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Conjugate systems in the construction of heterocycles and quaternary stereocenters*

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Abstract: The synthetic application of 4,5-bis-alkylidene-1,3-oxazolidin-2-ones led to the efficient and regioselective synthesis of 2-(3*H*)-benzoxazolones and diarylamines with a short methodology. They were also valuable synthons in a total synthesis of naturally occurring carbazoles. New enantiopure 4-oxazoline-2-one and 4-methylene-2-oxazolidinone were prepared via a one-pot microwave (MW)-promoted condensation of α-ketols and an enantiopure isocyanate. These enamides were efficient nucleophiles when added to Michael acceptors to give a series of compounds with quaternary stereocenters in fairly good stereoisomeric ratios. The novel approach for the synthesis of benzofurans and indoles by intramolecular cyclization of enaminones has been applied in the preparation of furobenzofurans starting from benzo-bis-enaminones.

Keywords: 4,5-dimethylene-2-oxazolidinone dienes; carbazoles; 4-oxazolin-2-ones; enaminones; furobenzofurans.

INTRODUCTION

Among the conjugate π-systems, dienes, enones, enamines, and enaminones are some of the most useful building blocks in organic synthesis. Dienes are intimately related to the milestone Diels–Alder reaction for the preparation of the core of substituted cyclohexenyl derivatives [1]. Enones have also been involved in Diels–Alder additions as dienophiles [1] and heterodienes [2]. Moreover, they have proved to be conjugate acceptors in Michael nucleophilic additions [3]. Among these, enaminones are also privileged Michael acceptors in the addition of a large variety of nucleophiles, due to the activation of the conjugate π-system by the amino group [4]. In contrast, enamines and enamides are currently associated to nucleophilic species as neutral enolate equivalents [5].

Over the years, our interest in Diels–Alder reactions led to the design of a one-pot synthesis of novel dienes, the N-substituted 4,5-bis-alkylidene-1,3-oxazolidin-2-ones **1**, through tandem condensation of aliphatic α-diketones **2** with isocyanates **3** [6] (Scheme 1). These dienes proved to be highly reactive Diels–Alder substrates, and readily underwent stereoselective and regioselective cycloadditions, yielding the corresponding adducts **4**, which were useful starting materials for the synthesis of aryl-

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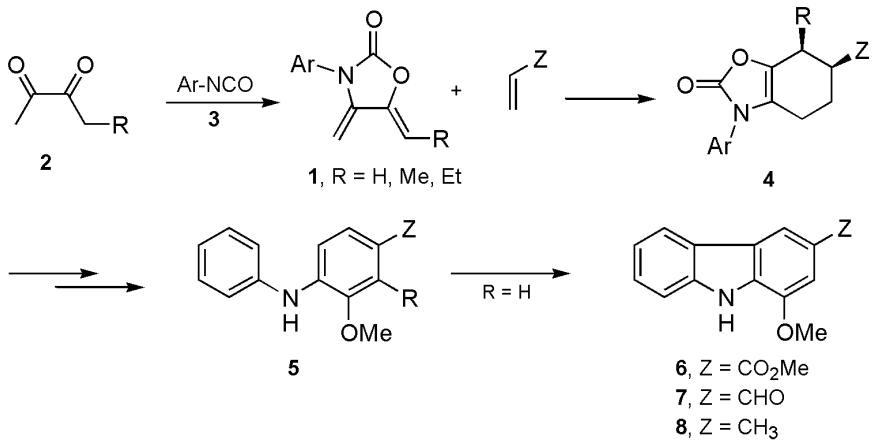
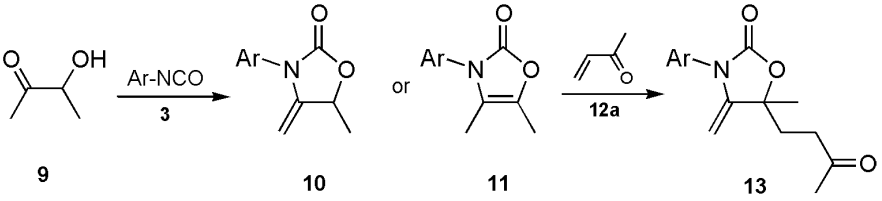


Scheme 1

anilines **5**, as precursors in the total synthesis of carbazole alkaloids mukonine (**6**) [7], murrayanine (**7**), and murrayafoline A (**8**) [8].

