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Recent developments in the one-pot synthesis of 1,4-benzoxazines, 1,4-benzodioxins and their 2,3-dihydro derivatives

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Running Title : One-pot synthesis of 1,4-benzoxazine and 1,4-benzodioxin derivatives

ABSTRACT

1,4-Benzoxazine and 1,4-benzodioxin derivatives have received great attention in chemical and medicinal research due to their natural occurrence and important biological activities. These compounds are known to be central nervous system depressants, antipsychotic agents, calcium antagonists, diuretic and antibacterial agents, while others are potential drugs for treating neurodegenerative, inflammatory, autoimmune, cardiovascular and diabetic disorders.

Past syntheses of 1,4-benzoxazine and 1,4-benzodioxin derivatives have relied predominantly upon multistep procedures, using 2-aminophenols and catechols as the starting materials, respectively. However, these methods suffered some limitations in the generation of molecular diversity. The recent development of new synthetic strategies such as metal-catalyzed reactions, cascade reactions or microwave irradiation, which allow one-pot multiple functionalization, contributes to revitalize interest in the 1,4-benzoxazine and 1,4-benzodioxin cores.

The present review mainly highlights, through contributions published after 2000 in chemical journals, the recent synthetic strategies allowing the one-pot synthesis of these biologically relevant N- and O-heterocycles.

INTRODUCTION

The 1,4-benzoxazine and 1,4-benzodioxin subunits **1a** and **2a**, and their 2,3-dihydro analogs **1b** and **2b** (Figure 1), are present in some naturally occurring substances and synthetic bioactive compounds [1,2]. For example, various glycosides of the 2-hydroxy-2H-1,4-benzoxazine skeleton have been found to occur in gramineous plants such as maize, wheat, rye, and rice, and have been suggested to act as plant resistance factors against microbial diseases and insects [3-6]. The 1,4-benzoxazine moiety is also found in various antibiotics such as enediynes [7-9] or ofloxacin, a third generation quinolone antibacterial agent which is currently on the market [10]. Likewise, flavolignans bearing a 1,4-benzodioxin nucleus have been shown to display activity against murine lymphocytic leukaemia P-388 cell line [11,12]. Some naturally occurring compounds possessing the 1,4-benzodioxin framework also serve as effective insecticidal agents [13], whereas some synthetic compounds act as potent antihypertensive or anti-depressant drugs [14-16].

Furthermore, various 1,4-benzoxazine and 1,4-benzodioxin derivatives themselves have been shown to display very interesting pharmacological properties. Some of them are antipsychotic agents, calcium antagonists, diuretic and antibacterial agents, while others are potential drugs for treating neurodegenerative, inflammatory, autoimmune, cardiovascular and diabetic disorders [1,2].

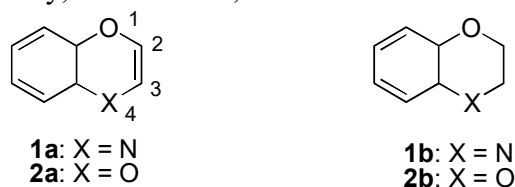


Figure 1. 1,4-benzoxazine and 1,4-benzodioxin subunits and their 2,3-dihydro analogs

As a consequence, 1,4-benzoxazine and 1,4-benzodioxin derivatives have attracted special attention from the synthetic community and several methods have been reported to synthesize these N- and O-heterocycles. However, past syntheses often required a tedious multistep sequence using 2-aminophenols and catechols as the starting materials [17-19]. Furthermore, most of the procedures targeted the synthesis of specific molecules and lacked generality.

Therefore, the development of new, efficient and general synthetic strategies proved to be essential to revitalize interest in the 1,4-benzoxazine and 1,4-benzodioxin cores. Among them, the use of palladium catalysis has recently gained great importance because of the possibility of constructing highly functionalized heterocyclic rings, with the desired substitution pattern in one-step procedures, through an ordered sequence of processes mediated by the metal center, under mild conditions and with high selectivity, using very simple and readily available starting materials [20-22]. Likewise, cascade reactions have been shown to constitute an interesting one-pot strategy which can fall under the banner of “green chemistry”, as only a single reaction solvent, workup procedure and purification are required to provide a product whose the synthesis normally would involve several individual steps [23]. Lastly, microwave irradiation has been successfully applied to heterocyclic chemistry, as spectacular accelerations, high yields under mild reaction conditions and high product purities have been reported [24-26]. Because of its speed (5 to 10 minutes as opposed to several hours in a conventional protocol), microwave-assisted organic synthesis is ideally suited for high-throughput chemistry, allowing the development of libraries of heterocycles [26].

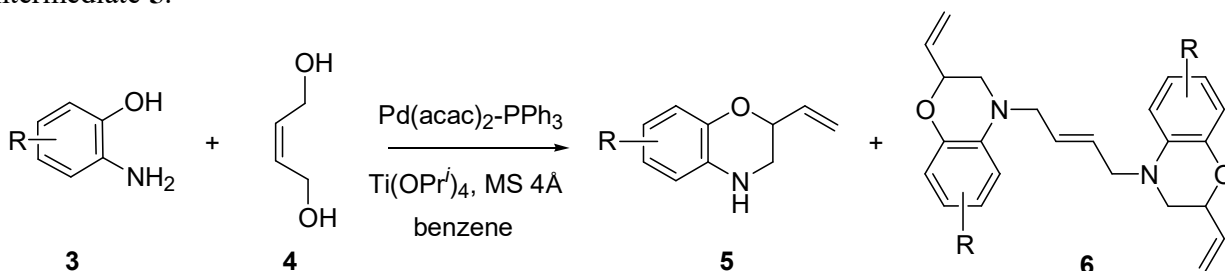
The synthesis of the 1,4-benzoxazine and 1,4-benzodioxin derivatives has been summarized in several reports [1,2,17-19], in which papers published before 2000 are extensively cited. Accordingly, the aim of this review is to show, through contributions published after 2000, how the aforementioned recent synthetic strategies have been used efficiently to improve the synthesis of the 1,4-benzoxazine and 1,4-benzodioxin derivatives and, consequently, to reinforce the interest in these biologically relevant N- and O-heterocycles. The developed one-pot synthetic protocols leading to the 1,4-benzoxazine and 1,4-benzodioxin derivatives have been grouped into three classes of reactions: metal-catalyzed reactions, cascade reactions and microwave irradiation.

