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Recent advances in the transformation reactions of the Betti base derivatives

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Betti bases are the products resulting from the one-pot multicomponent reaction involving 1-naphthol/2-naphthol, aliphatic/aromatic aldehydes, and secondary amines. This chemical process is commonly referred to as the Betti reaction. The significance of Betti bases in medicinal chemistry has grown substantially due to their diverse array of pharmacological applications. Furthermore, their synthetic utility is considerable, given their use as catalysts and ligands in asymmetric synthesis. Moreover, Mannich products, incorporating diverse functional groups such as –OH and –NH, find application in a range of organic reactions. This utilization enables the synthesis of novel C–C bond linkages and diverse heterocycles, including biologically active naphthoxazines, which hold biological applications such as antibacterial, antifungal and anticancer. The focus of this review article is on the application of aminonaphthol derivatives in transformation reactions and the synthesis of organic compounds, with particular emphasis on heterocycles.

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1 Introduction

Straightforward synthesis of 1-(α-aminobenzyl)-2-naphthol (the Betti base) from 2-naphthol, benzaldehyde, and ammonia was reported for the first time by Betti at the beginning of the 20th century.[1–4] The Betti procedure can be understood as an expansion of the Mannich condensation. In this process, formaldehyde is substituted with an aromatic aldehyde, the secondary amine is replaced by ammonia, and the C–H acid is substituted with an electron-rich aromatic compound, such as 2-naphthol. This modification in reactants results in a distinct chemical transformation, broadening the scope of the traditional Mannich condensation and yielding unique products through the Betti procedure. As a result of the potential utility of

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Mannich-type phenolic bases, the aminoalkylation of naphthol derivatives is a subject of current chemical interest. In recent years, numerous methodologies have reported for synthesizing these aminobenzylnaphthols, also known as Betti bases, and their bis-Betti base derivatives. These methods involve the utilization of diverse substrates such as various types of naphthols, aromatic amines, heteroaromatic amines, aliphatic and cyclic amines, instead of ammonia or diamines. Additionally, aliphatic and aromatic aldehydes or dialdehyde compounds have been employed under various conditions in recent research efforts. The typical process for the formation of the Betti bases begins with the generation of an *ortho*-quinone methide (*o*-QM) through the reaction between naphthol and aldehyde. Subsequently, the *o*-QM undergoes a Michael addition with an amine, resulting in the formation of the Betti base. These compounds exhibit a wide range of applications, including: enantioselective addition of diethylzinc to aldehydes,[5] crystallization-induced diastereoisomer transformation,[6] asymmetric hydrogenation and allylic substitution,[7] optoelectronic applications (fluorescent chemosensors,[8] fluorescence detection of Hg^{2+} and Cr^{3+} ions[9] and electrochemical activity[10]) and biological properties such as anticancer agents[11] (**A**), antioxidant[12] (**B**), anti-bacterial[13] (**C**), antitubercular agents[14] (**D**), pesticidal agents[15] (**E**), anti-Alzheimer agents[16] (**F**), topoisomerase I inhibitors[17] (**G**) and DNA binding and cleavage activity[18] (**H**) as depicted in Fig. 1. Active –OH & –NH functionalities in Betti bases are employed in different organic reactions to synthesize new C–C bond linkages and various medicinally

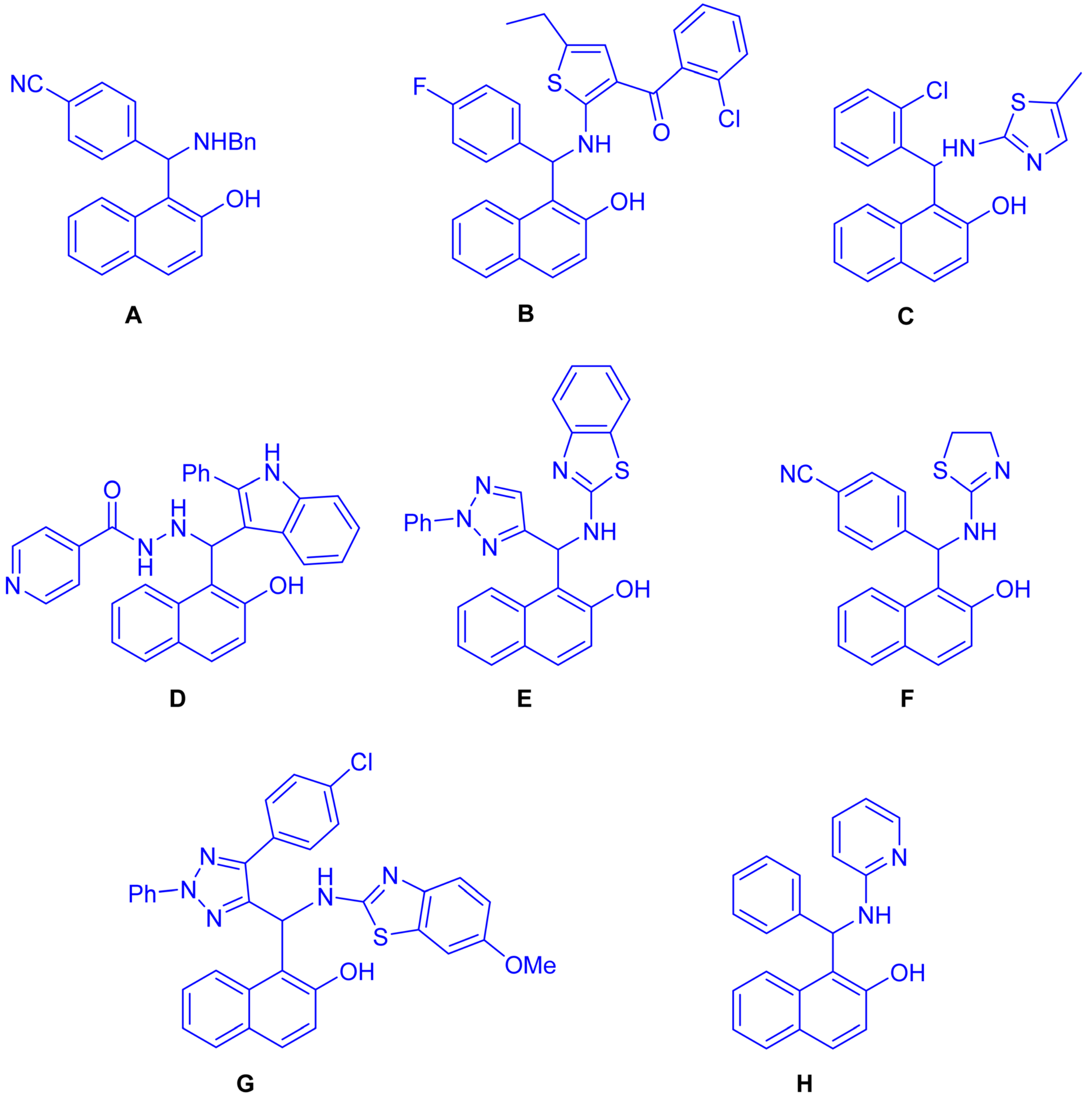


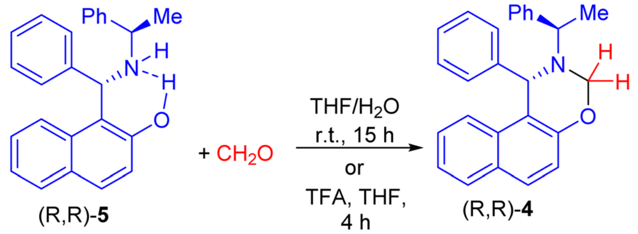
Fig. 1 Structures of Betti bases exhibiting biological activities.

important heterocycles such as biologically active 1,3-oxazine and naphthoxazine derivatives. Because of their broad significance in the medicinal and pharmaceutical industries, research on the synthesis of Betti bases has been ongoing since the early twentieth century. Up to now, a limited number of reviews have been published covering the synthesis of Betti base derivatives and their applications. Indeed, there has been limited discussion on the transformation of these compounds into various organic compounds. The exploration of subsequent reactions and the diversification of Betti base derivatives into different organic compounds is an aspect that has received relatively less attention in the existing review papers.[19–24] In this review, we aim to offer a comprehensive overview of a wide range of methodologies pertaining to the transformation of Betti base derivatives in the synthesis of various organic compounds. Our review examines the diverse strategies employed in these transformations and explores the applications of the resulting organic compounds.

2 Synthesis of naphthoxazines

In 1999, Naso and co-workers reported the reaction of Betti base (*S*)-(+)-**1** with *n*-butanal in EtOH at room temperature for 24 h to produce naphthoxazine (−)-**2** in 68% yield. It was reduced to l-(α-*N*-butylaminobenzyl)-2-naphthol (*S*)(+)-**3** in 60% yield with $NaBH_4$ in CH_3OH at room temperature for 6 h (Scheme 1).[25]

After that, Palmieri *et al.* described synthesis of naphthoxazine **4** by the reaction of enantiopure aminonaphthol **5** with formaldehyde in THF/H_2O at room temperature for 15 h.[26] Also, methylation of (*R*,*R*)-**5** with formaldehyde in the presence of trifluoroacetic acid in THF at room temperature for 4 h afforded naphthoxazine derivative (*R*,*R*)-**4** in 90% yield as depicted in Scheme 2.[27]



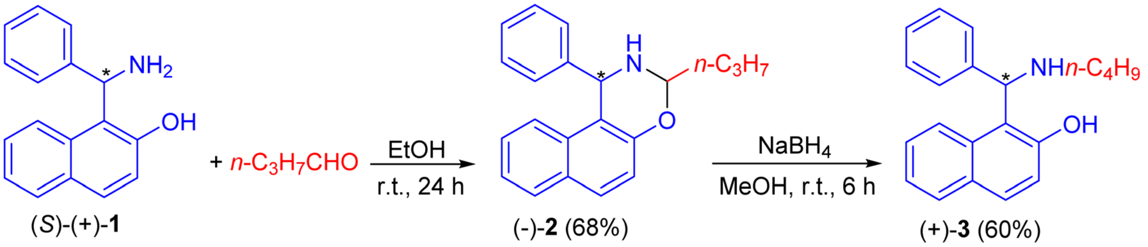
Scheme 2 Synthesis of naphthoxazine **4**.

After that, condensation of Betti base analogue amino naphthols **6** with substituted benzaldehydes in absolute MeOH at ambient temperature for 24 h led to the formation of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **7** in 67–93% yields. The ^{1}H-NMR spectra of **7** revealed that, in $CDCl_3$ solution at 300 K, the members of each set of compounds **7** participated in three-component ring chain tautomeric equilibria containing C-3 epimeric naphthoxazines (**7B** and **7C**) besides the open tautomer **8**. For the 3-(*p*-dimethylaminophenyl)-substituted derivatives, the tautomeric equilibria contained only one ring-closed form (**7B**). Moreover, 3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **9** were also prepared in 72–83% yields from the readily available 1-aminomethyl-2-naphthol (**10**) and aromatic aldehydes in absolute MeOH at ambient temperature for 24 h. In $CDCl_3$ at 300 K, compound **11** proved to participate in ring chain tautomeric equilibria. Moreover, the influence of aryl substituents at position on the ring-chain tautomeric equilibria described by the Hammett equation (Scheme 3).[28]

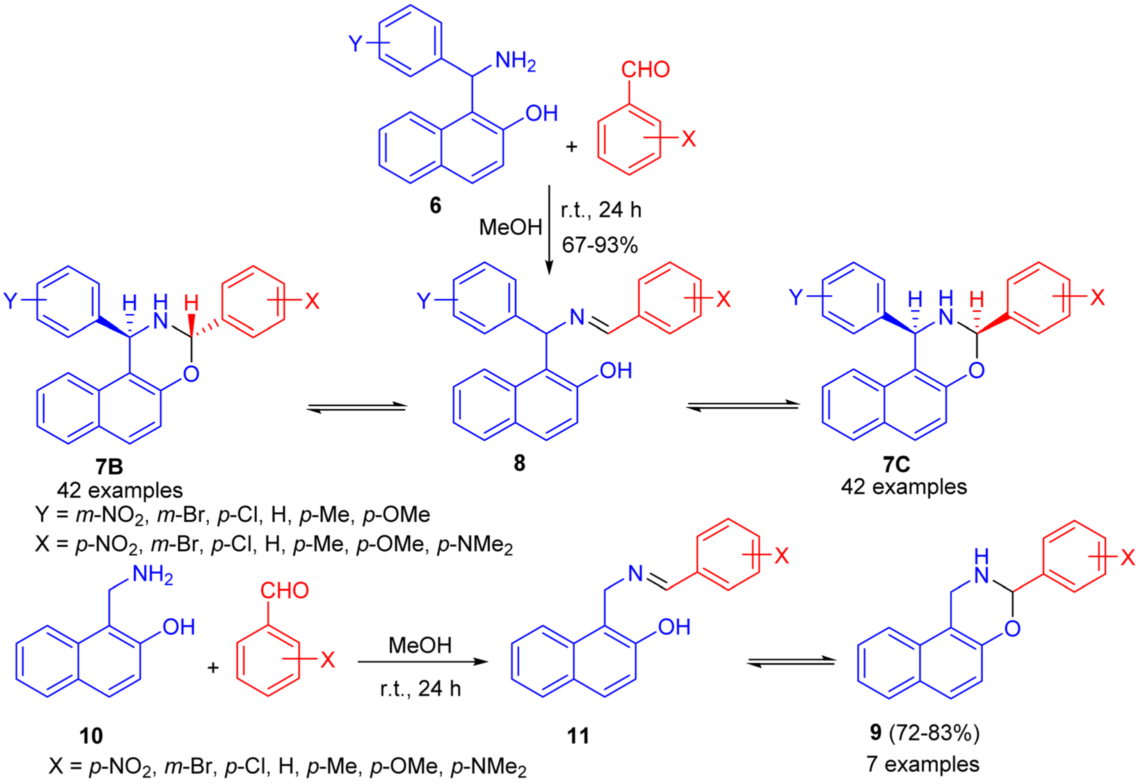
In 2004, Fulop and co-workers synthesized 2,4-diaryl-3,4-dihydro-2*H*-naphth-[2,1-*e*][1,3]oxazines **12** by condensations of aminonaphthol hydrochlorides **13** with equivalent amounts of aromatic aldehydes in the presence of Et_3N in absolute MeOH at ambient temperature for 24 h. The ^{1}H-NMR spectra of **12** proved that, in $CDCl_3$ solution at 300 K, the members of each set of compounds **12** formed three-component tautomeric mixtures, containing C-2 epimeric oxazines **12B** and **12C** together with the open-chain tautomer **12A** as shown in Scheme 4.[29]

Next, a one-pot preparation of chiral *N*-methyl-*N*-alkyl Betti base **14** developed by highly regioselective *N*-alkylation of (*S*)-(+)-Betti base (*S*)-**1**. 2-(*R*)-4-Phenyl-naphtho[1,2-*e*][1,3]oxazine **15**, obtained by condensation of (*S*)-**1** and aldehyde in MeOH at room temperature for 30 min, which *N*-methylated with $BtCH_2OH$ under essentially neutral conditions to yield 2-(*R*)-*N*-benzotriazolylmethyl-4-phenyl-naphtho[1,2-*e*][1,3]oxazine **16** after 1 h. Chiral *N*-methyl-*N*-alkyl Betti base **14** was then obtained by simultaneously cleaving the C–Bt bond and C–O bond in the structure of **16** *via* $LiAlH_4$ in THF under reflux conditions for 0.5 h (Scheme 5).[30]

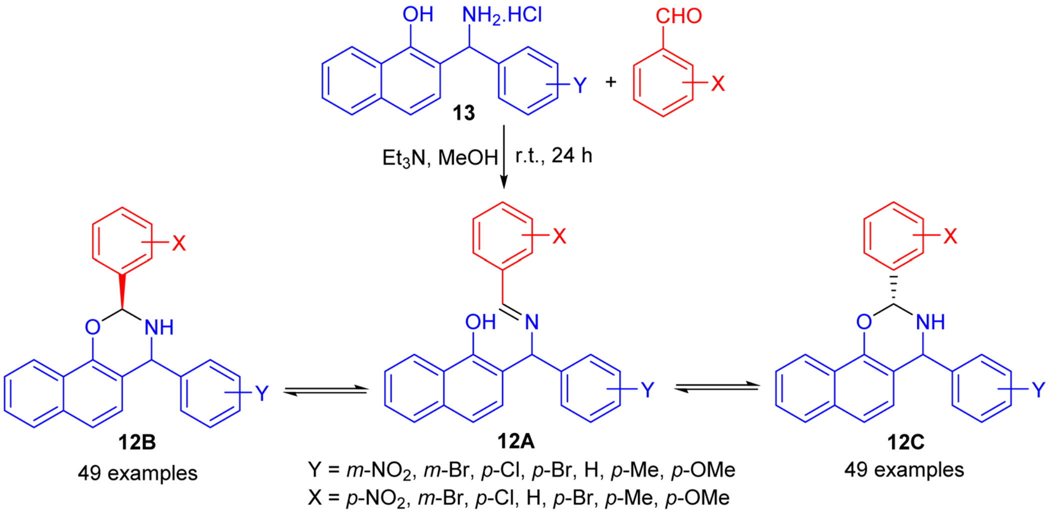
After that, an efficient kinetic resolution of racemic Betti base with L-(+)-tartaric acid in acetone was developed based on a enantioselective *N*,*O*-deketalization, by which the enantiopure *R*- and *S*-enantiomers of Betti base **1** were obtained as the corresponding *N*,*O*-ketal compound **17** and salt with L-(+)-tartaric acid, respectively, in excellent yields with a practically foolproof operation (Scheme 6).[31]



Scheme 1 Preparation of l-(α-*N*-butylaminobenzyl)-2-naphthol (*S*)(+)-**3**.



Scheme 3 Synthesis of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines **7**, **9**.

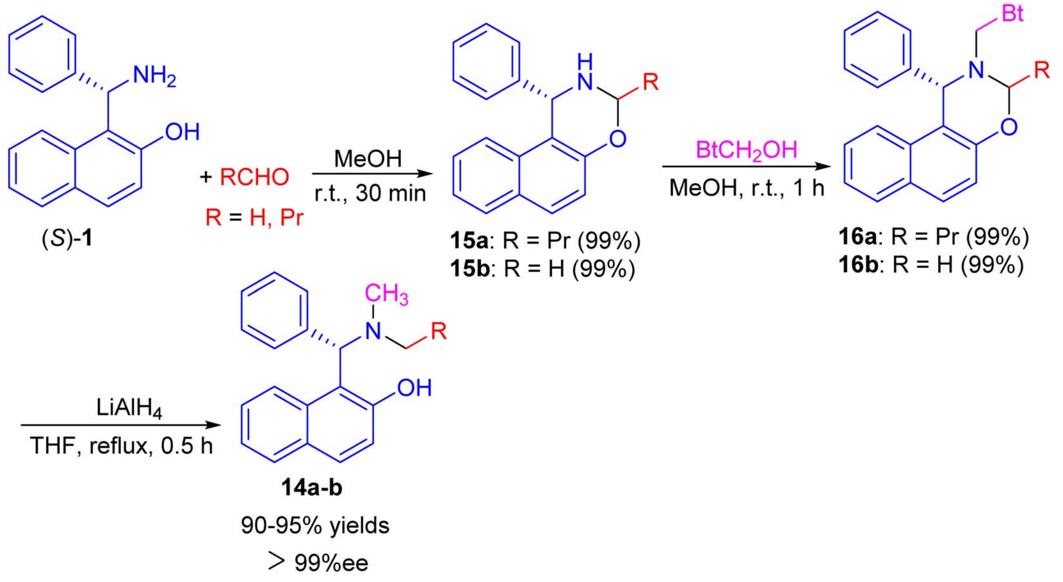


Scheme 4 Synthesis of 2,4-diaryl-3,4-dihydro-2*H*-naphth-[2,1-e][1,3]oxazines **12**.

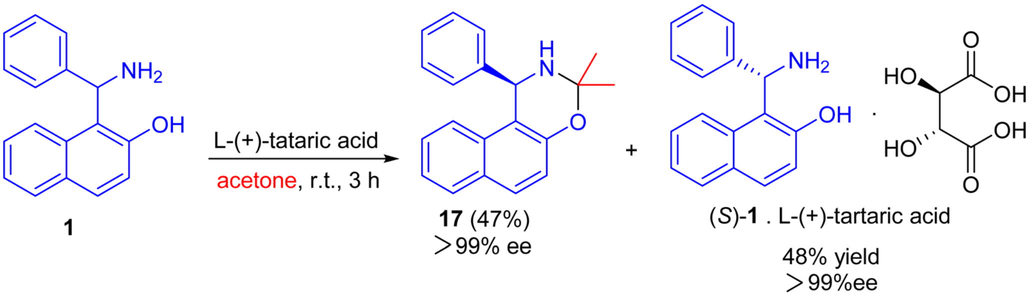
In 2006, Fulop *et al.* developed condensation of aminonaphthol hydrochlorides **18** with substituted benzaldehydes under microwave irradiation in the presence of Et_3N in MeOH at 80 °C for 10 min. The product 1-alkyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **19** was obtained in 15–81% yields, which proved to be three-component tautomeric mixtures in $CDCl_3$ at 300 K. The members of each set of compounds exist in three-component ring-chain tautomeric mixtures containing the C-3 epimericnaphthoxazines (**19a** and **19b**) and also the open tautomer **20** as illustrated in Scheme 7.[32]

In addition, 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **21** prepared in 42–53% yields through the ring-closure reactions of the aminonaphthols **22** with substituted aryl- and heteroaryl aldehydes in MeOH at room temperature for 48 h as depicted in Scheme 8.[33]

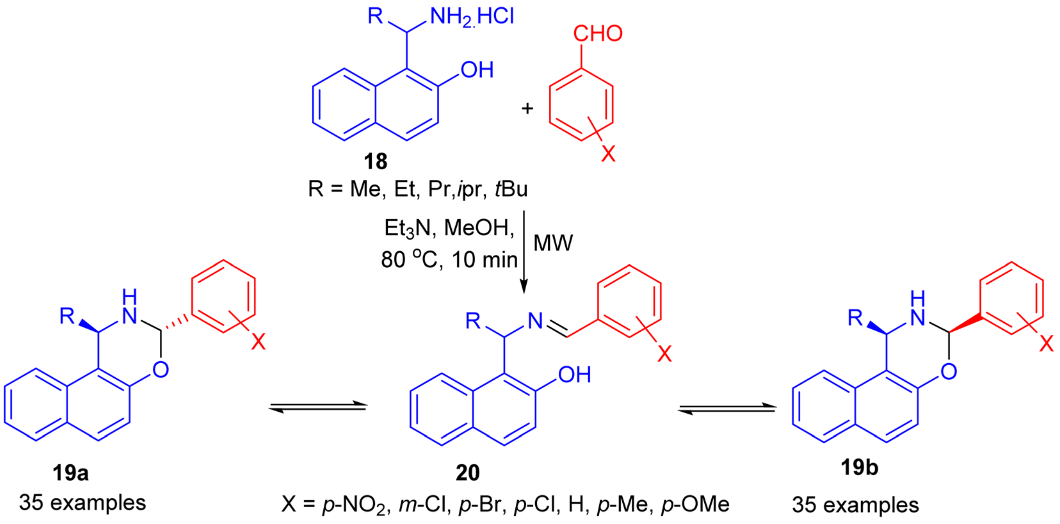
In 2008, naphthoxazine derivatives **23a** and **23b** synthesized in 92–95% yields by the reaction of Betti base derivatives **24a** and



Scheme 5 Synthesis of chiral *N*-methyl-*N*-alkyl Betti bases **14**.

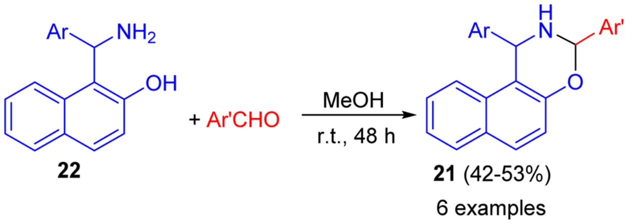


Scheme 6 Kinetic resolution of racemic Betti base **1**.



Scheme 7 Preparation of 1-alkyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **19**.

