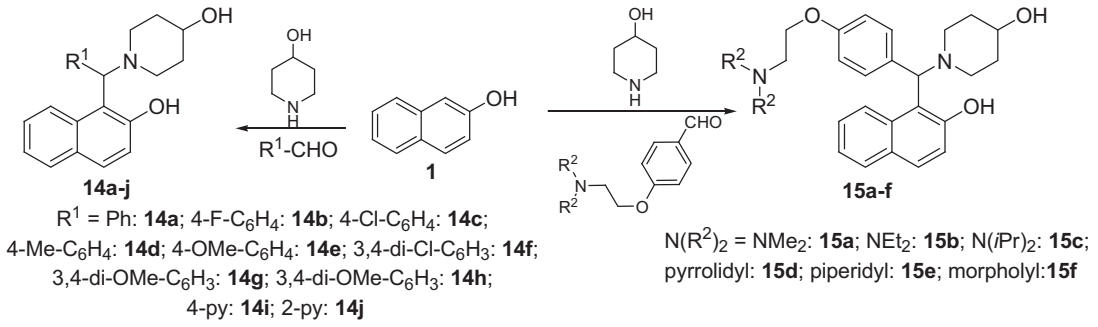
were designed and synthesized by Jha et al. via the mMR protocol from 2-naphthol (**1**), 4-piperidinol and 10 different aromatic aldehydes.[28] With the aim of a better biological effect, the structure of **14** was extended with different dialkylaminoethoxy substituents at position-4 of the aryl group (**15a**–**f**, Scheme 6).[29]

The syntheses of naphth[2,1-*e*][1,3]oxazines **16** or naphth[1,2-*e*][1,3]oxazines **17** from amine, 2 equiv of formalin and 1- or 2-naphthol with water as solvent were described by Nath et al.[30] The same reaction was achieved by Shingare et al. with $KAl(SO_4)_2 \cdot 12H_2O$ as a reusable, non-toxic inexpensive catalyst. It should be mentioned that, in this case, water was applied as solvent (Scheme 7).[31]

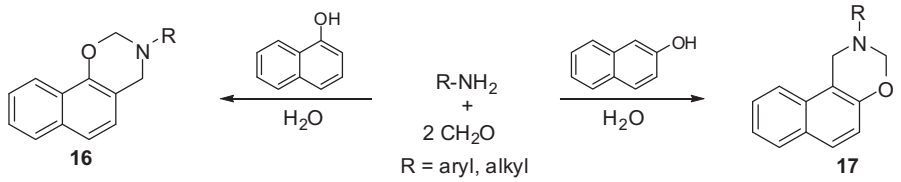
Technically, one of the most important areas of the chemistry of mMRs is the synthesis of enantiopure aminonaphthol derivatives and their application as chiral ligands. The syntheses and applications of these non-racemic aminonaphthols up to 2004 were reviewed earlier.[6] In spite of the excellent chiral induction of those aminonaphthols, only a few publications have subsequently appeared in this field. For instance, the insertion of a bulkier aromatic ring (e.g., naphthyl) at different positions proved successful. From 2-naphthol (**1**), 1-naphthaldehyde (**20a**) and (*R*)-(+)-α-methylbenzylamine (**19a**) or (*R*)-(+)-*N*-methyl-α-methylbenzylamine (**19b**), **21a** and **21b**, respectively (Table 1), have been prepared.[32] The bulkier naphthyl ring was inserted through the amine



Scheme 5. Syntheses of secondary (**12**) and tertiary (**13**) aminonaphthols.



Scheme 6. Syntheses of 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ol derivatives.



Scheme 7. Aminoalkylation of 1- and 2-naphthols with primary amines and formaldehyde.

moiety when 2-naphthol (**1**) was aminoalkylated by using benzaldehyde (**20c**) and (*R*)-(+)-1-(1-naphthyl)ethylamine (**19c**), (*R*)-(+)-*N*-methyl-1-(1-naphthyl)ethylamine (**19d**) or (*R*)-(+)-1-(2-naphthyl)ethylamine (**19e**), resulting in **21c**–**e** (Table 1), while **21c** and **21e** were also transformed into **22c** and **22e** through cyclization with formaldehyde, followed by reduction with $LiAlH_4$.[33]

A series of new tertiary aminonaphthol ligands with diverse substituted groups (**22f**–**q**) were prepared from 2-naphthol (**1**), (*S*)-(−)-α-methylbenzylamine (**19f**) and aldehydes (**20f**–**q**) via N-methylation of **21f**–**q** with formaldehyde followed by reduction with $NaBH_4$.[34]

The synthesis of enantiomerically pure naphthylglycinates (**21r**–**u**) was achieved by the reaction between naphthol derivatives (**1**, **4a** and **18**) and enantiopure α-imino glyoxylate formed from (*R*)-(+)-α-methylbenzylamine (**19r**) and ethyl glyoxylate (**20r**) (Table 1).[35]

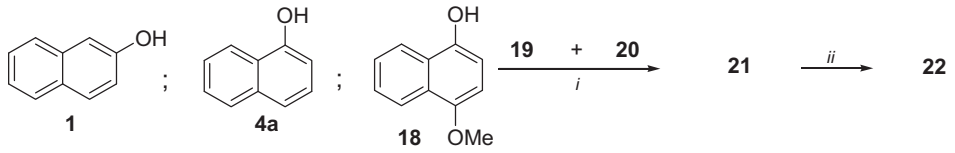
A recent approach in the mMRs involves insertion of a chiral group into the final product by using non-racemic aldehydes. In this field, Palmieri et al. reported the stereoselective synthesis of vicinal aminodiols (**26a**–**d**), diamines (**26e** and **26f**) and a diaminol (**26g**; Table 2) starting from amines **23**, non-racemic aldehydes (**24**) followed by removing the protecting groups of compounds **25**.[36]

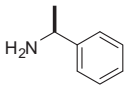
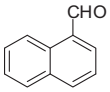
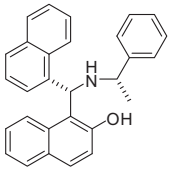
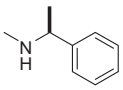
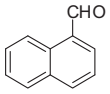
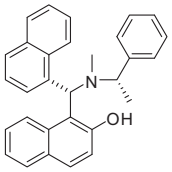
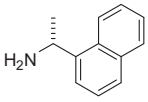
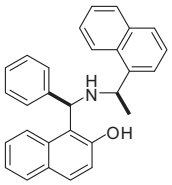
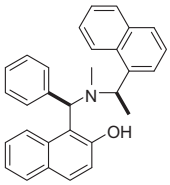
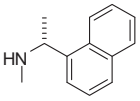
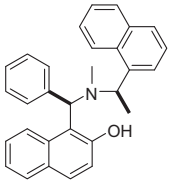
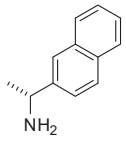
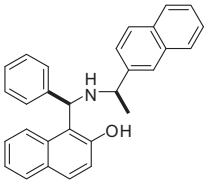
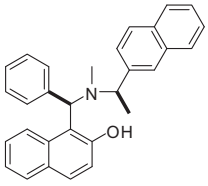
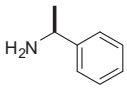
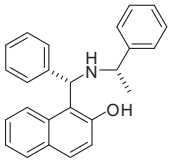
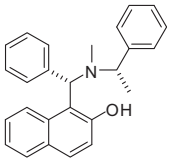
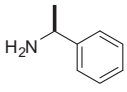
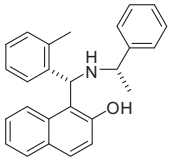
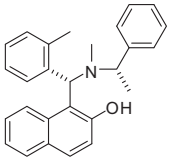
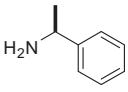
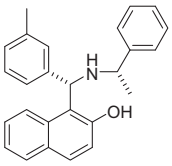
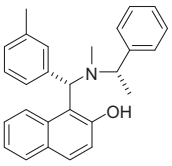
Diastereoselective syntheses of chiral 1,2-diaminoalkylnaphthols **27**–**29** from an amine, chiral α-*N*,*N*-dibenzylamino aldehyde and 1-or 2-naphthol were achieved by Rondot and Zhu.[37] The diastereoselectivity of the reaction was found to depend on the temperature, with a low reaction temperature (−20 °C) favouring formation of the *anti* adduct, and higher temperature (60 °C) mainly that of the *syn* isomer (Scheme 8).

Through mMRs, a series of new aminonaphthol derivatives (**30**, Scheme 9) were prepared from 2-naphthol, aromatic aldehydes and heteroaryl amines in water at room temperature. A study of the enantiomeric resolution of **30** with the aid of ^1H NMR spectroscopy and use of a chiral europium shift reagent was also presented.[38] The series of *N*-heteroaryl-substituted aminonaphthols was extended by using water as solvent[39] or solvent-free conditions.[40]

An efficient and environmentally friendly approach for the synthesis of 2′-aminobenzothiazolomethyl-2-naphthols (**32**) via the condensation of an aromatic aldehyde, 2-naphthol and 2-aminobenzothiazole (**31**) in water as solvent has been reported by Shaabani et al. (Scheme 10).[41]

Table 1
Syntheses of enantiopure aminonaphthols **21** and **22**



Compd	Amine (**19**)	Aldehyde (**20**)	*i*	**21**	*ii*	**22**	Ref.
a			Solvent-free, 85 °C, 72 h		—	—	32
b			Solvent-free, 85 °C, 72 h		—	—	32
c			Solvent-free, 65 °C, 72 h		1. CH_2O, rt 2. $LiAlH_4$, rt		33
d			Solvent-free, 65 °C, 72 h		—	—	33
e			Solvent-free, 65 °C, 72 h		1. CH_2O, rt 2. $LiAlH_4$, rt		33
f			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
g			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
h			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34

(*continued on next page*)

Table 1 (*continued*)

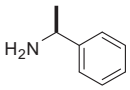
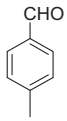
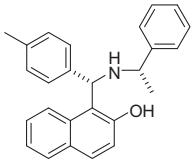
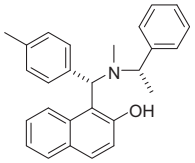
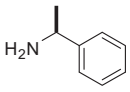
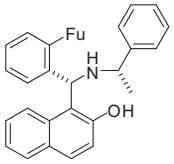
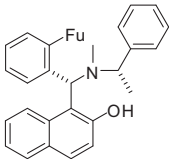
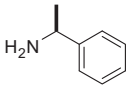
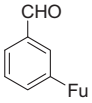
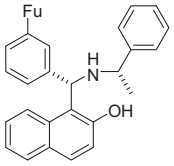
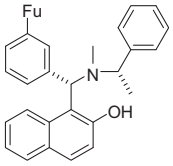
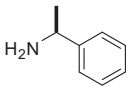
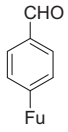
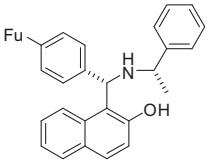
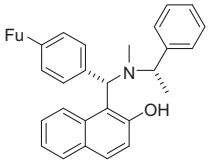
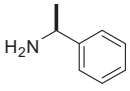
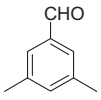
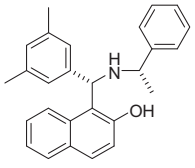
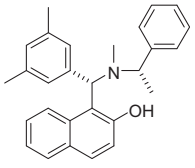
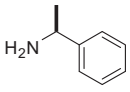
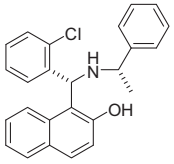
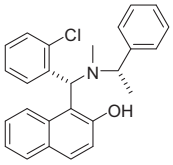
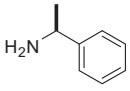
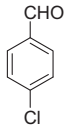
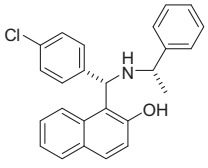
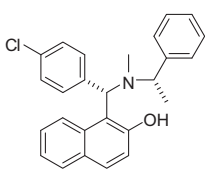
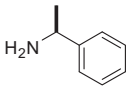
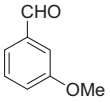
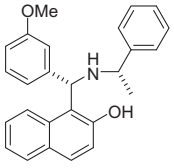
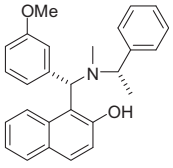
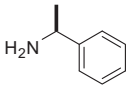
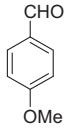
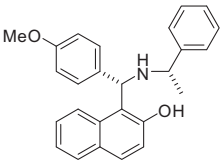
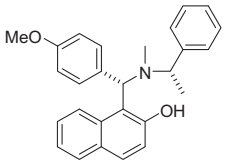
Compd	Amine (**19**)	Aldehyde (**20**)	*i*	**21**	*ii*	**22**	Ref.
i			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
j			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
k			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
l			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
m			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
n			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
o			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
p			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34
q			Solvent-free, 60 °C, 8–36 h		1. CH_2O, rt 2. $NaBH_4$, rt		34

