1. Introduction

The Mannich reaction is one of the most frequently applied multicomponent reactions in organic chemistry. 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.
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 Bettí 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 Bettí base, and the protocol as the Bettí 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 Bettí base derivatives were recently reviewed,7 with special attention to their use as versatile building blocks. With regard to the synthetic potential of this class of compounds again becoming a hot topic.14 Their promising biological activity has led to the chemistry of these intermediates being treated in the following sections and will not be discussed separately.

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 (NH4OOCNH2), which yielded 3a–d or 6a–h.7

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 (2f–i–l) was performed only in some cases (3f–h, Scheme 1).10

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 5l 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 (+)-tartaric acid in a ratio of 1:1. The products of this reaction were (5R)-3a H tartarate, 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-dihydropyran-1,3-diaryl-2,3-dihydro-2-azaphenalenones 11a–m from aromatic aldehydes, 2,7-naphthalediols (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)arylmethylpiperidin-4-ol derivatives (14a–j) as novel selective oestrogen receptor modulators
were designed and synthesized by Jha et al. via the mMR protocol from 2-naphthol (1), 4-piperidinol and 10 different aromatic aldehydes. 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).

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. The same reaction was achieved by Shingare et al. with KAl(SO₄)₂·12H₂O as a reusable, non-toxic inexpensive catalyst. It should be mentioned that, in this case, water was applied as solvent (Scheme 7).

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. 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. The bulkier naphthyl ring was inserted through the amine
moiety when 2-naphthol (1) was aminolylated 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 21f and 21g were also transformed into 22c and 22e through cyclization with formaldehyde, followed by reduction with LiAlH₄.³³

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 NaBH₄.³⁴

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-diaminoalkynylphosphatidynols 27–29 from an amine, chiral α-NN-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 enantioselective 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 solvent³⁹ or solvent-free conditions.⁴⁰

An efficient and environmentally friendly approach for the synthesis of 2’-aminobenzothiazolomethyl-2-naphtholes (32) via the condensation of an aromatic aldehyde, 2-naphthol and 2-aminobenzothiazole (31) in water as solvent has been reported by Shaaban et al. (Scheme 10).⁴¹
Table 1
Syntheses of enantiopure aminonaphthols 21 and 22

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<tr>
<th>Compd</th>
<th>Amine (19)</th>
<th>Aldehyde (20)</th>
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<td>CHO</td>
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<td></td>
<td>33</td>
</tr>
<tr>
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<td>N</td>
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<td></td>
<td>33</td>
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<td>Solvent-free, 65°C, 72 h</td>
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<td>CHO</td>
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<td></td>
<td>34</td>
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<td>CHO</td>
<td>Solvent-free, 60°C, 8–36 h</td>
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<td>CHO</td>
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(continued on next page)
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<th>Aldehyde (20)</th>
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<th>21</th>
<th>ii</th>
<th>22</th>
<th>Ref.</th>
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<td>Solvent-free, 60 °C, 8–36 h</td>
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<td></td>
<td>34</td>
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<tr>
<td>o</td>
<td>H₂N</td>
<td>CHO</td>
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<td>p</td>
<td>H₂N</td>
<td>CHO</td>
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<td>Solvent-free, 60 °C, 8–36 h</td>
<td>1. CH₂O, rt 2. NaBH₄, rt</td>
<td></td>
<td></td>
<td>34</td>
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</table>
Table 1 (continued)

<table>
<thead>
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<th>Compd</th>
<th>Amine (19)</th>
<th>Aldehyde (20)</th>
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<th>ii</th>
<th>Ref.</th>
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</thead>
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<td>r</td>
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<td>O(\text{O})</td>
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<td>s</td>
<td></td>
<td>O(\text{O})</td>
<td>Toluene, (-15,^\circ\text{C}, 3\text{--}10,\text{h})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>O(\text{O})</td>
<td>Toluene, (-15,^\circ\text{C}, 3\text{--}10,\text{h})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>u</td>
<td></td>
<td>O(\text{O})</td>
<td>Toluene, (-15,^\circ\text{C}, 3\text{--}10,\text{h})</td>
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<td>-</td>
</tr>
</tbody>
</table>