24b with paraformaldehyde in toluene at room temperature for 10–12 h. The compound **23** was also reduced with $LiAlH_4$ in THF at room temperature for 4–6 h affording aminonaphthol derivatives **25a** and **25b** in 96–98% yields (Scheme 9). The aminonaphthols **24** were found to catalyze the enantioselective ethylation of aryl aldehydes to 1-aryl-1-propanols (up to 92% ee).[34]

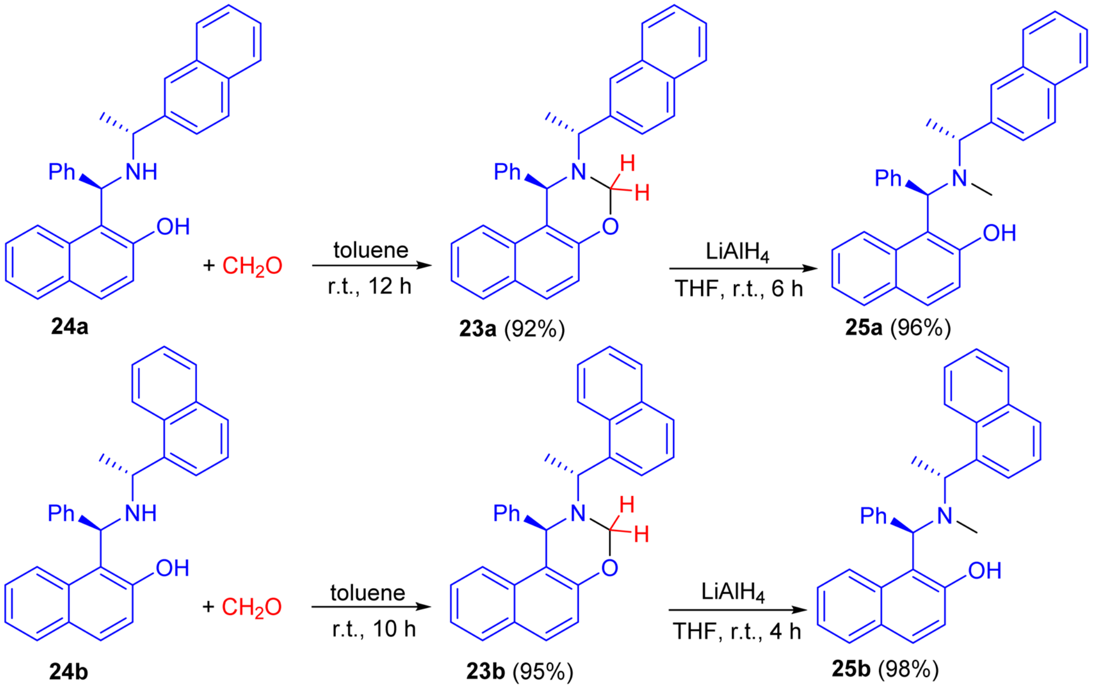


Scheme 8 Synthesis of 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines **21**.

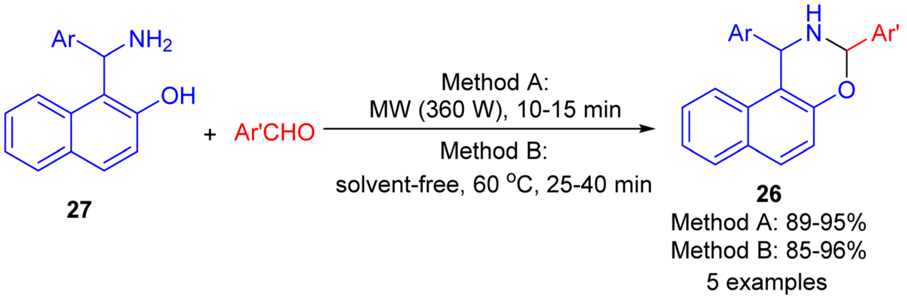
In 2009, synthesis of 1,3-oxazine derivatives **26** reported in 85–96% yields by the reaction of Betti base **27** with aromatic/heteroaromatic aldehydes under microwave irradiation (360 W) for 10–15 min or solvent-free conditions at 60 °C for 25–40 min. The simplicity of the reaction conditions, their efficiency, and the excellent results in shorter reaction times using both method A and method B under solvent and catalyst-free conditions, constitute an attractive contribution among the existing methodologies (Scheme 10).[35]

After that, the condensation of Betti base **1** and aliphatic aldehydes such as 1-butanal and $(MeO)_2CHCHO$ in MeOH at room temperature for 30–60 minutes afforded the corresponding *N*,*O*-acetal **28** and **29** in almost quantitative yields even without the use of an acidic catalyst. Also, alkylation of **29** by RMgBr was accomplished quickly in THF at room temperature within 30 minutes to give the desired product **30** in 85–96% isolated yield. Then, the diaryl benzylamine **30** was *N*-debenzylated quantitatively under mild Pd/C catalytic hydrogenolysis conditions in $ClCH_2CHCl_2$/MeOH at room temperature for 2–6 h, afforded 1-substituted 2,2-dimethoxyethylamine hydrochlorides **31** in 90–99% yields. The method reported is extremely convenient and highly efficient with wide substrate scopes (Scheme 11).[36]

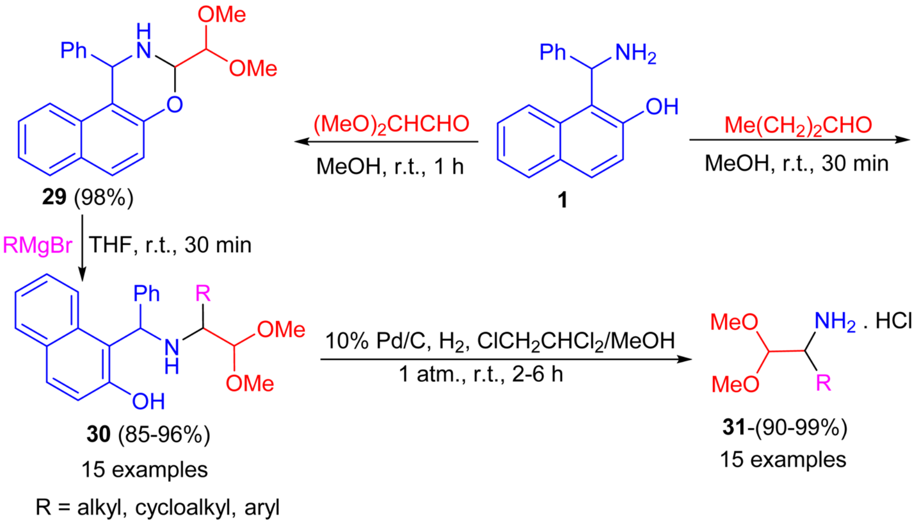
Next, the reaction of aminomethylnaphthols **32a** and **32b** and **33a** and **33b** with paraformaldehyde using Et_3N in $CHCl_3$



Scheme 9 Synthesis of naphthoxazine derivatives **23** and chiral aminonaphthols **25**.



Scheme 10 Synthesis of 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-e][1,3]-oxazines **26**.



Scheme 11 Preparation of naphthoxazines **28** and **29** and 1-substituted 2,2-dimethoxyethylamine hydrochlorides **31**.

for 6 h, phosgene in toluene/H_2O in the presence of Na_2CO_3 for 10 min and 4-chlorophenyl isothiocyanate in the presence of Et_3N for 6 h followed by the reaction with MeI in MeOH using KOH at room temperature for 4 h led to naphthoxazine derivatives **34**, **35**, **38**, **39** and **41** as shown in Scheme 12.[37]

In 2010, Shi and co-workers described synthesis a series of naphtho[1,2-*e*][1,3]oxazine derivatives such as *trans*-1,3-diaryl-1*H*-naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl chloride **42**, 1-aryl-2-benzyl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazine-3-one **43**, and *trans*-1,3-diaryl-1*H*-naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbaldehyde **44** in 65–96% yields *via* a chemoselective reaction of compound **45** with triphosgene or triethyl orthoformate in THF under reflux conditions, respectively, induced by different low-valent titanium/M systems. In these reactions, when the $TiCl_4$/Mg system was used, $TiCl_4$ is reduced by Mg dust to give low-valent titanium species, which catalysed the reaction of ring-closed tautomer and triphosgene to give product **42**. When the $TiCl_4$/Sm system was used, $TiCl_4$ is reduced by Sm to give low valent titanium species and Sm^{2+}. In the initial step, the open tautomer was reduced by Sm^{2+} and low-valent titanium to aminophenol intermediate **46.** Then products **42** were obtained by the reaction of **46** and triphosgene catalyzed by low-valent titanium species. This method has the advantages of short reaction time, high chemoselectivity, accessible materials, and convenient manipulation (Scheme 13).[38]

After that, a series of 8-bromo-1,3-bis(aryl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines **47** synthesized in 52–69% yields by the reaction of Betti base **48** with substituted aryl and heteroarylaldehydes in MeOH at ambient temperature for 48 h (Scheme 14). Some of the compounds found to exhibit good activity against tested bacterial and fungal strains. Compounds having fluoro, chloro and methyl substituted phenyl group attached to naphthoxazine showed promising activity.[39]

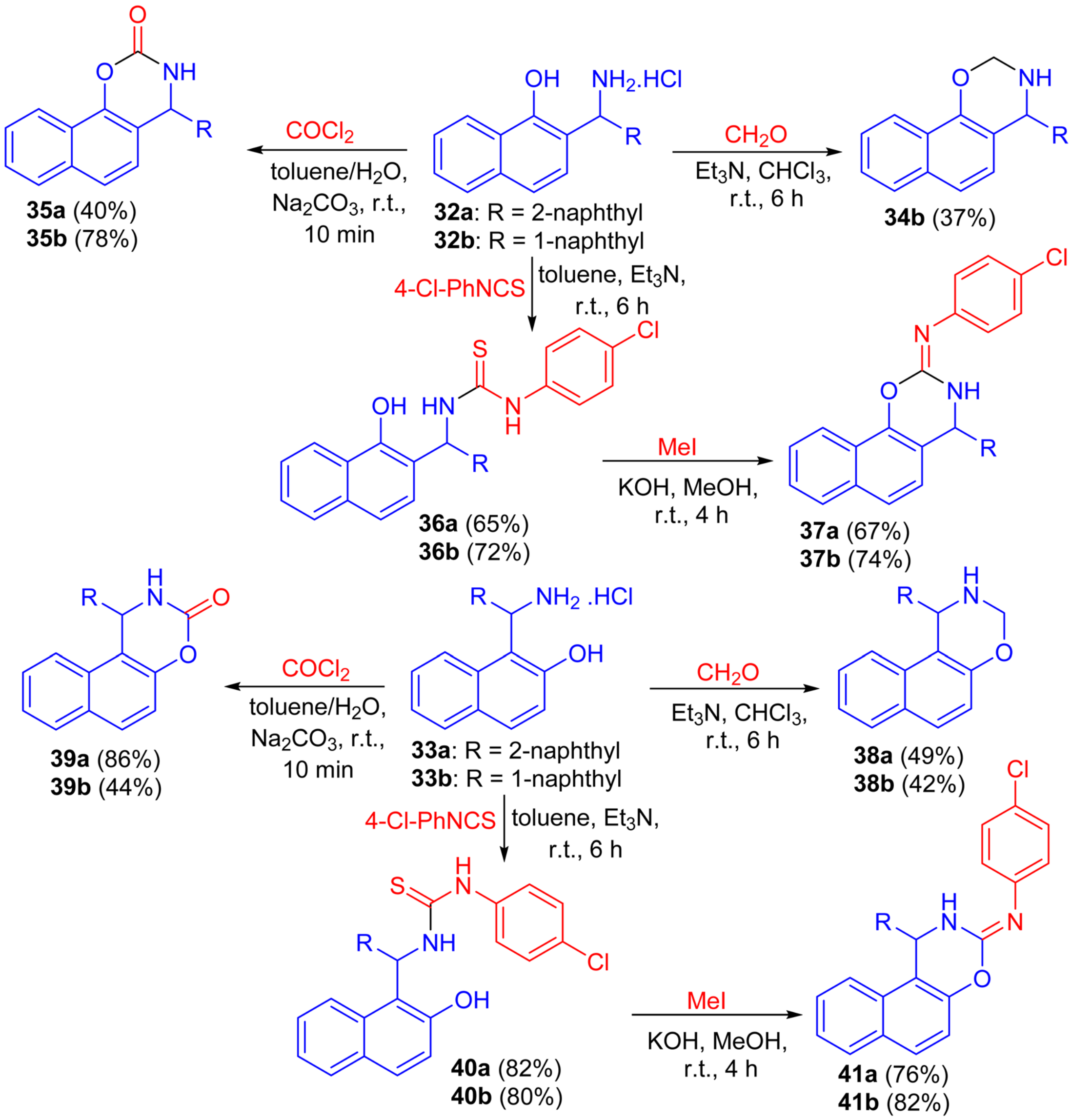
In addition, the reaction of aminonaphthol derivatives **49** with formaldehyde in THF at room temperature for 15 h gave naphthoxazine derivatives **50** in 90–95% yields, which were reduced with sodium boronhydride in THF/HOAc at room temperature to afford the target chiral aminonaphthol ligands **51** in 78–87% yields (Scheme 15). The results of asymmetric phenyl transfer to aromatic aldehydes catalyzed by these chiral ligands **51** indicated that enantioselectivities were greatly influenced by the electronic and steric effects of the ligands.[40]

In 2013, Dimitrov and co-workers have demonstrated Betti base derivatives **52** were easily transformed into the corresponding 1,3-oxazines **53a–e** in 24–99% yields by reacting them with formaldehyde (in the form of paraformaldehyde or formalin) in EtOH at 20 °C or 55 °C for 30 min to 24 h (Scheme 16).[41]

In 2014, Khosropour and his group described stereoselective synthesis of *trans*-3-(5-methylisoxazol-3-yl)-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine derivatives **54** in high yields (75–98%) by the reaction of 1-(aryl (5-methyl-isoxazol-3-ylamino) methyl)naphthalen-2-ols **55** with aromatic aldehydes using *p*-TSA as catalyst under solvent-free conditions at 100 °C for 30–40 min. This reaction includes some important aspects like straightforward operation, easy workup procedure and absence of transition metal catalysts. In the proposed mechanism, first, the Betti base attacks aryl aldehyde in the presence of the catalyst to generate the corresponding imine as the pivotal intermediate. Finally, the intermediate undergoes 6-*endo*-dig to give the corresponding [1,3]oxazine **54** as illustrated in Scheme 17.[42]

Next, Srimannarayana *et al.* reported preparation of (*S*)-naphthoxazines **56** with diastereoisomeric ratios (dr) in almost equal in 69–89% yields by the treatment of L-(+)-tartaric acid salt of the (*S*)-enantiomer **1** with various racemic α-alkyl dihydrocinnamic aldehydes (2-alkyl-3-phenylpropanals) **57** in MeOH at 60 °C for 25 h (Scheme 18).[43]

Further, a number of chiral racemic and enanthiopure thiophosphorylated thioureas **58** synthesized by the reaction of 1-(α-aminobenzyl)-2-naphthol **1** with *O*,*O*-diethyl thiophosphoryl isothiocyanate **59** in dry benzene at room temperature for 24 h. It was found that such thioureas undergo the cyclization reaction under basic conditions with hydrogen sulfide elimination



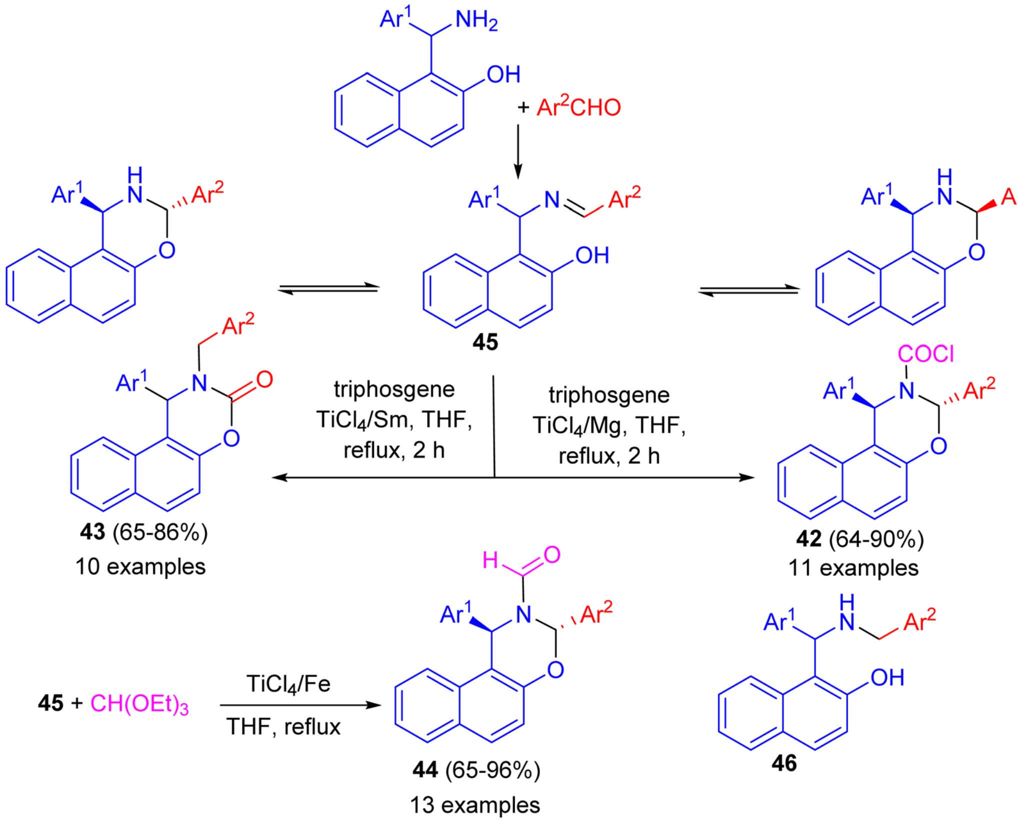
Scheme 12 Synthesis of naphthoxazine derivatives **34**, **35**, **38**, **39** and **41**.

via two methods (method A: in dry acetone, triethylamine or 4-(dimethylamino)pyridine at room temperature for 7 days; method B: in chloroform and hexane, *N*,*N*′-dicyclohexylcarbodiimide at reflux for 4 h) and afforded thiophosphorylated oxasines **60** as depicted in Scheme 19.[44]

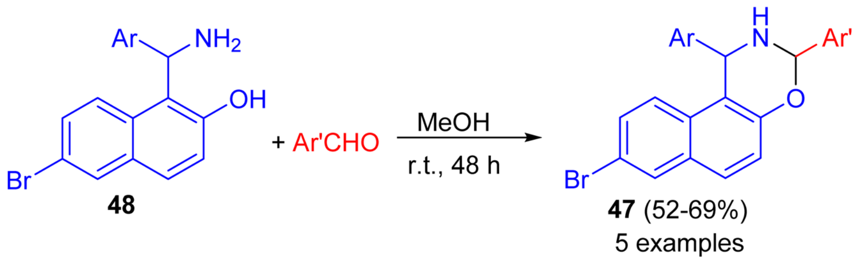
In 2017, Paolucci and co-workers accomplished synthesis of naphthoxazines **61** in 75–94% yields by the reaction of α-epimerizable 4-hydroxybutyraldeydes **62** with (*S*)-Betti base **1** in MeOH at room temperature for 2 h or 2.5–20% AcOH in MeOH at 60 °C for 16–69 h. The diastereoisomeric naphthoxazines **61** underwent hydrolysis by using pre-washed resin 20 in a mixture of aq. H_2SO_4, THF and acetic acid within 3–5 hours, and the aldehydes are obtained with higher enantiomeric enrichment (Scheme 20).[45]

In 2018, Alfonsov *et al.* developed a method to synthesize oxazines **63** in 69–76% yields by the reaction of the racemic Betti base **1** with 2-, 3-, and 4-pyridinecarbaldehydes in benzene under reflux for 4 h. In the solution, a three-component ring-chain equilibrium is established between the imine form and *cis*- and *trans*-oxazines. It should be noted that the content of the imine form ($CDCl_3$) in a series of compounds **63** is significantly lower compared with 1,3-diphenylnaphthoxazine. *Trans* form is predominant in all cases (Scheme 21). It can be assumed that the imine/oxazine ratio is mainly influenced by electronic interactions, while the *cis*-/*trans*-1,3-oxazine ratio is more influenced by steric factors.[46]

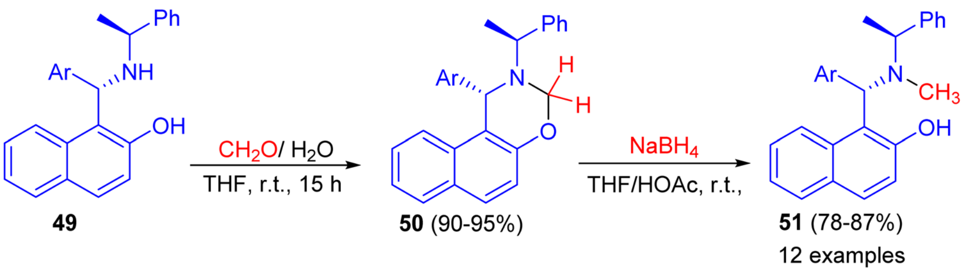
In 2020, a series of naphtho[1,2-*e*][1,3]oxazines **64** in 43–78% yields bearing arylsulfonamide moiety synthesized *via* a one-pot reactions of 1-(amino(aryl)methyl)naphthalen-2-ol hydrochloride **65**, dimethyl arylsulfonylcarbonimido dithioate **66** using Na_2CO_3 in H_2O/EtOH (1 : 3) under reflux conditions for 2 h (Scheme 22). All of the compounds examined for their *in vitro* anticancer activity against breast (MCF-7), colon (HCT116), and B-CLL (Waco3-CD5) cancers. Some of these compounds showed



Scheme 13 Synthesis of naphtho[1,2-*e*][1,3]oxazine derivatives **42–44**.

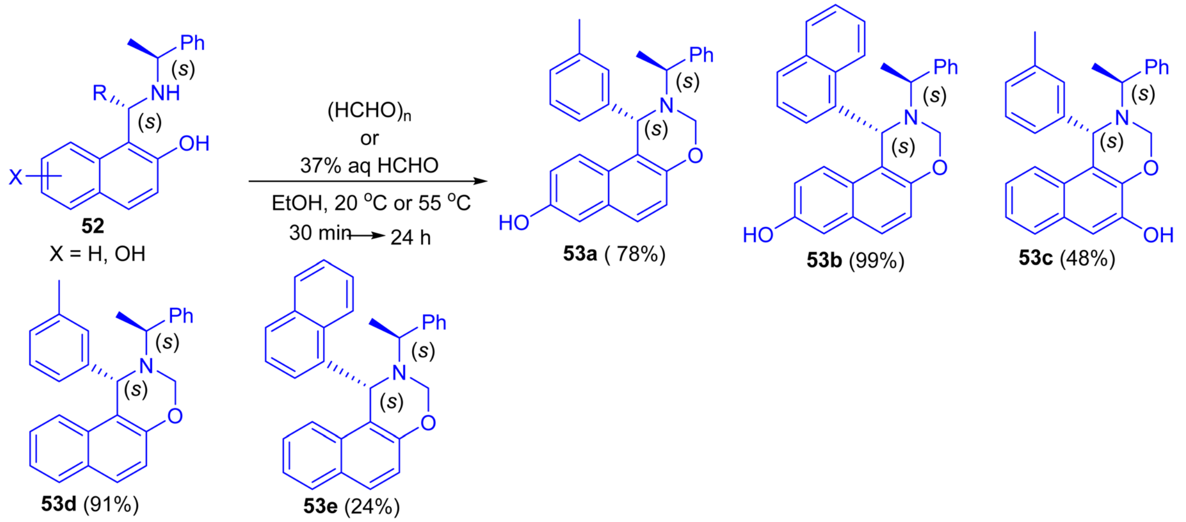


Scheme 14 Synthesis of 8-bromo-1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines **47**.