Table 1 (*continued*)

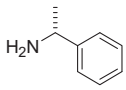
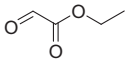
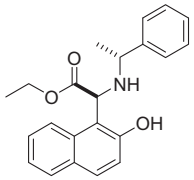
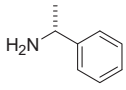
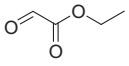
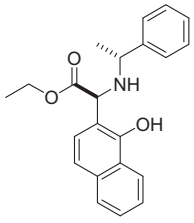
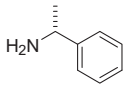
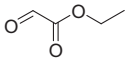
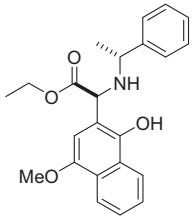
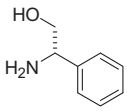
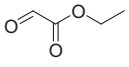
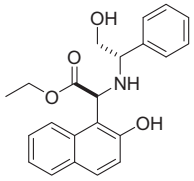
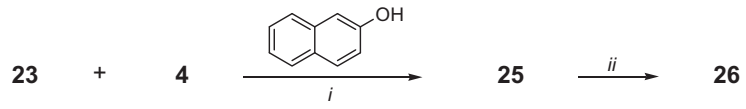
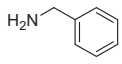
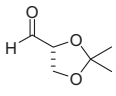
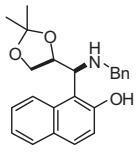
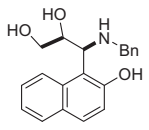
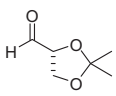
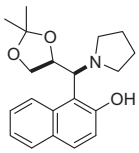
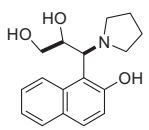
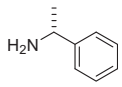
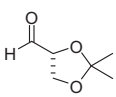
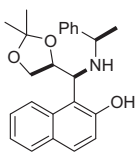
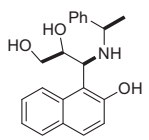
Compd	Amine (**19**)	Aldehyde (**20**)	*i*	**21**	*ii*	**22**	Ref.
r			Toluene, −15 °C, 3–10 h		—	—	35
s			Toluene, −15 °C, 3–10 h		—	—	35
t			Toluene, −15 °C, 3–10 h		—	—	35
u			Toluene, −15 °C, 3–10 h		—	—	35

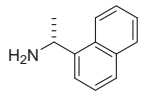
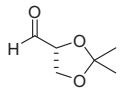
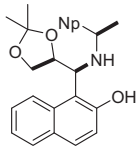
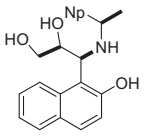
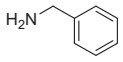
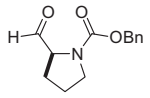
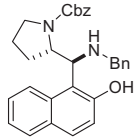
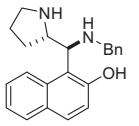
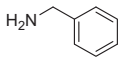
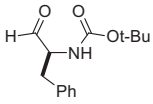
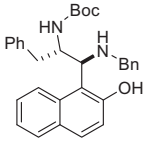
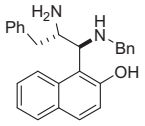
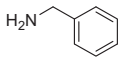
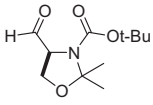
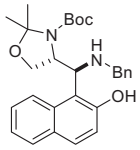
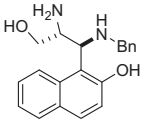
Table 2
Syntheses of aminodiols and diaminoalcohols **25** and **26**

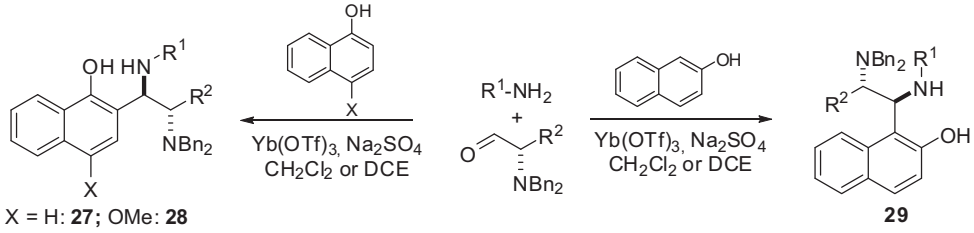


Compd.	Amine (**23**)	Aldehyde (**24**)	*i*	**25**	*ii*	**26**
a			Solvent-free, rt, 12–72 h		6 M HCl, THF, reflux, 2 h	
b			Solvent-free, rt, 12–72 h		6 M HCl, THF, reflux, 2 h	
c			Solvent-free, rt, 12–72 h		6 M HCl, THF, reflux, 2 h	

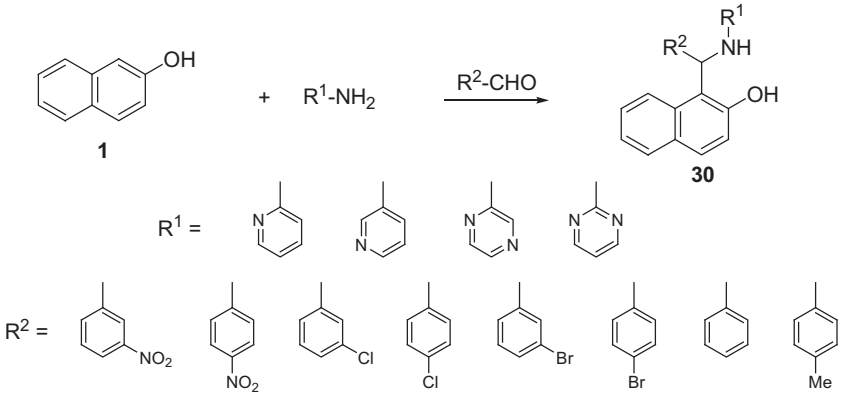
(*continued on next page*)

Table 2 (*continued*)

Compd.	Amine (**23**)	Aldehyde (**24**)	*i*	**25**	*ii*	**26**
d			Solvent-free, rt, 12–72 h		6 M HCl, THF, reflux, 2 h	
e			Solvent-free, rt, 12–72 h		6 M HCl, THF, reflux, 2 h	
f			Solvent-free, rt, 12–72 h		6 M HCl, THF, reflux, 2 h	
g			Solvent-free, rt, 12–72 h		6 M HCl, THF, reflux, 2 h	



Scheme 8. Syntheses of non-racemic diaminonaphthols **27**–**29**.

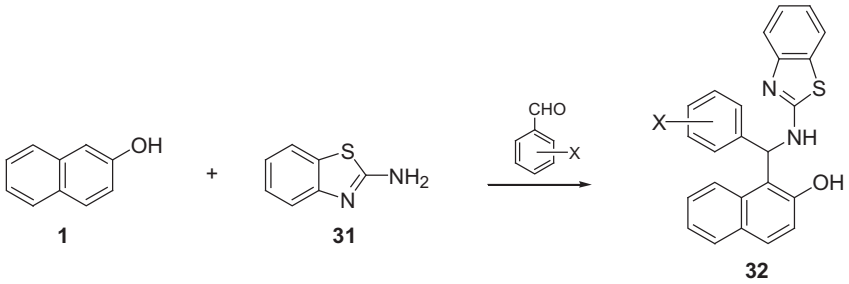


Scheme 9. Aminoalkylation of 2-naphthol with heteroaryl amines and aromatic aldehydes.

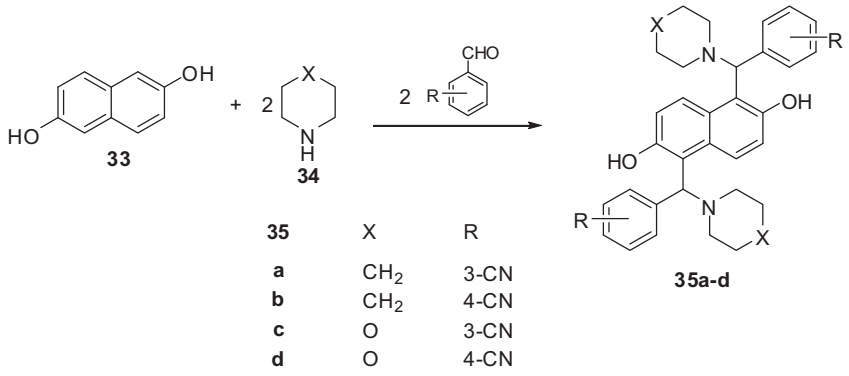
The preparation of novel bis-aminonaphthol derivatives is another new approach in the chemistry of the mMR. 2,6-Dihydroxynaphthalene (**33**) can be interpreted as an electron-rich aromatic system with two activated positions. When it was reacted with 2 equiv of aromatic aldehyde and 2 equiv of cyclic amine (piperidine or morpholine **34**), **35a**–**d** could be isolated (Scheme 11).[42]

Synthesis of the bis-product **36** was achieved from 2-naphthol, (*S*)-(−)-α-methylbenzylamine and *m*-phthalaldehyde,[43,44] and it was transformed into **37** by reaction with 2,6-bis-(chloromethyl) pyridine (Scheme 12).[45]

Jha et al. reported the syntheses of the bis-Mannich bases **38a**–**l** and **39a**,**b** of 2-naphthol, derived from aromatic aldehydes and

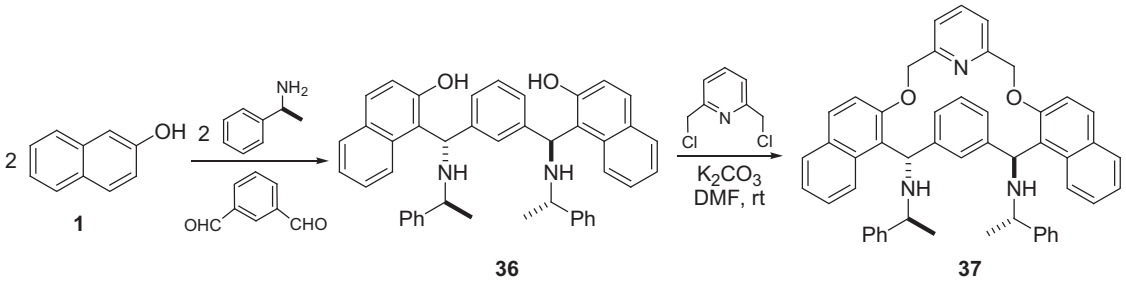


Scheme 10. Syntheses of 2′-aminobenzothiazolomethyl-2-naphthols **32**.



35	X	R
a	CH_2	3-CN
b	CH_2	4-CN
c	O	3-CN
d	O	4-CN

Scheme 11. Syntheses of bis-aminonaphthol derivatives **35**.