Table 2
Syntheses of aminodiols and diaminoalcohols 25 and 26

\[
\text{23} + \text{4} \xrightarrow{i} \text{25} \xrightarrow{ii} \text{26}
\]

<table>
<thead>
<tr>
<th>Compd</th>
<th>Amine (23)</th>
<th>Aldehyde (24)</th>
<th>i</th>
<th>ii</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td>O(\text{O})</td>
<td>Solvent-free, rt, 12--72 h</td>
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<td>-</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>O(\text{O})</td>
<td>Solvent-free, rt, 12--72 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>O(\text{O})</td>
<td>Solvent-free, rt, 12--72 h</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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), 35a–e could be isolated (Scheme 11).42

Synthesis of the bis-product 36 was achieved from 2-naphthol, (S)-(-)-a-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–e and 39a,b of 2-naphthol, derived from aromatic aldehydes and

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Amine (23)</th>
<th>Aldehyde (24)</th>
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<th>25</th>
<th>ii</th>
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<tr>
<td>e</td>
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<td>Solvent-free, rt, 12–72 h</td>
<td></td>
<td>6 M HCl, THF, reflux, 2 h</td>
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<tr>
<td>f</td>
<td>H2N-NH2</td>
<td>O=O-Ot-Bu</td>
<td>Solvent-free, rt, 12–72 h</td>
<td></td>
<td>6 M HCl, THF, reflux, 2 h</td>
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<tr>
<td>g</td>
<td>H2N-NH2</td>
<td>O=O-Ot-Bu</td>
<td>Solvent-free, rt, 12–72 h</td>
<td></td>
<td>6 M HCl, THF, reflux, 2 h</td>
</tr>
</tbody>
</table>


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

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).

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

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.

6-Isouquinolinol (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.

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. 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).

The mMRs of anilines, benzaldehydes and 8-quinolinols yielded 7-\( \alpha \)-anilinoalkyl-8-quinolinols 50 (Scheme 17). The simplicity of these three-component reactions led to the combination of aliphatic aldehydes and substituted anilines (49) to obtain 7-anilinoalkyl-8-
Scheme 13. Aminoalkylation of 2-naphthol with symmetric diamines and aldehydes.

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

Scheme 15. Syntheses of tertiary aminoquinolinol and aminoisoquinolinol.


Scheme 17. Syntheses of 7-arylaminomethyl-substituted 8-quinolinol derivatives.
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-aminquinoline, leading to 54 (Scheme 19). It is interesting to note that 2,6-diaminopyrididine appeared to react at only one amino group.11

Shaaban 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, NaNO3, Na2SO4, LiNO3 or Li2SO4, 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

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...
(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 (69e–71e) were transformed into their N-methylated derivatives (72e–74e) by using formaldehyde, followed by reduction with NaBH4.

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-1H-naphth[1,2-e][1,3]oxazines (75a–g–79a–g), which proved to be three-component tautomeric mixtures in CDCl3 at 300 K, involving C-3 epimeric naphthoxazines (B and C) besides the open tautomer (A).12 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-1H-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-

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.
dihydro-1H-naphth[1,2-e][1,3]oxazines revealed a significant dependence on the inductive effect of substituent Y \((\sigma_f)\), which was further evidence of the anomeric effect in the trans ring form.  

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.  

For 1-alkyl-3-aryl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazines \((\text{75}a-\text{g})\), 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 \((\sigma^*)\). 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.  

The highly functionalized aminonaphthol \(3\text{e}\) was converted into naphth[1,2',5,6][1,3]oxazino[3,4-c][1,3]benzoxazines \((\text{80}, \text{Scheme 26})\), 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.  

A novel method for the synthesis of 1-substituted 2,2-dimethoxyethylamines \((\text{83})\) was introduced by Hu et al. The synthetic pathway involved the reaction of \(3\text{a}\) with an aqueous solution of 2,2-dimethoxyacetaldehyde to yield \(6\text{a}\), which was alkylated with Grignard reagents, followed by catalytic (Pd/C) hydrogenolysis of benzylamines \(82\), to give the target products \(83\) directly (Scheme 26).  