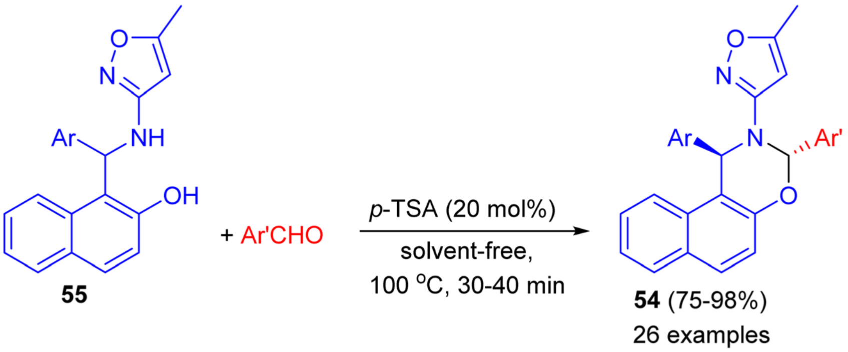


Scheme 15 The preparation of chiral aminonaphthol ligands **51**.

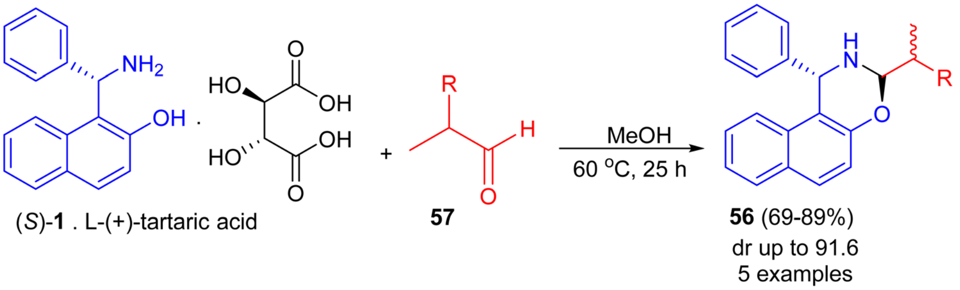
remarkable activities against MCF-7 (breast) and HCT116 (colon) cancers with comparable IC_{50} (the half maximal inhibitory concentration) values as that of known drugs such as 5-fluorouracil (5-FU). *In vitro* antimicrobial activities of all compounds were also evaluated against five human pathogenic fungi strains and two bacteria (one Gram positive and one Gram



Scheme 16 Synthesis of 1,3-oxazines **53a–e**.



Scheme 17 Diastereoselective synthesis of *trans*-3-(5-methylisoxazol-3-yl)-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazines **54**.



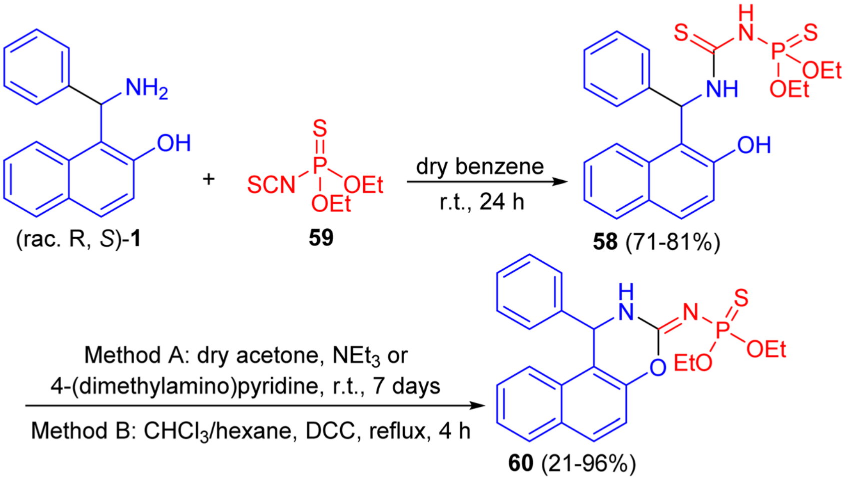
Scheme 18 Preparation of (*S*)-naphthoxazines **56**.

negative). The best MICs (Minimum Inhibitory Concentrations) were found against the *C. albicans*.[47]

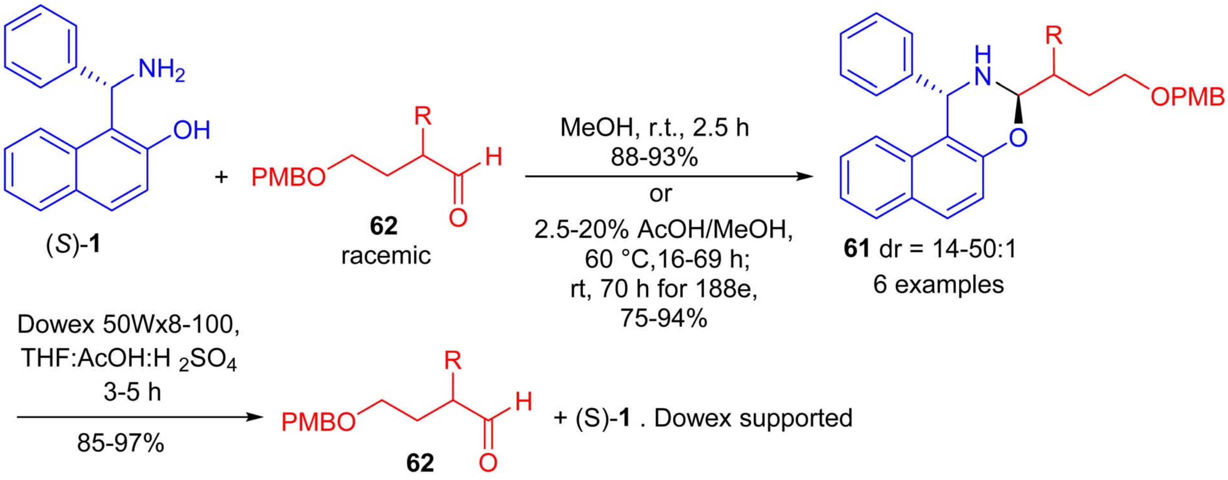
3 Synthesis of bis-naphthoxazines

In 2014, synthesis of bis-(isoxazolyl-1,3-oxazine)naphthalenes **67** in 76–89% yields accomplished by the reaction of Betti bases **68** with formaldehyde (37%) in acetonitrile under reflux conditions for 5 h. The synthesized compounds were evaluated for *in vitro* antimicrobial activity. Compounds **67a** and **67b** were proved to possess remarkable antimicrobial activity (Scheme 23).[48]

In 2016, Paolucci *et al.* described the synthesis of *trans*, *trans*-bisdihydrooxazinic compounds **69** in 50–98% yields from (*R*)-Betti base **1** and various dialdehydes in THF or MeOH at room temperature for 24 h to 4 days. Reduction of **69** with diisobutylaluminium hydride (DIBAL-H) in CH_2Cl_2 at room temperature for 2 h gave the corresponding compound **70** in very good



Scheme 19 Synthesis of thiophosphorylated oxazines **60**.



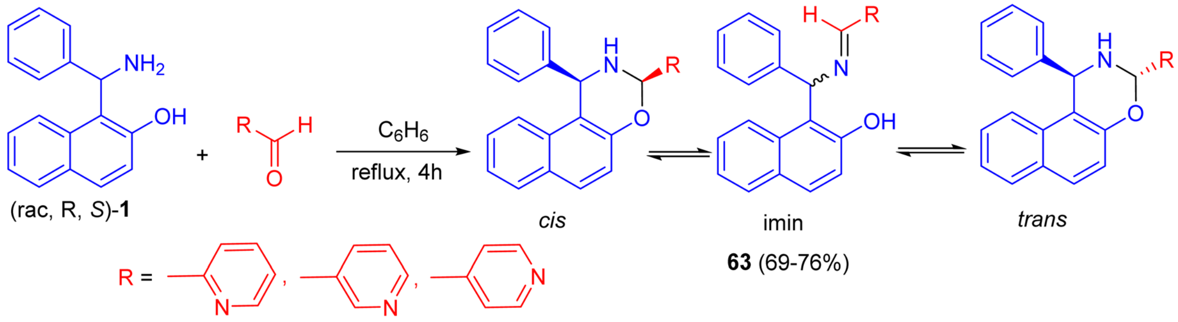
Scheme 20 Synthesis of naphthoxazines **61**.

yields. The oxidation of compound **69a** with $PhI(OAc)_2$ in MeOH for 2 h afforded bisoxazinic compound **71** in 68% yield as shown in Scheme 24. Two Cu complexes and one Sc complex were prepared from compound **71**. The metal complexes were employed in some reactions to test their ability to promote the transformation and the asymmetric induction.[49]

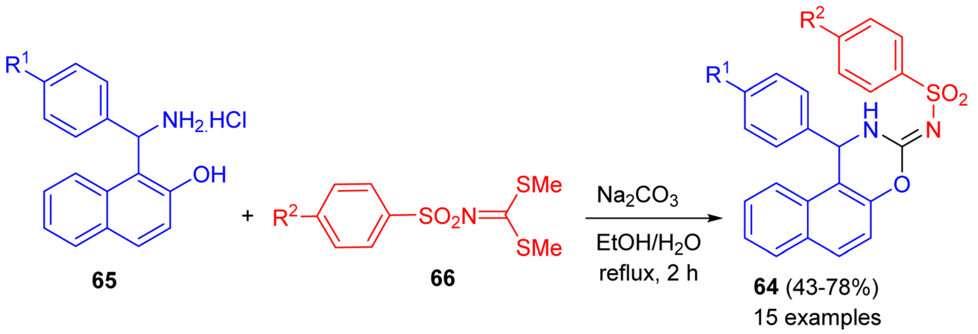
4 Synthesis of naphthopyrrolooxazines, naphthopyridooxazines and naphthooxazinoazepines

In 2002, Hu *et al.* synthesized unsubstituted piperido[2,1-*b*] oxazine derivative **72a** in 61% yield by the reaction of (*S*)-**1** with 1,5-pentanedial in the presence of $NaBH_3CN$ in a buffer solution (aqueous EtOH solution of Na_2HPO_4–KH_2PO_4) at 0 °C for 1.5 h. Similarly, **72b** (59%) and **72c** (51%) were obtained smoothly by using 1,4-butanedial and 1,6-hexanedial, respectively. When compounds **72** were treated with $LiAlH_4$, the CO bond was cleaved selectively to yield the desired cycloamine-phenols without any loss of enantiomeric excess at −10 °C in 1.5 h. The asymmetric addition of $ZnEt_2$ to benzaldehyde was tested in toluene with 10 mol% of cycloamine-phenol ligands to give the products in 93–96% yields and 73–99% ee (Scheme 25).[50]

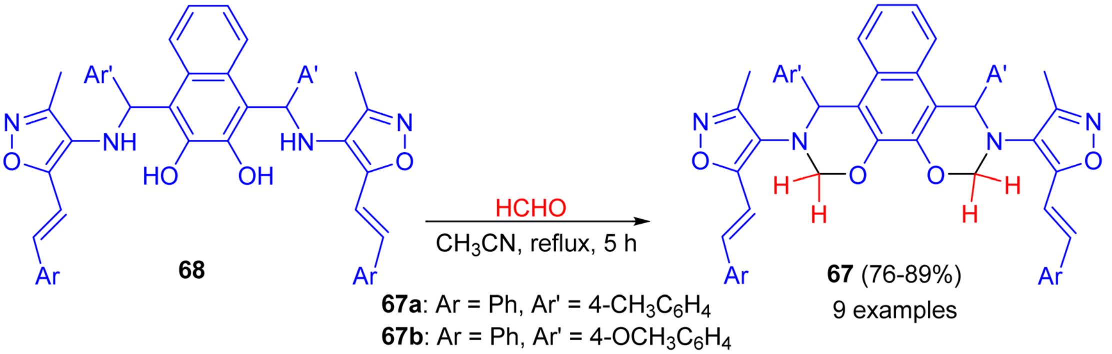
After that, unsubstituted tetrahydropyrido-[2,1-*b*]oxazine **72d** was obtained in 76% yield *via* the reaction of (*S*)-**1** with pentane-1,5-dial in the presence of $NaBH_3CN$ in an aqueous buffer solution (Na_2HPO_4–KH_2PO_4) at room temperature for 12 days. Also, the salt of (*S*)-**1** with L-(+)-tartaric acid, which is a precursor of (*S*)-**1** in its optical resolution, was used directly as the starting material and **72d** was obtained in 61% yield within 30 min in 50% aqueous EtOH. Similarly, **72e** (59%) and **72f** (51%) were prepared respectively by the replacement of pentane-1,5-dial with butane-1,4-dial and hexane-1,6-dial under the same conditions. These compounds converted to non-racemic 1-[-(1-azacycloalkyl)benzyl]-2-naphthols **72g–i** by the selective



Scheme 21 Synthesis of oxazines **63**.



Scheme 22 Synthesis of naphtho[1,2-*e*][1,3]oxazines **64**.

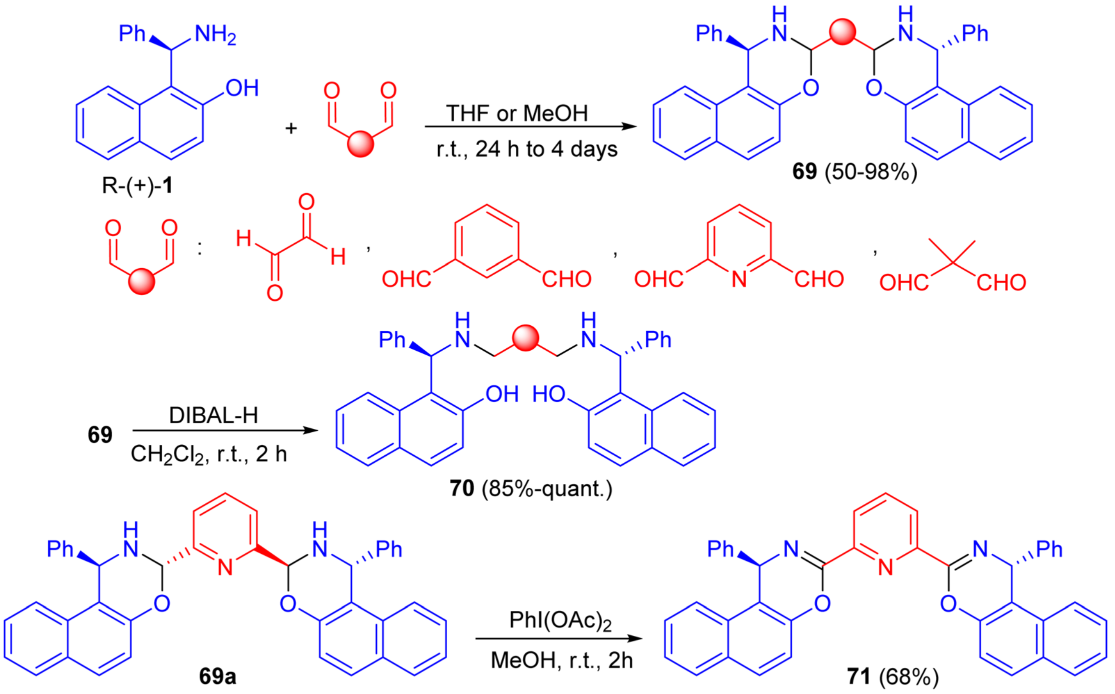


Scheme 23 Synthesis of bis-(isoxazolyl-1,3-oxazine)naphthalenes **67**.

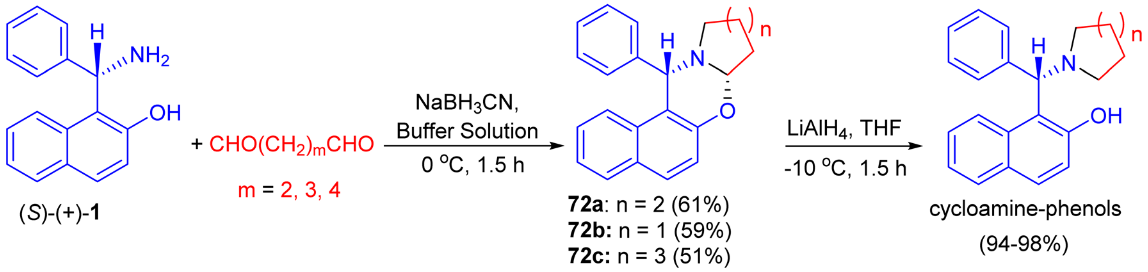
cleavage of a C–O bond with $LiAlH_4$ in THF at −10 °C for 1.5 h. The ligands with pyrrolidine and piperidine lead to highly efficient asymmetric induction in the addition of diethylzinc to aryl aldehydes with up to 96% yield and 99% ee (Scheme 26).[51]

In 2004, following Katritzky's procedure, a mixture of *S*-**1** [as a salt of L-(+)-tartaric acid], pentane-1,5-dial and BtH in CH_2Cl_2 was stirred at 0 °C for 5 hours. As expected, the diastereopure α-benzotriazolyl-piperido[2,1-*b*][1,3]-oxazine **73a** was obtained in 91% yield (Scheme 2). Similarly, replacement of pentane-1,5-dial by butane-1,4-dial and hexane-1,6-dial, the five- and seven membered azacyclic analogues **73b** and **73c** were obtained respectively in high yields (93% and 91%) and diastereoselectivities. Moreover, both C–Bt and C–O bonds in the oxazines **73** were cut clearly *via* $LiAlH_4$ within half hour at 0 °C to afford chiral Betti bases in high yields, which have been proved to be excellent chiral ligands in the asymmetric addition of $ZnEt_2$ to aldehydes (Scheme 27).[52]

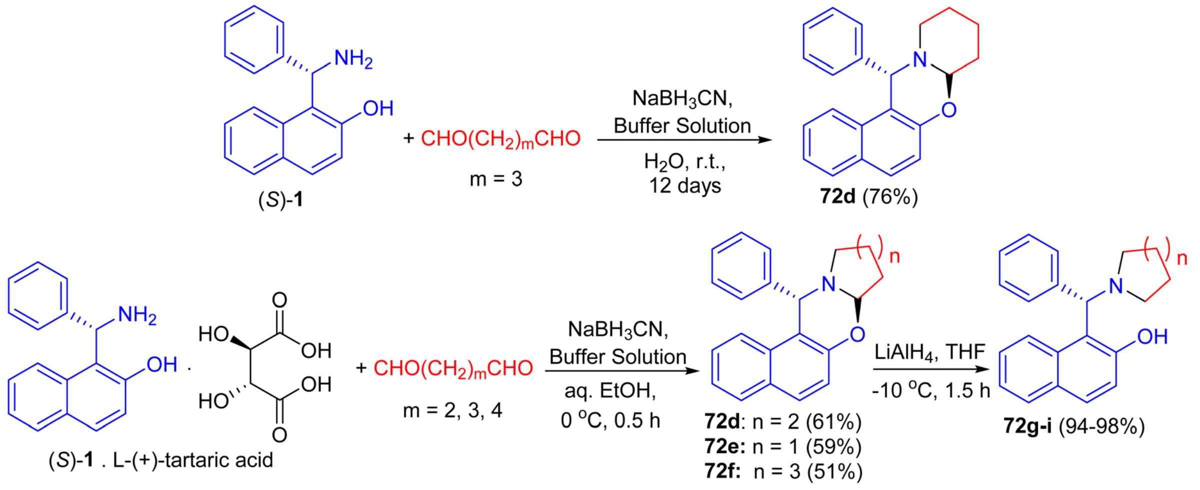
In 2005, total syntheses of enantiopure alkaloidal natural products (2*S*,6*R*)-dihydropinidine (**74a**, as hydrochloride) and (2*S*,6*R*)-isosolenopsins (**74b–e**, as hydrochlorides) achieved with the shortest steps and unprecedented high total yields by using a strategy of the formation-cleavage of 1,3-oxazinane. First, Betti base (*S*)-**1** [as a salt of L-(+)-tartaric acid] condensed with pentane-1,5-dial and benzotriazole to diastereopurely yield **75** in 92% yield. By using THF as solvent, a solvent controlled monoalkylation of **75** was achieved to give diastereopure **76** in 96% yield. Then **76** was alkylated with the corresponding Grignard reagent followed by *N*-debenzylation straightforward



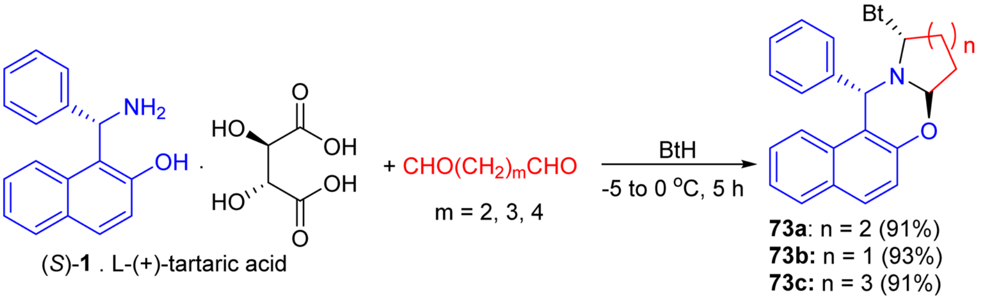
Scheme 24 Synthesis of compounds **69–71**.



Scheme 25 Synthesis of oxazine derivatives **72**.



Scheme 26 Synthesis of tetrahydropyrido[2,1-*b*]oxazines **72d–f**.