Scheme 12. Syntheses of enantiopure aminonaphthols **36** and **37**.

diamines such as piperazine and *N*,*N*′-dialkylethylenediamines. Although refluxing in ethanol provided products with higher purity, the use of microwave-assisted conditions was found to be the most efficient method of synthesizing these compounds in terms of atom economy, energy consumption and time required (Scheme 13).[46]

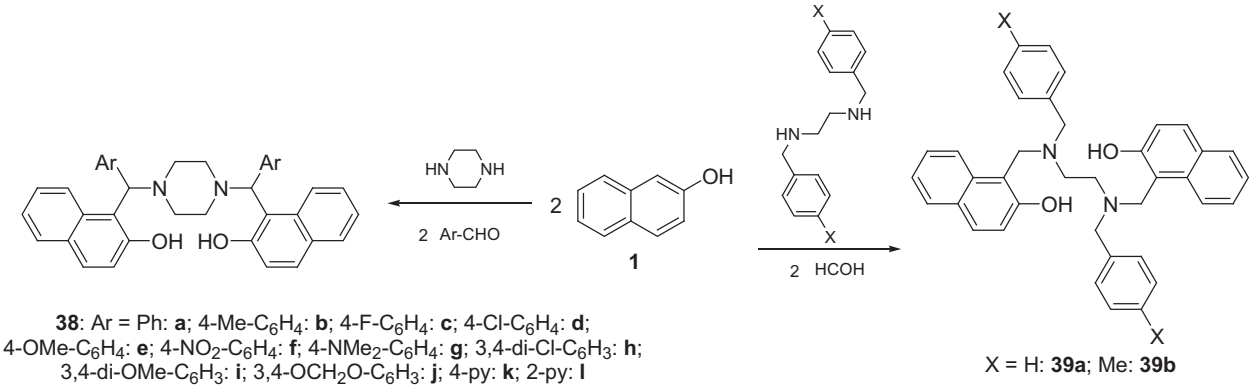
2.2.2. Syntheses from quinolinol or isoquinolinol derivatives. The reaction of **40** with dimethylamine in the presence of formaldehyde led to Mannich base **41** together with by-product **42**. The results and the analytical data indicated that the structure of **42** is 1,1′-dichloro-3,3′-methylenedi(4-isoquinolinol) (Scheme 14).[47]

On the use of primary amines with 2 equiv of formaldehyde, cyclization of the Mannich bases formed led to **43a** and **43b**.[47]

Möhrle and Miller applied an mMR to prepare **44a** (Scheme 15) from 8-quinolinol (**4b**), formaldehyde and piperidine as a cyclic secondary amine, or **44b** when formaldehyde was replaced by benzaldehyde.[48] 6-Isoquinolinol (**45**) was successfully aminoalkylated with the iminium salt of morpholine and benzaldehyde prepared in situ in the presence of lithium perchlorate in diethyl ether, yielding **46**.[49]

Electron-rich aromatic compounds such as 2-naphthol can be easily aminoalkylated with (*R*)-1-phenylethylamine (**47**) and benzaldehyde. The diastereoselectivity of the reaction has been explained in terms of an asymmetric transformation of the second kind induced by the preferential crystallization.[50] In comparison with 2-naphthol, the less reactive 8-quinolinol (**4b**) gave **48** in moderate yield (44%) and with poor dr (1.4). The reaction was performed under solvent-free conditions in which a mixture of 8-quinolinol, (*R*)-1-phenylethylamine and benzaldehyde in a molar ratio of 1.0:1.05:1.2 was stirred and heated at 60 °C for the time required, under an inert atmosphere (Scheme 16).[50]

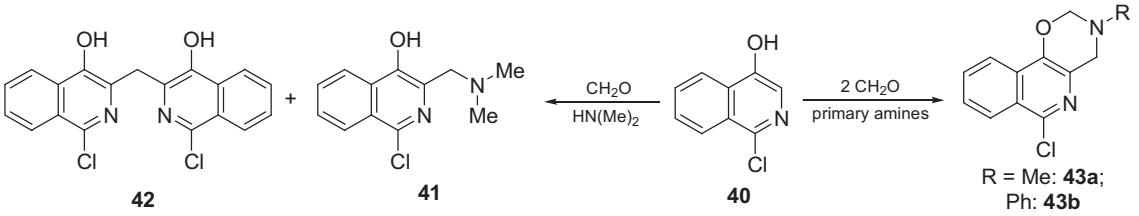
The mMRs of anilines, benzaldehydes and 8-quinolinols yielded 7-α-anilinobenzyl-8-quinolinols **50** (Scheme 17).[51–54] The simplicity of these three-component reactions led to the combination of aliphatic aldehydes and substituted anilines (**49**) to obtain 7-anilinoalkyl-8-



38: Ar = Ph: **a**; 4-Me-C_6H_4: **b**; 4-F-C_6H_4: **c**; 4-Cl-C_6H_4: **d**; 4-OMe-C_6H_4: **e**; 4-NO_2-C_6H_4: **f**; 4-NMe_2-C_6H_4: **g**; 3,4-di-Cl-C_6H_3: **h**; 3,4-di-OMe-C_6H_3: **i**; 3,4-OCH_2O-C_6H_3: **j**; 4-py: **k**; 2-py: **l**

X = H: **39a**; Me: **39b**

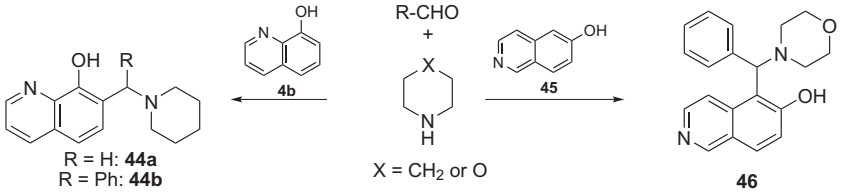
Scheme 13. Aminoalkylation of 2-naphthol with symmetric diamines and aldehydes.



42 **41** **40**

R = Me: **43a**;
Ph: **43b**

Scheme 14. Aminoalkylation of 1-chloro-4-isoquinolinol.

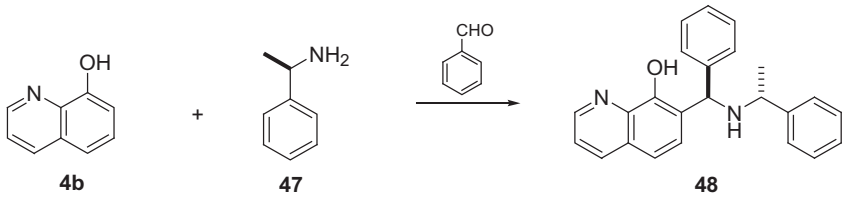


R = H: **44a**
R = Ph: **44b**

X = CH_2 or O

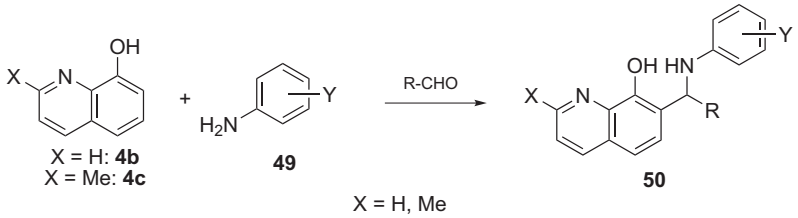
46

Scheme 15. Syntheses of tertiary aminoquinolinol and aminoisoquinolinol.



4b **47** **48**

Scheme 16. Synthesis of non-racemic aminoquinolinol **48**.



X = H: **4b**
X = Me: **4c**

49

50

X = H, Me

Y = H, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 3-Cl, 4-Cl, 3-F, 4-Cl,2-NO_2, 2-Me, 4-Me, 3-Et, 2-OMe, 4-OMe, 2-OEt, 4-OEt, 2-COOH, 2-COOEt, 4-COOH, 4-COO*n*Pr, 4-COO*n*Bu

R = $Me_3(CH_2)_5$-, $Me_3(CH_2)_2$-, Ph, 2-OH-C_6H_4, 3-OH-C_6H_4, 4-OMe-C_6H_4, 3-NO_2-C_6H_4, 4-*i*Pr-C_6H_4, 6-Br,3-OH-C_6H_3, 3-OMe,4-OH-C_6H_3, 5-Br,3-OMe,4-OH-C_6H_2, 2-furyl, 2-py

Scheme 17. Syntheses of 7-arylaminomethyl-substituted 8-quinolinol derivatives.

quinolinols.[53,55] The aminoalkylation was extended to the use of **4b** and **4c** as electron-rich aromatic compounds.[53,55–57]

Hamachi et al. carried out the addition of 8-quinolinol (**4b**) to the Schiff bases formed from 2-pyridinecarboxaldehyde and different substituted aniline derivatives. The procedure was very simple and involved an ethanolic solution of equivalent amounts of the Schiff base and 8-quinolinol being allowed to stand at room temperature, when the desired 7-substituted quinolinols were obtained in good-to-excellent yields.[58]

The series of anilines was extended with anthranilic acid and ethyl anthranilate,[54] or with a series of *p*-aminobenzoates (Scheme 17),[59] yielding the desired Mannich products **50**.

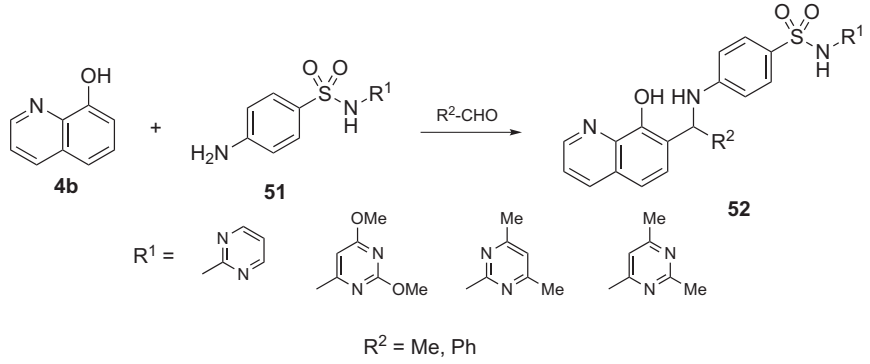
Sulphonamides **51** are special substituted aniline derivatives of established therapeutic importance. Their reactions with 8-quinolinol in the presence of acetaldehyde or benzaldehyde furnished 7-substituted-8-hydroxyquinolines (**52**) (Scheme 18).[60,61]

2.3. Aza-Friedel–Crafts reactions of naphthol derivatives with imines

The aza-Friedel–Crafts reactions of naphthol derivatives with different imines can be interpreted as a special variant of the mMR.

The enantioselective reactions of 2-naphthol or its 6-substituted derivatives and 1-naphthol or its 4-substituted derivatives with *N*-sulphonyl imines were recently achieved by catalysis with cinchona-derived compounds. The Mannich products obtained (**61** and **62**, Scheme 22) were isolated with good-to-excellent ee.[62,63]

The present authors reported the first syntheses of 1-(hydroxynaphthyl)-substituted 1,2,3,4-tetrahydroisoquinolines (**64a**–**c** and **65a**,**b**, Table 3), in which 1- or 2-naphthol was reacted with 3,4-dihydroisoquinolines (**63**) either in MeCN or under solvent-free conditions with microwave irradiation.[64] A Canadian research group later described the syntheses of some 1-(hydroxynaphthyl)-



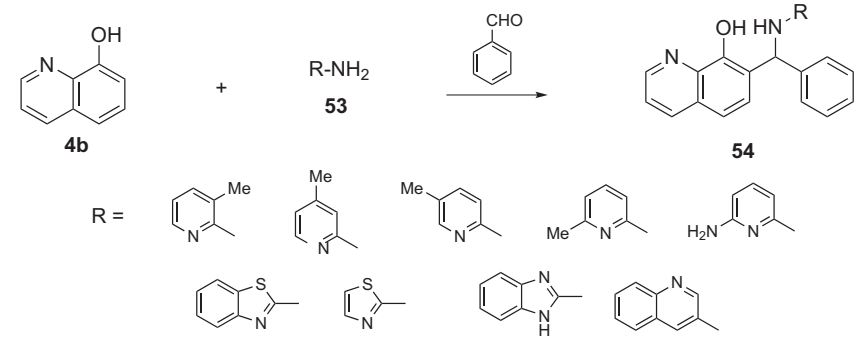
Scheme 18. Syntheses of 7-substituted 8-quinolinol derivatives containing a sulphonamide moiety.

The reaction of **4b**, benzaldehyde and aniline has been extended to heteroaromatic amines (**53**) such as 2-amino-3-methylpyridine, 2-amino-4-methylpyridine, 2-amino-5-methylpyridine, 2-amino-6-methylpyridine, 2,6-diaminopyridine, 2-aminobenzothiazole, 2-aminothiazole, 2-aminobenzimidazole and 3-aminoquinoline, leading to **54** (Scheme 19).[53] It is interesting to note that 2,6-diaminopyridine appeared to react at only one amino group.[11]

Shaabani et al. devised an efficient and environmentally friendly approach for the synthesis of 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines (Scheme 20, **56**) via the condensation of a substituted benzaldehyde, 6-quinolinol (**55**) and 2-aminobenzothiazole (**31**) in water as solvent. In the presence of ionic solutes such as LiCl, NaCl, $NaNO_3$, Na_2SO_4, $LiNO_3$ or Li_2SO_4, the yields of the reactions were improved.[41]

The reactions of **4b** with substituted oxazoles (**57**) and thiazoles (**58**) in the presence of benzaldehyde led to the Mannich bases **59** and **60**, as depicted in Scheme 21.[12]

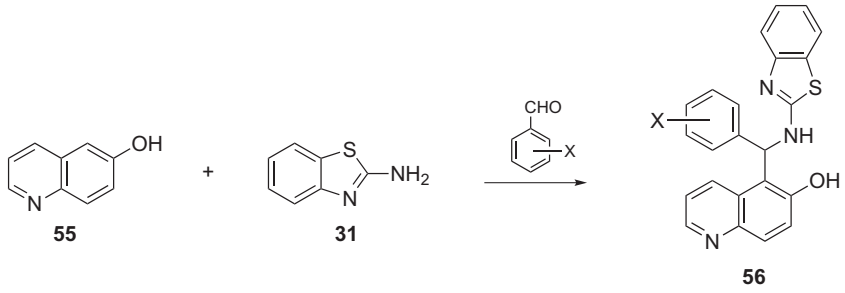
substituted 1,2,3,4-tetrahydroisoquinoline derivatives (**64a**,**d**–**n**) by the same route, but with some modifications.[65,66] Compounds **64o**–**t** were prepared in enantiomerically pure form from 2-naphthol analogues and (*R*)-3-phenyl-3,4-dihydroisoquinoline. The arrangement of the naphthyl and R^2 substituents in **64o**–**t** was found to be cis (Table 3).[67]



Scheme 19. Aminoalkylation of 8-quinolinol with primary amines and benzaldehyde.