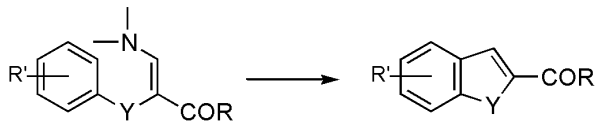
As an extension of our tandem methodology for the preparation of dienes **1**, we have also described the regioselective synthesis of N-substituted 4-methylene-2-oxazolidinones **10** or 4-oxazolin-2-ones **11**, starting from α-ketol **9** and isocyanates **3** [9] (Scheme 2). The enamide compounds **11** underwent nucleophilic addition to the Michael acceptor methyl vinyl ketone (**12a**), to provide adduct **13** regioselectively.



Scheme 2

Recently, and with the aim of evaluating the effect of the electron-donating groups on the reactivity of the double bond, we reported the synthesis of methyl 2-aryloxy-3-dimethylaminopropenoates **14** as useful precursors in a novel synthesis of 2-methoxycarbonylbenzofurans **15** by an intramolecular Friedel–Crafts cyclization, promoted by Lewis acid catalysis [10] (Scheme 3). Moreover, the cyclization of the enaminone analogs 2-aryloxy-3-dimethylamino-3-buten-2-ones **16** was much faster than that of substrates **14**, leading to the formation of 2-acylbenzofurans **17**, which included some natural products of the genus *Calea* [11]. This strategy was also a valuable new route for the synthesis of the crucial heterocycle indoles [12]. Thus, 2-acyl- and 2-alkoxycarbonyl-indoles, **20** and **21**, were prepared by an intramolecular Friedel–Crafts heteroannulation of enaminones **18** and **19**, respectively (Scheme 3).

Herein, we present an account of our recent results about the general approach toward the synthesis of 2-(3*H*)-benzoxazolones and diarylamines, which are important synthetic targets themselves that can be used in the total synthesis of naturally occurring carbazoles. A new diastereoselective construction of quaternary stereocenters by asymmetric conjugate addition of enantiopure 4-oxazolin-2-ones onto Michael acceptors is also presented in this work, as is the development of a convergent and stereocontrolled synthesis of 2-oxazolidinone chiral auxiliaries.



14, Y = O, R = OMe
16, Y = O, R = Me
18, Y = NH, R = OMe
19, Y = NH, R = Me

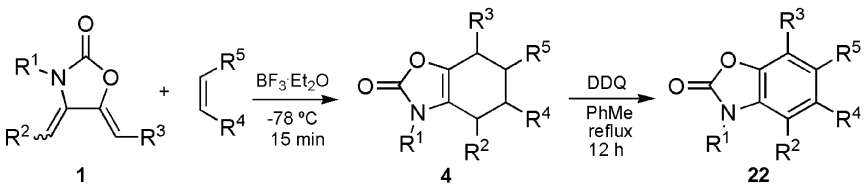
15, Y = O, R = OMe
17, Y = O, R = Me
20, Y = NH, R = OMe
21, Y = NH, R = Me

Scheme 3

2-(3*H*)-BENZOXAZOLONES AND DIARYLAMINES IN THE SYNTHESIS OF NATURAL CARBAZOLES

In accordance with Scheme 1, the synthesis of carbazoles can be achieved by a palladium-promoted cyclization of diarylamines **5**, which in turn can be derived from cycloadducts **4**, and these from the suitable dienes **1** (Scheme 1). The first approach toward the preparation of **5** consisted of a tandem basic hydrolysis/cyclohexene oxidation of adducts **4**, followed by a treatment with dimethyl sulfate [13]. The latter step was modified for the synthesis of mukonine (**6**), since the methylation reaction was more efficient when the phenol was treated with MeI in the presence of K_2CO_3 in acetone as the solvent [7]. In the synthesis of murrayanine (**7**) and murrayafoline A (**8**) [8], the yields were improved when the Diels–Alder adducts were previously oxidized to the 2-(3*H*)-benzoxazolones **22** with DDQ (Table 1).