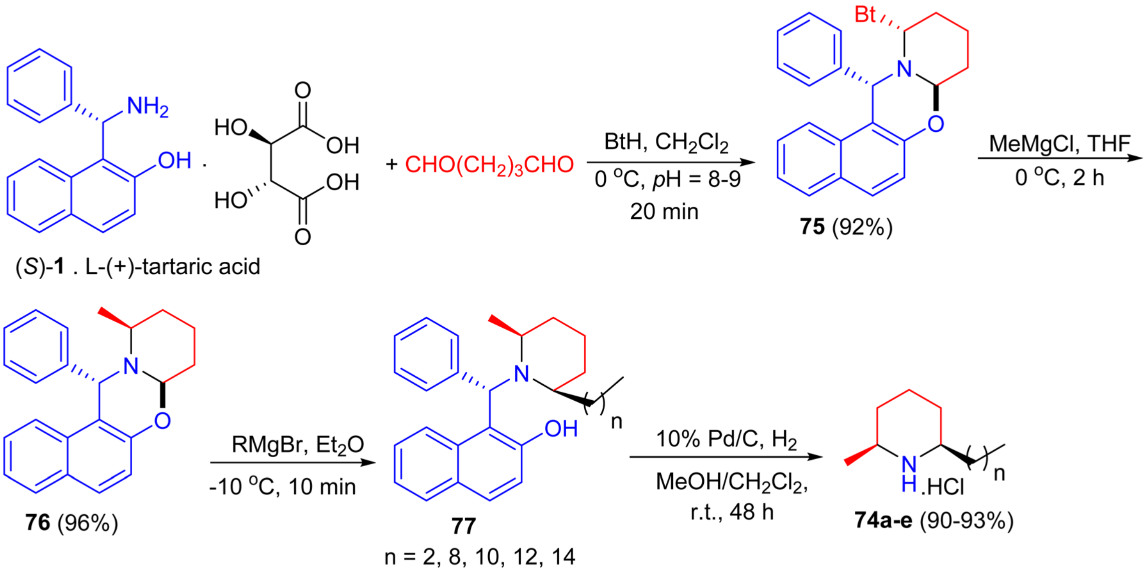
Scheme 27 Preparation of α-benzotriazolyl 1-piperido[2,1-*b*][1,3]-oxazine **73a–c**.

to amine hydrochloride by Pd/C-catalyzed hydrogenolysis in the presence of CH_2Cl_2 to yield target products **74a–e** in 90–93% yields (two steps), respectively (Scheme 28).[53]

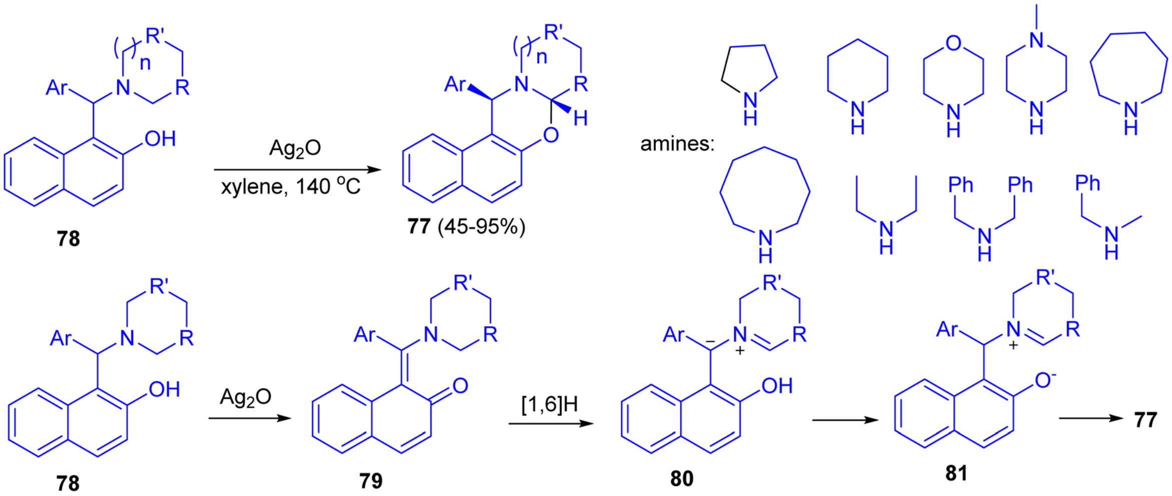
In 2014, Jana and co-workers reported diastereoselective α-C–H functionalization of aliphatic N-heterocycles for the synthesis of ring fused oxazines **77**. The reaction of Betti base derivatives **78** with Ag_2O in xylene at 140 °C afforded the desired product **77** in 45–95% yields. A probable mechanism is depicted in Scheme 29. First, Betti base **78** reacted with Ag_2O to provide the corresponding *o*-quinone methide **79**. Thus a 1,6-H (alpha to the nitrogen) transfer can be operative on **79** to furnish the zwitterionic intermediate **80**. Alternatively, **80** can also be formed *via* mesomerization of quinone methide **79** followed by a proton transfer. Protonation of **80** and subsequent diastereoselective cyclization of the resulting iminium ion **81** gave rise to *trans*-oxazine **77**. The electron-withdrawing group on Ar and the electron donating nature of R will stabilize the zwitterionic intermediate **80**. The expected lower yields for morpholine derivatives are due to the reduced stability of the zwitterionic intermediate **80** because of the negative inductive effect of the ring oxygen atom.[54]

In 2016, Karade *et al.* synthesized a series of 1,3-napthoxazines **82** in 58–81% yields by the reactions of 1-(α-aminoalkyl)-2-naphthols **83** with (diacetoxyiodo)benzene (DIB) in CH_2Cl_2 at room temperature for 6–24 h. This synthesis of 1,3-naphthoxazine involves transition metal-free cross-dehydrogenative C–O bond formation at sp^3 C–H bond adjacent to tertiary nitrogen. The tentative mechanism is shown in Scheme 30. The reaction of DIB with phenolic substrate **83** can inhibit the oxidative dearomatization due to the formation of putative six membered iodine(III) heterocycle **84**. The propensity of **84** for reductive elimination of iodobenzene will generate the requisite iminium ion **85** which will be intramolecularly trapped by phenoxide anion to form *trans*-1,3-naphthoxazine **82**.[55]

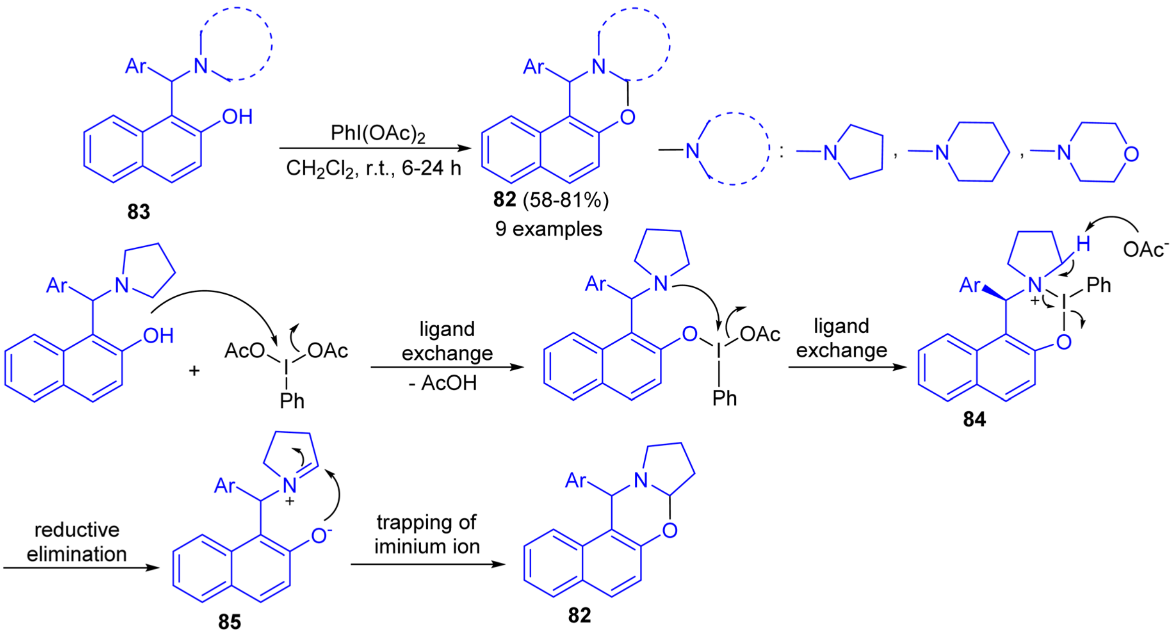
Deb and co-workers developed an iodine-*tert*-butylhydroperoxide for the synthesis of 1,3-oxazines **86** in 85–94% yields from Betti bases **87** under heating at 130 °C in DMF as solvent within 15–30 min. The method uses inexpensive and nonhazardous I_2 catalyst and TBHP as the oxidant. Moreover, the reaction could easily be scaled up to multigram scale with excellent yield, in which the product can be successfully isolated by recrystallization. The proposed a tentative mechanism for the reaction is outlined in Scheme 31. First, **87** is converted to



Scheme 28 Total syntheses of enantiopure (2*S*,6*R*)-dihydropinidine and (2*S*,6*R*)-isosolenopsins **74**.



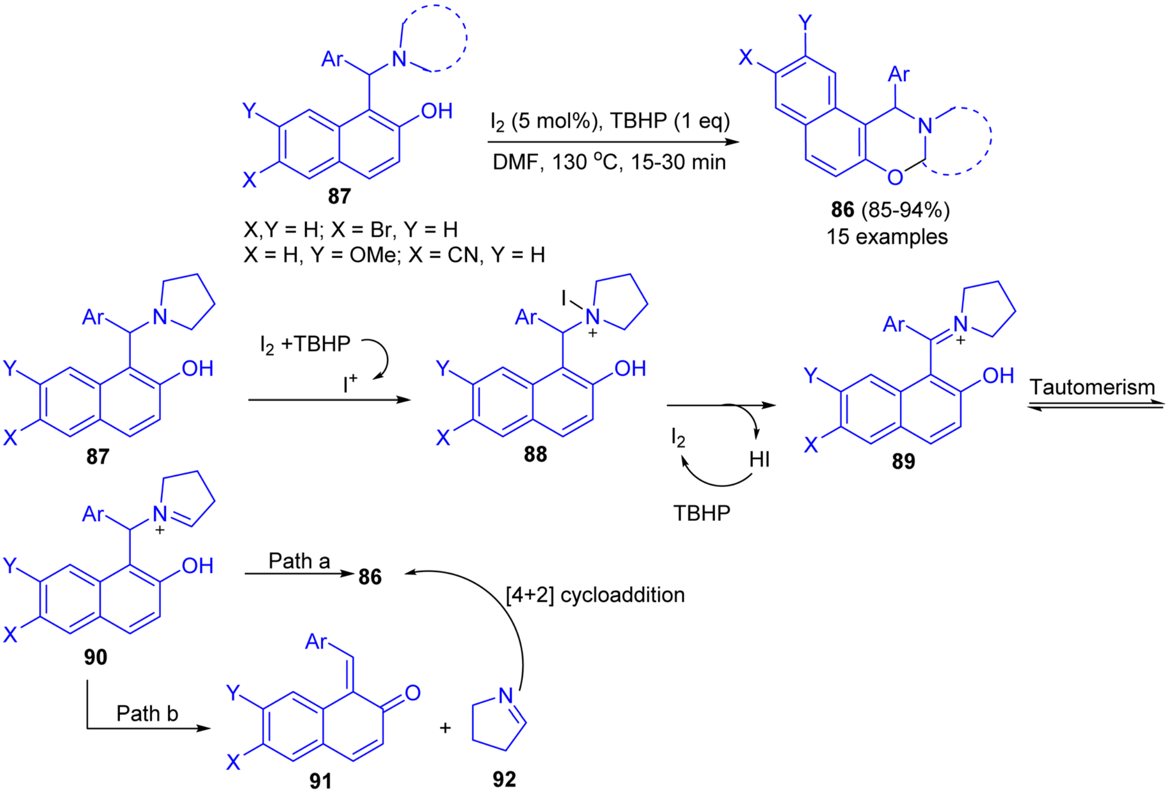
Scheme 29 Synthesis of ring fused oxazines **77**.



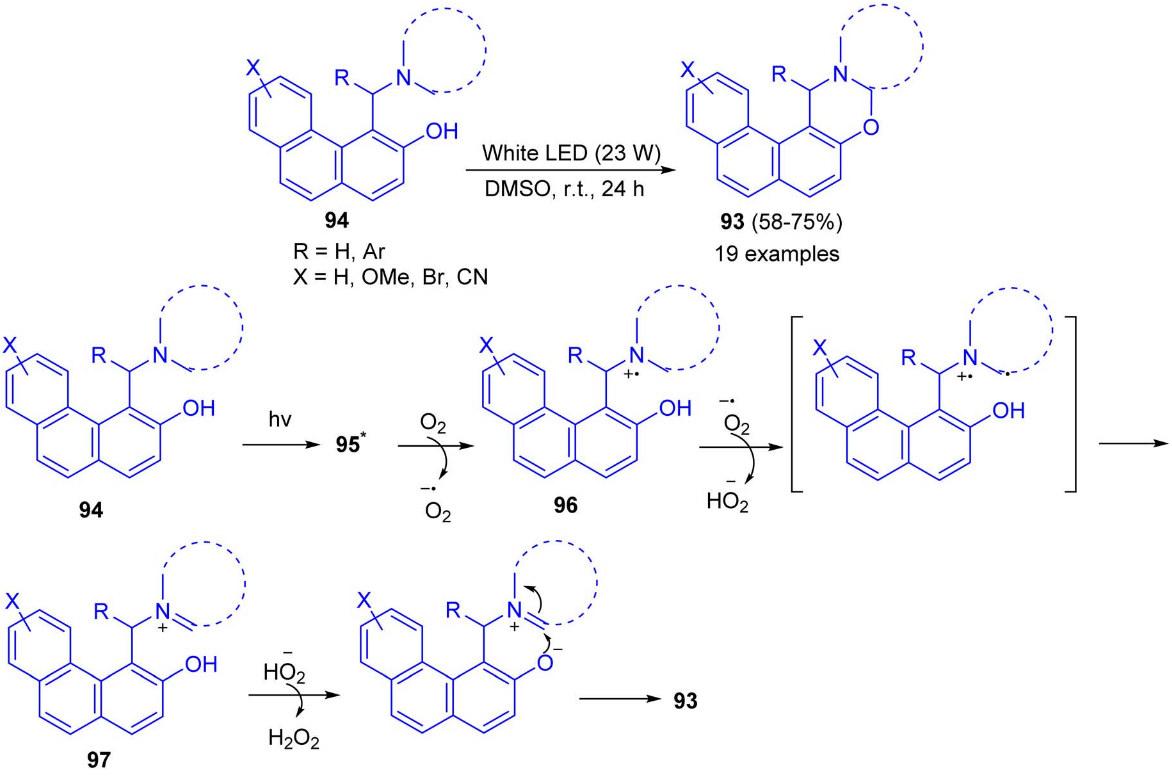
Scheme 30 Synthesis of 1,3-naphthoxazines **82**.

iodopyrrolidinium **88** in the presence of iodine source. The intermediate **88** then releases a molecule of HI to form iminium ion **89**, which undergoes tautomerisation to iminium ion **90**. Next, **90** undergoes cyclization by two different pathways. In path a, **90** directly cyclizes to the final product **86.** On the other hand, in path b, **90** first undergoes fragmentation to **91** and **92**. Subsequently **91** and **92** coupled through the [4 + 2]-cycloaddition reaction to form **86.**[56]

Recently, a catalyst-free cross-dehydrogenative coupling reaction accomplished by visible light for the synthesis of 1,3-oxazines **93**. When α-aminoalkylnaphthols **94** are irradiated with white light-emitting diode (LED, 23 W) in dimethyl sulfoxide as solvent in an open reaction vessel at room temperature for 24 h, cyclization takes place *via* α-C–H activation of tertiary amine moiety and forms a new C–O bond. Biologically important 1,3-oxazines are obtained in 58–85% yields. The various advantages of this methodology are (i) the reaction is catalyst-free, (ii) only aerial oxygen is needed as the oxidant and (iii) the reaction is visible light-promoted. A mechanism is proposed in Scheme 32. The Betti base **94** is first excited by visible light to **95** which reacts with O$_2$ and transfer a single electron to O$_2$. This generates a radical cation **96** and a superoxide. The superoxide then abstracts a hydrogen atom from **96** which forms the iminium ion **97** and hydroperoxide anion. The formation of iminium ion proves that C–H activation takes place rather than O–H activation, though in some cases O–H activation may prefer. The hydroperoxide anion then removes a proton from –



Scheme 31 Intramolecular CDC of Betti base leading to 1,3-oxazines **86**.



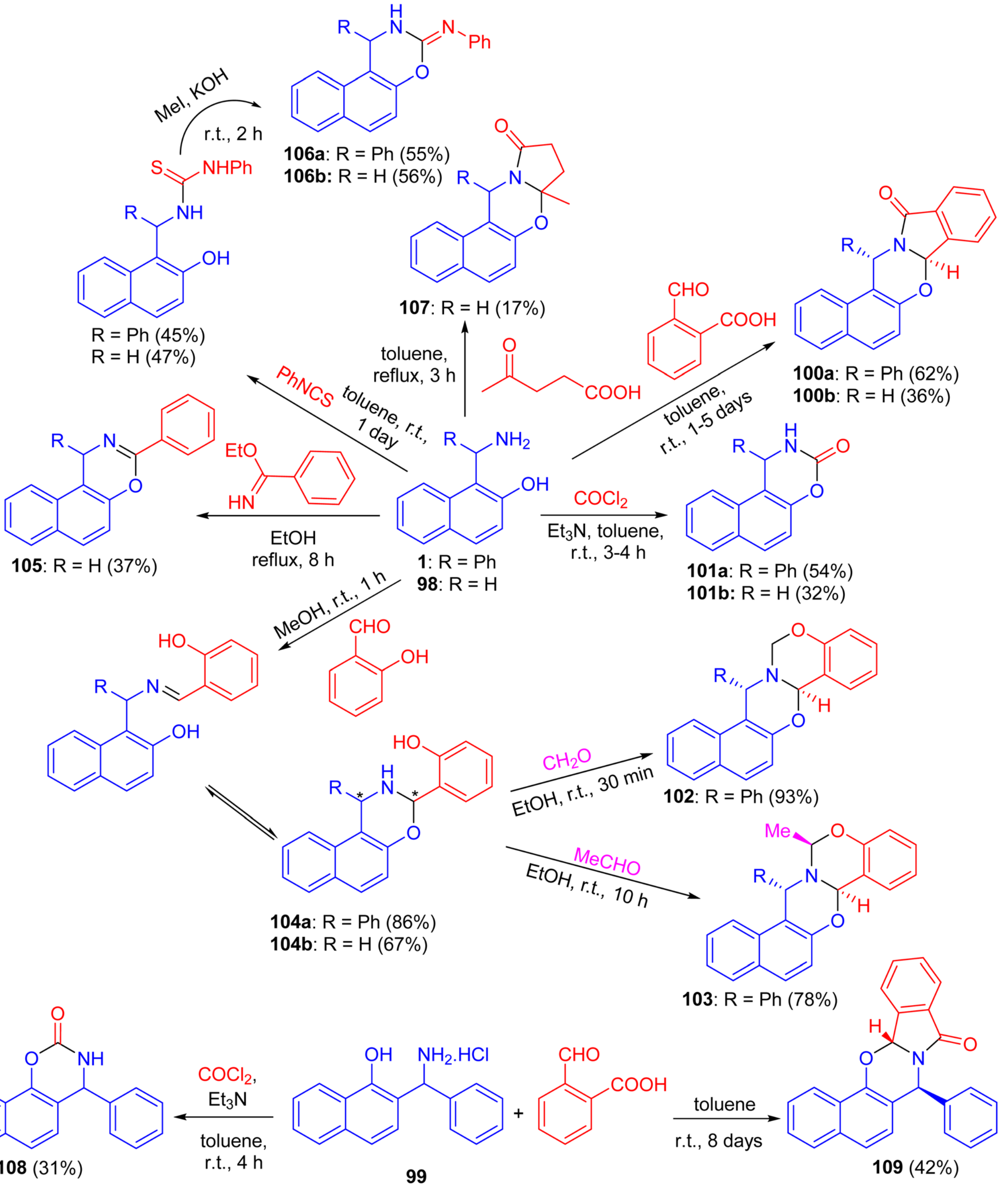
Scheme 32 Preparation of 1,3-oxazines **93**.

OH group of **97** followed by cyclization with the elimination of a molecule of hydrogen peroxide.[57]

5 Synthesis of naphthoxazinobenzoxazines

In 2004, Fulop *et al.* described domino ring-closure reactions of 1-(α-aminobenzyl)-2-naphthol (**1**), 1-aminomethyl-2-naphthol (**98**) and 2-(α-aminobenzyl)-1-naphthol (reverse Betti base: **99**) with phosgene, ethylbenzimidate, phenylisocyanate/MeI, 2-carboxybenzaldehyde, levulinic acid, salicylaldehyde/formalin or salicylaldehyde/acetaldehyde which afforded naphth[1,2-*e*][1,3]oxazine and naphth[2,1-*e*][1,3]oxazine derivatives **100–109** in 17–93% yields (Scheme 33).[58]

After that, a functional group, the hydroxy group, was inserted into a Betti base **1** by reaction with salicylaldehyde, and the naphthoxazine derivatives thus obtained were converted by ring-closure reactions with formaldehyde, acetaldehyde, propionaldehyde or phosgene to the corresponding naphth[1′2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine derivatives **110.** Moreover, condensation of 1-aminomethyl-2-naphthol **98** with salicylaldehyde led to the Schiff base **111**, which could be easily



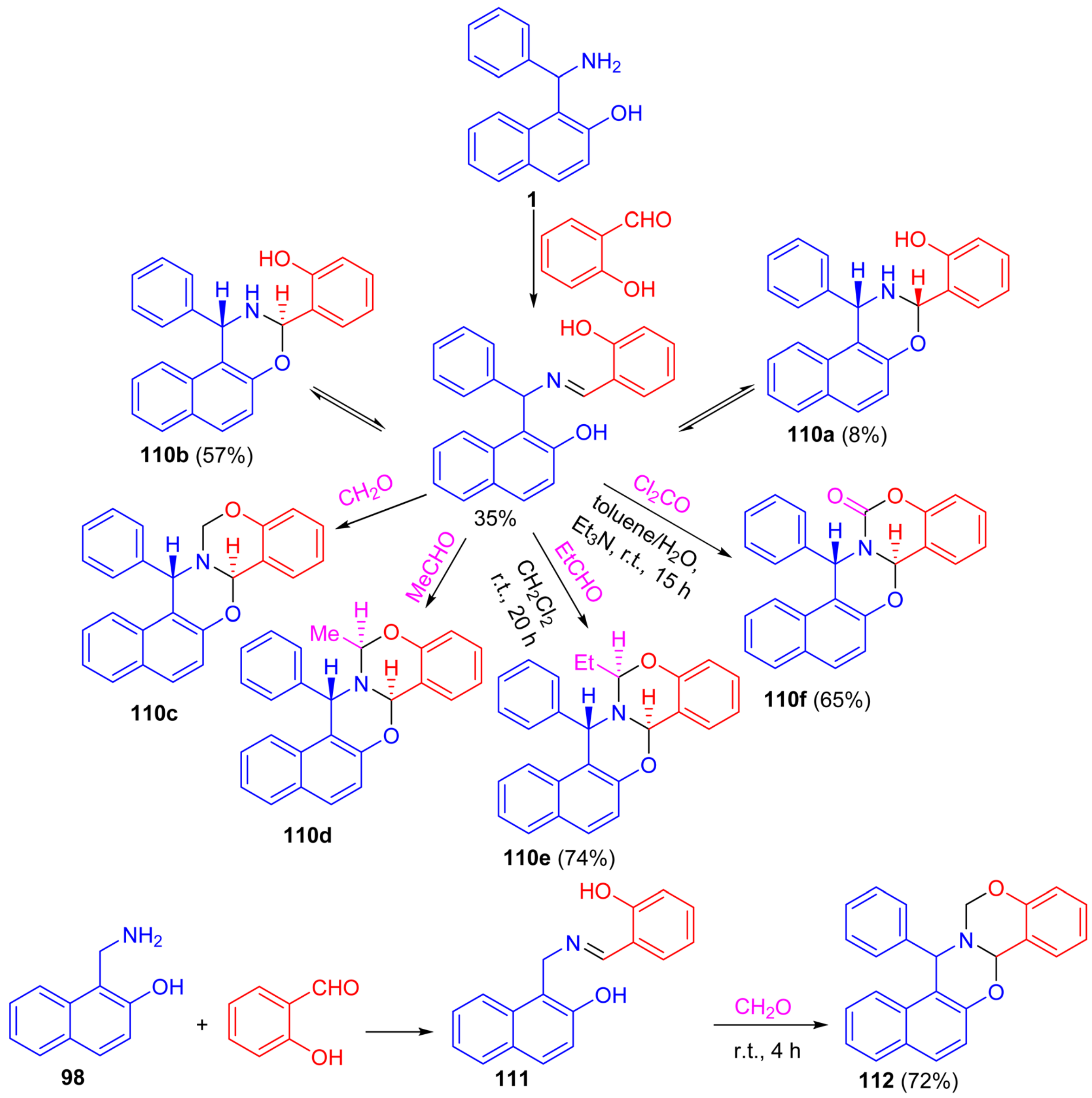
Scheme 33 Synthesis of naphthoxazine derivatives 100–109.

converted into the unsubstituted naphth[1′,2′:5,6][1,3]-oxazino[3,2-*c*][1,3]benzoxazine derivative **112** in 72% yield. Further, by NMR spectroscopy and an accompanying molecular modelling, both quantitative anisotropic ring current effects of the aromatic moieties and steric substituent effects were employed to determine the stereochemistry of the naphthoxazinobenzoxazine derivatives (Scheme 34).[59]

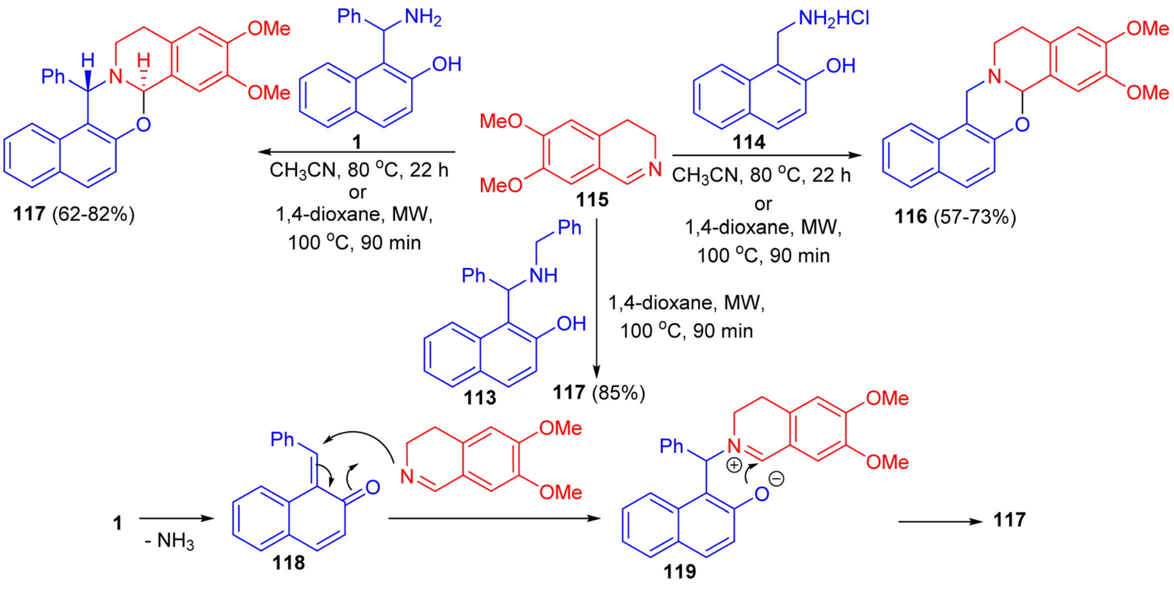
6 Synthesis of naphthoxazinoisoquinolines/naphthoxazinoquinolines