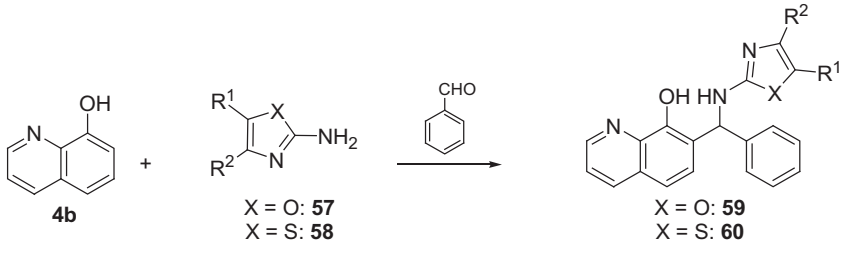
The solvent-free syntheses of 1-hydroxyquinolyl- and 1-hydroxyisoquinolyl-1,2,3,4-tetrahydroisoquinoline derivatives (**66** and **67**, Scheme 23) from *N*-containing 1-naphthol or 2-naphthol derivatives were achieved through 3,4-dihydroisoquinolines (**63**) using classical heating at 80–100 °C or microwave agitation at the same temperature. Both reaction conditions yielded the products in good yields (57–92%), but the use of microwave conditions allowed a decrease of the reaction time from 10–50 h to 1.5–3.5 h.[68]

The reaction has been extended by starting from five- and six-membered cyclic imines (**68a**, **68b**) and 1- or 2-naphthol analogues to give **69a**,**b** and **71a**,**b**, or from 3,4-dihydroisoquinoline



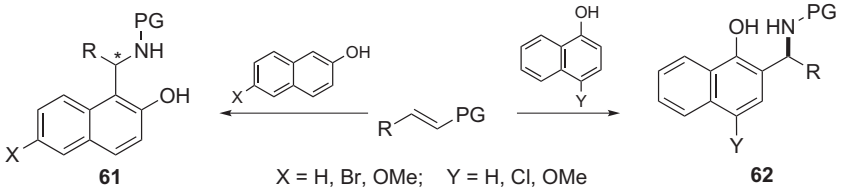
X = H, 4-Me, 4-OMe, 4-Cl, 4-Br, 3-OMe, 3-NO_2

Scheme 20. Aminoalkylation of 6-quinolinol with aminobenzothiazole and substituted benzaldehydes.



R^1 = H, Cl, Br;
R^2 = Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-OH-C_6H_4, 4-OMe-C_6H_4, 4-Me-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-Me-C_6H_4, 1-Nph, 2-Nph

Scheme 21. Syntheses of 7-substituted 8-quinolinol derivatives containing an oxazole or thiazole moiety.



X = H, Br, OMe; Y = H, Cl, OMe

PG = Ts, Bs, Boc

R = Ph, 2-F-C_6H_4, 4-F-C_6H_4, 2-Me-C_6H_4, 4-Me-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2-OMe-C_6H_4, 4-OMe-C_6H_4, 4-Br-C_6H_4, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2-Nph, furyl, *i*-Pr, Pr, *n*-Bu

Scheme 22. Syntheses of aminonaphthols **61** and **62** from naphthol analogues and imines.

(**68c**) and 4-methoxy-1-naphthol or 2-naphthol to give **70c** and **71c**, respectively (Scheme 24). The absolute configurations of **69a** and **69b** were ascertained by X-ray analysis and chiroptical methods (ECD) after resolution of the corresponding racemates with (*R*,*R*)-tartaric acid. Additionally, all the prepared racemic compounds (**69**–**71**) were transformed into their *N*-methylated derivatives (**72**–**74**) by using formaldehyde, followed by reduction with $NaBH_4$.[69]

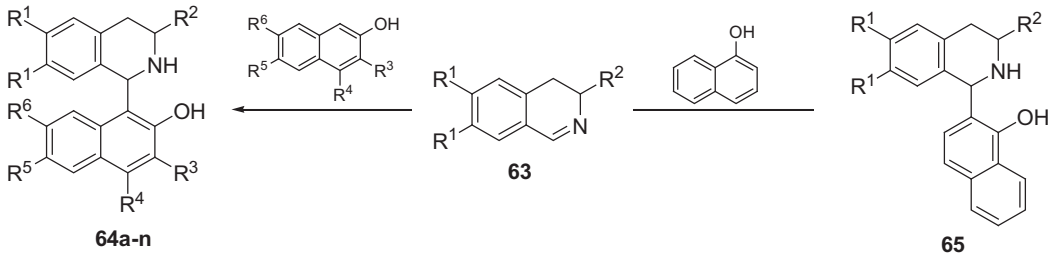
3. Applications of Mannich bases synthesized via mMRs

3.1. Transformations of aminonaphthol derivatives

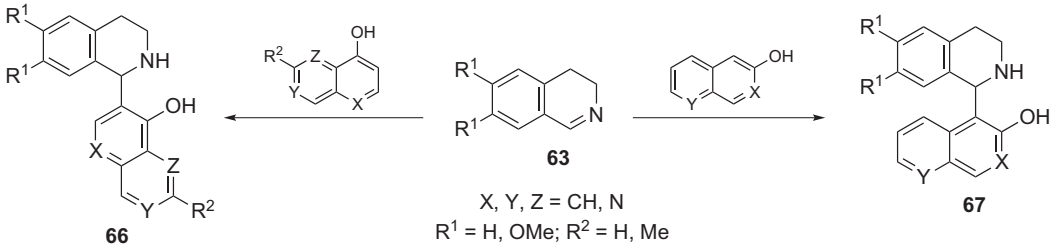
Thanks to the two or more functional groups present in the structures of the Mannich bases prepared via mMR (as presented in Section 2.2), such transformations have become a highly important field of application of these aminonaphthol derivatives.

The present authors condensed **3d**,**o**–**r** with substituted benzaldehydes with the aid of microwave irradiation to obtain 1-alkyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**75**(**a**–**g**)–**79**(**a**–**g**), Scheme 25), which proved to be three-component tautomeric mixtures in $CDCl_3$ at 300 K, involving C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**).[21] These compounds served as an excellent model system for further study of the influence of the double substituents on the tautomeric equilibria of disubstituted naphthoxazines. Quantitative investigations of the ring-chain tautomeric equilibria of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines have recently led to the first precise mathematical formulae with which to characterize the effects of substituents situated elsewhere than between the heteroatoms. It was demonstrated, for example, that the tautomeric ratio was influenced not only by the aryl substituent at position-3, but also by that at position-1. The additional stabilization effect was explained as an anomeric effect in the trans ring form.[70–72] The results of multiple linear regression analysis of the log K_R values of the tautomeric equilibria of 3-alkyl-1-aryl-2,3-

Table 3
Aza-Friedel–Crafts reaction between naphthols and dihydroisoquinolines



Products	R^1	R^2	R^3	R^4	R^5	R^6	Ref.
64a	H	H	H	H	H	H	64,65
64b	OMe	H	H	H	H	H	64
64c	OMe	Me	H	H	H	H	64
64d	H	H	H	H	OMe	H	65
64e	H	H	OMe	H	H	H	65
64f	H	H	H	H	H	OMe	65
64g	H	H	H	H	–COPh	H	65
64h	H	H	H	H	Br	H	65
64i	H	H	COOH	H	H	H	66
64j	H	H	CH_2OH	H	H	H	66
64k	H	H	OH	H	H	H	66
64l	H	H	H	H	H	OH	66
64m	H	H	H	OH	H	H	66
64n	H	H	H	H	H	H	66
(1*S*,3*R*)-**64o**	H	Ph	Ph	H	H	H	67
(1*S*,3*R*)-**64p**	H	Ph	4-OMe–C_6H_4	H	H	H	67
(1*S*,3*R*)-**64q**	H	Ph	3-OMe-C_6H_4	H	H	H	67
(1*S*,3*R*)-**64r**	H	Ph	3,5-Di-(*t*-Bu)–C_6H_3	H	H	H	67
(1*S*,3*R*)-**64s**	H	Ph	2-Nph	H	H	H	67
(1*S*,3*R*)-**64t**	H	Ph	CH_2OH	H	H	H	67
65a	H	H	H	H	H	H	64,65
65b	OMe	H	H	H	H	H	64



Scheme 23. Syntheses of 1-hydroxyquinolyl- and 1-hydroxyisoquinolyl-1,2,3,4-tetrahydroisoquinolines.

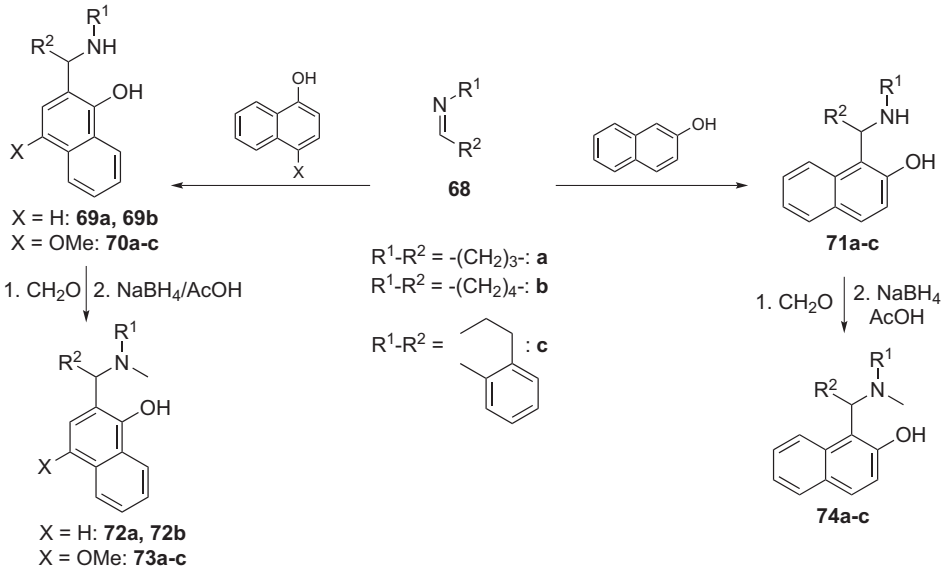
dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines revealed a significant dependence on the inductive effect of substituent Y (σ_F), which was further evidence of the anomeric effect in the trans ring form.[72] Systematic quantitative investigations of the ring-chain tautomeric equilibria of 2,4-diarylnaphth[2,1-*e*][1,3]oxazines demonstrated an analogous inductive influence on the ring^{trans}-chain tautomeric equilibria.[73]

For 1-alkyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**75**(**a**–**g**)–**79**(**a**–**g**), Scheme 25), the influence of the alkyl substituent at position-1 on the ring-chain tautomeric equilibria could be described by the Meyer parameter, and that of the aryl substituent at position-3 by the Hammett–Brown parameter (σ^+). The slopes of the Meyer parameter V^a for the trans and cis forms displayed a significant difference, which was explained in terms of an alkyl-substituent-controlled stereoelectronic effect in the trans ring form.[74]

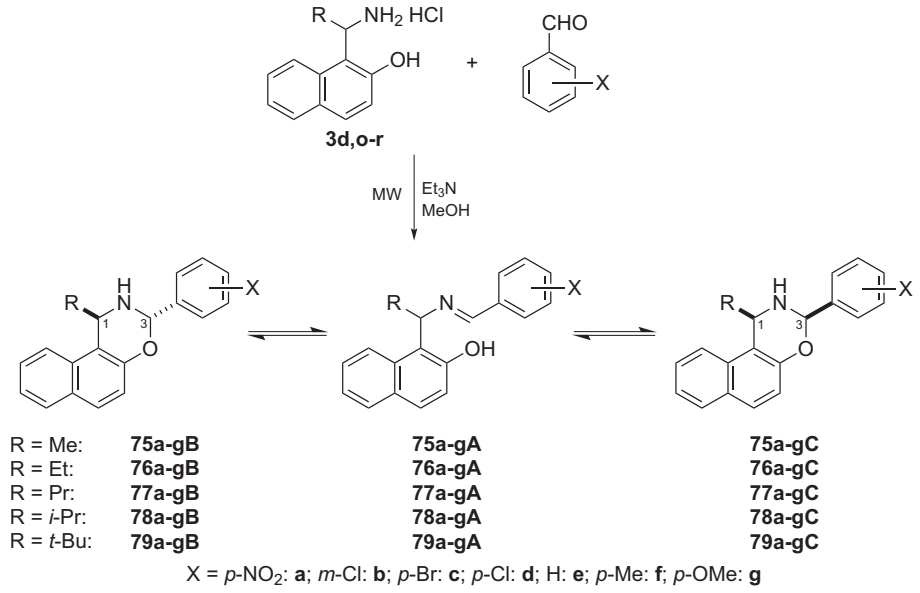
The highly functionalized aminonaphthol **3e** was converted into naphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazines (**80**, Scheme 26), which were subjected to conformational analysis by NMR spectroscopy and accompanying molecular modelling. In particular, quantitative anisotropic ring-current effects of the aromatic moieties and steric substituent effects were employed to determine the stereochemistry of the naphthoxazinobenzoxazine derivatives.[18]