METAL-CATALYZED REACTIONS

1. Synthesis of 1,4-benzoxazine derivatives and 3,4-dihydro-2*H*-1,4-benzoxazine derivatives

1.1 Palladium-catalyzed reactions

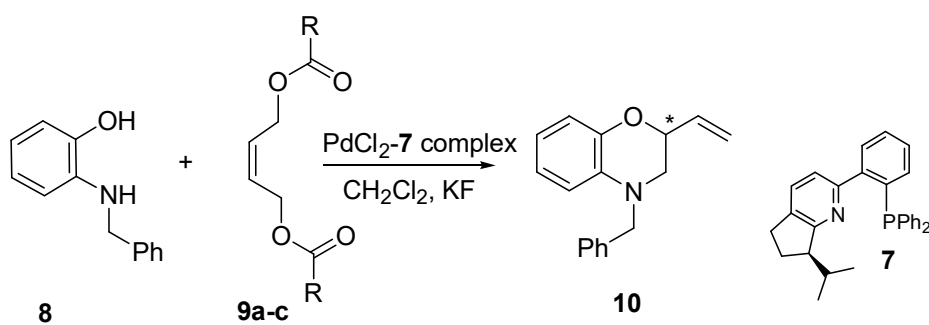
Introduction of palladium-catalyzed heteroannulation proved to be useful in organic synthesis. In particular, some successful applications of a process involving C-O bond cleavage, with direct use of allylic alcohols, catalyzed by palladium complexes were reported [27-30]. Accordingly, Yang et al. developed a one-pot palladium-catalyzed regioselective tandem allylation of 2-aminophenol substrates **3** with 2-butene-1,4-diol **4** for the synthesis of 3,4-dihydro-2-vinyl-2*H*-1,4-benzoxazine derivatives **5** [31]. The addition of a titanium reagent $\text{Ti}(\text{OPr}^i)_4$ to promote the palladium-catalyzed allyl-OH bond cleavage, together with phosphine ligand PPh_3 to reinforce the catalytic activity of palladium catalyst, markedly enhanced both the reaction rate and yield of product (Scheme 1). A comparative study of different catalysts was reported. As the catalyst precursor, $\text{Pd}(\text{acac})_2$, $\text{Pd}(\text{OAc})_2$, $\text{Pd}_2(\text{dba})_3$ and $\text{PdCl}_2(\text{MeCN})_2$ showed good catalytic activity. Other palladium complexes such as PdCl_2 and $\text{Pd}(\text{PPh}_3)_4$ were less active, leading to lower yields. Moreover, the amination of 2-butene-1,4-diol **4** worked well with 2-aminophenols containing an electron-donating group ($\text{R} = \text{Me}$), whereas 2-aminophenols bearing strong electron-withdrawing groups ($\text{R} = \text{NO}_2$ or SO_2Et) gave lower yields (Scheme 1). In some cases, compound **6** was isolated as a result of two successive nucleophilic substitution on the diol **4** via intermediate **5**.



3	R	Yield (%) (5 : 6)
3a	H	90 (50:50)
3b	4-Me	86 (70:30)
3c	5-Me	89 (45:55)
3d	4-Cl	60 (70:30)
3e	4-NO ₂	44 (100:0)
3f	4-SO ₂ Et	37 (100:0)

Scheme 1

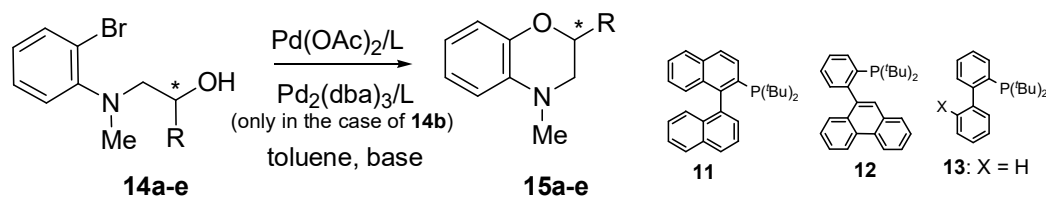
Palladium-catalyzed asymmetric allylic substitution is a major topic in catalytic asymmetric synthesis and various chiral ligands have been developed for this reaction [32,33]. Katsuki et al. have demonstrated that 2-(phosphinophenyl)pyridine **7**, bearing an isopropyl group at C7, is an efficient chiral auxiliary for palladium-mediated intramolecular allylic amination. In this context, they have examined the reaction of 2-benzylaminophenol **8** with (*Z*)-1,4-diacetoxy- and (*Z*)-1,4-bis(alkoxycarbonyloxy)-2-butene **9a-c**, in the presence of $\text{PdCl}_2\text{-7}$ complex as the catalyst and KF as the base (Scheme 2). Optically active 4-benzyl-2-vinyl-1,4-benzoxazine **10** could then be isolated in high yields ranging from 92 to 98%. In all cases, the *R*-isomer was isolated as the major product. Interestingly, the reaction of **9b** at 0°C improved the enantioselectivity up to 86% ee [34].



9a-c	R	T(°C)	10 Yield (%) (%ee)
9a	Me	rt	98 (66)
9b	O ⁱ Pr	0	96 (86)
9c	^t Bu	rt	92 (67)

Scheme 2

The intramolecular palladium-catalyzed C-O bond formation is also a potentially attractive means to assemble oxygen heterocycles [20-22]. Buchwald et al. showed that bulky, electron-rich *o*-biphenylphosphines were effective in a variety of palladium-catalyzed cross-coupling reactions [35-38]. Especially, attempts were made to apply di-*tert*-butylphosphinobiaryl ligands **11-13** to cyclize 2-bromoaniline-derived substrates **14a-e** into 1,4-benzoxazine derivatives **15a-e** (Scheme 3).



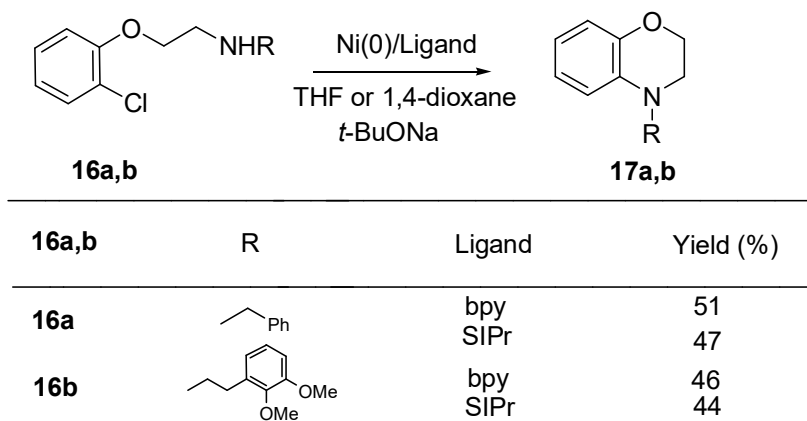
14a-e	R	ee (%)	Ligand L	base	Yield (%) 15a-e	ee (%)
14a	H	–	12	Cs ₂ CO ₃	74	–
14b	Me	99	11	Cs ₂ CO ₃	78	94
14c	OH	97	13	K ₃ PO ₄	80	97
14d	<i>n</i> Pr	98	13	K ₃ PO ₄	86	98
14e	OMe	99	11	K ₃ PO ₄	80	99

Scheme 3

The reactions proceeded under mild conditions, using weak bases such as Cs₂CO₃ or K₃PO₄. A variety of functional groups was tolerated and enantioenriched alcohols could be coupled without erosion of optical purity [39]. The analogous 2-chloroaniline-derived substrates were also prepared and their cyclization reactions were examined. The yield in 1,4-benzoxazine derivatives was found to be close to that obtained using the corresponding 2-bromoaniline-derived substrates.