In 2011, unexpected reactions between 1-α-aminobenzyl-2-naphthol (**1**), *N*-benzyl-1-α-aminobenzyl-2-naphthol (**113**), 1-aminomethyl-2-naphthol hydrochloride (**114**) and 6,7-dimethoxy-3,4-dihydroisoquinoline (**115**) to furnish naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines **116** and **117** were reported. The reaction conditions involved classical heating at 80 °C in MeCN for 22 h, or the use of microwave conditions (100 °C), which allowed a reduction of the reaction time to 90 min and resulted in somewhat higher yields of the product. The proposed reaction pathway for the formation of **117** is depicted in Scheme 35. The first step is the loss of ammonia, leading to **118**. The next step involves nucleophilic attack of the dihydroisoquinoline nitrogen on the C═C bond, forming **119**. The driving force for this step is aromatization. The ionic intermediate **119** is stabilized by attack of the phenolic ion on the imine carbon of the dihydroisoquinoline, leading to **117**.[60]

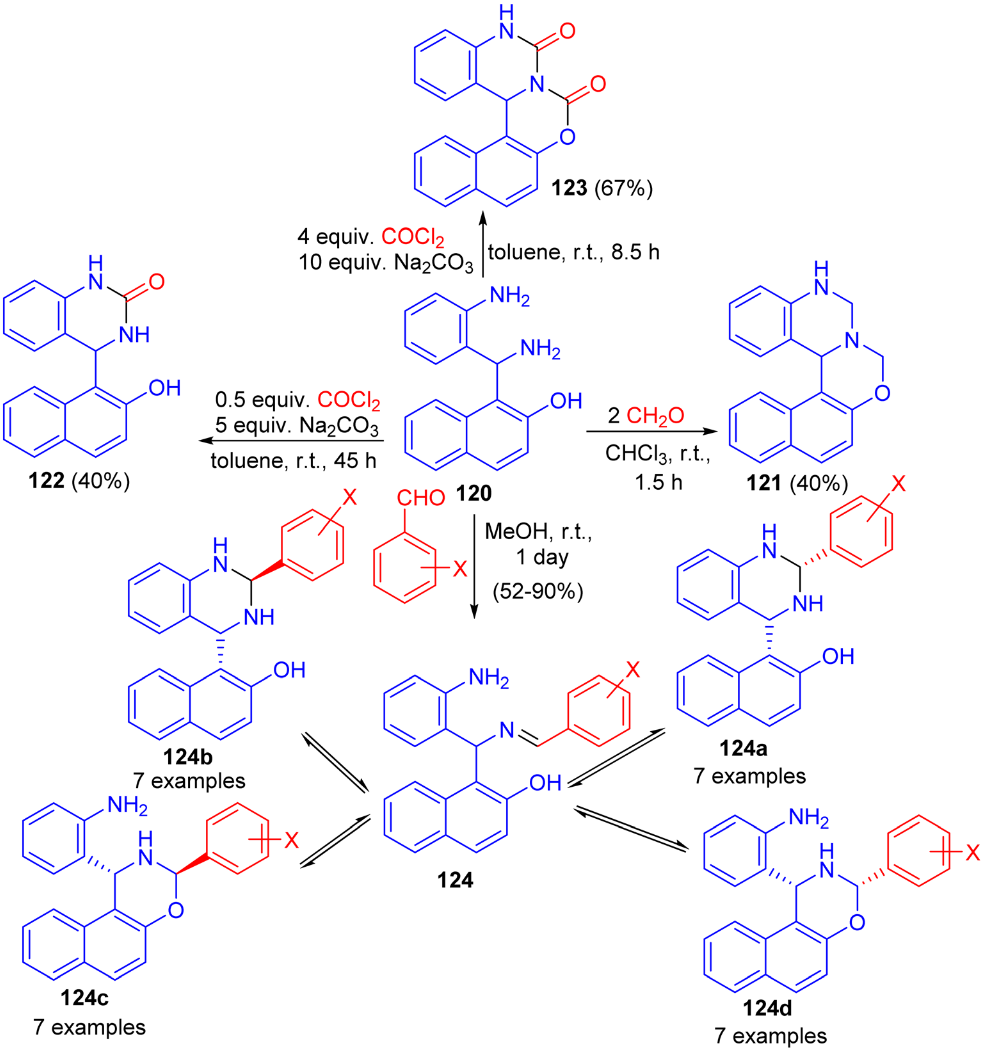
Next, Folup and co-workers described a highly functionalized aminonaphthol derivative **120** converted to the corresponding naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline



Scheme 34 Synthesis of naphth[1′2′:5,6][1,3]oxazino[3,2-c][1,3]benzoxazines 110 and 112.



Scheme 35 Synthesis of pentacyclic oxazinoisoquinolines **116** and **117**.



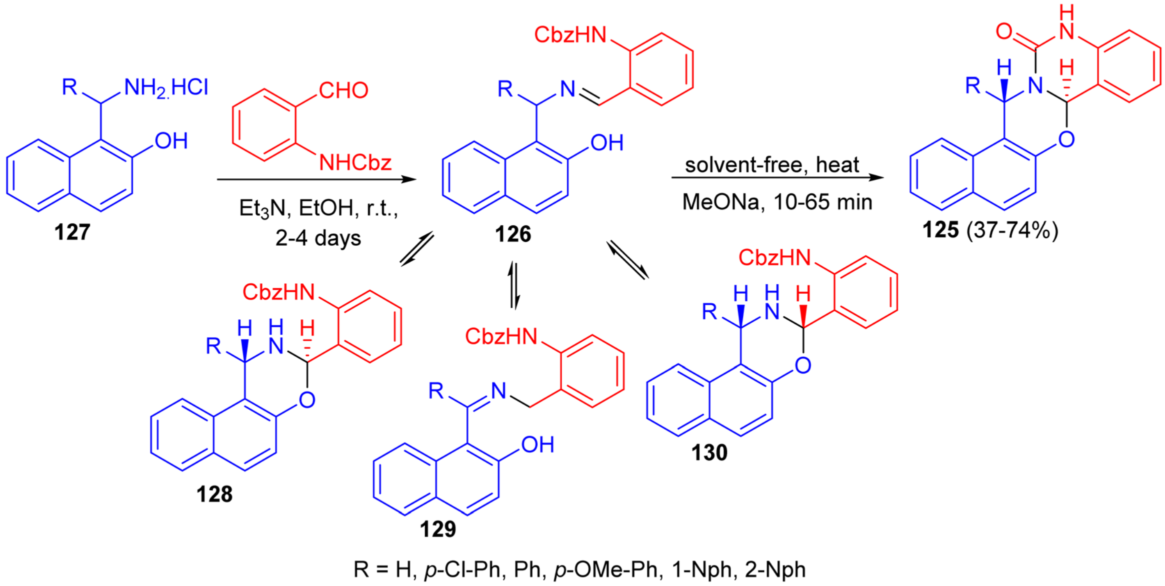
Scheme 36 Synthesis of naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivatives **121–124**.

derivatives **121–124** in ring-closure reactions with formaldehyde in $CHCl_3$, benzaldehyde in MeOH and/or phosgene in toluene at room temperature. The products obtained *via* the reactions of **120** with substituted benzaldehydes can potentially furnish five-component tautomeric mixtures **124** in CD_2Cl_2 at 300 K (Scheme 36).[61]

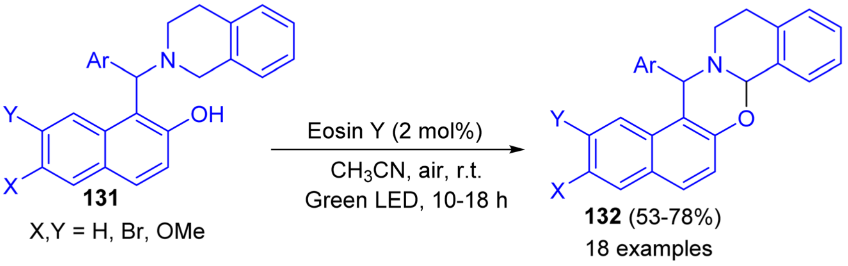
In 2012, the syntheses of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives **125** in 37–74% yields were reported by the solvent-free heating of benzyloxycarbonyl-protected intermediates **126** with MeONa for 10–65 min. For intermediates **126**, prepared by the reactions of substituted aminonaphthols **127** with benzyl *N*-(2-formylphenyl)carbamate in the presence of Et_3N in EtOH for 2–4 days at room temperature, not only the expected *trans* ring form **128** and chain form **126**, but also the rearranged chain form **129** as a new tautomer were detected in DMSO at room temperature. The quantity of **130** in the tautomeric mixture was changed with time. Moreover, conformational analyses of the target heterocycles **125** by NMR spectroscopy and accompanying theoretical calculations at the DFT level of theory revealed that the oxazine ring preferred a twisted chair conformation and the quinazolone ring was planar. Besides the conformations, both the configurations at C-7a and C-15 and the preferred rotamers of the 1-naphthyl substituent at C-15 were assigned, which allowed evaluation of the aryl substituent-dependent steric hindrance in this part of the molecules (Scheme 37).[62]

In 2017, Baruah and co-workers developed visible light intramolecular cross dehydrogenative coupling of 1-aminoalkyl-2-naphthols **131** to 1,3-oxazines **132** in 53–78% yields using green LED lamp as the light source and eosin Y functions as photoredox catalyst in CH_3CN at room temperature for 10–18 h. Organic photoredox catalyst eosin Y is used which is very cheap and non-hazardous. Moreover, aerial oxygen is used as the oxidant. In the proposed mechanism, the reaction proceeds through the formation of iminium ion intermediate (Scheme 38).[63]

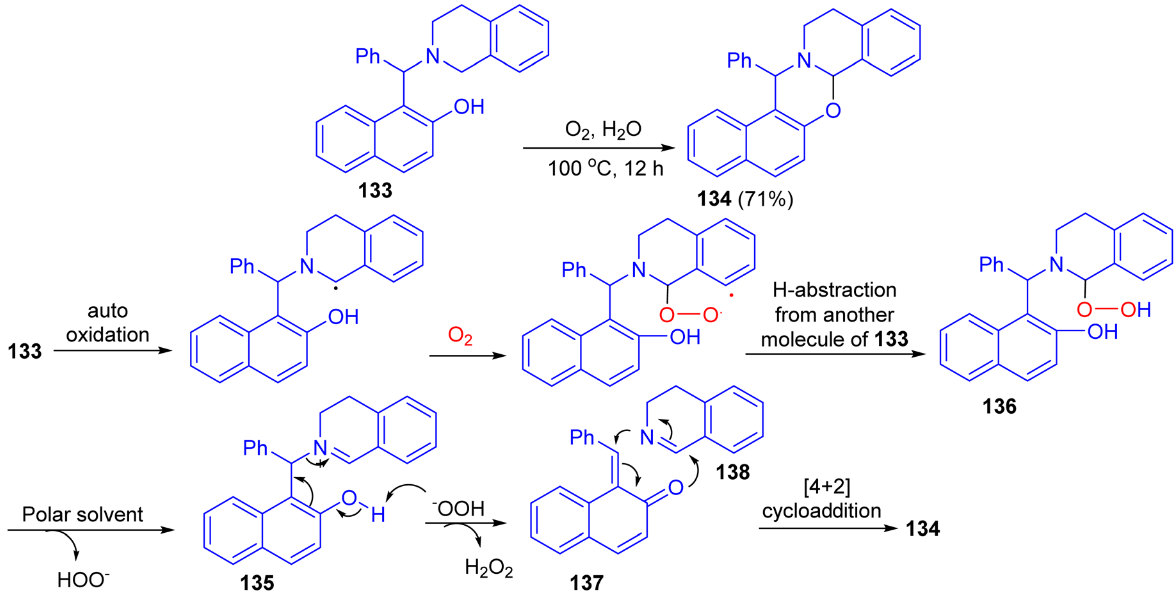
After that, the reaction of Betti base **133** in H_2O in the presence of O_2 as the sole oxidant at 100 °C afforded 1,3-oxazine **134** in 71% yield after 12 h. The proposed mechanism is illustrated in Scheme 39. Compound **133** gets oxidized by oxygen to iminium ion **135**. They believe that a polar solvent might help eliminate the –OOH group from **136** through solvation. The iminium ion **135** then undergoes fragmentation to quinone methide **137** and 3,4-dihydroisoquinoline **138**. These two



Scheme 37 Synthesis of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives **125**.



Scheme 38 Visible light-promoted synthesis of 1,3-oxazines **132**.



Scheme 39 Synthesis of 1,3-oxazine **134**.

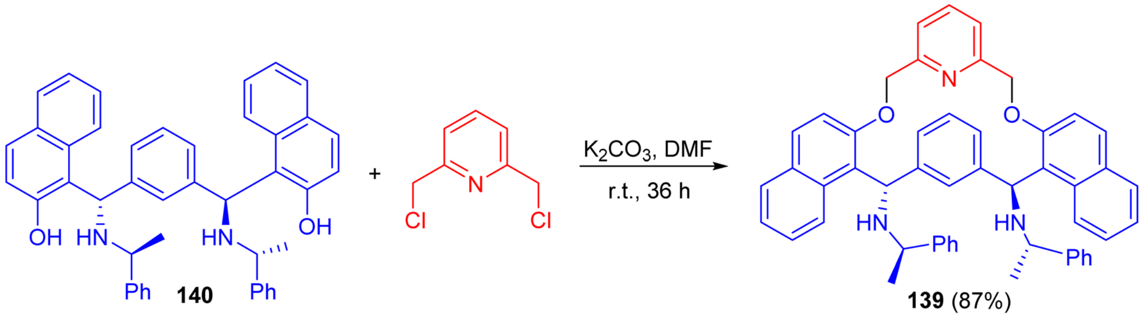
fragments are then coupled with each other through [4 + 2]-cycloaddition to form the product **134**.[64]

7 The other fused-heterocycles

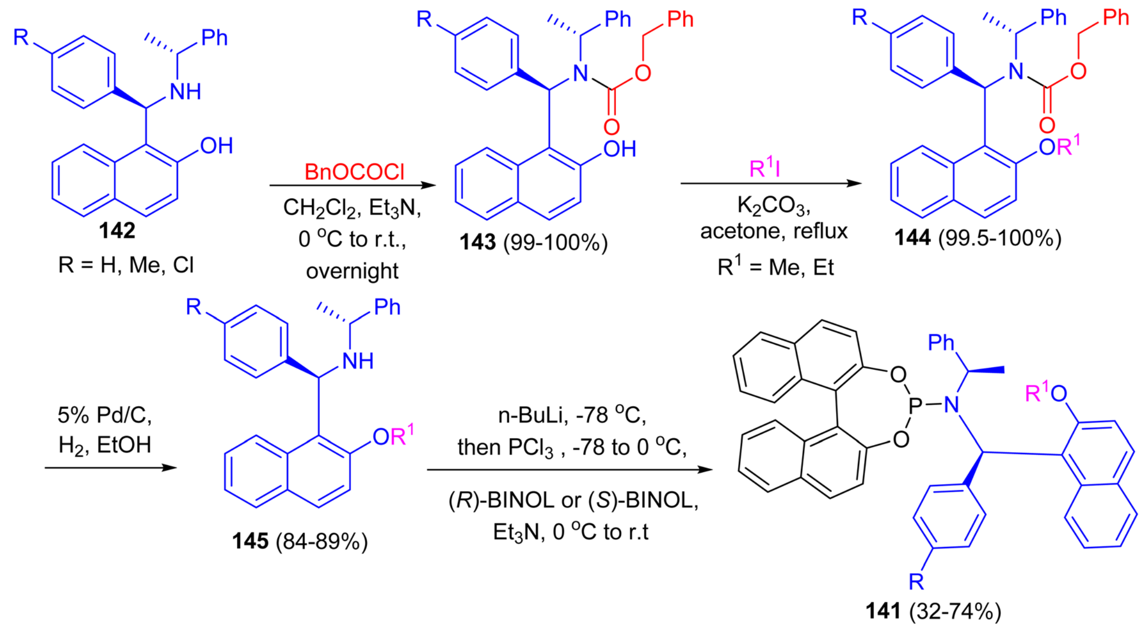
In 2007, Zhang and co-workers prepared macrocyclic compound **139** in 87% yield by the reaction of C_2-symmetric aminonaphthol **140** with 2,6-dichloromethylpyridine using K_2CO_3 in dry DMF at room temperature for 36 h. Compound **139** exhibited excellent ability to discriminate the enantiomers of a broad variety of carboxylic acids by ^{1}H-NMR spectroscopy (Scheme 40).[65]

After that, a series of chiral phosphoramidite ligands **141** were prepared in high yields from unsymmetrical secondary amines **142** and chiral BINOL. Alkylation of the hydroxy group of naphthols **142** with methyl or ethyl iodide in acetone after protection of the amino group with benzyl chloroformate **143** in dichloromethane provided **144** in quantitative total yields. Hydrogenolysis of carbamates **144** with 5% palladium on carbon in alcohol afforded free secondary amines **145** in good yields. The free amines reacted with phosphorus trichloride and chiral BINOL to provide chiral phosphoramidites **141** in 32–74% yield after flash chromatography (Scheme 41). The ligands with (*S*,*R*,*R*)-configuration were effective for the palladium-catalyzed enantioselective hydrosilylation of styrene derivatives. The resulting silanes were oxidized to provide secondary alcohols in medium to high yields (up to 96% yield) and good enantiomeric excesses (up to 97% ee).[66]

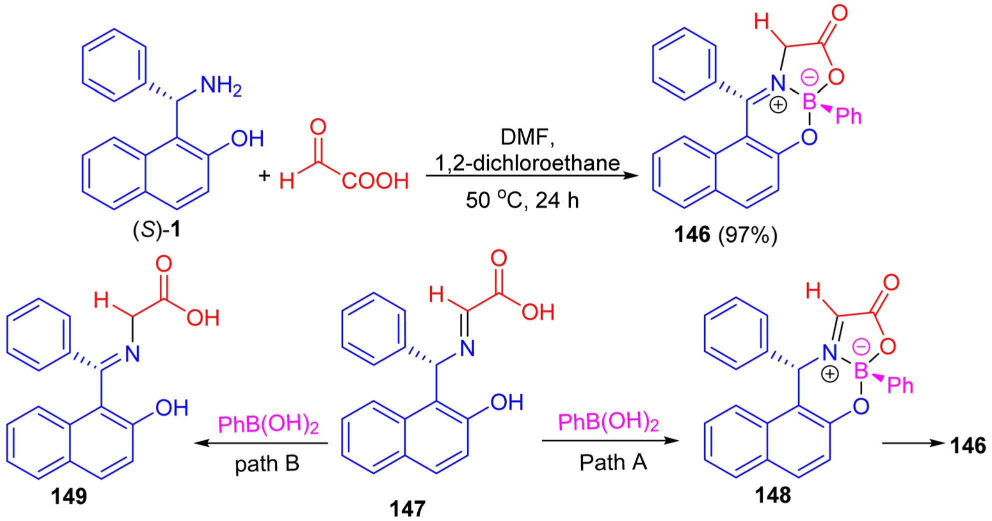
In addition, Hutton and co-workers constructed boronate complex **146** in 97% yield by the reaction of (*S*)-**1** with glyoxylic acid and phenylboronic acid in DMF/1,2-dichloroethane at 50 °C for 24 h. Formation of **146** must involve three processes: complexation of aldimine **147** with phenylboronic acid would generate boronate complex **148**, with subsequent tautomerization of the aldimine to the ketimine generating final complex **146** (path A). Alternatively, tautomerization of the aldimine to the ketimine **149** could precede complexation with the boronic acid (path B) as shown in Scheme 42. To achieve enantioselective formation of boronate complex **146**, the reaction must proceed by path A, with diastereoselective formation of glyoximine–boronate complex **148** controlled by the configuration at the carbon stereocenter. The alternative reaction sequence



Scheme 40 Synthesis of macrocyclic compound **139**.



Scheme 41 Synthesis of chiral phosphoramidite ligands **141**.



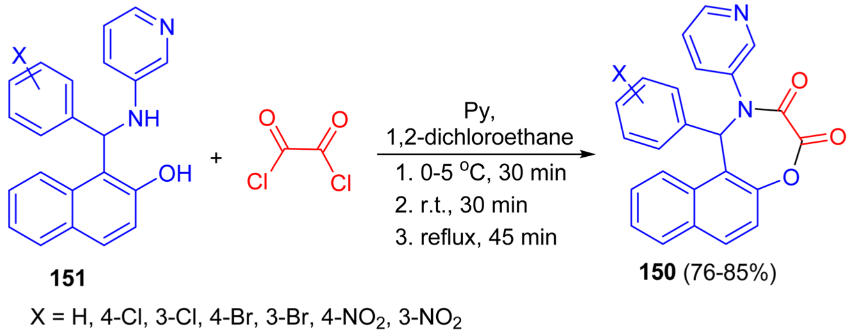
Scheme 42 Enantioselective preparation of a stable boronate complex **146**.

(path B), in which tautomerization of the aldimine **147** to the achiral ketimine **149** precedes complexation with boronic acid, would result in formation of complex **146** as a racemate.[67]

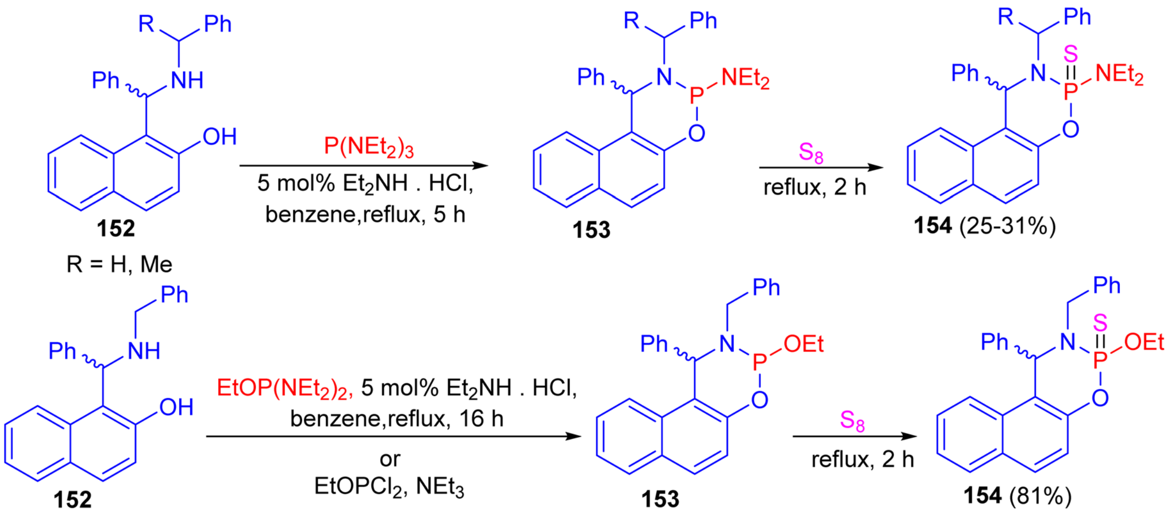
In 2009, Olyaei and his group reported synthesis of naphth[1,2-*f*][1,4]oxazepine-3,4-dione heterocycles **150** in 76–85% yields by the reaction of N-heteroaryl aminonaphthols **151** with oxalyl chloride in dry 1,2-dichloroethane containing pyridine under argon atmosphere. The reaction mixture was stirred for 30 min at 0–5 °C, then 30 min at room temperature, and refluxed for an additional 45 min. This method with the advantages, such as generality and simplicity of procedure, lower reaction time, elimination of acid catalyst, and obtaining excellent yields are worth noting (Scheme 43).[68]

In 2014, the reaction of *N*-substituted 1-(α-aminobenzyl)-2-naphthols **152** with phosphorus(III) compounds in refluxing benzene in the presence of diethylamine hydrochloride as catalyst for 5–16 h afforded cyclic phosphorylated diastereomeric derivatives **153**, followed by addition of elemental sulfur under reflux conditions for 2 h resulted cyclic thiophosphorylated diastereomeric derivatives **154** in 25–81% yields as depicted in Scheme 44.[69]

After that, Shahrisa and his group reported chemoselective sequential reactions for the synthesis of 12*H*-benzo[*a*]xanthenes **155** and dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines **156**. Depending on the used conditions selective, Ullmann-type arylation or α-C–H aryloxylation of 2-bromophenyl alkylaminonaphthols



Scheme 43 Synthesis of naphth[1,2-*f*][1,4]oxazepine-3,4-diones **150**.