A novel method for the synthesis of 1-substituted 2,2-dimethoxyethylamines (**83**) was introduced by Hu et al. The synthetic pathway involved the reaction of **3a** with an aqueous solution of 2,2-dimethoxyacetaldehyde to yield **81**, which was alkylated with Grignard reagents, followed by catalytic (Pd/C) hydrogenolysis of benzylamines **82**, to give the target products **83** directly (Scheme 26).[75]

Through the condensation of **3n**, **3o**, **6i** and **6j** with paraformaldehyde, 4-nitrobenzaldehyde, phosgene or 4-chlorophenyl isothiocyanate, naphthoxazine derivatives (**84**–**91**: Scheme 26 and **92**–**99**: Scheme 27) were synthesized. The conformation of the oxazine ring moiety was found to depend on the hybridization of the carbon at position-3 or-2. The compounds that contained an sp^3 carbon preferred a twisted-chair conformation, whereas the insertion of an sp^2 carbon led to a nearly flat naphthoxazine ring moiety.[20]



Scheme 24. Aza-Friedel–Crafts reactions between naphthol analogues and cyclic imines.



Scheme 25. Syntheses of 1-alkyl-3-arylnaphth[1,2-*e*][1,3]oxazines.

1-Aryl-*N*,*N*-dimethyl-1*H*-naphth[1,2-*e*][1,3]oxazine-3-amine derivatives (**101**, Scheme 28) were synthesized in the reactions of 2-naphthol, aromatic aldehydes and *N*,*N*,*N*′,*N*′-tetramethylguanidine through the intermediate **100**, under microwave irradiation.[76]

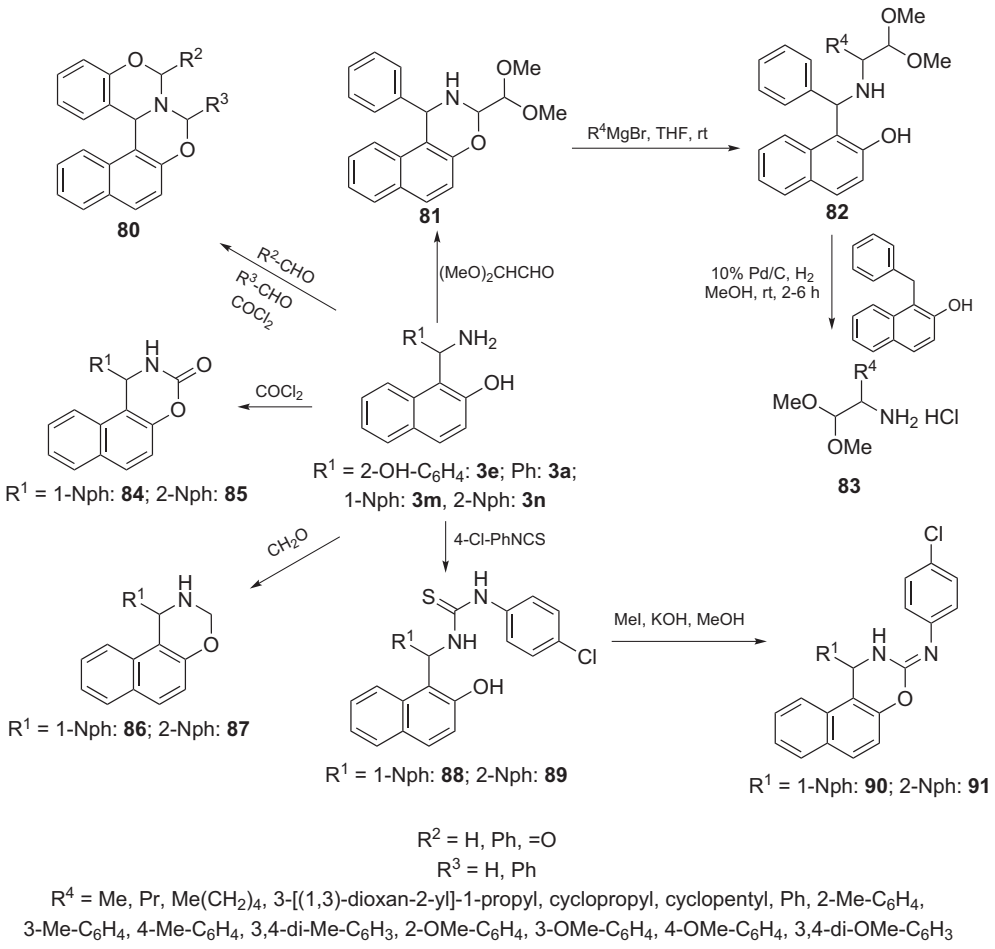
The condensations of *N*-heteroaryl aminonaphthols (**30**) with oxalyl chloride led to the formation of 1,2-disubstituted naphth[1,2-*f*][1,4]oxazepine-3,4-diones (**102**, Scheme 29)[39]

The intramolecular cyclization of **103** by use of the Vilsmeier reagent (DMF 12 equiv, $POCl_3$ 8 equiv) afforded dialdehydes **104**; Perumal et al. extended the reaction to amidoalkylnaphthols **105**, leading to **106** (Scheme 30).[77]

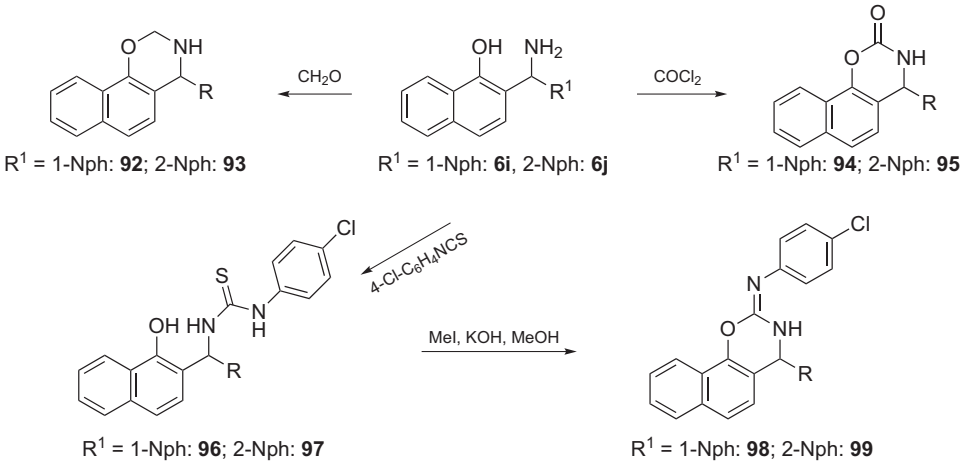
A series of *trans*-1,3-diaryl-1*H*-naphth[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl chlorides (**109**) and 1-aryl-2-benzyl-1*H*-naphth[1,2-*e*][1,3]oxazin-3-ones (**110**) were prepared by the chemoselective reaction of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**108**) and triphosgene induced by different low-valent titanium systems, while the transformation of **108** with triethyl orthoformate in the same catalytic system led to the formation of *trans*-1,3-diaryl-1*H*-naphth[1,2-*e*][1,3]oxazine-2(3*H*)-carbaldehydes (**111**: Scheme 31).[78]

The benzyloxycarbonyl-protected intermediates (**112a**–**f**) in the syntheses of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives (**113a**–**f**, Scheme 32), formed through the reactions of substituted aminonaphthol derivatives (**3**) with benzyl *N*-(2-formylphenyl)carbamate, existed not only as the expected trans ring form **B** and chain form $\mathbf{A^1}$, but also as the rearranged chain form $\mathbf{A^2}$ as a new tautomer in DMSO at room temperature. The quantity of $\mathbf{A^2}$ in the tautomeric mixture varied with time. Compounds **112a**–**f** were transformed into naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives (**113a**–**f**) by solvent-free heating with MeONa.[79]

Itoh et al. reported the synthesis of novel sulphonamide derivatives **114a**–**i** and **115** from non-racemic aminonaphthol **3a** and various sulphonyl chlorides (Scheme 33).[80]



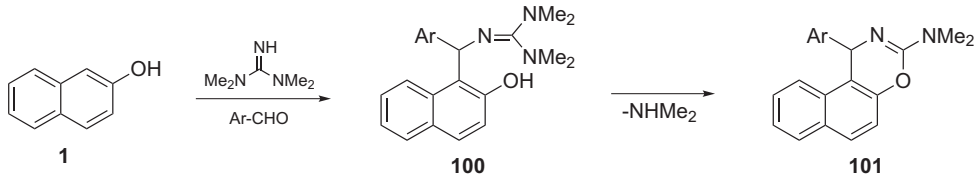
Scheme 26. Transformations of aminonaphthol derivatives **3**.



Scheme 27. Transformations of aminonaphthol derivatives **6**.

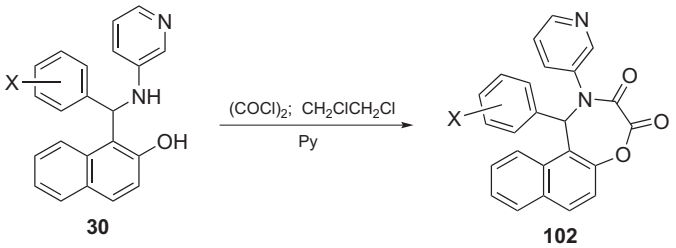
Intermediates **8**, isolated from the reactions of 6-bromo-2-naphthol (**7**) and aromatic aldehydes in the presence of ammonia, were in turn reacted with 4-nitroaniline to obtain **116** as novel mordant and disperse azo-azoimine dyes (Scheme 34).[81]

The cyclization of **65a**,**b** and **64a**,**b** with formaldehyde, phosgene, *p*-nitrobenzaldehyde or *p*-chlorophenyl isothiocyanate resulted in 8-substituted 10,11-dihydro-8*H*,15b*H*-naphth[2,1-*e*][1,3]oxazino[4,3-*a*][1,3]isoquinolines (**117a**,**b**–**121a**,**b**, Scheme 35) and 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[4,3-*a*][1,3]isoquinolines (**122a**,**b**–**126a**,**b**, Scheme 36). Conformational analysis of the piperidine and 1,3-oxazine moieties of these heterocycles by NMR spectroscopy and an accompanying theoretical ab initio study revealed that these two conformationally flexible six-membered ring-moieties prefer twisted half-chair conformers.[82,83]



Ar = Ph, 3-Me-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 2-Br-C_6H_4, 2-thienyl, 2-furyl

Scheme 28. Syntheses of 1-aryl-*N*,*N*-dimethylnaphth[1,2-*e*][1,3]oxazine-3-amines.



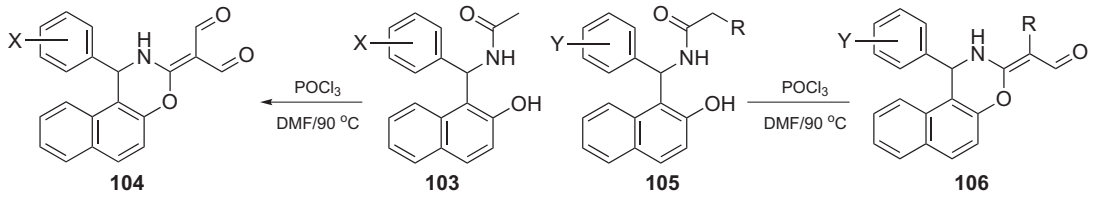
X = H, 4-Cl, 4-F, 4-Br, 4-OMe, 4-Me, 2-Cl, 3-Br, 2-OMe

Scheme 29. Synthesis of 1,2-disubstituted naphth[1,2-*f*][1,4]oxazepine-3,4-diones.

from that time, which are mostly restricted to the technical and/or substrate modifications in the test reactions.