1.2 Nickel-catalyzed reactions

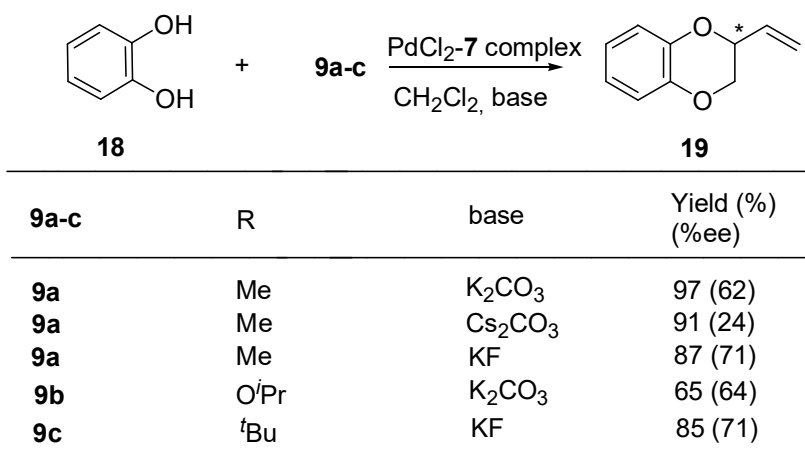
Nickel-catalyzed intramolecular cyclization of 2-chlorophenol-derived substrates have been described by Fort et al. [40] as a variant of the aforementioned palladium-catalyzed cross-coupling reactions. The use of an *in situ* generated Ni(0) catalyst, associated with 2,2'-bipyridine (bpy) or N,N'-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene (SIPr) as a ligand and *t*-BuONa as the base, allowed the intramolecular cyclization of 2-chlorophenol-derived substrates **16a,b** into 1,4-benzoxazine derivatives **17a,b** in moderate yields (Scheme 4).



Scheme 4

2. Synthesis of 1,4-benzodioxin derivatives and 2,3-dihydro-1,4-benzodioxin derivatives by palladium-catalyzed reactions

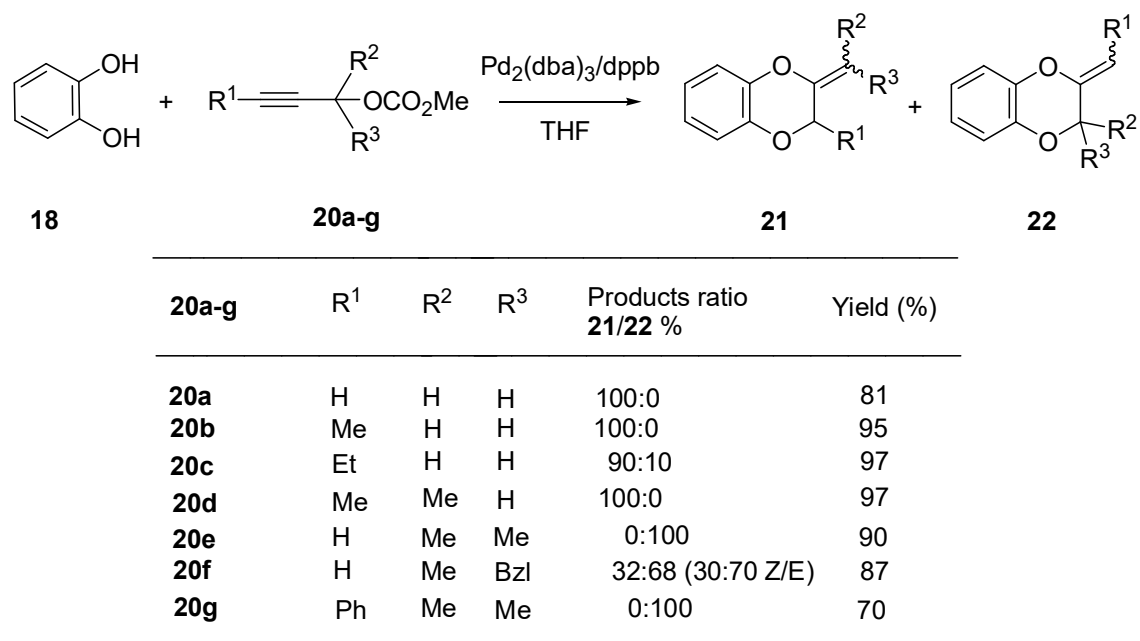
The aforementioned palladium-catalyzed asymmetric tandem allylic substitution of (*Z*)-1,4-diacyloxy- and (*Z*)-1,4-bis(alkyloxycarbonyloxy)-2-butene **9a-c** (Scheme 2), replacing 2-benzylamino phenol **8** by catechol **18** as the nucleophile, allowed the synthesis of optically active 1,4-benzodioxin derivative **19**. Katsuki et al. showed that the highest enantioselectivity (71% ee) was observed when KF was used as the base (Scheme 5) [34].



Scheme 5

Sinou et al. [41] reported that the palladium-catalyzed condensation of catechol **18** with various propargylic carbonates **20a-g**, in the presence of a palladium complex generated *in situ* by mixing Pd₂(dba)₃ and 1,4-bis(diphenylphosphino)butane ligand (dppb), provided a versatile and easy access to various 2-alkylidene-2,3-dihydro-1,4-benzodioxin derivatives **21** and **22** with good yields and regioselectivity. The stereochemistry of the double bond in the resulting heterocycle depended on the

substitution pattern of the propargylic carbonate: primary and secondary carbonates afforded mainly the *Z* alkene, while tertiary carbonates gave predominantly the *E*-isomer (Scheme 6). This reaction was recently extended to propargylic carbonates bearing different functionalized groups (hydroxyl, *t*-butyldimethylsilyloxy, ester, diethylamino). The regioselectivity of the palladium-catalyzed annulation between catechol and functionalized propargylic carbonates strongly depended on the nature of the substituent and on the chain length between the triple bond and the function [42].



Scheme 6

Asymmetric versions (up to 97% ee) of these reactions were also achieved by the same group using chiral (*R*)- or (*S*)-2,2'-bis(diphenylphosphanyl)-1,1'-binaphtyl (Binap) ligand instead of dppb [43-45]. This methodology was successfully extended to the asymmetric palladium-catalyzed annulation of catechol with racemic secondary propargylic carbonates and acetates bearing two different substituents (\neq H), both on the *sp* carbon and on the carbon atom bearing the carbonate (or acetate) function [46].

Buchwald et al. showed that the aforementioned intramolecular palladium-catalyzed C-O bond formation, using 2-bromophenol derived substrates **23a-e** instead of 2-bromoaniline-derived substrates **14a-e**, and di-*tert*-butylphosphinobiaryl ligand **11** or **24**, alternatively, was attractive for the synthesis of 1,4-benzodioxin derivatives **25a-e** (Scheme 7) [38,39]. Once again, aryl bromides bearing stereogenic centers at the carbinol carbon were cyclized in high yields, without racemization. The analogous aryl chloride substrates can also be efficiently cyclized with the palladium catalyst system, but small amount of epimerization (7-10%) was observed.