Scheme 44 Phosphorylation of Betti bases **152**.

157 occurred. The two-step sequence proceeded efficiently in a one-pot manner by heating of **157** in the presence of CuI (10 mol%), picolinic acid (20 mol%) and K_3PO_4 at 100 °C in DMSO for 18 h to afford the desired product **155** in 78–83% yields. Moreover, compounds **156** were achieved in 63–77% yields by heating of **157** in toluene at 110 °C using Cs_2CO_3, CuI and L-proline for 6–8 h (Scheme 45).[70]

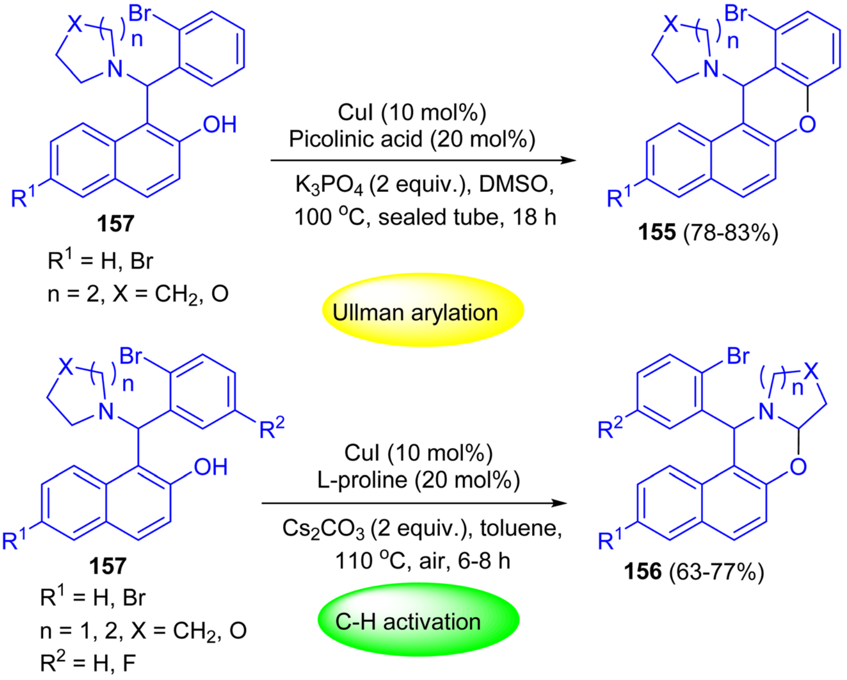
Next, the reaction of (*R*,*R*)-Betti base **158** with commercially available dichloro(methoxy)phosphine in the presence of triethylamine in tetrahydrofuran (THF) at 0 °C to room temperature for 3 h led to the formation of two phosphorus-containing species phosphoramidites **159**, in a ratio of $(S_p):(R_p)/80:20$. Subsequent, the mixture of P-epimers **159** was treated with a solution of $BH_3 \cdot SMe_2$ at room temperature for 14 h to give the borane adducts **160**·BH_3 in 84% yield. When the same reaction sequence was carried out in CH_2Cl_2 or THF with triethylamine or *n*-BuLi as base, phosphoramidochloridite **161** was formed. In the following reaction with methanol the P-epimers of the resulting phosphoramidite **160** were obtained (Scheme 46).[71]

In 2016, the ring closure of the Betti bases **163–166** by using a 35% solution of CH_2O as cyclizing agent in CH_2Cl_2 at room temperature led to the formation of naphthoxazines, isoquinolinoxazines and quinolinoxazines **167–170** in 78–92% yields. The reactions proved to be complete after relatively short reaction times (20–30 min) and the desired products **167–170** were isolate (Scheme 47).[72]

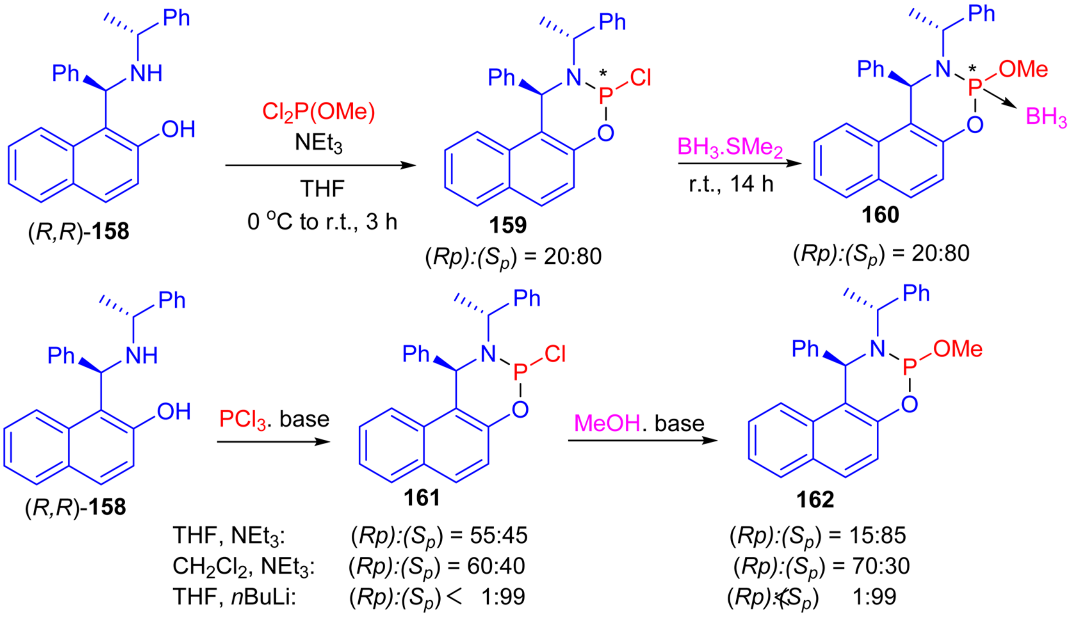
In 2017 Teimuri-Mofrad *et al.* reported synthesis of oxazepine derivatives **171** in 75–83% yields *via* intramolecular Ullmann reaction of Betti bases **172** in the presence of catalytic amount of CuI, L-proline and K_2CO_3 in DMF at 110 °C for 18 h followed by subsequent oxidation reaction as shown in Scheme 48.[73]

Further, a series of naphth[1,3]oxazino-benzazepines **173** in 7–48% yields and -thienopyridines **174** in 10–49% yields were synthesized using a modified Mannich-type synthetic pathway by the reaction of 4,5-dihydro-3*H*-benz[*c*]azepine **175** or 6,7-dihydrothieno[3,2-*c*]pyridine **176** and different substituted aminonaphthols **177** and **178** using microwave irradiation in 1,4-dioxane in the presence of Et_3N at a temperature of 80 °C for 20–80 min. In these reactions, the mixture of diastereomers was formed and the conversion and the diastereomeric ratio were monitored by crude product NMR spectra in all cases (Scheme 49).[74]

Fulop and co-workers reported synthesis of non-racemic naphth[1,3]oxazino[3,2-*a*]quinoxalinones **179** and **180** in 51–66% yields starting from (4a*S*,8a*S*)-4a,5,6,7,8,8a-hexahydro-2-



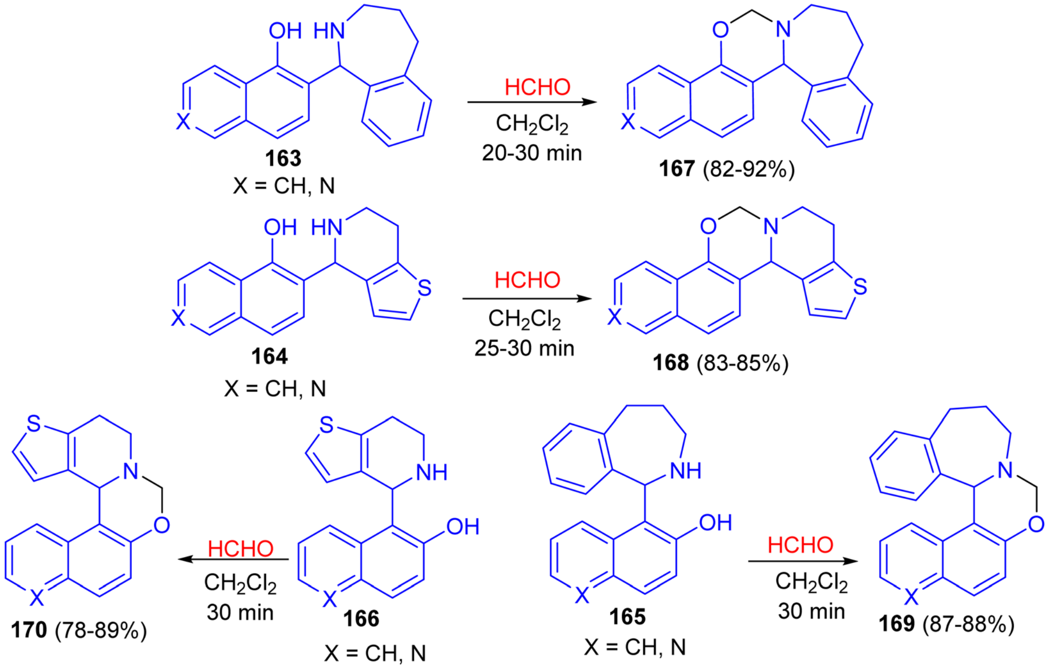
Scheme 45 Chemoselective sequential Betti–Ullmann coupling and Betti-C–H activation reactions of **157**.



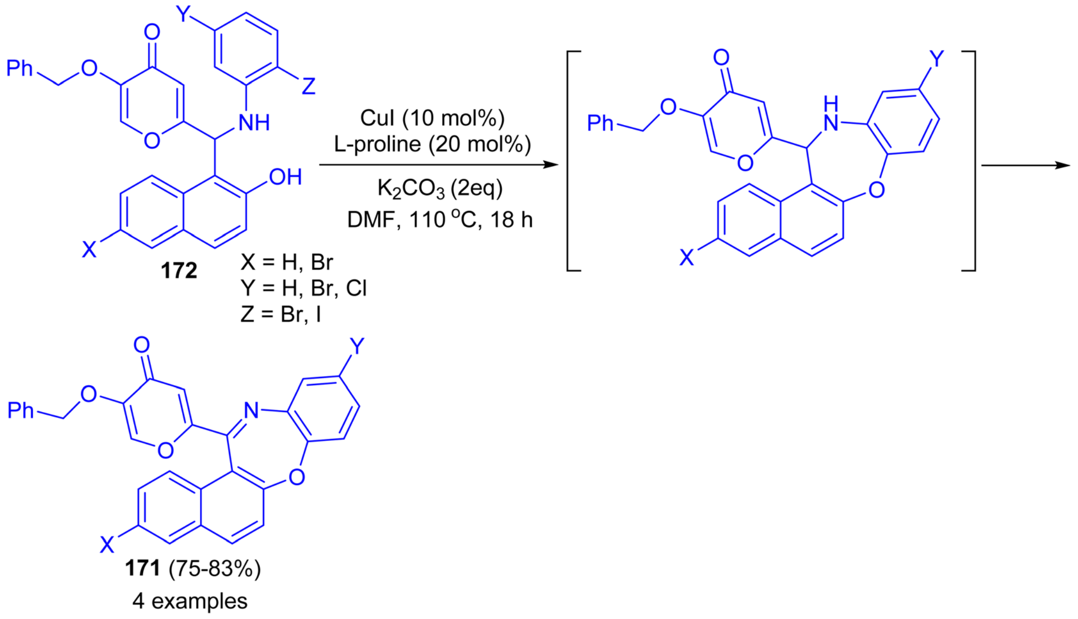
Scheme 46 Synthesis of *P*-stereogenic phosphoramidites **159–162**.

quinoxalinone **181** and 1-aminoalkyl-2-naphthols **182** or 2-aminoalkyl-1-naphthols **183** in 1,4-dioxane under microwave irradiation at 80 °C for 60–180 min (Scheme 50). In all cases, NMR studies were performed to analyse the structures and diastereoselectivities of the products.[75]

In 2019, Szatmari and co-workers described synthesis of O,N- or N,N-heterocycles by the reactions of highly functionalized aminonaphthol **184** with different cyclic imines *via* [4 + 2] cycloaddition. Initially, *o*-QM intermediate **185** was formed by thermal decomposition of **184.** Then, the reaction of **185** with β-carboline **186**, 4,5-dihydro-3*H*-benz[*c*]azepine **187** and 6,7-dihydrothieno[3,2-*c*]pyridine **188** in 1,4-dioxane under microwave irradiation at 80 °C for 20 min led to the formation of aminonaphthol **192** with different cyclic imines **186–188** under the same reaction conditions afforded quinazolines **193–195** in 89–92% yields. The reactions were found to be diastereo- and



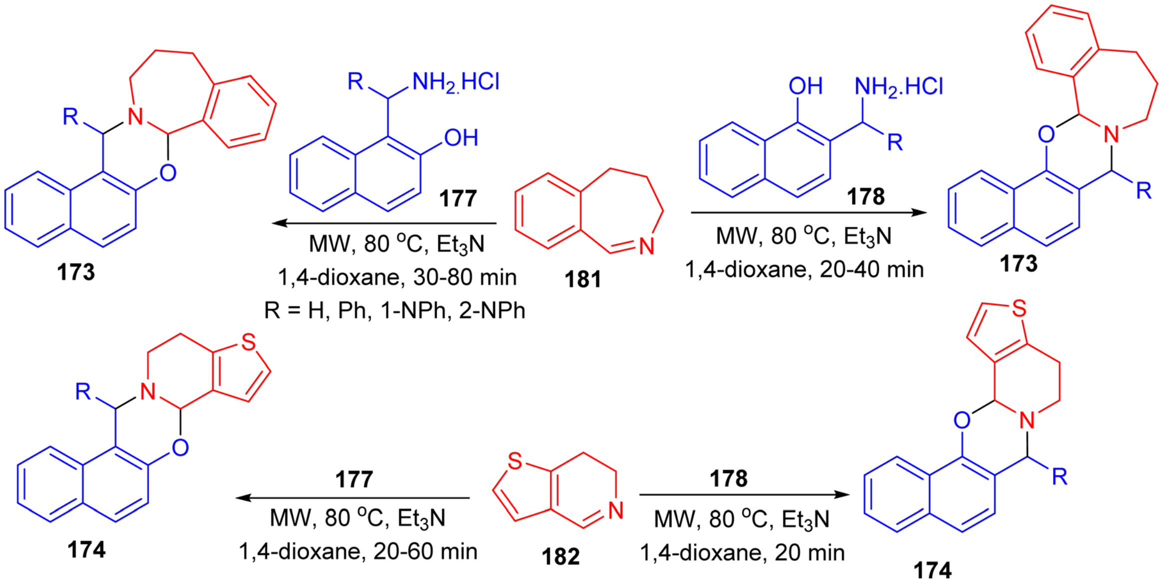
Scheme 47 Synthesis of naphthoxazines, isoquinolinoxazines and quinolinoxazines **167–170**.



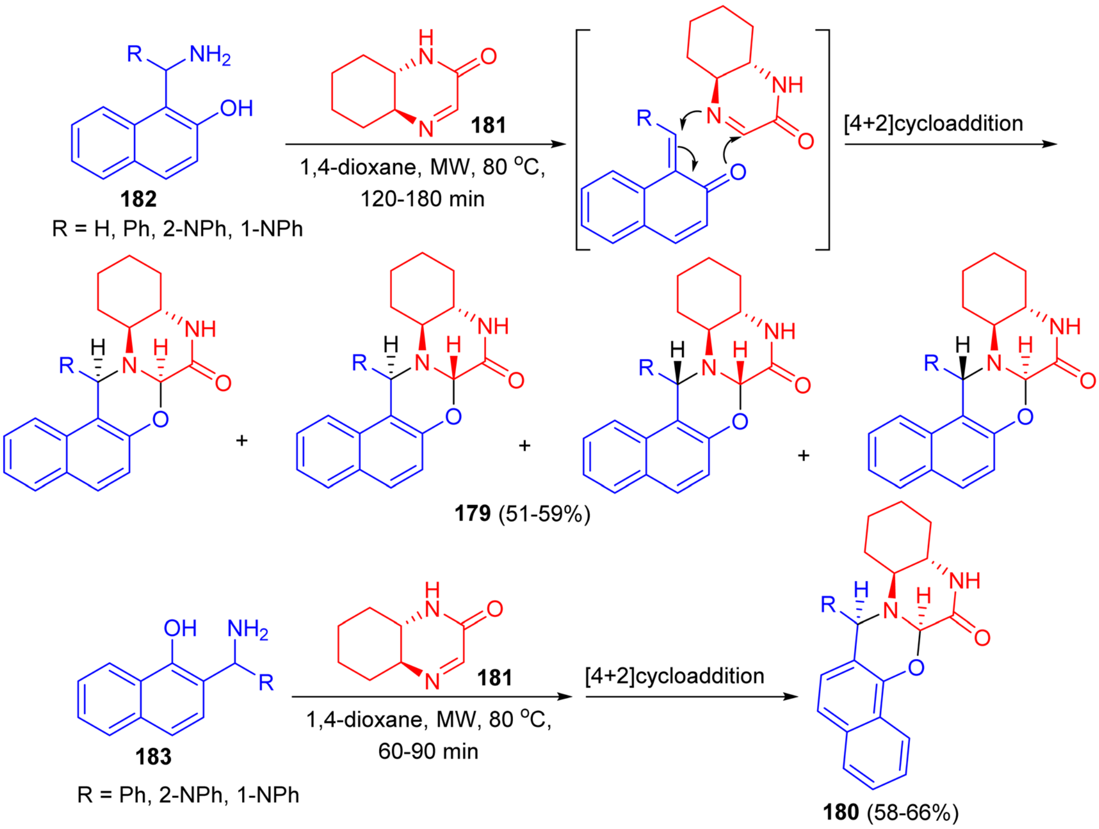
Scheme 48 Synthesis of oxazepine derivatives **171**.

regioselective naphthoxazines **189–191** in 87–92% yields. Also, the reaction of leading to *trans* naphthoxazine. Its structure was proved by DFT computed structures in comparison with the experimental $^{1}H/^{13}C$-NMR spectra, and a detailed analysis of the spatial magnetic properties of the preferred diastereomers. The possible reaction pathway *via* formation of the *o*-QM intermediate **196** (Scheme 51).[76]

In 2022, Shaabani *et al.* reported an efficient and convenient approach for the synthesis of naphtho[1,2-*f*][1,4]oxazepines **197** in 42–67% yields based on the consecutive Betti/Bargellini multicomponent reactions of aminobenzylnaphthols **198** with aliphatic ketones in chloroform in the presence of sodium hydroxide at 0 °C to room temperature for 3 h. A plausible mechanism for the formation of **197** is depicted in Scheme 52. At first, sodium hydroxide abstracts a proton from chloroform to afford the carbanion **199**, which subsequently attacks acetone and generates the unstable carbinol **200**. Next, the intermediate **200** cyclizes to produce the Bargellini epoxide **201**.



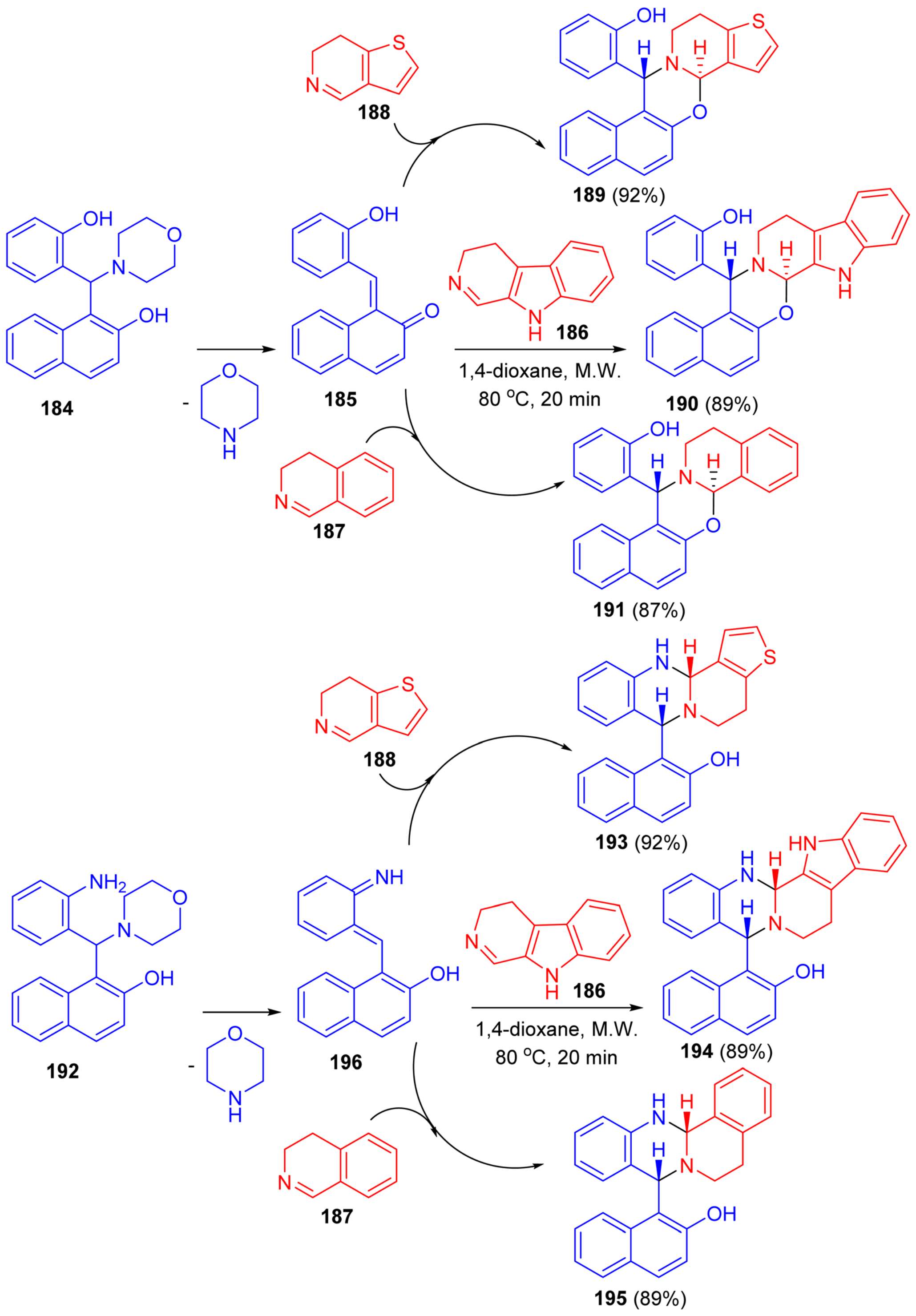
Scheme 49 Synthesis of naphth[1,3]oxazino-benzazepines **173** and -thienopyridines **174**.



Scheme 50 Preparation of naphth[1,3]oxazino[3,2-*a*]quinoxalinones **179** and **180**.