Table 1 Yields of adducts **4a–4p** and 2-(3*H*)-benzoxazolones **22a–22p**.[a]



1 **4** **22**

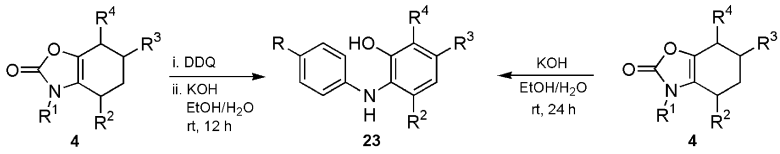
Entry	R_1	R_2	R_3	R_4	R_5	**4** (%)	**22** (%)
1	C_6H_5	H	H	H	CHO	**4a** (80)	**22a** (60)
2	C_6H_5	H	H	H	$COCH_3$	**4b** (97)	**22b** (50)
3	C_6H_5	H	CH_3	H	CHO	**4c** (80)	**22c** (54)
4	C_6H_5	H	CH_3	H	$COCH_3$	**4d** (95)	**22d** (66)
5	C_6H_5	H	CH_3CH_2	H	CHO	**4e** (83)	**22e** (62)
6	C_6H_5	H	CH_3CH_2	H	$COCH_3$	**4f** (95)	**22f** (76)
7[b]	C_6H_5	H	CH_3	CO-N(Ph)-CO		**4g** (61)	**22g** (66)
8	C_6H_4-*p*-Cl	H	CH_3	H	CHO	**4h** (95)	**22h** (72)
9	C_6H_4-*p*-Cl	H	CH_3	H	$COCH_3$	**4i** (86)	**22i** (50)
10	C_6H_4-*p*-OCH_3	H	CH_3CH_2	H	CHO	**4j** (73)	**22j** (53)
11	C_6H_4-*p*-OCH_3	H	CH_3CH_2	H	$COCH_3$	**4k** (79)	**22k** (60)
12	C_6H_5	CH_3	CH_3	H	CHO	**4l** (80)	**22l** (50)
13	C_6H_5	CH_3	CH_3	H	$COCH_3$	**4m** (75)	**22m** (45)
14	Bn	H	H	H	CHO	**4n** (87)	**22n** (25)
15	Bn	H	H	H	$COCH_3$	**4o** (88)	**22o** (16)
16[c]	C_6H_4-*p*-Cl	H	CH_3	CO-CH=CH-CO		**4p** (84)	**22p** (57)

[a]In the presence of 3.0 mol equiv of dienophile, and 0.1 mol equiv of BF_3·Et_2O at –78 °C in CH_2Cl_2.
[b]In the absence of catalyst in xylene at 180 °C for 1 h.
[c]In EtOH at 20 °C for 15 h.

Considering that compounds **22** have attracted special attention due to their significant anticonvulsant, anti-inflammatory, antifungal, and antibacterial activities [14], and their use as potent drugs against mental disorders [15], we investigated the preparation of a wide series of polysubstituted 2-(3*H*)-benzoxazolones **22**. We found that they can be prepared by this methodology in good overall yields starting from dienes **1**, except for the case of *N*-benzyl derivatives **4n**–**4o**, which were oxidized to **22n**–**22o** in poor yields (Table 1).

Upon hydrolysis of some members of the series **22** and other analogs under basic conditions, diarylamines **23** were obtained in fairly good overall yields (52–60 %) (Table 2). In order to avoid using dichlorodicyano-*p*-benzoquinone (DDQ), we carried out the opening/aromatization sequence in a one-pot procedure. Thus, by treating **4** with KOH (6.0 mol equiv) in ethanol/water (5:2) at reflux for 24 h, the corresponding diarylamines **23** were obtained in moderate yields (45–65 %) (Table 2). The efficiency of both methods was comparable. It is noteworthy that diarylamines have recently attracted great interest from synthetic and technological points of view [16].