Chan et al. successfully applied **21a** and **21b** as highly efficient ligands for asymmetric catalytic phenyl transfer to aromatic aldehydes. By means of this reaction, a variety of chiral diarylmethanols were prepared with high (up to 99%) ee values and in high chemical yields.[32] Dahmen and Lormann highlighted the value of arylboranes as precursors for arylzinc reagents in asymmetric catalysis. On the application of **21a**, the desired diarylmethanols were isolated with high (up to 98%) ee values.[86]

In tests of the enantiomeric induction of **21c**–**e**, **22c** and **22e** in the addition of diethylzinc to arylaldehydes, comparison of the results with the literature data demonstrated that the bulkier naph-



X = H; 3-NO_2; 4-NO_2; 4-Cl; 2,4-diCl; 4-Me; 4-OMe; 4-Br; 2-Cl
Y = H; 2-NO_2; R = Me; Ph

Scheme 30. Transformations of amidoalkylnaphthols **103** and **104** with Vilsmeier reagent.

The N-substitution of 1-(1,2,3,4-tetrahydroisoquinolin-1-yl) naphthalen-2-ol (**64a**) on reaction with alkyl halides yielded **127a**–**e**. The separation of the enantiomers of **127a**–**d** was achieved by using dibenzoyl L-tartaric acid, while for **127e** the semi-preparative chiral HPLC method proved successful (Scheme 36).[67]

Unexpected reactions between 1-α-aminobenzyl-2-naphthol (**3a**) or 1-aminomethyl-2-naphthol (**129**) and 6,7-dimethoxy-3,4-dihydroisoquinoline (**63**; R^1=R^2=H; Table 3) furnished naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines (**128** and **130**, Scheme 37). The reaction conditions involved classical heating at 80 °C in MeCN for 22 h (*i*), or the use of microwave conditions (100 °C, *ii*), which allowed a decrease of the reaction time to 90 min and resulted in somewhat higher yields.[84]

Chiral calix[4]arenes **132**–**135** were synthesized from **131** and chiral aminonaphthols by Sirit et al. (Scheme 38).[85]

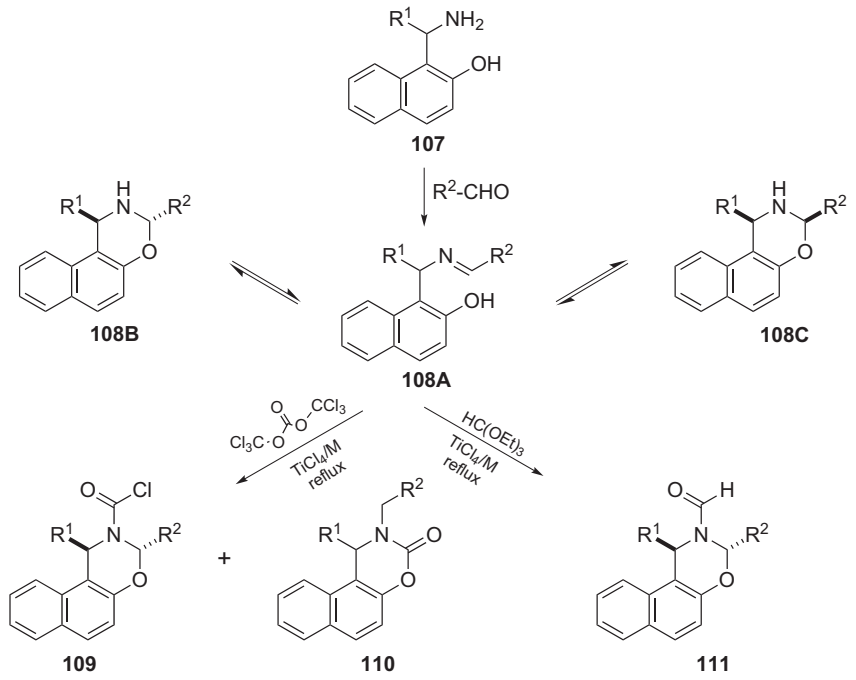
3.2. Applications in enantioselective transformations

The use of non-racemic aminonaphthol derivatives as chiral ligands is one of the most important areas of application of these types of compounds. The enantiopure aminonaphthols proved to be good-to-excellent chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde (Noyori reaction). The results of their enantiomeric inductions have been fully reviewed up to 2004.[6] The present review covers the results that have appeared

thylethyl group on the *N* atom did not cause significantly higher enantioselectivity in the enantioselective alkylation of arylaldehydes.[6] Furthermore, the tertiary aminonaphthols did not improve the ee values significantly. Concerning the influence of the aryl substituents on the addition of diethylzinc to arylaldehydes, higher ee values were achieved in all cases for the *p*-OMe substituent than for *p*-Me or H. All the reactions were substantially accelerated by using microwave irradiation, and temperature increase (depending on the structure of the chiral ligands) led to the same ee values or to the formation of the racemic 1-aryl-propanol.[33] Li et al. tested the catalytic behaviour of ligands **21f**–**q** and **22f**–**q** in the asymmetric phenyl transfer to aromatic aldehydes, and found that *ortho* electron-donating substituents on the aldehyde moiety of the ligands promoted higher enantioselectivities, while strongly electron-attracting groups were unfavourable to the ee values.[34]

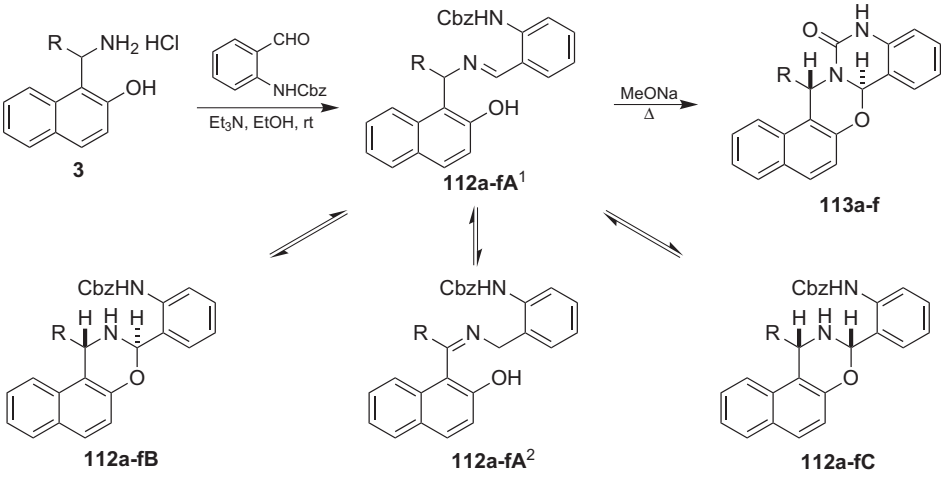
The same model reaction was used to test the enantioselectivity of **127a**. In order to improve the moderate ee values (up to 70%),[65] **127b**–**e** were synthesised and examined.[67] It emerged that modifications at the *N* atom reduced the efficiency of these ligands, whereas modifications at position-3 of the 1,2,3,4-tetrahydroisoquinoline ring and position-3 of the naphthyl ring ((1*S*,3*R*)-**64o**–**t**) improved (ee up to 96%) the enantioselectivity.[67]

Another model reaction in which the enantioinductions of non-racemic sulphonamide derivatives **114a**–**i** and **115** were tested was the hetero-Diels–Alder reaction of ethyl glyoxylate with



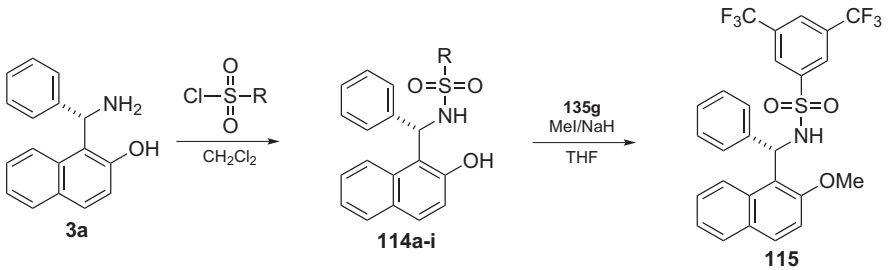
R^1 = 4-Br-C_6H_4, Ph, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-F-C_6H_4
R^2 = 4-Br-C_6H_4, Ph, 4-Cl-C_6H_4, 4-F-C_6H_4, 3,4-di-Cl-C_6H_3, 4-Me-C_6H_4, 2-thienyl

Scheme 31. Syntheses of 1,3-diarylnaphth[1,2-*e*][1,3]oxazines.



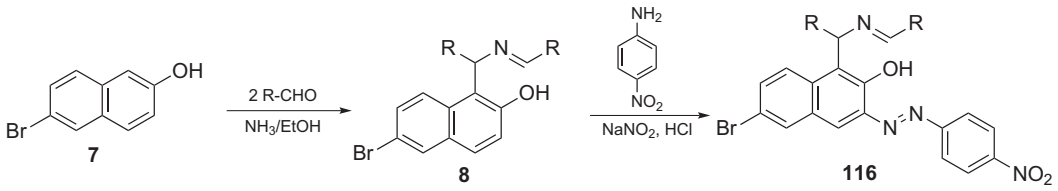
R = H: **a**; 4-Cl-C_6H_4: **b**; Ph: **c**; 4-OMe-C_6H_4: **d**; 1-Nph: **e**; 2-Nph: **f**

Scheme 32. Syntheses of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones.

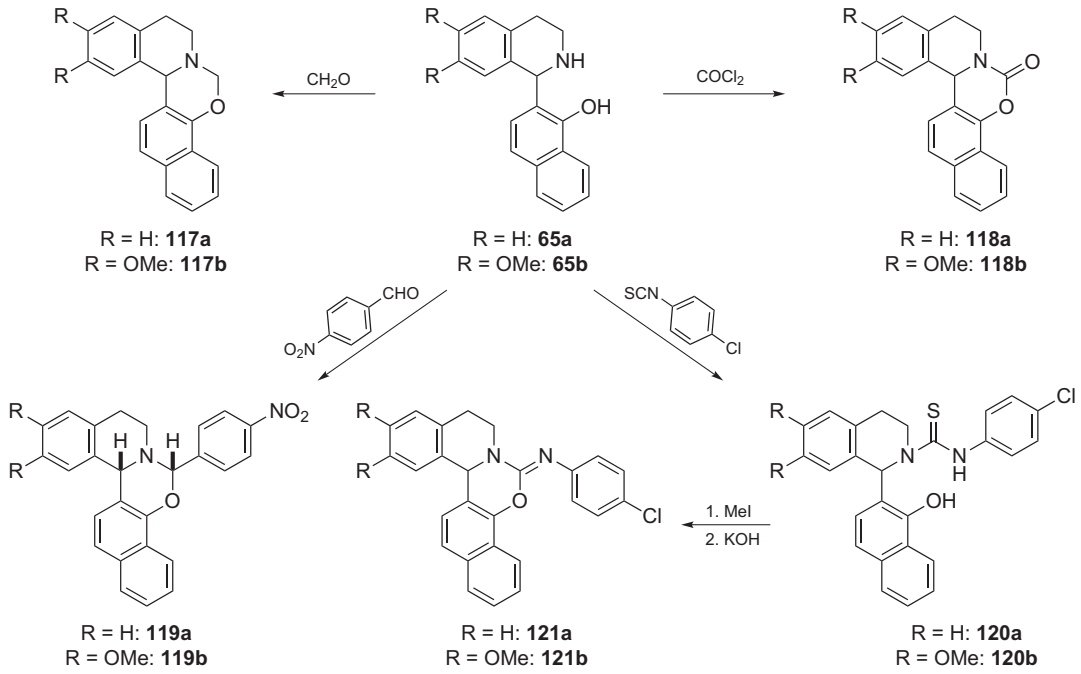


R = CF_3: **a**, C_4F_9: **b**, Ph: **c**, 4-Me-C_6H_4: **d**, 4-NO_2-C_6H_4: **e**,
2,4-di-NO_2-C_6H_3: **f**, 3,6-di-CF_3-C_6H_3: **g**, 1-Nph: **h**, 2-Nph: **i**

Scheme 33. Syntheses of aminonaphthols containing a sulphonamide moiety.



Scheme 34. Syntheses of azo-azoimine dyes **116**.



Scheme 35. Transformations of 1-(1-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinolines.