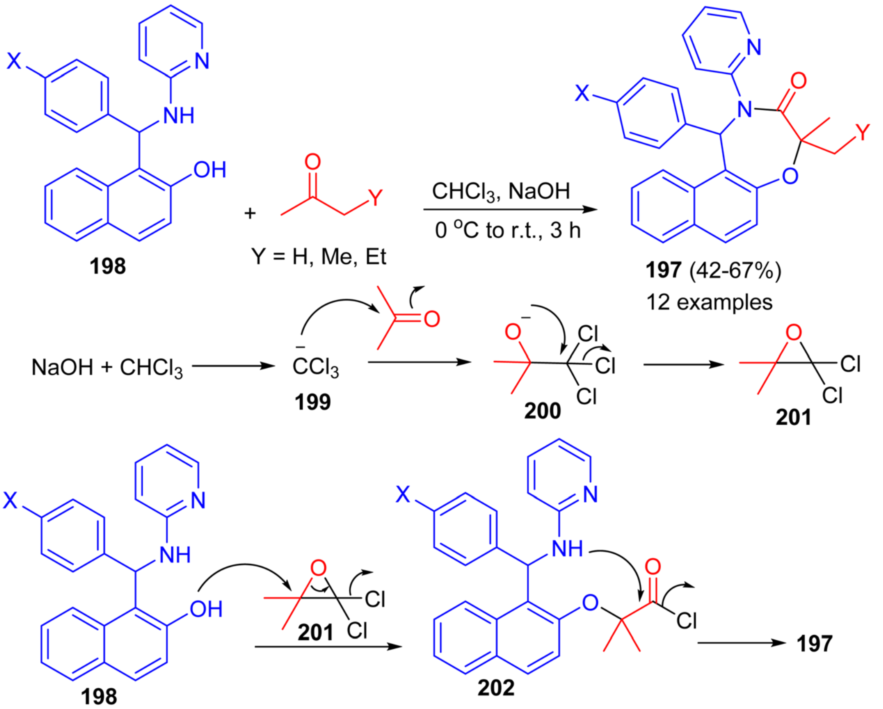
Afterward, the intermediate **202** is formed *via* the attack of oxygen nucleophile of the Betti base to intermediate **201**. Finally, intramolecular cyclization occurs and leads to the formation of desired oxazepine scaffold **197**.[77]

Ahmed and co-workers developed Cu–Cu_2O combination synergic effects in catalyzing intramolecular Ullmann coupling reaction for halo-Betti bases **203** in 2-ethoxyethanol at 130 °C for 5 h to afford fused benzo-xanthenes **204** in 72–92% yields from both electron-rich and electron-deficient aromatic systems in



Scheme 51 Synthesis of O,N- or N,N-heterocycles **189–191** and **193–195**.

good yield under mild reaction conditions. However, without *ortho*-halo substituted Betti-bases failed to afford fused benzoxanthene derivatives. Exploring the reaction optimization without Cu metal, serendipitously it was produced 1,3-oxazine derivatives **205** in 76–90% yields in DMF at 100 °C for 30 min *via* intramolecular cross-dehydrogenative coupling (CDC) reaction. Similarly, electron-rich, electron-deficient and sterically hindered Betti-bases provided the products in good to excellent yield under mild condition. A possible mechanism for the formation of **204** is proposed in Scheme 53. The abstraction of proton from **203** by K_2CO_3 led to Betti base anion **206** (soft nucleophile) which reacts with Cu(I) to give intermediate **207**. Then, intermediate **207** undergoes intramolecular Ullmann oxidative addition step to afford intermediate **208.** Followed by,



Scheme 52 Synthesis of naphtho[1,2-*f*][1,4]oxazepines **197**.

reductive elimination of CuX led the product **204** formation. In the proposed mechanism for the synthesis of **205**, abstraction of proton from Betti base **203** by K_2CO_3 led to Betti base anion **209** (soft nucleophile) which reacts with Cu(I) to form intermediate **210**. Then, intermediate **210** undergoes coordination with heterocycle N-atom which causes positive charge on atom. This resulted in alpha hydrogen abstraction in basic condition to afford imine intermediate **211**. Finally, nucleophilic addition to imine intermediate **211** gave the product **205**.[78]

After that, the reaction of Betti bases **212** and **213** with different cyclic imines (3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine, 3,4-dihydro-β-carboline) in [4 + 2] cycloaddition in 1,4-dioxane under MW irradiation at 100 °C for 80–360 min afforded the desired naphthoxazines **214–219** in 70–78% yields (Scheme 54). During the reaction *via* loss of morpholine, the presence of partially aromatic *ortho*-quinone methide intermediates proved and they were transformed with dienophiles to new α-amino acid esters. Regarding the biological results, it can be concluded that in the case of some compounds antibacterial effect was observed on the reference *S. aureus* ATCC 25923 strain.[79]

8 The other reactions

In 1998, Naso and co-workers reported synthesis of [(2-methoxynaphth-1-yl)benzyl]dimethylamine (**220**) in 90% yield by the reaction of 1-(α-aminobenzyl)-2-naphthol (**1**) with CH_3I in the presence of NaOH in THF at room temperature for 6 h as illustrated in Scheme 55.[80]

Next, the reaction of the Betti base 1-(α-aminobenzyl)-2-naphthol (**1**) with 1,3-dicarbonyl compounds at room temperature in CH_3OH in the presence of *p*-toluenesulfonic acid led to the corresponding enamino carbonyl products **221** after 2–72 h, in high yield (71–95%) and with high chemical purity (Scheme 56).[81]

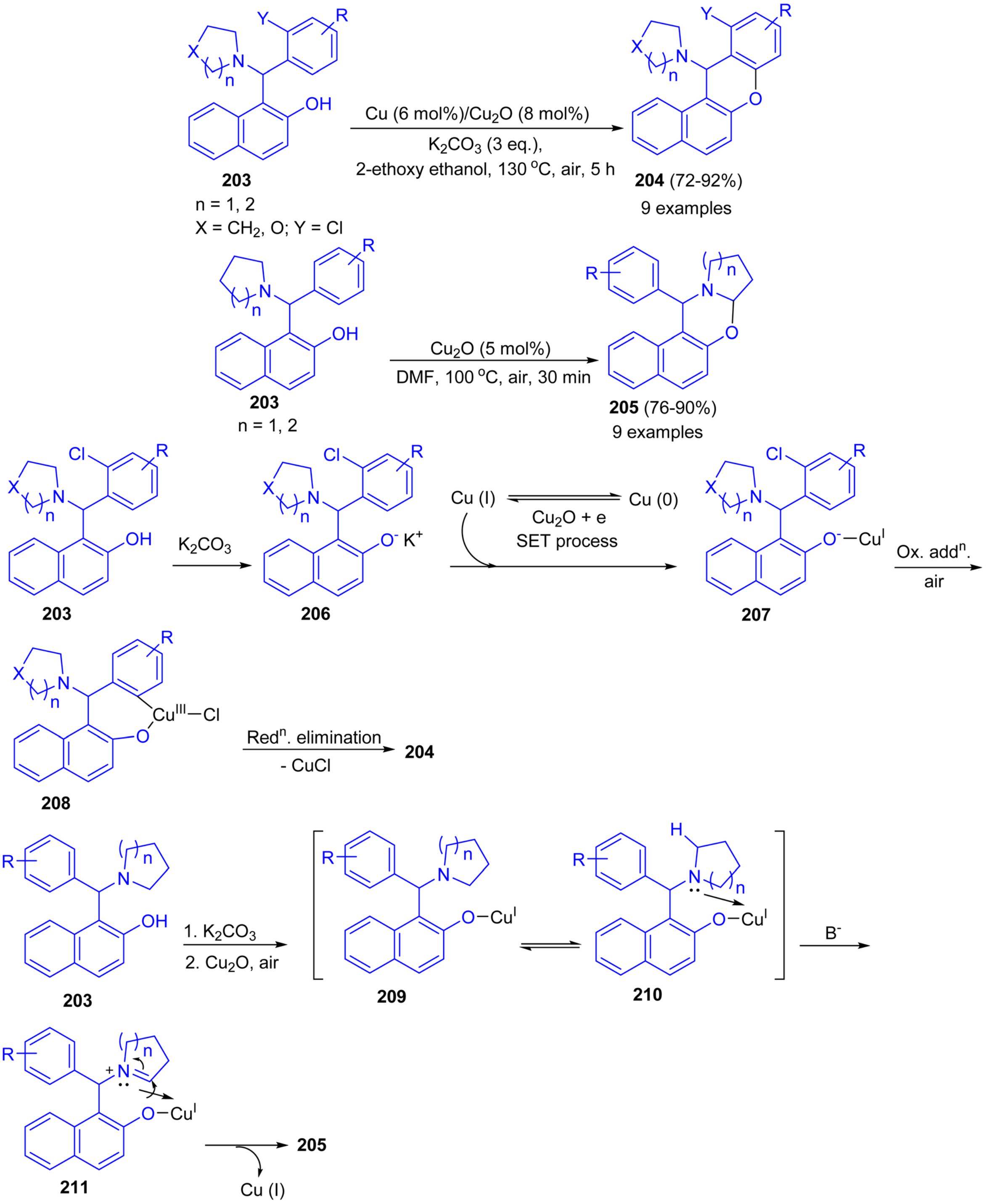
After that, Betti base-derived tetradentate ligand **222** was designed and synthesized in good yield through the condensation of Betti base **1** with aqueous glyoxal in MeOH at room temperature for 6 h (Scheme 57). The application of the ligand **222** in copper-catalyzed *N*-arylation of imidazoles was investigated briefly, and good yields of the products were obtained.[82]

In 2010, Witte *et al.* described synthesis of *N*-tylosil-1-α-amino-(3-bromophenyl)-methyl-2-naphthol (TBN) (**223**) in 81% yield by the reaction of Tylosin (**224**) with Betti-base **225** in EtOH in the presence of HCOOH at room temperature for 24 h (Scheme 58).

TBN dramatically increased the P-gp-mediated cellular uptake of the fluorescent substrate rhodamine 123. Similarly, TBN was found to act as a very potent enhancer of the cytotoxicity of doxorubicin on the resistant cell line.[83]

In 2011, a variety of mono-sulfonamide organocatalysts **226** prepared in 12–56% yields by coupling of (*S*)-**1** with various sulfonyl chlorides in CH_2Cl_2 at room temperature for 24 h and applied as catalyst to the asymmetric hetero-Diels–Alder reaction of ethyl glyoxylate with Danishefsky's diene. The sulfonamides exhibited catalytic activity as hydrogen bond donor (Scheme 59).[84]

In 2015, Baruah *et al.* converted 1-(α-aminoalkyl) 2-naphthols **227** to 1-alkyl-2-naphthols **228** *via* a metal-free transfer hydrogenation with Hantzsch 1,4-dihydropyridine **229** in CH_3CN using *p*-TSA (10 mol%) as catalyst under microwave irradiation (500 W) for 5–9 min.

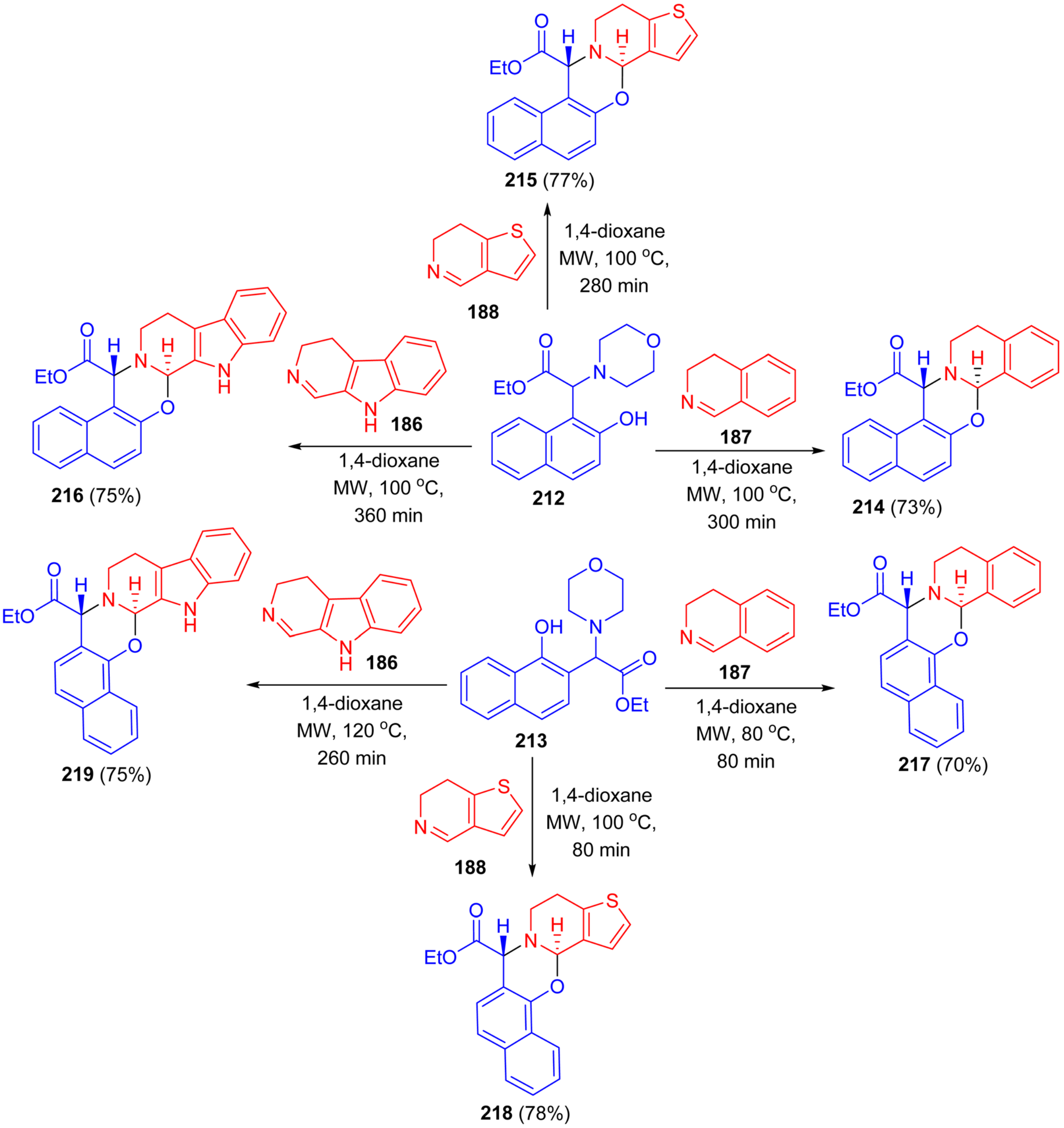


Scheme 53 Synthesis of benzo-xanthenes **204** and 1,3-oxazine derivatives **205**.

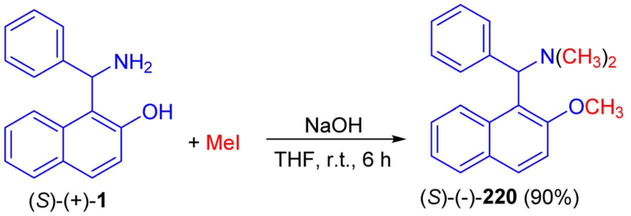
The corresponding aryl methylnaphthols which contain a wide range of substituents, could be obtained in 71–89% yields. The reaction does not use any hazardous metal catalyst or reductant. The method uses *p*-TSA as catalyst which is a convenient, easily available and cheap reagent. Moreover, the reaction is general and having wide substrate compatibility. A mechanistic proposal involving elimination–addition mechanism is described in Scheme 60.[85]

In addition, the Betti bases **230** were diazotized by treating with equivalent amounts of sulfanilamide or *p*-aminoacetophenone in the presence of sodium nitrite and hydrochloric acid at 0–5 °C. After 5–10 min, azo dye compounds **231** obtained in 54–92% yields (Scheme 61).[86]

In 2016, Deb and co-workers reported the reaction of Betti bases **232** with various heterocycles like indole, 5-pyrazolone, 6-aminouracil, and 4-hydroxycoumarin for the formation of



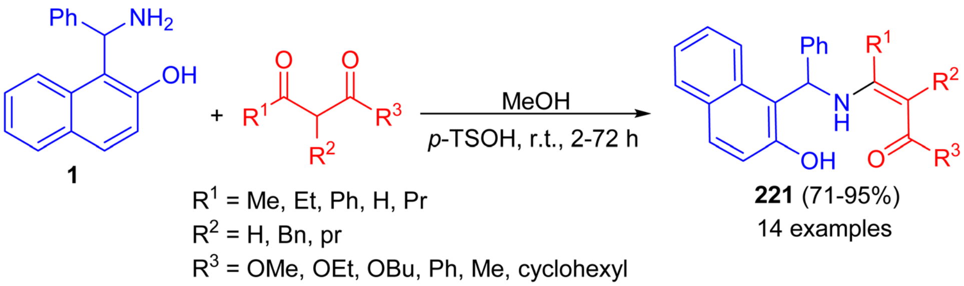
Scheme 54 Synthesis of naphthoxazines **214–219** *via* [4 + 2] cycloaddition reactions.



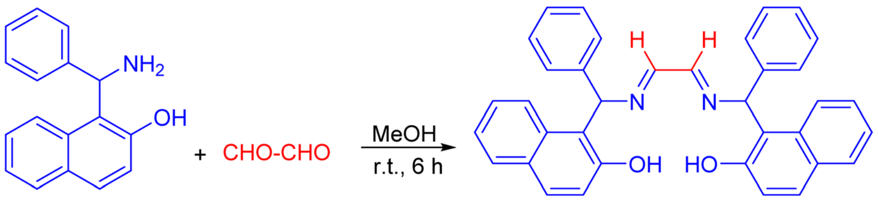
Scheme 55 Synthesis of [(2-methoxynaphth-1-yl)benzyl]dimethylamine (**220**).

bis(heterocycle)methanes **233** using *p*-toluenesulphonic acid in CH_3CN under microwave irradiation at 100 °C for 7–11 min. A plausible mechanism for the reaction is proposed in Scheme 62. *p*-TSA first helps to eliminate the *tert*-amine moiety of the Betti base by protonating nitrogen, which generates *o*-quinone methide **233**. Subsequently a molecule of indole attacks **233**, producing 3-(α,α-diarylmethyl) indole **234.** In the presence of *p*-TSA, a naphthol ring of **234** gets protonated and eliminated as free naphthol through the formation of alkylideneindoleninium ion **235.** Then another molecule of indole attacks **235**, producing bis(indolyl)methanes **233** in 25–88% yields.[87]

Alfonsov and co-workers published the synthesis of phosphoric acid derivatives containing chiral Betti base fragment **236** by reacting racemic and enantiopure *N*-Boc-protected 1-(α-aminobenzyl)-2-naphthol **237** with diethyl chlorophosphate in anhydrous benzene using potassium *tert*-butylate for 24 h followed by deprotection with bromotrimethylsilane in CH_2Cl_2 at

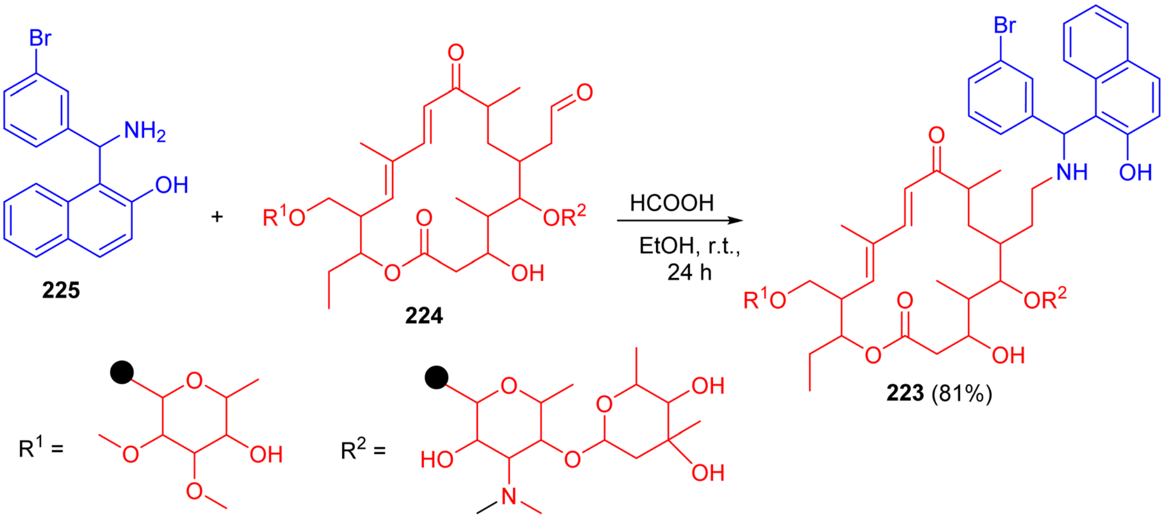


Scheme 56 Condensations of Betti base **1** with 1,3-dicarbonyl compounds.



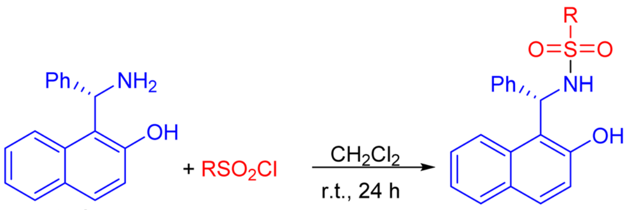
1 **222**

Scheme 57 Synthesis of tetradentate Betti base derivative **222**.



225 **224** **223** (81%)

Scheme 58 Preparation of *N*-tylosil-1-α-amino-(3-bromophenyl)-methyl-2-naphthol (**223**).



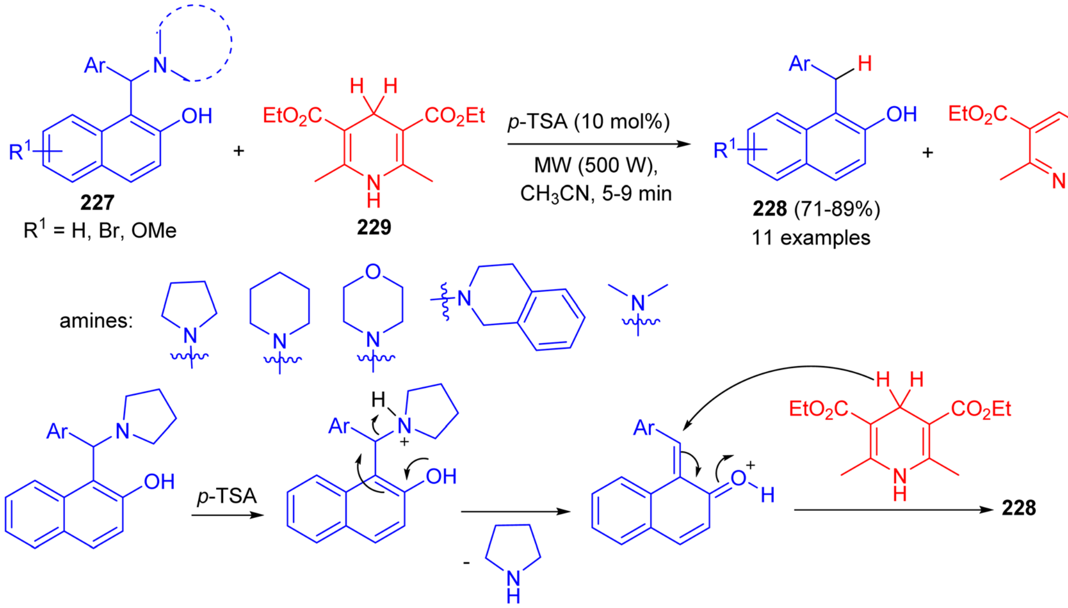
(*S*)-**1** **226** (12-56%)

R = CF_3, C_4F_9, C_6H_5, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, 3,5-$(CF_3)_2C_6H_3$, 1-naphthyl, 2-naphthyl

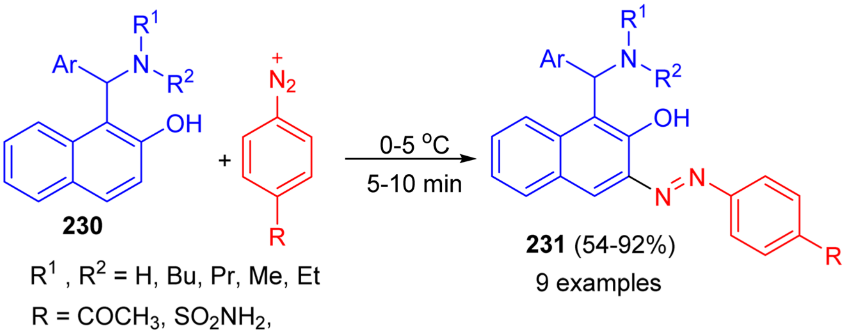
Scheme 59 Synthesis of mono-sulfonamide organocatalysts **226**.

room temperature under argon for 24 h. It should be noted that *N*-Boc-protected Betti base **237** synthesized in 80.3% yield by the reaction of (±)- and (*S*)-(+)-1-(α-aminobenzyl)-2-naphthol (**1**) with di-*tert*-butyl dicarbonates in CH_2Cl_2 at room temperature for 1 h followed by refluxing for 5 h. This method is simple and effective approach to synthesis of racemic and enantiopure phosphoric acids containing chiral Betti base fragment with free amino group (Scheme 63).[88]

Next, an efficient route for benzoylation or formylation of naphthols for the synthesis of hydroxyaryl ketones **238** developed *via* oxidative deamination of Betti bases **239** in the presence of copper salt catalyst with TBHP as an oxidant in water as a reagent as well as solvent. The products were obtained in 62–



Scheme 60 Synthesis of 1-alkyl-2-naphthols **228**.