23a-e	R	ee (%)	Ligand L	base	Yield (%) 25a-e	ee (%)
23a	H	–	24	CS ₂ CO ₃	81	–
23b		96	24	CS ₂ CO ₃	80	95
23c		99	11	K ₃ PO ₄	72	99
23d		98	11	K ₃ PO ₄	84	98
23e		99	11	K ₃ PO ₄	83	99

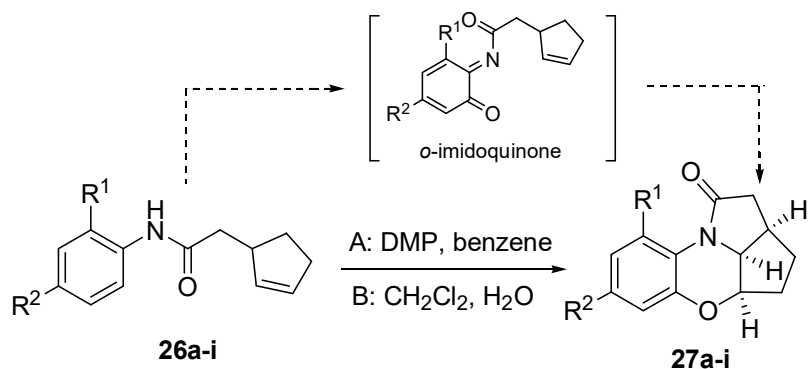
Scheme 7

CASCADE REACTIONS

The undeniable benefits of cascade reactions are now well established. Among them, the possibility of carrying out several transformations in only one synthetic operation is of particular interest from a green chemistry perspective. For example, only a single reaction solvent, workup procedure and purification step may be required to provide a product whose the synthesis normally would involve several individual steps. Recently, Nicolaou et al. presented a broad variety of strategies developed for the construction of complex molecules using cascade reactions [23]. In this part, the term “cascade” encompasses not only cascade sequence but also tandem reaction allowing the synthesis of polyfunctionalized 1,4-benzoxazine and 1,4-benzodioxin derivatives.

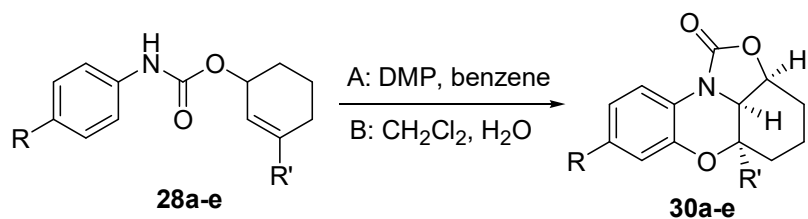
1. Synthesis of 1,4-benzoxazine derivatives and 3,4-dihydro-2*H*-1,4-benzoxazine derivatives

Nicolaou et al. reported an elegant Dess-Martin periodinate (DMP)-mediated cascade polycyclization reaction of simple anilides, urethanes and ureas for the synthesis of 1,4-benzoxazine-containing polycycles [47,48]. This reaction delivered complex structures equipped with numerous heteroatoms, useful functionalities and several stereochemical centers in a single step. For example, the reaction of easily accessible substituted anilides **26a-i** with DMP:H₂O (2:1) reagent, either in refluxing benzene or in CH₂Cl₂ at room temperature, led to the 1,4-benzoxazine derivatives **27a-i** (Scheme 8). A wide variety of groups were tolerated on the aryl residue, ranging from the electronwithdrawing nitro and trifluoromethyl groups to the synthetically fertile halides. Similarly, urethanes **28a-e** and urea **29** produced the related complex benzoxazine-containing polycycles **30a-e** and **31** (Scheme 9). Furthermore, a detailed mechanistic study of the cascade reaction revealed the *in situ* formation of an *o*-imidoquinone intermediate (Scheme 8), which reacted as a diene in an intramolecular inverse-electron-demand Diels-Alder (IEDDA) reaction with the proximate olefin, to furnish the observed polycycle [48]. Later, Nicolaou et al. were able to isolate pure *o*-imidoquinone entities, which proved to be willing partners for diverse olefins in the intermolecular variant of the aforementioned process, affording polyfunctionalized 1,4-benzoxazine derivatives in high yields ranging from 71 to 95% [49, 50].

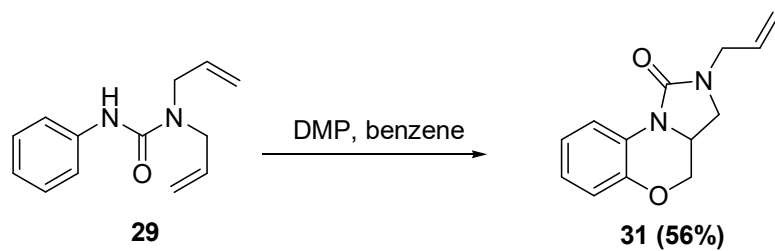


26a-i	R¹	R²	conditions	Yield (%) 27a-i
26a	H	H	A	52
26b	H	Et	B	44
26c	H	Cl	B	48
26d	H	NO ₂	B	37
26e	H	CF ₃	B	57
26f	OH	H	B	35
26g	CF ₃	H	B	39
26h	I	H	B	31
26i	Me	F	B	25

Scheme 8

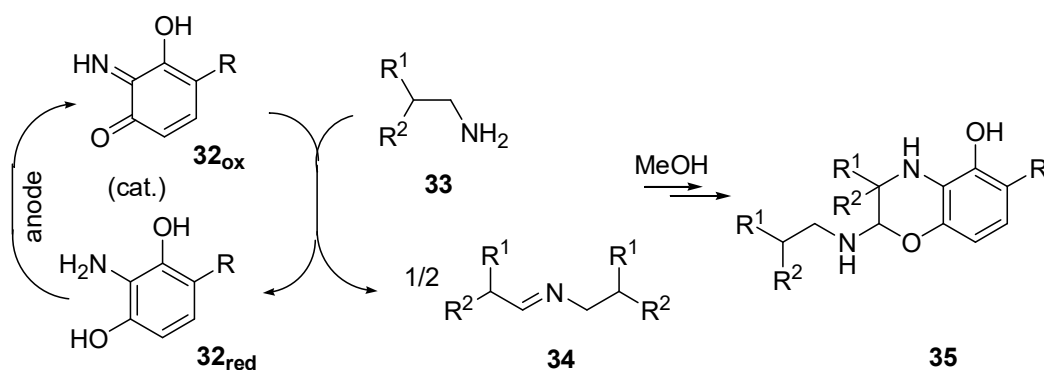


28a-e	R	R'	conditions	Yield (%) 30a-e
28a	H	H	A	50
28b	Et	H	B	30
28c	CN	H	B	37
28d	NO ₂	H	B	25
28e	H	Me	A	42



Scheme 9

Our group recently revealed that electrochemically induced cascade reactions, which combine the synthetic potential of cascade reactions with the pre-eminent green advantages of electrochemical synthesis (especially the utilization of electricity as energy instead of chemical reagents, high atom economy and room temperature), were also effective for the synthesis of 1,4-benzoxazine derivatives [51]. This one-pot cascade of transformations required the utilization of electrogenerated 3,4-azaquinone species **32_{ox}** as effective organic catalyst for the autorecycling oxidation of (R^1R^2)CHCH₂NH₂ aliphatic primary amines **33**. The catalytic cycle produced the reduced catalyst **32_{red}** and an alkylimine **34** as the product of amine oxidation [52]. After a certain number of turnovers, the catalytic process ceased as the catalyst **32_{ox}** was trapped through IEDDA reaction, with the simultaneously electrogenerated tautomeric enamine form of the alkylimine extruded during the catalytic process. This cascade sequence, wherein both chemically nonaccessible cycloaddition partners were generated *in situ*, at room temperature, under metal-free conditions, led to the rapid construction of polyfunctionalized 1,4-benzoxazine derivatives **35** in a regioselective manner and allowing diastereospecific annellation [53-55]. The synthetic utility of this process was proven through the variation of the structure of both cycloaddition partners (Scheme 10).