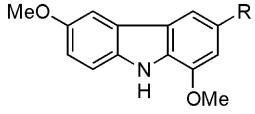
Table 2 Overall yields in the synthesis of diarylamines **23a–23i**.[a]



23	R	R^2	R^3	R^4	DDQ (%)[b]	KOH (%)[c]
23a	H	H	CHO	H	55	45
23b	H	H	$COCH_3$	H	60	62
23c	OMe	H	CHO	H	57	48
23d	OMe	H	$COCH_3$	H	53	52
23e	H	H	CHO	Me	52	50
23f	H	H	$COCH_3$	Me	58	61
23g	Cl	H	CHO	Me	54	65
23h	Cl	H	$COCH_3$	Me	60	60
23i	H	Me	CHO	Me	59	55

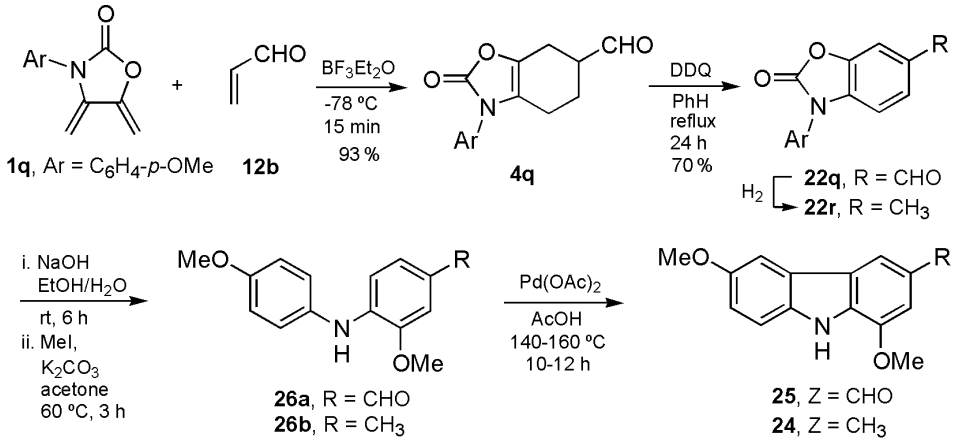
[a]1.0 mmol equiv of **4**.
[b]DDQ (4.0 mol equiv) in 20 mL of toluene at reflux 24 h and then KOH (6.0 mol equiv) in $EtOH/H_2O$ (5:2) at room temperature 12 h.
[c]KOH (6.0 mol equiv) in $EtOH/H_2O$ (5:2) at reflux 24 h.

Carbazoles **6–8** belong to an extensive family of natural carbazoles mainly isolated from species of the genera *Murraya* and *Clausena*, and are characterized by a methoxy group at C-1 and by a substituent at C-3 [17]. It has been established that mukonine (**6**) and murrayanine (**7**) biogenetically arise from the in vivo oxidation of murrayafoline A (**8**) [17a,18]. Similarly, it is likely that clausenine (**24**) was the bioprecursor of the naturally occurring carbazole 3-formyl-1,6-dimethoxycarbazol (**25**) [19]. Clausenine (**24**) was isolated from the ethanolic extract of the bark of *Clausena anisata*, exhibiting moderate antifungal and *Gram*-positive as well as *Gram*-negative bactericidal activities [20].



24, Z = CH_3
25, Z = CHO

Following a similar synthetic strategy to that designed for carbazoles **7** and **8**, we achieved a total synthesis of carbazoles **24** and **25**, via a highly regioselective cycloaddition of diene **1q** with acrolein (**12b**) (Scheme 4). Thus, adduct **4q** was obtained in high regioselectivity (*para/meta*, 98:2), which was aromatized with DDQ to give 2-(3*H*)-benzoxazolone **22q** in good yield. Hydrolysis and methylation of the latter provided diaryl amine **26a** in 77 % overall yield. Finally, carbazole **25** was obtained in 79 % yield by $Pd(OAc)_2$-mediated cyclization of **26a**. On the other hand, when the formyl group of **22q** was reduced by hydrogenation, derivative **22r** was obtained in almost quantitative yield (98 %) (Scheme 4). After hydrolysis of **22r** under mild basic conditions, the arylphenylamine **23r** was obtained in good yield (83 %). Then, methylation using methyl iodide in acetone and potassium carbonate (reflux, 3 h) yielded **26b** [21]. The coupling of the aromatic rings of the latter, promoted by palladium acetate in acetic acid [22], provided clausenine (**24**) in 55 % overall yield from **22r** (Scheme 4).