Through the condensation of \(3\text{n}, 3\text{o}, 6\text{i}\) and \(6\text{j}\) with paraformaldehyde, 4-nitrobenzaldehyde, phosgene or 4-chlorophenyl isothiocyanate, naphthoxazine derivatives \((\text{84} - 91): \text{Scheme 26} \text{ and} 92 - 99: \text{Scheme 27})\) 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.  

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

<table>
<thead>
<tr>
<th>Products</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>(R^4)</th>
<th>(R^5)</th>
<th>(R^6)</th>
<th>Ref.</th>
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<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>64,65</td>
</tr>
<tr>
<td>(64\text{b})</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>64</td>
</tr>
<tr>
<td>(64\text{c})</td>
<td>OMe</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>64</td>
</tr>
<tr>
<td>(64\text{d})</td>
<td>H</td>
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<td>65</td>
</tr>
<tr>
<td>(64\text{f})</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
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<td>65</td>
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<tr>
<td>(64\text{g})</td>
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<td>H</td>
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</tr>
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<td>66</td>
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<tr>
<td>(15,3\text{R}^6)-(64\text{o})</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>67</td>
</tr>
<tr>
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<td>H</td>
<td>Ph</td>
<td>4-OMe – C₆H₄</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>67</td>
</tr>
<tr>
<td>(15,3\text{R}^6)-(64\text{q})</td>
<td>H</td>
<td>Ph</td>
<td>3-OMe – C₆H₄</td>
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<td>H</td>
<td>H</td>
<td>67</td>
</tr>
<tr>
<td>(15,3\text{R}^6)-(64\text{r})</td>
<td>H</td>
<td>Ph</td>
<td>3,5-Di-(t-Bu) – C₆H₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>67</td>
</tr>
<tr>
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<td>Ph</td>
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<td>H</td>
<td>H</td>
<td>67</td>
</tr>
<tr>
<td>(65\text{a})</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>64</td>
</tr>
</tbody>
</table>

**Scheme 23.** Syntheses of 1-hydroxyquinolyl- and 1-hydroxyisoquinolyl-1,2,3,4-tetrahydroisoquinolines.
1-Aryl-N,N-dimethyl-1H-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,N0,N0-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, POCl3 8 equiv) afforded dialdehydes 104; Perumal et al. extended the reaction to amidoalkynaphthols 105, leading to 106 (Scheme 30).77

A series of trans-1,3-diaryl-1H-naphth[1,2-e][1,3]oxazine-2(3H)-carbonyl chlorides (109) and 1-aryl-2-benzyl-1H-naphth[1,2-e][1,3]oxazin-3-ones (110) were prepared by the chemo-selective reaction of 1,3-diaryl-2,3-dihydro-1H-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-1H-naphth[1,2-e][1,3]oxazine-2(3H)-carbaldehydes (111: Scheme 31).78

The benzyloxycarbonyl-protected intermediates (112a-e) in the syntheses of naphth[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-one derivatives (113a-e, Scheme 32), formed through the reactions of substituted aminonaphthol derivatives (3) with benzyl N-(2-formyl-phenyl)carbamate, existed not only as the expected trans ring form B and chain form A1, but also as the rearranged chain form A2 as a new tautomer in DMSO at room temperature. The quantity of A2 in the tautomeric mixture varied with time. Compounds 112a-e were transformed into naphth[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-one derivatives (113a-e) 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 25. Syntheses of 1-alkyl-3-arylnaphth[1,2-e][1,3]oxazines.
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).\textsuperscript{81}

The cyclization of 65a,b, 64a,b with formaldehyde, phosgene, \( p \)-nitrobenzaldehyde or \( p \)-chlorophenyl isothiocyanate resulted in 8-substituted 10,11-dihydro-8H,15bH-naphth[2,1-e][1,3]oxazino[4,3-\( a \)][1,3]isoquinolines (117a,b–121a,b, Scheme 35) and 10,11-dihydro-8H,15bH-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.\textsuperscript{82,83}
Me2N
NMe2
O
Y
R
N

The N-substitution of 1-(1,2,3,4-tetrahydroisoquinoline-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).57