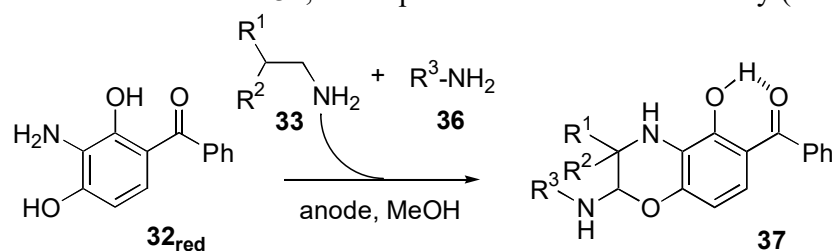


32_{red}	amine substrate 33		35
R	R ¹	R ²	Yield (%)
COPh	Ph	Ph	55
COPh	(CH ₂) ₅		77
COPh	Me	Ph	52
COPh	Me	Et	70
COPh	Me	Me	71
COPh(4-SO ₂ Me)	Me	Me	74
COPh(2-OMe)	Me	Me	84
COPh(2,6-Me)	Me	Me	72
COMe	Me	Me	71
CO ^t Bu	Me	Me	76
COC ₆ H ₁₁	Me	Me	78
NO ₂	Me	Me	75

Scheme 10

To increase the molecular diversity, we have also electrogenerated enamines in which the substituents on the amino group were different from those linked to the double bond. For this purpose, the amine R^1R^2 CHCH₂NH₂ was catalytically oxidized by *o*-azaquinone **32_{ox}**, in the presence of a second

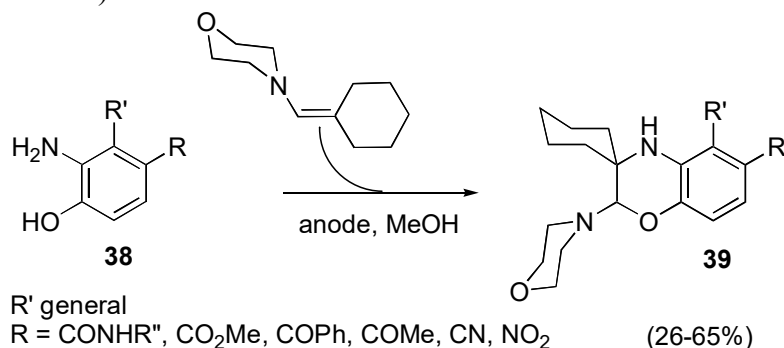
R^3NH_2 primary aliphatic amine **36** [53]. Then, the 32_{ox} -mediated cascade reaction led to the construction of complex 1,4-benzoxazine derivatives **37**, with up to five elements of diversity (Scheme 11).



Amine 33		Amine 36	37 Yield (%)
R ¹	R ²	R ³	
Me	Me		70
Me	Me		50
Me	Me		60
Me	Me		68
Me	Et		66
(CH ₂) ₅			62

Scheme 11

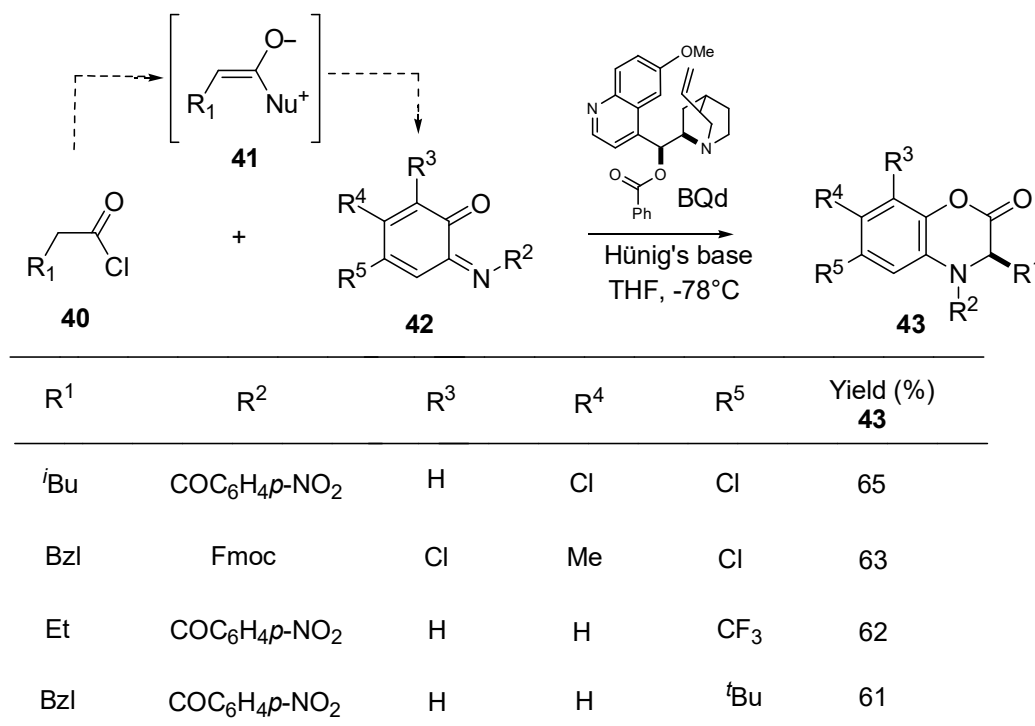
However, two limitations of our electrochemical procedure were delineated. First, it can not produce tertiary alkylenamine. Accordingly, when the primary amine R^3NH_2 was replaced by a secondary amine R^3NHR^4 , alkyimine **34** continued to be formed leading to the unwanted 1,4-benzoxazine derivatives **35**. Second, the cascade reaction was found to be general only with electron-poor *o*-azaquinone entities, generated from substituted 2-aminoresorcinol substrates 32_{red} . In the case of *o*-aminophenol derivatives **38**, which lack the 2-hydroxyl group, the *in situ* produced *o*-azaquinone species failed to catalyze the oxidation of the amine to the corresponding alkyimine, precursor of the alkylenamine dienophile, due to the absence of an intramolecular hydrogen bond at the origin of a highly reactive Schiff base cyclic transition state [55]. To overcome these problems, a tandem oxidation-IEDDA reaction, in which the *o*-azaquinone was generated in the presence of a preformed tertiary alkylenamine, was developed as an alternative, affording 1,4-benzoxazine derivatives **39** with complete regioselectivity (Scheme 12).