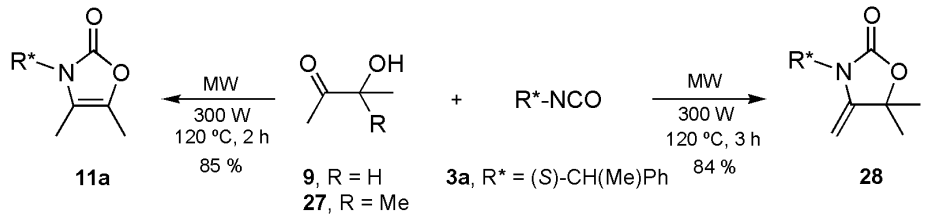


Scheme 4

ENANTIOPURE 4-OXAZOLIN-2-ONES AND DIASTEREOSELECTIVE GENERATION OF QUATERNARY STEREOCENTERS

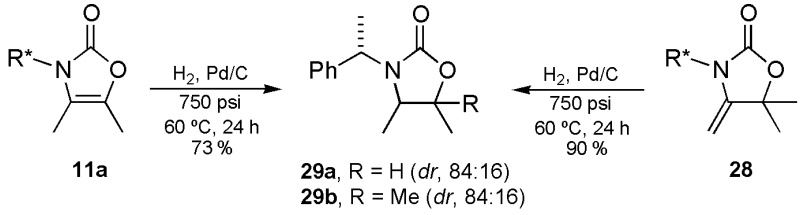
Chiral auxiliaries have played a key role in the development of efficient and elegant routes to a variety of enantiomerically pure compounds. Oxazolidin-2-ones have been widely used as valuable intermediates for the synthesis of β-amino alcohols and β-amino acids, which form a large group of natural products [23]. They have been precursors of important chiral auxiliaries [24], and valuable synthons in the preparation of biologically active compounds [25].

Enantiopure 4-oxazolidin-2-ones have been commonly prepared from optically pure amino acids [24a] or β-amino alcohols [24b]. The palladium-catalyzed [3+2] cycloadditions of vinyloxiranes with arylisocyanates provide a direct route to these heterocycles but in relatively low *er*'s [26]. We devised a diastereoselective strategy for the synthesis of enantiopure oxazolidin-2-ones, taking advantage of the straightforward access to 4-methylene-2-oxazolidinones (**10**) and 4-oxazolin-2-ones (**11**) that we have recently developed [9] (Scheme 2). These heterocycles were readily prepared by a microwave (MW)-promoted one-step tandem condensation of α-ketols **9** and **27** with the enantiopure isocyanate **3a** (Scheme 5).



Scheme 5

Unlike the previously reported cascade method of the heterocyclic ring formation, which was conducted in the presence of triethylamine and depended on the polarity of the solvent [9], this new procedure was carried out under solvent-free conditions and only promoted by MW irradiation. Products **11a** and **28** were obtained in high and comparable yields (Scheme 5). The hydrogenation reaction of these compounds was catalyzed by Pd/C (10 %) in EtOAc/AcOH under pressure (750 psi) at 60 °C for 24 h, and proceeded with identical diastereoselectivity in each case (*dr*, 84:16), to give the saturated heterocycles **29a–29b** (Scheme 6). This selectivity is fairly good considering that the chiral auxiliary moiety (*N*-(*S*)-methylbenzyl) is relatively far away from the reactive center and might have a high conformational mobility.