Danishefsky's dienes. Most of the ligands gave the desired 2-substituted 2,3-dihydropyran-4-ones with moderate ees (50–55%), although with somewhat higher enantioinduction (ee=70–74%) on the use of **115** as chiral organocatalyst.[80]

The applications of non-racemic aminonaphthols were recently extended to their use for the synthesis of other chiral compounds, e.g., chiral auxiliaries. These investigations mostly start from the non-racemic Betti base (**3a**). An efficient kinetic method for the resolution of racemic **3a** with L-(+)-tartaric acid in acetone, based on a novel N,O-deketalization, was developed by Hu et al.[87]

Hutton et al. succeeded in achieving the stereoselective asymmetric synthesis of **137** via **136** (Scheme 39) through a novel chirality-transfer process, yielding compounds exclusively stereogenic at the boron.[88]

By the reaction of (*S*)-**3a** and dialdehydes, diastereopure α-benzotriazolyl (Bt) 1-azacycloalka[2,1-*b*][1,3]oxazines **138a**–**c** were prepared,[89,90] from which the enantioselective syntheses of **139a**–**c** and **141** (via **140**) were performed (Scheme 40).[90]

A series of enantiopure piperidines (**144**)[87] or (2*S*,6*R*)-disubstituted piperidines (**147**)[90] were prepared by Hu et al. via intermediates **138a**–**c**, **142** and **143**, or **145** and **146** starting from (*S*)-**3a** as an excellent chiral auxiliary (Scheme 41). The process was extended to the syntheses of non-racemic 2,5-disubstituted pyrrolidines (**150**) through **148** and **149**, which proved to be good precursors for (−)-cocaine and (−)-ferruginine (Scheme 41).[91]

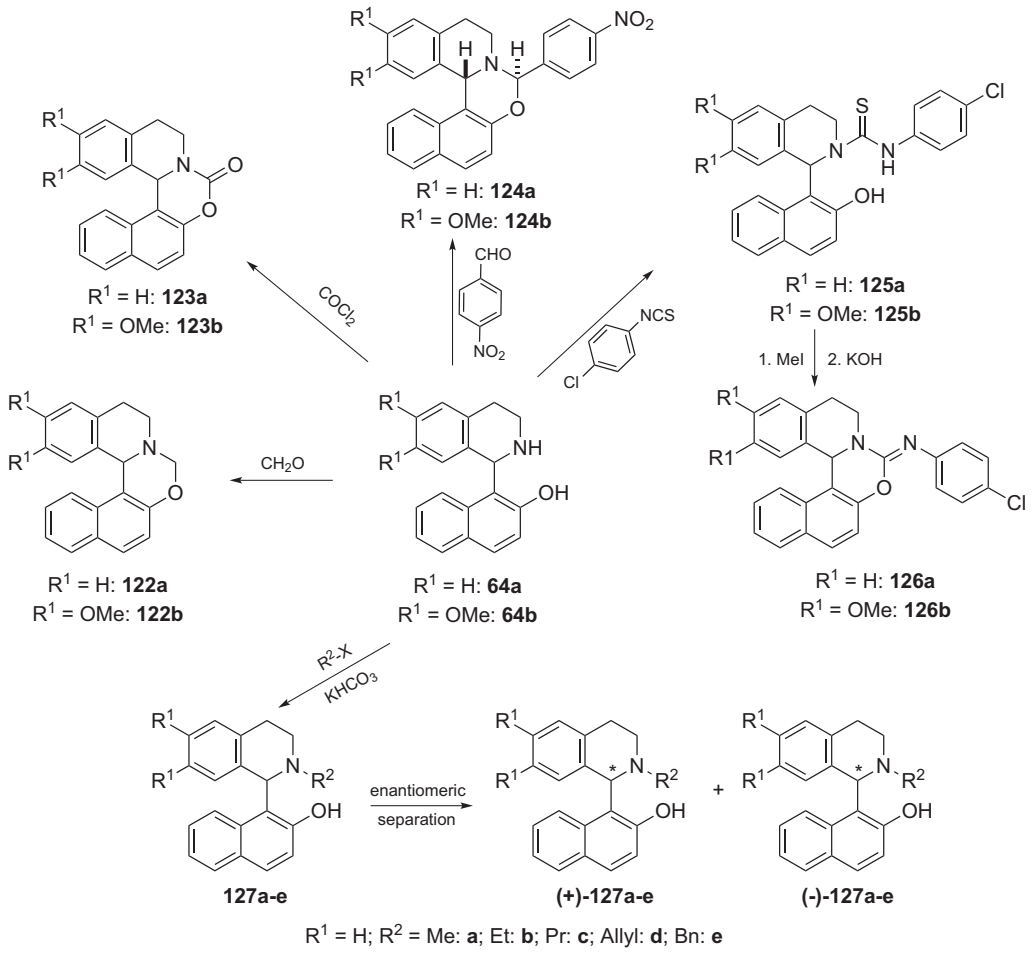
A general method for the synthesis of enantiopure 2-alkene- or 2-alkyne-substituted piperidines (**152**) was devised by starting from **138b** (Scheme 42).[92,93] It is interesting to note that a novel base-catalysed N-debenzylation of **149** and **151** was applied instead of hydrogenolysis for the synthesis of **150** and **152** in order to avoid saturation of the alkene or alkyne side chain.

A simple and efficient approach to enantiopure α-aminophosphonic acids (**155a**–**c**), based on the reactions of chiral benzylidenes (**153a**–**c**) derived from the enantiomers of **3a** with trialkyl phosphites in the presence of TFA (Scheme 43), through the intermediates **154a**–**c** was described by Alfonsov et al.[94,95]

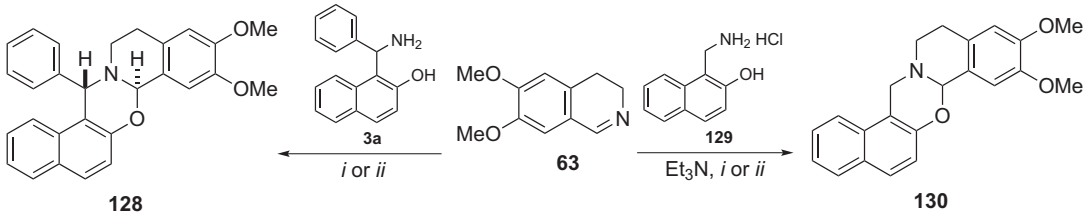
A series of new chiral phosphoramidate ligands (**160**; Scheme 44) were synthesized from the *O*-protected non-racemic aminonaphthol derivatives **159** and BINOL, starting from the enantiopure aminonaphthol **156**, via **157** and **158**. The ligands were tested in the palladium-catalysed enantioselective hydrosilylation of styrene derivatives. The ligands with the (*S*,*R*,*R*) configuration were found to be effective catalysts (ees up to 97%) of these model reactions.[96]

3.3. Miscellaneous applications

The high number of that papers have recently appeared with special applications indicate that the uses of these compounds are not restricted solely to enantioselective transformations.



Scheme 36. Transformations of 1-(2-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinolines.



Scheme 37. Syntheses of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines.

The aminonaphthol analogues **13** and **21f** have been used as ligands in the palladium-catalysed Mizoroki–Heck reaction. Interestingly, high turnover numbers were observed in the reactions with aryl bromides and iodides, whereas aryl chlorides were inert.[97]

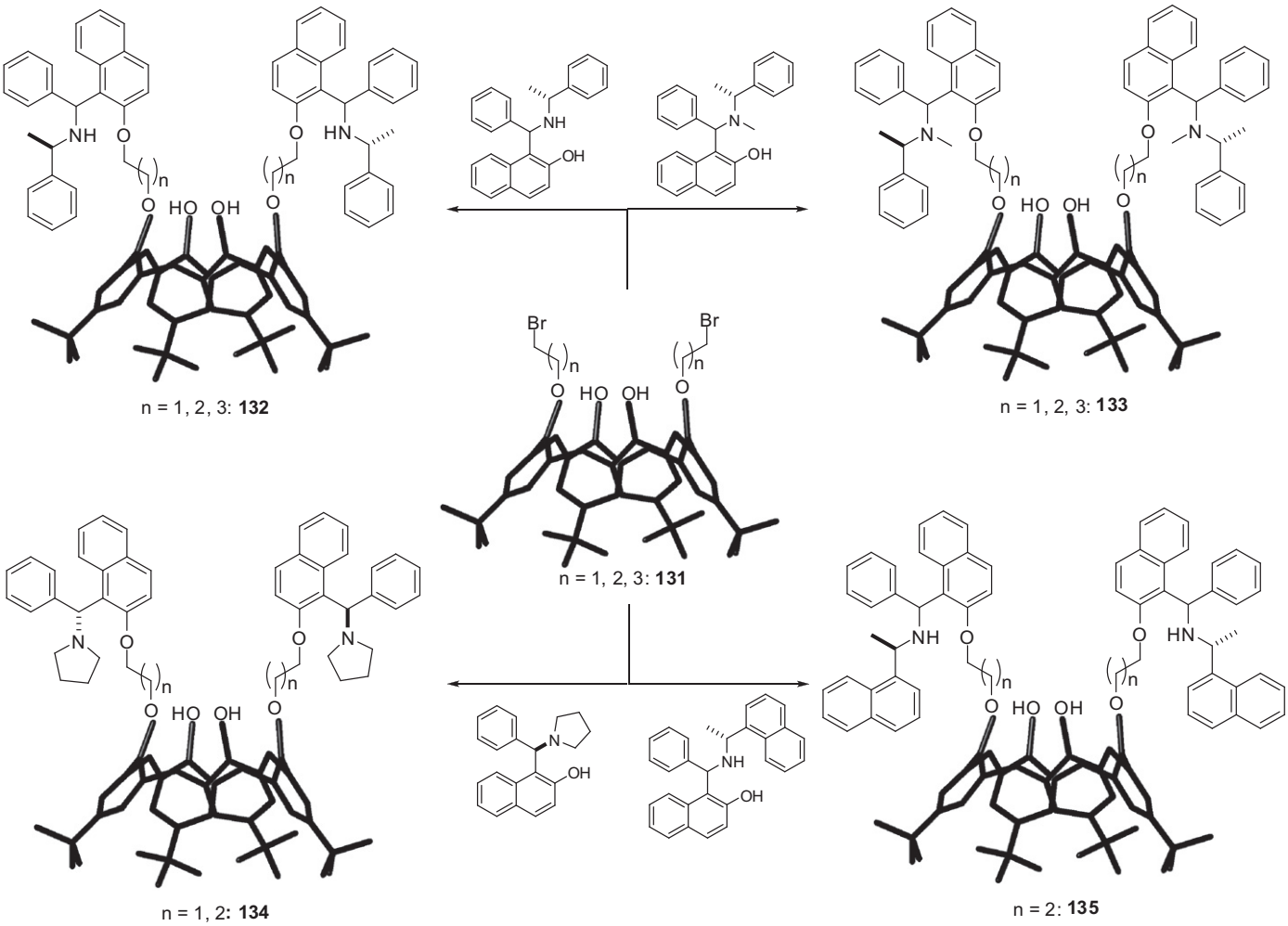
When the inter- or intramolecular N···H–O or N–H···O H-bonding in **3a**, **3d** and **6a** and their derivatives was examined, it was found that the strength of the intramolecular H bond depends on the steric and electronic effects of the substituents.[98]

In recent studies, 1-(α-aminoarylmethyl)-2-naphthol, 1-α-aminoalkyl-2-naphthol and 2-(α-aminoarylmethyl)-1-naphthol enantiomers were separated on different chiral HPLC columns. Quantitative investigations were also made of the relationships between the HPLC parameters and the substituents on the aminonaphthols.[99–104] The structures of **21c** and **21e** contain two stereogenic centres, and the enantioseparation of such racemic and non-racemic aminonaphthols was achieved on an AmyCoat™ or CelluCoat™ HPLC stationary phase.[105,106]

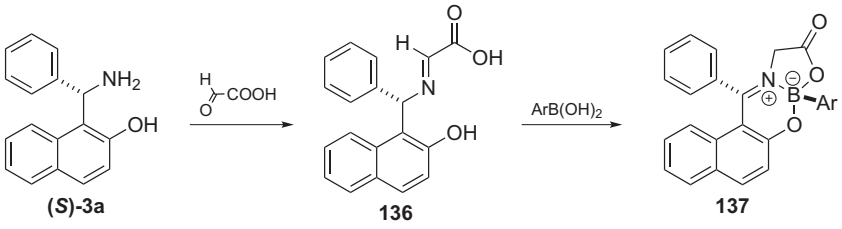
Naphthoxazinobenzoxazines **80** and their derivatives (pyrrolonaphthoxazinones) were studied by using mass spectrometry in order to establish the effects of the regioisomers and substituents on the fragmentation.[107]

3.4. Biological activity

Naphthoxazinone derivatives have received considerable attention in view of the interesting pharmacological properties associated with this heterocyclic scaffold.[108–110] It has been reported that they act as antibacterial agents,[111] while a benzoxazinone derivative was approved by the FDA as a non-nucleoside reverse transcriptase inhibitor in 1998, and is currently in clinical use for the treatment of AIDS.[112]



Scheme 38. Syntheses of chiral calix[4]arenes **132**–**135**.