Scheme 12

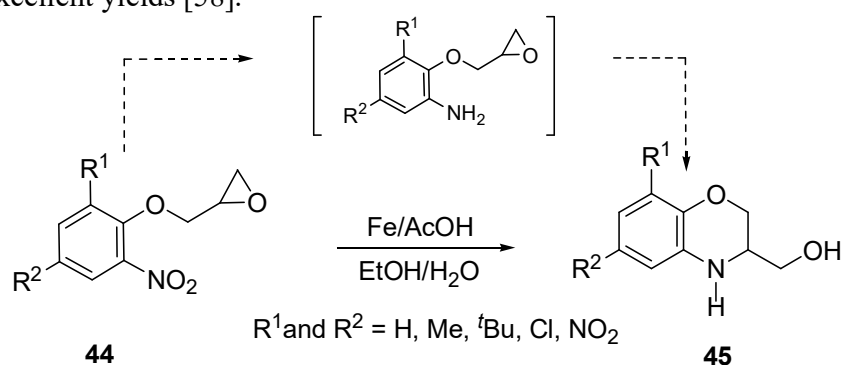
These one-pot electrochemical methodologies, which offer the opportunity to introduce variations in both cycloaddition partners, were found to be particularly useful for the development of libraries of biologically relevant 1,4-benzoxazine derivatives. In this respect, some of these compounds were found to be significant targets as neuroprotective agents both *in vitro* and *in vivo* [56].

Lectka et al. recently described the first catalytic asymmetric synthesis of 1,4-benzoxazinone derivatives, traversing through a chiral ketene enolate intermediate [57]. This tandem reaction consisted of the transformation, in the presence of benzoyl-quinidine (BQd) as the catalyst and Hünig's base, of an acyl chloride **40** into a chiral ketene enolate intermediate **41**, which served as a dienophile for [4+2] cycloaddition with an *o*-imidoquinone heterodiene **42**, leading to 1,4-benzoxazinone derivatives **43**, in good yield with uniformly excellent enantiomeric excess (>99%) (Scheme 13).



Scheme 13

Zhao et al. have described a tandem reduction-oxirane opening of 2-nitroaroxymethyloxiranes **44**, in the presence of iron powder and acetic acid, for the synthesis of biologically relevant 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine derivatives **45**. The yields were not given but the authors indicated moderate to excellent yields [58].

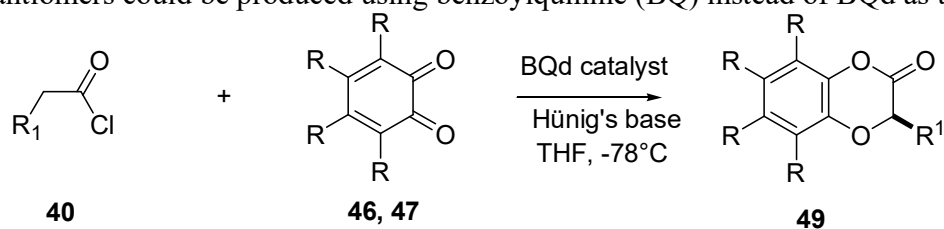


Scheme 14

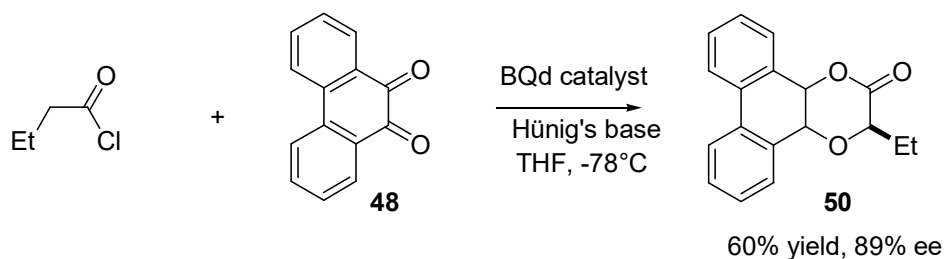
Among these compounds, 6,8-dichloro-2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine was found to be the most effective molecule in promoting vascular endothelial cells (VEC) apoptosis and inhibiting A549 cell proliferation, whereas 6-amino-2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine could inhibit VEC apoptosis and might induce the formation of microvessel [58].

2. Synthesis of 1,4-benzodioxin derivatives and 2,3-dihydro-2H-1,4-benzodioxin derivatives

The aforementioned catalyzed tandem nucleophilic substitution-[4+2] cycloaddition of ketene enolate **41** (Scheme 13) could also be used for the synthesis of optically active 1,4-benzodioxinone derivatives, using *o*-chloranil **46**, *o*-bromanil **47** or 9,10-phenanthrene-quinone **48** as heterodienes [59]. 1,4-Benzodioxinone derivatives **49** were isolated in high yields, the (R)-enantiomers being formed preferentially (Scheme 15). The reactivity of 9,10-phenanthrene quinone proved to be lower than that of *o*-chloranil or *o*-bromanil, affording 1,4-Benzodioxinone **50** in moderate yield (89% ee). Interestingly, the (S)-enantiomers could be produced using benzoylquinine (BQ) instead of BQd as the catalyst.

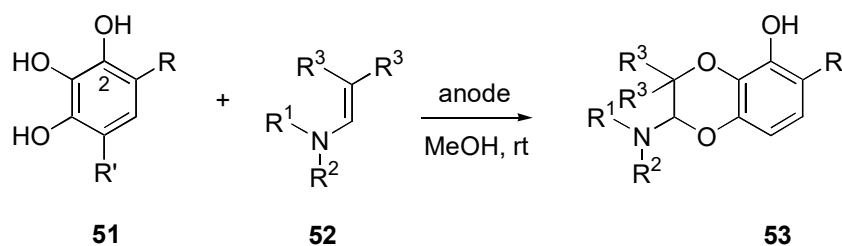


<i>o</i> -quinone	R	R ¹	Yield (%) 49	ee (%)
46	Cl	Et	91	99
46	Cl	<i>i</i> Pr	75	93
46	Cl	Ph	90	90
46	Cl	Bzl	72	99
46	Cl	<i>p</i> OMePh	58	99
46	Cl	<i>p</i> MePh	75	93
47	Br	Et	90	95



Scheme 15

The aforementioned tandem oxidation-IEDDA reaction (Scheme 12), in which the *o*-azaquinone was replaced by an electrogenerated *o*-quinone species, could also be used for the regiospecific synthesis of diverse 1,4-benzodioxin derivatives [60]. Accordingly, the anodic oxidation of pyrogallol derivatives **51** produced putative *o*-quinone heterodienes, which were trapped *in situ* by enamine dienophiles **52**. The possibility of introducing variations in both cycloaddition partners gave rise to highly substituted 1,4-benzodioxin cycloadducts **53**, with up to five elements of diversity (Scheme 16).