Unexpected reactions between 1-α-aminobenzyl-2-naphthol (3α) or 1-aminomethyl-2-naphthol (129) and 6,7-dimethoxy-3,4-dihydroisoquinoline (63; R1=R2=H; Table 3) furnished naphth[1,2-e][1,3]oxazino[2,3-e]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).35

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 this 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 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 dialkylzincs 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 aryldiazene reagents in asymmetric catalysis. On the application of 21a, the desired diarylzincs 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 aryldiazene, comparison of the results with the literature data demonstrated that the bulkier naphthylation group on the N atom did not cause significantly higher enantioselectivity in the enantioselective alkylation of arylaldehydes.6 Furthermore, the tertiary aminonaphthol did not improve the ee values significantly. Concerning the influence of the aryl substituents on the addition of diethylzinc to aryldiazene, higher ee values were achieved in all cases for the p-OMe substituent than for p-Br or p-OMe. 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 ([15,3R]-64a–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...
Scheme 31. Syntheses of 1,3-diarylnaphth[1,2-e][1,3]oxazines.

\[ R^1 = 4-\text{Br-C}_6\text{H}_4, \text{Ph}, 4-\text{Cl-C}_6\text{H}_4, 4-\text{Me-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4 \]
\[ R^2 = 4-\text{Br-C}_6\text{H}_4, \text{Ph}, 4-\text{Cl-C}_6\text{H}_4, 4-\text{F-C}_6\text{H}_4, 3,4-\text{di-Cl-C}_6\text{H}_3, 4-\text{Me-C}_6\text{H}_4, 2-\text{thienyl} \]


R = H: a; 4-Cl-C\(_6\)H\(_4\): b; Ph: c; 4-OMe-C\(_6\)H\(_4\): d; 1-Nph: e; 2-Nph: f

Scheme 33. Syntheses of aminonaphthols containing a sulphonamide moiety.

R = CF\(_3\): a; C\(_2\)F\(_5\): b; Ph: c; 4-Me-C\(_6\)H\(_4\): d; 4-NO\(_2\)-C\(_6\)H\(_4\): e; 2,4-di-NO\(_2\)-C\(_6\)H\(_4\): f; 3,6-di-CF\(_3\)-C\(_6\)H\(_3\): g; 1-Nph: h; 2-Nph: i
Danishefsky’s dienes. Most of the ligands gave the desired 2-substituted 2,3-dihydropyran-4-ones with moderate enantioinduction (ee = 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 enantioselective piperidines (144)97 or (25,6R)-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-amino-phosphonic 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 amonaphthol 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.
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 (pyrrolo-naphthoxazinones) 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
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; \(X=\text{Me}, \ Y=\text{H}, \ R=\text{Ph} \); 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; \(X=\text{H}, \ Y=\text{H}, \ R=\text{Ph} \); Scheme 17) were found to be a promising new class of nonpeptide inhibitors of the MDM2-p53 interaction.14

Another virtual screening demonstrated that 7-[(3-fluorophenylamino)(pyridin-2-yl)methyl]-8-quinolinol (50; \(X=\text{H}, \ Y=\text{H}, \ R=\text{Ph} \); Scheme 17) was an MIF-CD74 inhibitor at low micromolar concentrations, acting as a weak tautomerase inhibitor.15

The in vitro efficacy of compounds 52 against Escherichia coli, Vibrio cholerae, Chromobacter hydrophilis, Proteus mirabilis, Klebsiella pneumonaiæ, Salmonella typhi, 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.
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.\textsuperscript{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 \textit{3a} and tylosine by using human MDR1 gene-transfected and parental L5178 mouse lymphoma cell lines. The most promising compound was \textit{N}-tylosyl-1-\textit{x}-amino-(3-bromophenyl)methyl-2-naphthol.\textsuperscript{13}

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

Acknowledgements

The authors thank the Hungarian Research Foundation (OTKA No. K-75433) and TÁMOP-4.2.2/A-11/1/KONV-2012-0052 for
financial support. I.S. acknowledges the award of a János Bolyai Fellowship.

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6. Shaabani, A.; Rahmati, A.; Farhangi, E.


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