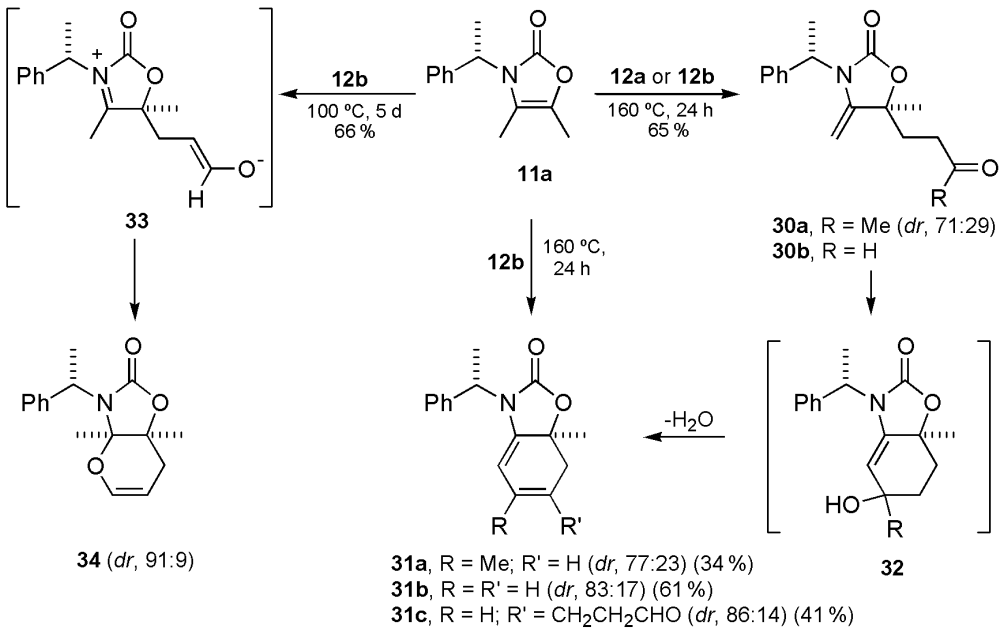


Scheme 6

Enantiopure enamines have proved to be efficient and highly stereoselective nucleophiles in asymmetric synthesis [5,27]. In particular, the in situ-generated enamines from pyrrolidine- or proline-based catalysts have been extensively studied [28], whereas the investigation of those from pipecolic acid only began recently [29]. Asymmetric aldol, Mannich, and Michael reactions are some of the most general and efficient asymmetric amino-catalyzed processes via the preformed enamines. The Michael reaction is a powerful tool for the C–C formation and the β-functionalization of carbonyl compounds, providing highly enantio- and diastereoselective conjugate addition products [30].

4-Oxazolin-2-ones **11** are enamides that behave as nucleophiles in conjugate additions to Michael acceptors [9] to yield 4-methylene-2-oxazolidinones **13** bearing a quaternary carbon center (Scheme 2). Similarly, enantiopure 4-oxazolin-2-one **11a** may undergo Michael additions with acceptors such as methyl vinyl ketone (**12a**) and acrolein (**12b**) to provide adducts **30**, in which the quaternary carbon center may be diastereoselectively generated (Scheme 7). Thus, when the thermal reaction of **11a** with **12a** was carried out at 160 °C for 24 h, a mixture of diastereoisomers **30a** (71:29) was obtained in 65 % yield. When the reaction was carried out at the same temperature for a longer time (96 h), the cyclohexadiene compound **31a** was obtained in low yield and in a slightly better *dr* (77:23) (Scheme 7).

This result prompted us to extend the process to other Michael acceptors such as **12b** under the same reaction conditions. However, the corresponding adduct **30b** was not observed, while a mixture of cyclohexadienes **31b–31c** was isolated in good *dr* (Scheme 7). Diene **31b** is probably formed through a tandem Michael/enamine-aldol reaction via the formation of the conjugate addition adduct **30b** and the alcohol intermediate **32**. Diene **31c** might be formed by a Michael addition of diene **31b** toward a second molecule of acrolein (**12b**).