51		52			53
R	R'	R ¹	R ²	R ³ ,R ³	Yield %
COMe	H				62
COMe	Br				66
CO ^t Bu	H				53
COPh	H				77
COPh	Br				76
CO ₂ Me	H				60
NO ₂	H				25
COPh	Br			Me,Me	75
COPh	Br			Et,Et	70
COPh	Br				70
COPh	Br			Me,Me	75
COPh	H	H		Ph,Ph	50

Scheme 16

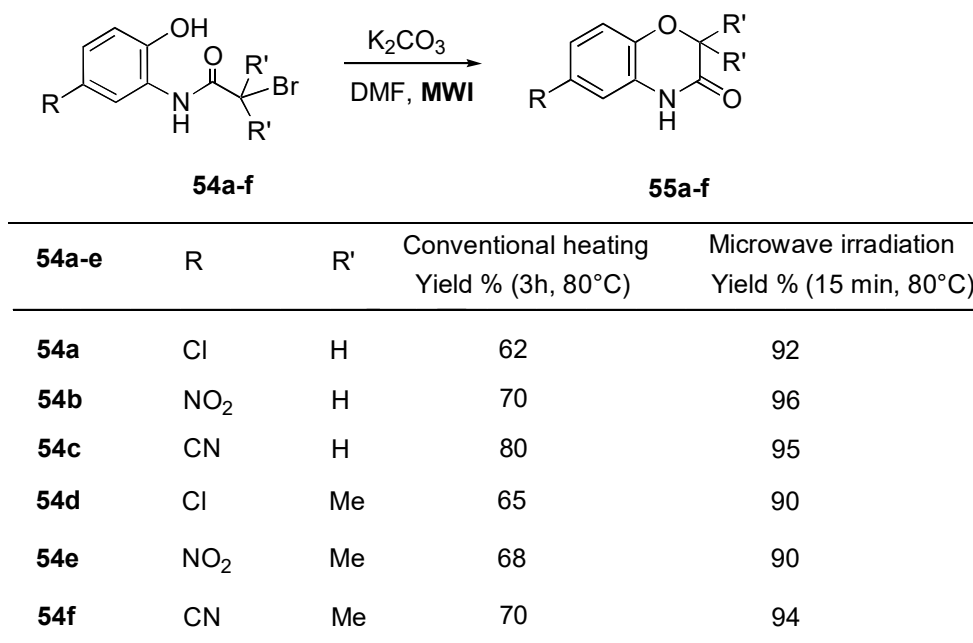
The regioselectivity of the cycloaddition reaction deserved special note because the regioselectivity of previously reported similar reactions was quite variable [61-63]. Furthermore, when the pyrogallol derivative **51** (R = COPh, R' = H) was replaced by its corresponding 2-methoxy analog, the electrochemically induced cycloaddition led to a 4:1 mixture of regioisomers (75% combined yields), highlighting the crucial role of the 2-hydroxyl group as the inducer of regioselectivity. In this respect, the related *o*-azaquinone species proved to be more versatile heterodienes, since the cycloaddition reactions were regioselective irrespective of the nature of the 2-substituent, thus ensuring their synthetic utility [55].

MICROWAVE IRRADIATION

The efficiency of microwave flash-heating chemistry in dramatically reducing reaction times (reduced from days and hours to minutes and seconds) has recently been proven in several different fields of organic chemistry [24-26, 64]. Especially, the ability of microwave technology to rapidly synthesize organic compounds would be of significant benefit for library generation and its potential as a feature tool for drug-discovery programs has recently been recognized [26].

Synthesis of 1,4-benzoxazine derivatives and 3,4-dihydro-2H-1,4-benzoxazine derivatives

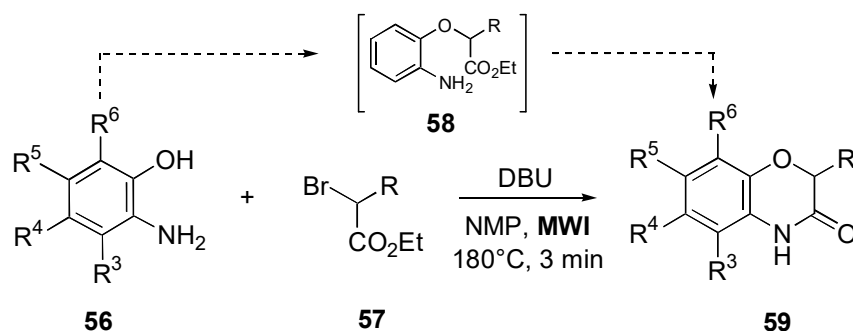
Caliendo et al. reported the first parallel synthesis in solution of 1,4-benzoxazine library using microwave irradiation (MWI) [65]. The procedure involved the use of a microwave oven especially designed for parallel synthesis of solution libraries. The optimal microwave conditions consisted of 2 min of irradiation at 300 W, followed by 3 min off, repeated three times, giving a total reaction event time of 15 min. Under these conditions, amides **54a-f** cyclized in the presence of potassium carbonate, in DMF, to afford benzoxazine derivatives **55a-f** in high yields ($\geq 90\%$) (Scheme 17).



Scheme 17

Interestingly, MWI approach gave the desired compounds **55a-f** in higher yields than those obtained by conventional heating and the overall time for the synthesis was considerably reduced from 3h to 15 min (Scheme 17), ensuring the synthetic utility of MWI to develop libraries for biological screening. Accordingly, Caliendo et al. used derivatives **55a-f** as the starting materials for the microwave-assisted synthesis of substituted N,N-dimethylamide benzoxazine derivatives, which showed *in vitro* a relaxant activity, higher on guinea pig trachea rings pre-contracted with carbachol than on rat aorta rings pre-contracted with phenylephrine [65].

Dai et al. have developed a regioselective one-pot synthesis of substituted 1,4-benzoxazine derivatives under controlled microwave heating (180°C for 3 min) [66]. Starting from commercially available substituted 2-aminophenols **56**, a base-mediated regioselective O-alkylation took place with 2-bromoalkanoates **57**, to give the acyclic intermediates **58**, which spontaneously underwent an intramolecular amidation reaction to furnish 2-alkyl-3-oxo-1,4-benzoxazine derivatives **59** in moderate to good yields (Scheme 18). Note that use of a base as DBU was critical for achieving the regioselectivity.

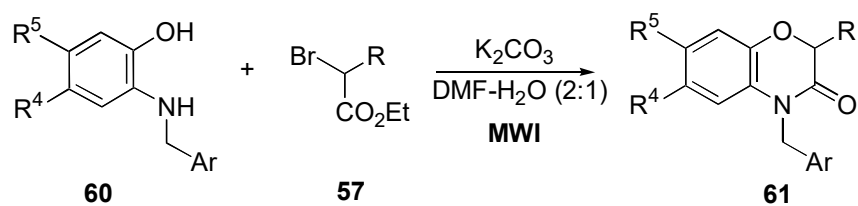


56				57	59
R ³	R ⁴	R ⁵	R ⁶	R	Yield %
H	H	H	H	Me	76
H	Me	H	H	Me	63
H	H	Me	H	Me	64
H	Me	H	Me	Me	61
H	^t Bu	H	H	Me	76
H	Ph	H	H	Me	58
H	OMe	H	H	Me	44
H	Cl	H	H	Me	80
H	Cl	NO ₂	H	Me	72
NO ₂	H	H	H	Me	60
H	NO ₂	H	H	Me	82
H	H	H	H	Et	56
H	H	H	H	<i>n</i> -Pr	47

Scheme 18

The aforementioned regioselective *o*-alkylation of 2-aminophenols by 2-bromoalkanoates **57** (Scheme 18) could also be extended to *N*-arylmethyl-2-aminophenols **60** to give acyclic intermediates, which cyclize spontaneously to afford the 1,4-benzoxazine derivatives **61**, in good to excellent yields (60-98%) [67]. It was found that microwave heating over 180°C was necessary for ring closure of the acyclic intermediates possessing an electron-withdrawing group (Scheme 19).