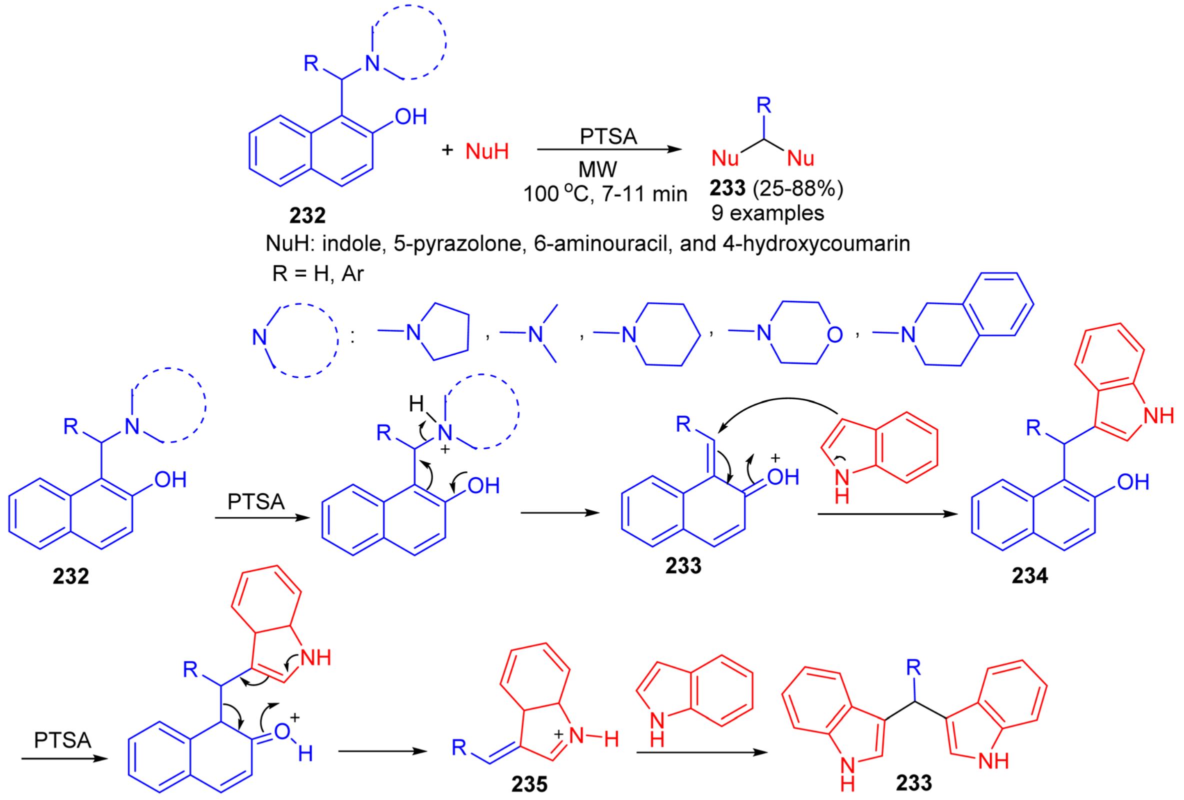


Scheme 61 Synthesis azo dye compounds **231**.

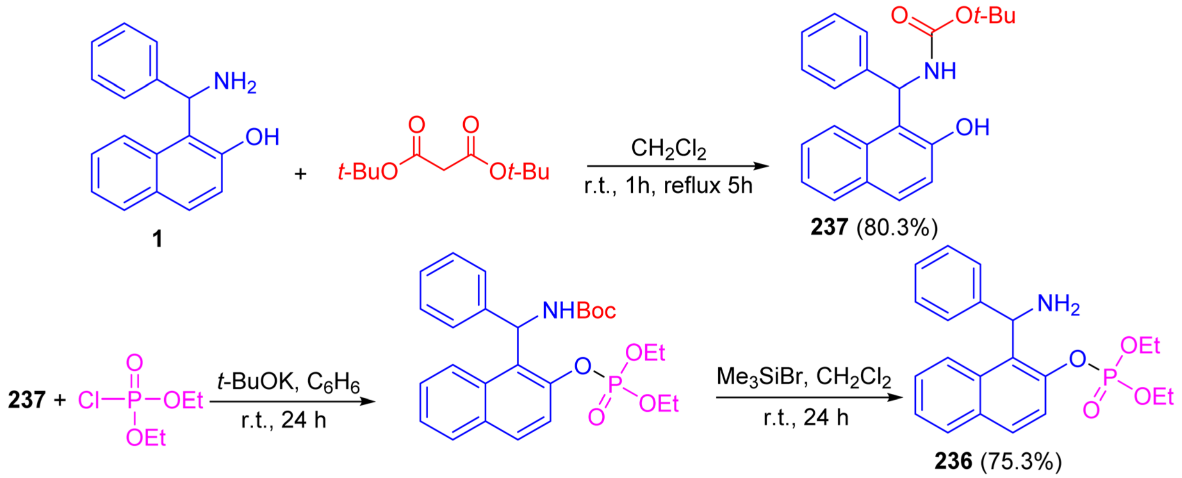
94% yields after 3–5 h. The obtained results showed that *o*/*m* substituted aryl ring of Betti base offered relatively lower yield of product with longer time. Electron withdrawing group on the R of Betti base increases the product yield, whereas electron releasing group decreases the yield. A tentative mechanism for the reaction is proposed in Scheme 64. The benzylic radical **240** could be formed through H-abstraction by *tert*-butoxy radical (formed by copper catalyzed decomposition of TBHP), which followed by a single-electron transfer (SET) from **240** to generate the benzylic iminium carbocation **241**. Subsequently, the intermediate **241** was attacked by a molecule of water giving ketone **238**.[89]

Baruah and co-workers published the synthesis of compounds **242** in 58–86% yields by the reaction of Betti bases **243** with indoles using *p*-TsOH·H_2O (0.1 eq.) as catalyst in toluene at 100 °C for 3–5 h. Electron-donating groups on the aryl ring of Betti bases decreased the product yield, whereas electron-withdrawing groups increased the yield. Betti bases having *ortho*-substituted aryl rings provided lower yields with longer reaction times. When the reaction was carried out by 2.0 equivalents of indoles in the presence of *p*-TsOH·H_2O (0.25 eq.), bis(indolyl)methanes **244** were obtained in 52–65% yields after 3–4 h. Also, the reaction of **243** with indoles using *p*-TsOH·H_2O (0.1 equiv.) in toluene at 100 °C for 3–5 h and then I_2 (0.1 equiv.) and TBHP (2.0 equiv.) afforded chromeno[2,3-*b*]indoles **245** after 2.5 h by stirring the mixture at room temperature. Moreover, the reactions do not use any expensive metal catalyst or solvent. Neither dry solvents nor precautions for an inert atmosphere are required (Scheme 65).[90]

In 2017, the reaction of racemic urea **246** with diethyl chlorophosphite in the presence of potassium *t*-butoxide in benzene/diethyl ether at room temperature for 4 h followed by the treatment with elemental sulfur at reflux conditions for 2 h furnished bis-thiophosphorylated thiourea **247** in 51.5% yield. Then, the reaction of thiourea **246** with diethyl chlorophosphate in the presence of potassium *tert*-butoxide as the base in benzene/diethyl ether at room temperature for 24 h resulted thiourea **248** in 71.3% yield. Also, the reaction of **248** with an excess of bromotrimethylsilane in methylene chloride at room temperature for 24 h afforded bisilylated phosphorylthiourea



Scheme 62 Synthesis of bis(heterocycle)methanes **233**.

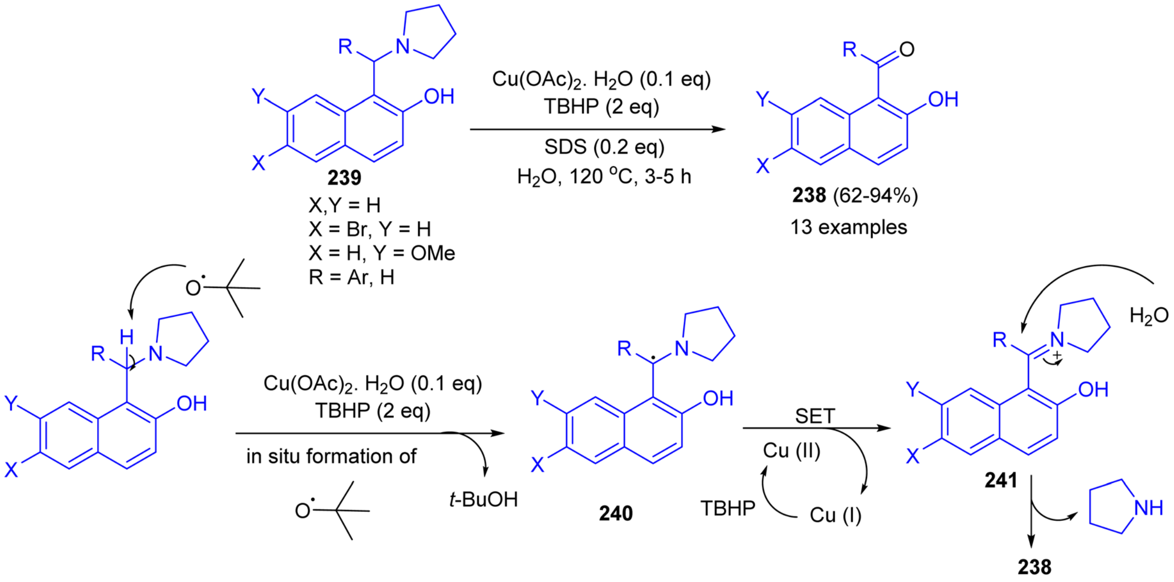


Scheme 63 Synthesis of (±)-*O*-1-[amino(phenyl)methyl]naphth-2-yl phosphate **236**.

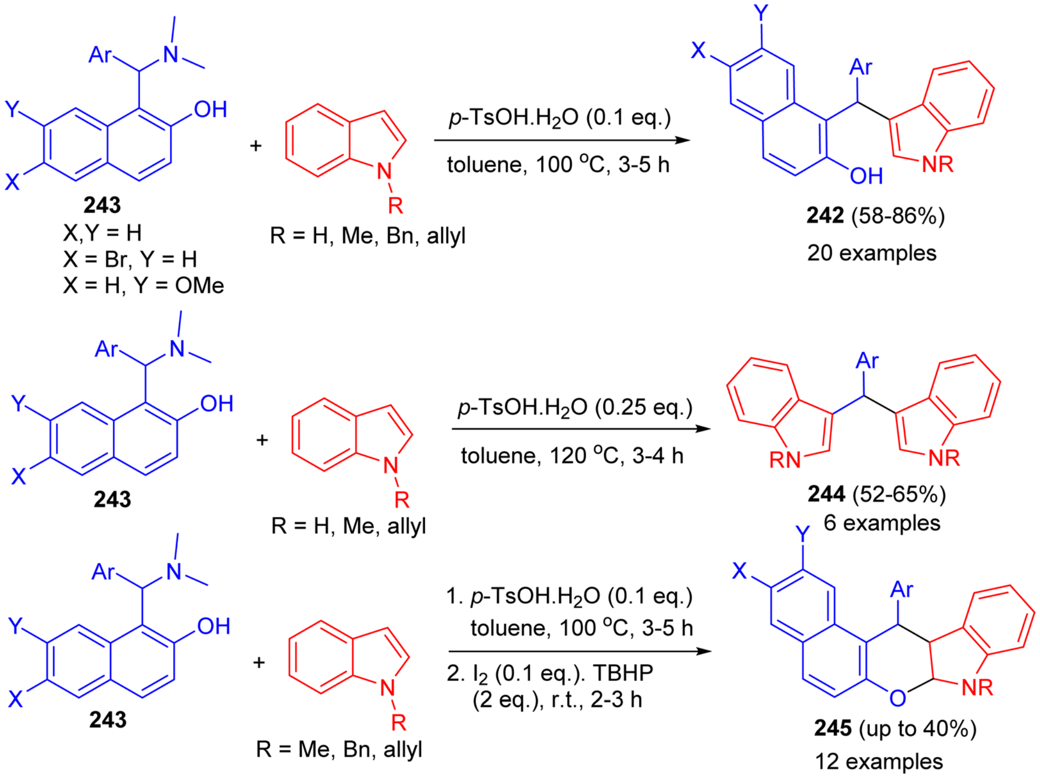
249 followed by the addition of methanol to the reaction mixture resulted in the synthesis of polyfunctional compound **250** in 79.1% yield containing a thiourea fragment, a thionamidophosphate ester group, and a free phosphate dibasic acid function (Scheme 66).[91]

In 2018, Alfonsov and co-workers described the reaction of the Betti base **1** with di-*tert*-butyl decarbonate (**251**) gave Boc-protection of the amino group of the Betti base **252**. The product **252** which reacted with tetra ethyl diamidochlorophosphate in the presence of potassium *tert*-butylate to form compound **253**. To remove the Boc protecting group, compound **253** without isolation was treated with trifluoroacetic acid to form trifluoroacetate **254** in 67.4% yield. The latter reacted with *O*,*O*-diethyl thiophosphorylisothiocyanate to give thiourea bearing a chiral Betti base fragment **255** (Scheme 67).[92]

After that, Vasudevan *et al.* described synthesis of phthalonitrile 4-((1-(phenyl(pyridin-2-ylamino)methyl)naphthalen-2-yl)



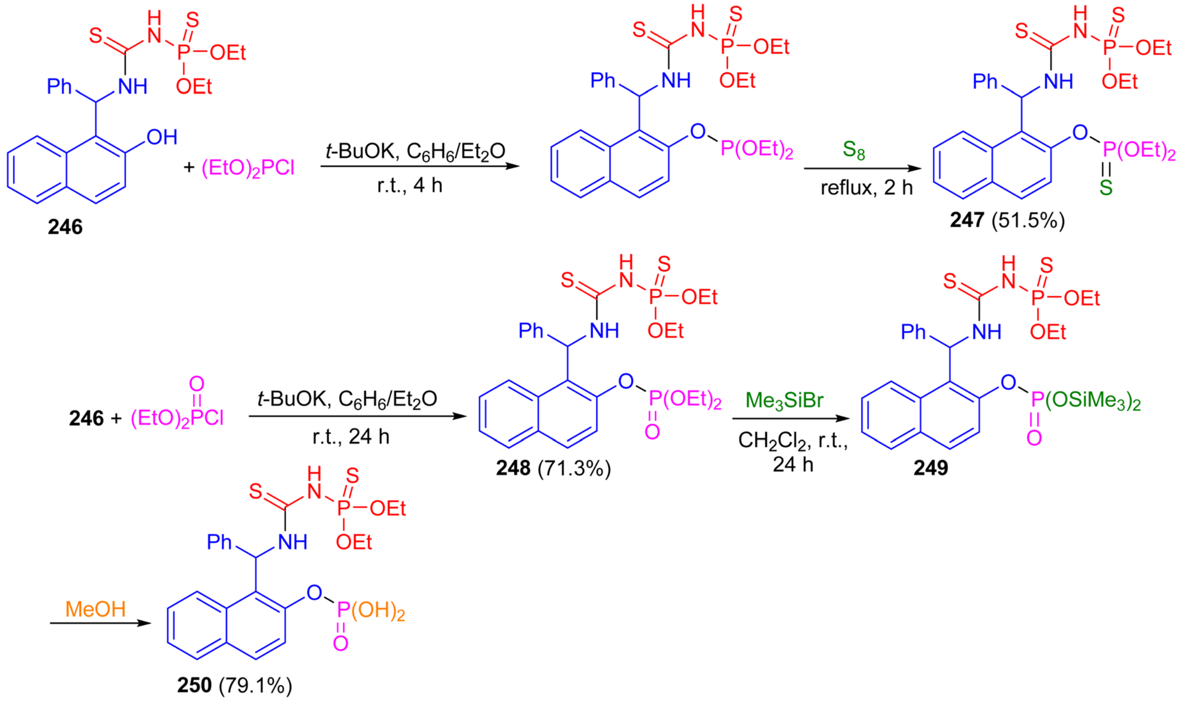
Scheme 64 Copper catalyzed synthesis of hydroxy aryl ketones **238**.



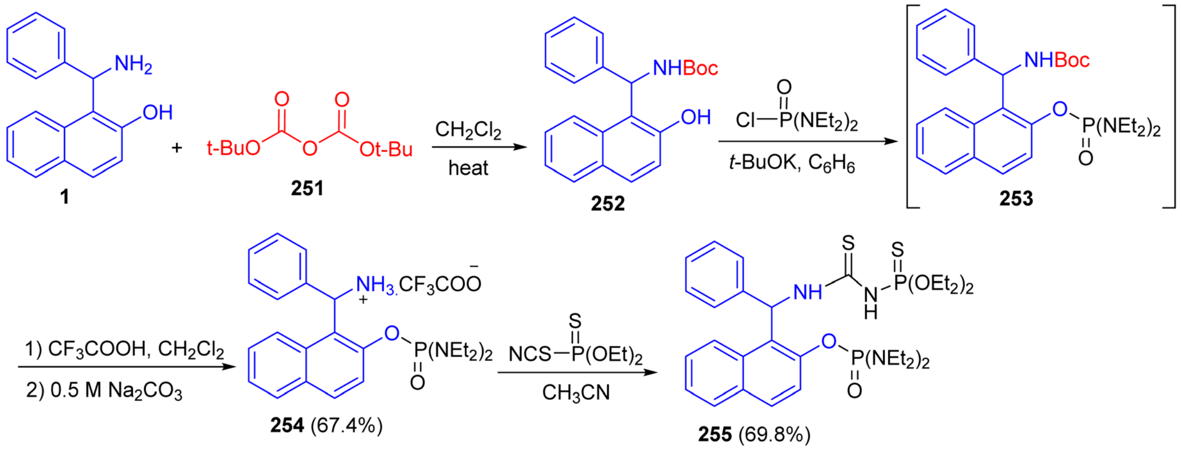
Scheme 65 Brønsted-acid-mediated divergent reactions of Betti bases with indoles.

oxy)phthalonitrile **256** in 82% yield by aromatic nucleophilic coupling reaction of 4-nitrophthalonitrile with phenyl-(2-pyridinylamino)-methyl-2-naphthalenol **257** in DMF using anhydrous K_2CO_3 at room temperature for two days under nitrogen atmosphere. The compound **256** exhibited a selective and sensitive fluorescence detection tendency towards chromium Cr^{3+} ion by the fluorescence turn on processes (Scheme 68).[93]

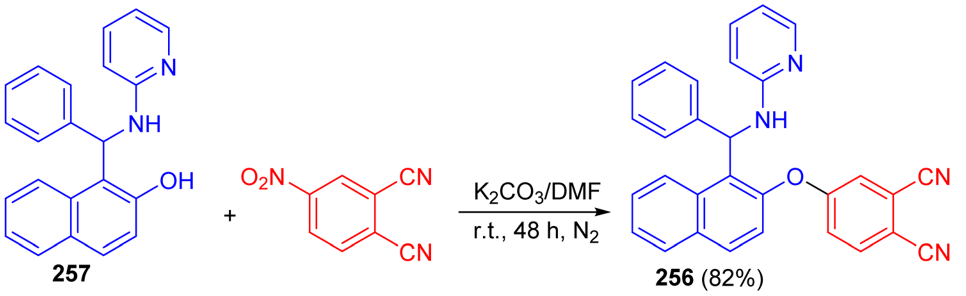
In 2022, the treatment of aminonaphthol derivatives **258** with thiols under catalyst-free in water at 100 °C for 4 h afforded thioethers **259** in 61–91% yields. A plausible mechanism illustrated in Scheme 69. The aerobic oxidation of the aminonaphthol could result in the formation of *ortho*-quinone



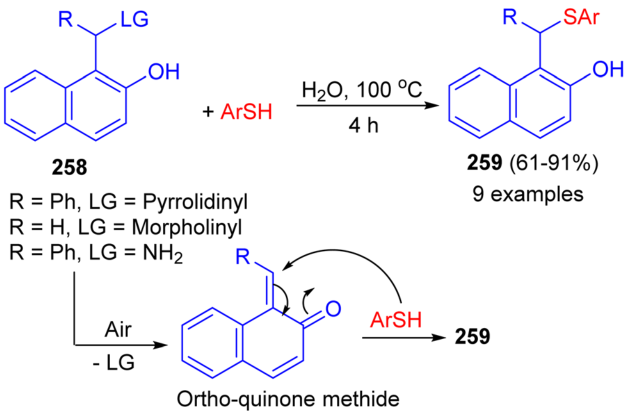
Scheme 66 Synthesis of thiourea derivatives **247–250**.



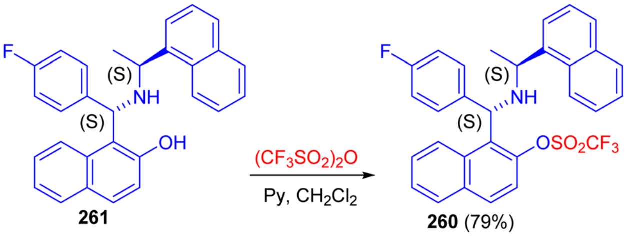
Scheme 67 Synthesis of the Betti base phosphorylated **254** and **255**.



Scheme 68 Synthesis of phthalonitrile 4-((1-(phenyl(pyridin-2-ylamino)methyl)naphthalen-2-yl)oxy)phthalonitrile **256**.



Scheme 69 Synthesis of thioethers **259** from aminonaphthol.



Scheme 70 Triflation of the Betti base **261**.

methide intermediate. The addition of thiol onto the *in situ* generated *ortho*-quinone methide could result in the formation of the desired product **259**. Saturated brine solution was identified as a suitable medium for the synthesis of thioethers from aminophenol derivatives. Control experiments revealed that the nature of leaving group and reaction atmosphere plays a vital role in determining the yield of the products.[94]

Recently, synthesis of 1-[(1*S*)-(4-fluorophenyl)-((1′*S*)-1′-naphthalen-1-yl-ethylamino)-methyl]-naphthalen-2-ol **260** in 79% yield reported by the triflation reaction of (*S*,*S*)-aminobenzylnaphthol **261** with trifluoromethanesulfonic anhydride in the presence of pyridine in dichloromethane at room temperature for 16 h as shown in Scheme 70. Compound **260** can be used as valuable intermediate in the future synthesis of aminophosphine, to be used in asymmetric catalysis.[95]

9 Conclusions

The Betti reaction is a multicomponent reaction that allows for the synthesis of various compounds containing C–C and C–N bonds in a single step. The Betti bases exhibit significant versatility as essential structural motifs in synthetic organic compounds, especially in the synthesis of heterocyclic molecules. This is attributed to their capacity for incorporating diverse functional groups, including –OH and –NH. This review explores transformations of the Betti base derivatives to the heterocyclic compounds such as naphthoxazines, bis-naphthoxazines, naphthopyrrolooxazines, naphthopyridooxazines, naphthooxazinoazepines, naphthoxazinobenzoxazines, naphthoxazinoisoquinolines, naphthoxazinoquinolines and the other fused-heterocycles. Furthermore, the review investigates the applications of these transformed compounds in relation to their pharmacological properties. We hope this review will promote the continued interest in the conversion of the Betti bases to the organic compounds and will provide a comprehensive and valuable insight to fill the gap in the reactions of Betti bases and their transformations into target compounds in the future.

Conflicts of interest

There are no conflicts to declare.

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