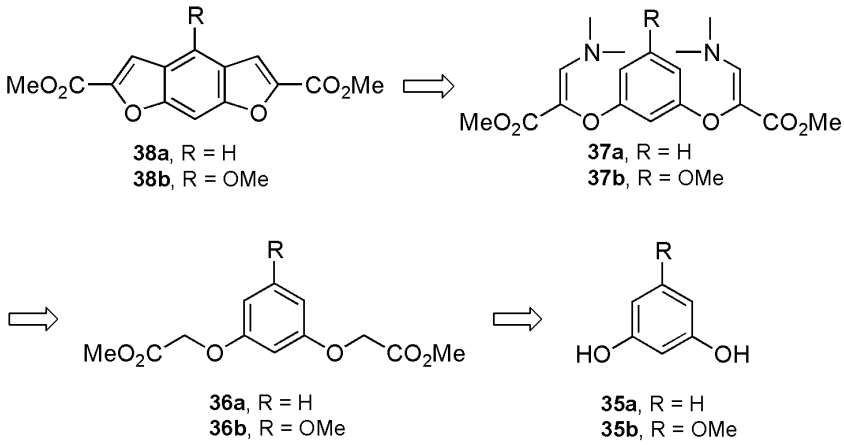


Scheme 7

With the aim of isolating the primary conjugate addition product **30b**, we carried out the reaction at a lower temperature (100 °C) for 5 days. Although the desired product was not obtained, the new bicyclic pyranyl compound **34** was isolated in high *dr* (91:9) (Scheme 7). It seems that a lower temperature, besides increasing the *dr*, led to the kinetically controlled product, which probably comes from the intramolecular cyclization of the zwitterionic species **33**, via *O*-addition of the enolate onto the deffficient iminium carbon center. The absolute configuration of **34**, as indicated in Scheme 7, was established by X-ray diffraction crystallography. This suggests that both the conjugate addition and the cyclization take place on the β-face of the double bond. It is likely that an analogous outcome gave rise to the major diastereoisomers of adducts **30a** and **31a**–**31c**, hence they would have the same configuration at the quaternary carbon center.

INTRAMOLECULAR FRIEDEL–CRAFTS HETEROANNULATION OF ENAMINONES IN THE SYNTHESIS OF BENZO-BIS-HETEROCYCLES

Benzo-bis-heterocycles have attracted increasing interest as potential pharmacological agents, many of them being widely distributed in nature [31]. Therefore, diverse strategies have been developed for the synthesis of these compounds, and most of them have focused on the heterocyclic ring closure, starting from the appropriately substituted benzene scaffold [32]. For these reasons, we have investigated the development of a new general approach to benzo-bis-heterocycles, being inspired by our recently described route to benzofurans and indoles (Scheme 3). Thus, alkylation of hydroxyphenols **35a–35b** with methyl bromoacetate under basic conditions may give rise to the bis-phenoxy compounds, **36a–36b**, which could be converted into the corresponding enaminones, **37a**–**37b**, by treatment with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (Scheme 8). Finally, as the last step, the Lewis acid-catalyzed cyclization of the latter should lead to the desired products **38a–38b**.



Scheme 8

The synthesis of **38** was started from commercially available phenols **35a–35b**. Thus, the latter were converted into phenoxyacetates **36a–36b** in good yields (87–93 %) by reacting with $BrCH_2CO_2Me$ and K_2CO_3. The corresponding compounds **37a–37b** were readily obtained by reacting **36a–36c** with an excess (4–6 mol equiv) of DMFDMA (Table 3). By decreasing the reaction time and the number of equivalents of DMFDMA, the process gave rise to monoalkylated compounds **39a–39b** as the main products (Table 3).

Table 3 Reaction conditions in the aminomethylation of compounds **36a–36b** and yields of products **37** and **39**.[a]

Entry	**36**	Y	R	DMFDMA (mol equiv)	*t* (h)	**37** (%)[b]	**39** (%)[b]
1	**36a**	O	H	6.0[a]	48	**37a** (85)	**39a** (3)
2	**36b**	O	OMe	6.0[a]	72	**37b** (60)	**39b** (15)
3	**36a**	O	H	3.0	24	**37a** (5)	**39a** (70)
4	**36b**	O	OMe	3.0[a]	24	[c]	**39b** (75)

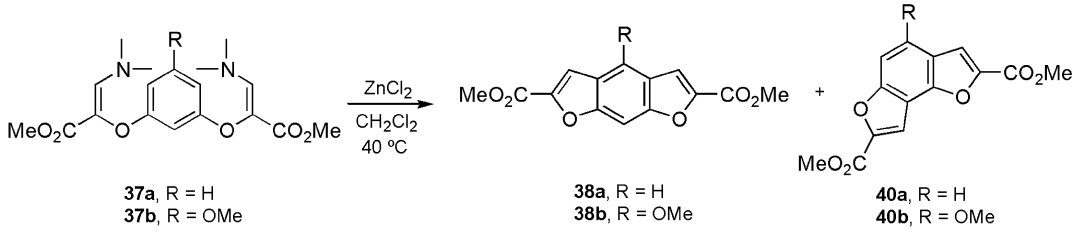
[a]0.1 mmol equiv of $ZnCl_2$, at 80 °C.
[b]After purification.
[c]No detected by ^{1}H NMR of the crude reaction mixture.