In the continuation of their preceding works [66,67], Dai et al. reported an original high-throughput synthesis of 1,4-benzoxazine derivatives, which combined the synthetic potential of multicomponent reactions (MCRs) with the benefits of controlled MWI [68]. Especially, the Ugi four-component reaction (U-4CR), which is one of the most popular isocyanide-based MCRs, offered a number of advantages originating from the unique reactivity of an isocyanide, which acts as a nucleophile and an electrophile [69-71]. Starting from the building blocks, 2-aminophenols **62**, aromatic aldehydes **63**, α -bromoalkanoic acids **64** and isocyanides **65**, highly functionalized 1,4-benzoxazinone derivatives **66** were synthesized, in good to high yields, through microwave-assisted one-pot U-4CR and intramolecular *O*-alkylation (Scheme 20).



60		57		61	
R ⁴	R ⁵	Ar	R	T(°C), t (min)	Yield %
H	H	2-furyl	Et	100, 20	75
H	H	2-furyl	<i>n</i> -Pr	100, 25	74
H	Me	2-furyl	Et	180, 20	81
H	Me	2-furyl	<i>n</i> -Pr	180, 20	80
NO ₂	H	2-furyl	Me	190, 40	74
NO ₂	H	2-furyl	Et	190, 45	71
NO ₂	H	2-furyl	<i>n</i> -Pr	190, 40	85
Cl	H	2-furyl	Et	180, 30	90
Cl	H	2-furyl	<i>n</i> -Pr	180, 30	96
Cl	H	Ph	<i>n</i> -Pr	180, 30	91
Cl	H	4-MeOPh	<i>n</i> -Pr	180, 30	98
Cl	H	3-pyridyl	<i>n</i> -Pr	180, 30	70

Scheme 19

CONCLUSION

In the past few years, recent one-pot synthetic strategies such as metal-catalyzed reactions, cascade reactions and microwave-assisted reactions, have been successfully exploited for the synthesis of 1,4-benzoxazine and 1,4-benzodioxin derivatives. The selected examples discussed in this review illustrate the power of each of the processes in the construction of these biologically relevant N- and O-heterocycles.

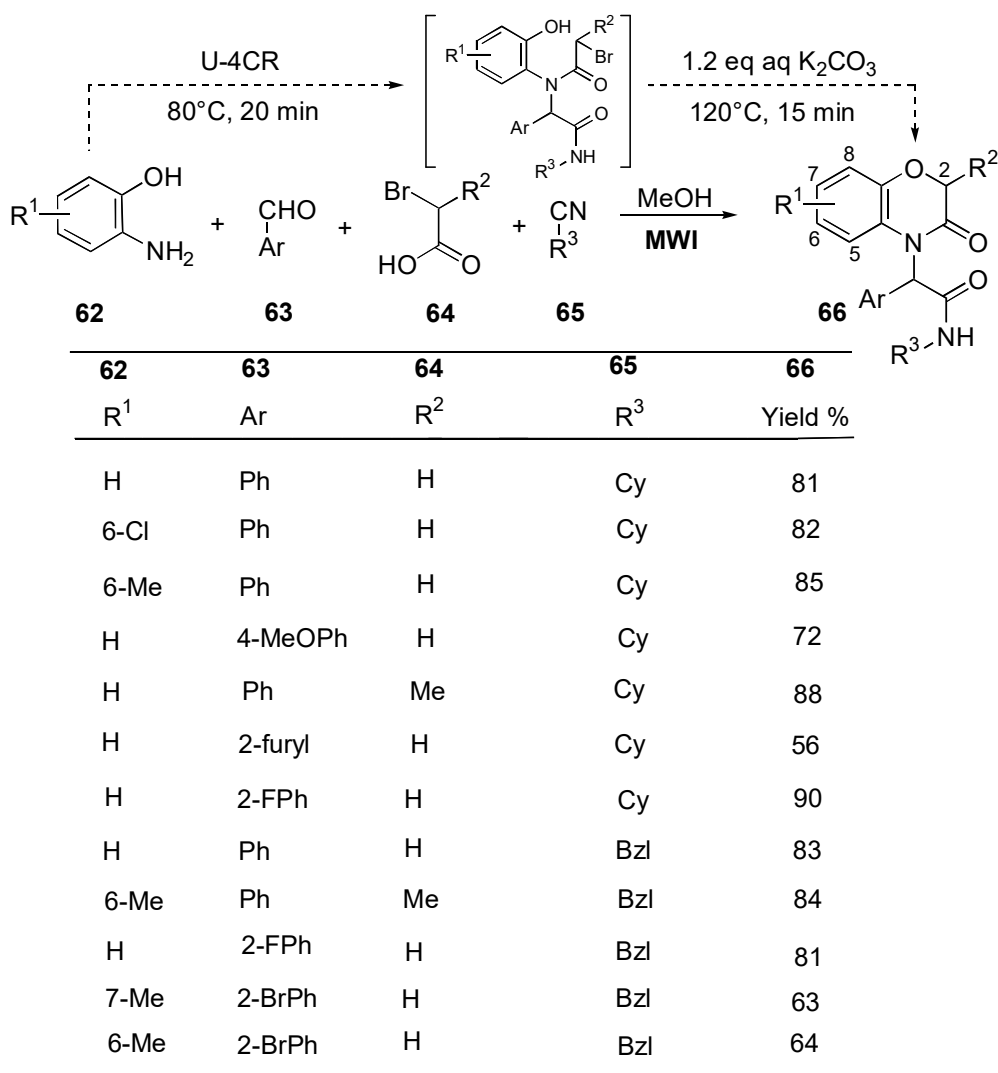
An important feature of the metal-catalyzed heteroannulation reactions is that highly functionalized derivatives can be constructed with the desired substitution pattern, through an ordered sequence of processes mediated by the metal center, under mild conditions and with high selectivity, using very simple and readily available starting materials. No doubt fundamental efforts will be pursued in developing stereoselective methodology using transition-metal catalysts but also chiral auxiliaries.

The undeniable benefits of cascade reactions include atom economy, as well as economies of time, labor, resource management, and waste generation. As such, cascade reactions can be considered to fall under the banner of “green chemistry”, as the savings involved when one carries out several transformations in one synthetic operation can be considerable. Such considerations will become increasingly important in years to come, as both chemists and society in general strive for evermore environmentally friendly methods. In this respect, the development of electrochemically induced cascade reactions, which combine the synthetic potential of cascade reactions with the pre-eminent green advantages of electrochemical synthesis, should be really interesting.

The advantages of controlled microwave heating are manifold. Most importantly, microwave processing leads to dramatically reduced reaction times, higher yields, and cleaner reaction profiles. As a result, microwave-assisted organic synthesis is ideally suited for high-throughput chemistry, allowing

the assembly of libraries. Consequently, in most pharmaceutical companies, microwave synthesis, which quickly affords lead generation, is the vanguard methodology today.

Finally, it is likely that combinations of these processes will become increasingly prominent in the future.



Scheme 20

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