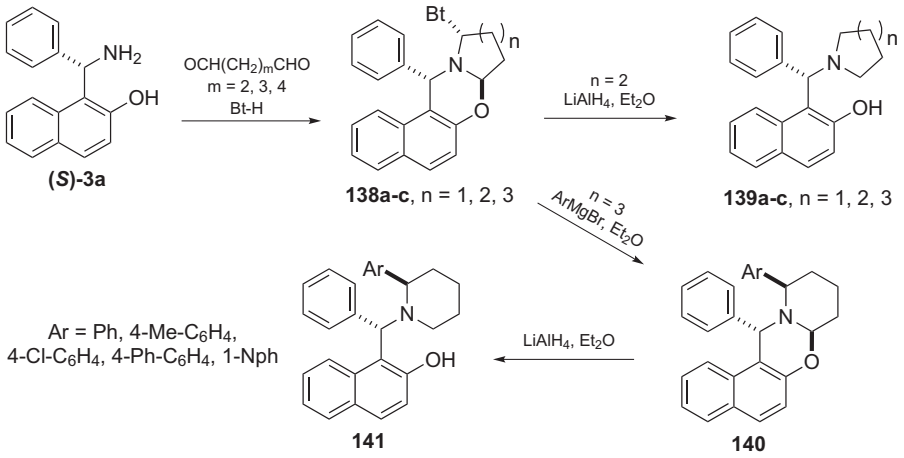
Scheme 39. Syntheses of boron derivatives **137**.

Many functionalized quinolines and isoquinolines are widely employed as antimalarial, anti-asthmatic or anti-inflammatory agents or as antibacterial, antihypertensive and tyrosine kinase PDGF-RTK-inhibiting agents. In an integrated, virtual database screening, their analogues containing a hydroxyl group, such as 7-[anilino(phenyl)methyl]-2-methyl-8-quinolinol (**50**; X=Me, Y=H, R=Ph; Scheme 17), were found to be a promising new class of nonpeptide inhibitors of the MDM2-p53 interaction.[14]

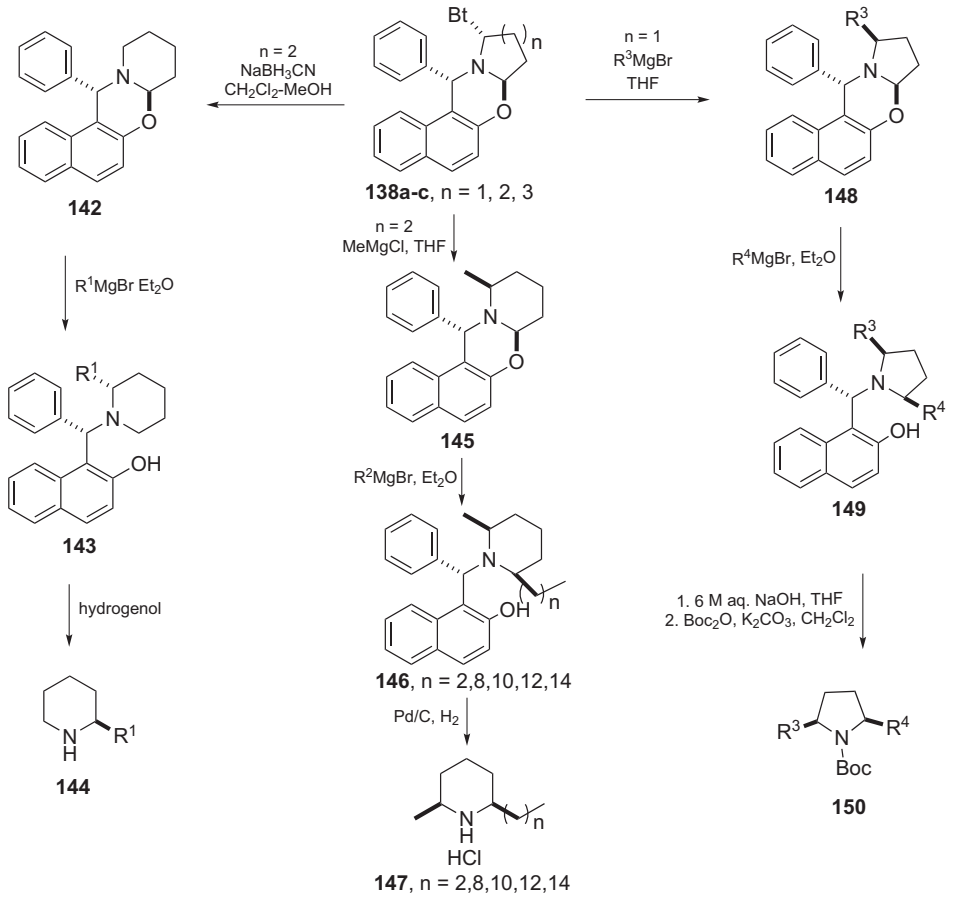
Recent, biochemical and X-ray crystallographic studies after a virtual screening confirmed that hydroxyquinolines (**50**; X=H, Y=H, 2-Me, 4-Me, 2-OMe, 4-OMe, 2-OEt, 4-OEt, 2-Cl, 4-Cl, R=2-Py; Scheme 17) were actually covalent inhibitors of MIF tautomerase.[15] Another virtual screening demonstrated that 7-[(3-fluorophenylamino)(pyridin-2-yl)methyl]-8-quinolinol (**50**; X=H, Y=3-F, R=2-Py; Scheme 17) was an MIF-CD74 inhibitor at low micromolar concentrations, acting as a weak tautomerase inhibitor.[16]

The in vitro efficacy of compounds **52** against *Escherichia coli*, *Vibria cholerae*, *Achromobacter hydrophilis*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Salmonella typhii*, *Plesiomonas schigellaides*, *Proteus vulgaris*, *Citrobacter* and *Citrobacter ovis* revealed that derivatives containing a 2-pyrimidinyl group on the sulphonamide moiety were the most effective.[61]

When compounds **59** and **60** were screened for their fungicidal activity against *Pyricularia oryzae* (Cav) and for their antibacterial activity against *E. coli* and *Staphylococcus aureus* by the usual methods,[12] almost all of them exhibited promising antifungal and antibacterial activities. Introduction of a halogen atom at C-5 of either the thiazole or the oxazole moiety augmented the activity.



Scheme 40. Transformations of (*S*)-**3a** into non-racemic aminonaphthols.

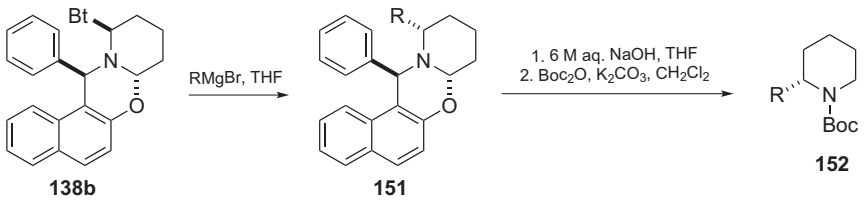


Scheme 41. Syntheses of enantiopure piperidines and pyrrolidines.

Chloro derivatives proved to be more active than bromo derivatives. Substituents on C-4 of the thiazole or oxazole nucleus contributed to the fungicidal activity in the following sequence: chlorophenyl≥-bromophenyl>naphthyl>nitrophenyl. The pathogenic bacteria were equally sensitive to the compounds at 100 ppm. It was also observed that thiazolyl-substituted compounds were generally slightly more active than the oxazolyl-substituted derivatives.[12]

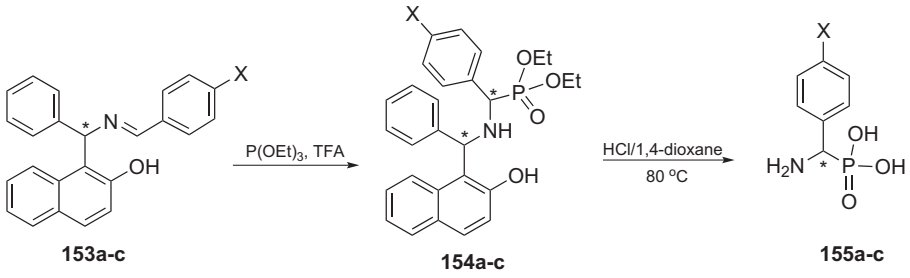
de Witte et al. evaluated the in vitro and in vivo P-glycoprotein (P-gp)-modulating activities of the products of some substituted analogues of **3a** and tylosine by using human MDR1 gene-transfected and parental L5178 mouse lymphoma cell lines. The most promising compound was *N*-tylosyl-1-α-amino-(3-bromophenyl)methyl-2-naphthol.[113]

A series of racemic 1-((4-(2-(dialkylamino)ethoxy)phenyl)-(2-hydroxynaphthalen-1-yl)methyl)piperidin-4-ols (**15a**–**f**) were evaluated against oestrogen-responsive human MCF-7 breast cancer cells. The moderate activities of **15a**–**f** were explained by the molecular bulk resulting in an inadequate fit at the receptor, and



138b 151 152

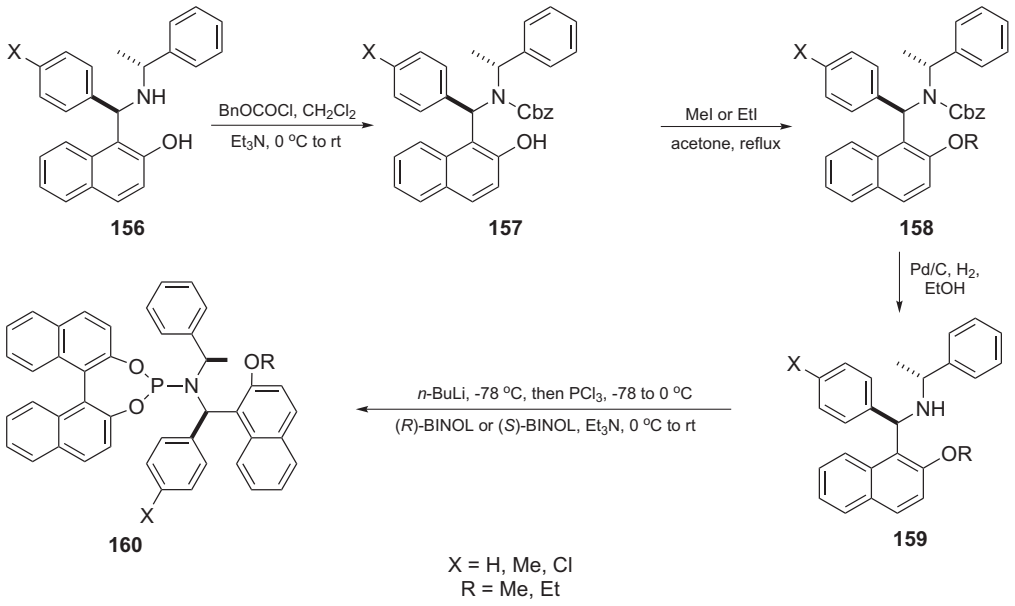
Scheme 42. Synthesis of non-racemic 2-substituted piperidines **152**.



153a-c 154a-c 155a-c

X = H, Me, Br

Scheme 43. Syntheses of enantiopure α-aminophosphonic acid derivatives.



156 157 158 159 160

X = H, Me, Cl
R = Me, Et

Scheme 44. Syntheses of chiral phosphoramidate ligands **160**.

the molecular motif was modified by removal of the piperidinol moiety to furnish achiral 1-(4-(2-(dialkylamino)ethoxy)benzyl) naphthalen-2-ols. This new series of compounds displayed significantly enhanced cytotoxicity against MCF-7 cells.[29]

4. Conclusions and outlook

The high number of publications that have recently appeared on the syntheses and applications of the mMR is a clear indication that this mode of synthesis has again become a hot topic in organic chemistry. It is also clear that the most important area of application of the non-racemic aminonaphthols prepared in this manner is their use in asymmetric transformations, either as chiral ligands or as chiral auxiliaries. It should be mentioned that the relatively high molecular weights of this type of non-racemic molecules is their only disadvantage of their use in organocatalytic reactions. The functional groups in these Mannich products offer many ring-closure possibilities. Some of these products or the starting bifunctional compounds possess biophore units with promising biological activity. Thanks to the immense number of possibilities for three-component mMR through the use of different amines and/or aldehydes, the continued evolution of the literature on these reactions appears guaranteed, while the synthetic behaviour of 2-naphthol will find interest in the context of other electron-rich aromatic compounds, such as quinolinols, isoquinolinols or phenols.

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financial support. I.S. acknowledges the award of a János Bolyai Fellowship.

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