Cyclization of compounds **37a–37b** was carried out by Lewis acid catalysis, using $ZnCl_2$ (Table 4). The reaction with **37a** proceeded successfully after 48 h at 40 °C to give a mixture of the expected product **38a** along with **40a** as the major regioisomer (Scheme 9). In a similar way, the cyclization of enaminone **37b** took place efficiently to give a mixture of furobenzofurans **38b/40b** (35:65) (Table 4). Interestingly, the preference for isomers **40**, in which the cyclization took place at the *ortho* position of the heteroatom of the other heterocycle, might be useful in the preparation of analogs whose structures are related to those benzo-bis-heterocycles previously reported [33].

Table 4 Reaction conditions and yields in the preparation of **38a–38b**, **40a–40b**, **41a–41b**, and **42**.[a]

Entry	Precursor	Y	R	Catalyst[b]	*T* (°C)	*t* (h)	Products[c]	Yield (%)[d]
1	**37a**	O	H	$ZnCl_2$	40	48	**38a/40a** (30:70)	73
2	**37b**	O	OMe	$ZnCl_2$	40	72	**38b/40b** (35:65)	70
3	**39a**	O	H	$ZnCl_2$	40	36	**41a** (70)	70
4	**39b**	O	OMe	$ZnCl_2$	40	72	**41b/42** (65:35)	71

[a]All the reactions in CH_2Cl_2.
[b]3.0 mol equiv.
[c]Determined by ^1H NMR of the reaction crude.
[d]After purification of the mixture.



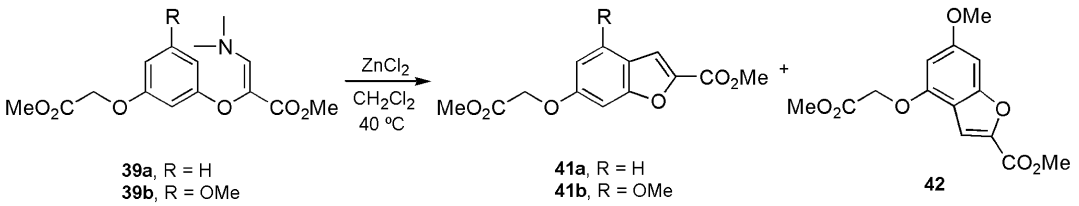
37a, R = H
37b, R = OMe

38a, R = H
38b, R = OMe

40a, R = H
40b, R = OMe

Scheme 9

In contrast, the cyclization process of monoenaminone **39a** was highly regioselective to provide benzofuran **41a**, exclusively (Scheme 10) (Table 4, entry 3). This regioselectivity is in agreement with that observed previously when the aryl ring was substituted by a methoxy group instead of the methoxy carbonylmethoxy group at the *meta* position [10,11]. However, the regioselectivity was lower when **39b** was cyclized under similar conditions, since a mixture of **41b** and **42** was obtained, where the former product was the major one (Table 4, entry 4).



39a, R = H
39b, R = OMe

41a, R = H
41b, R = OMe

42

Scheme 10

CONCLUSIONS

We have demonstrated how conjugate systems such as dienes, enamides, and enaminones can be useful synthons for the preparation of a wide variety of functionalized heterocycles and chiral quaternary carbon centers. The application of 2-oxazolidinone dienes has been extended to the efficient and regioselective synthesis of 2-(3*H*)-benzoxazolones and diarylamines through a short methodology, which was also valuable for a total synthesis of the natural carbazoles clausenine (**24**) and 3-formyl-1,6-dimethoxycarbazol (**25**). A new method was described for the preparation of enantiopure 4-oxazoline-2-one **11a** and 4-methylene-2-oxazolidinone **28** by MW-promoted condensation of α-ketols and an enantiopure isocyanate, in a one-pot reaction. Enamides **11a** and **28** behaved as efficient nucleophiles with Michael acceptors to give a series of addition products bearing a quaternary carbon center in good

dr. The novel Friedel–Crafts cyclization of enaminones was applied in a short synthesis of furobenzofurans.

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