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Synthesis of 3-Substituted and 2,3-Disubstituted-4*H*-1,4-Benzoxazines

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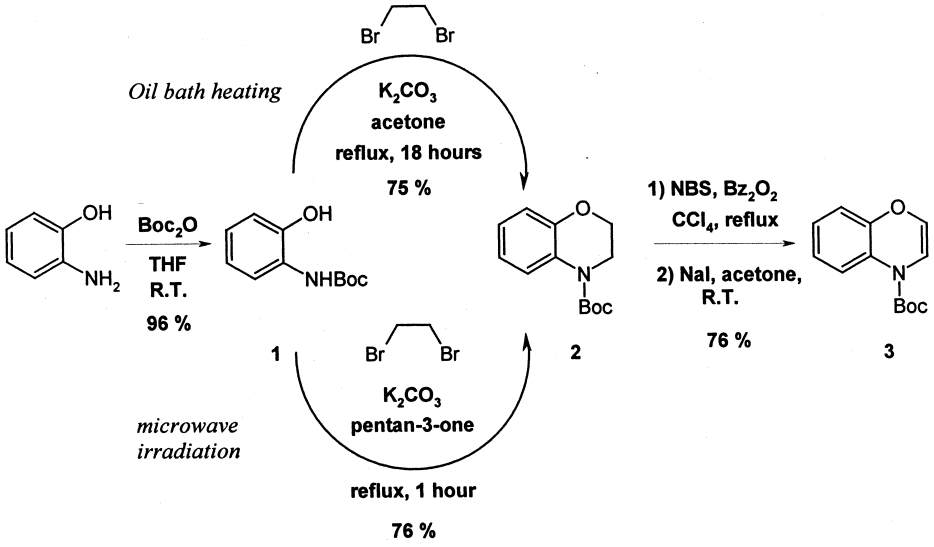
Abstract—Two new and efficient synthetic routes towards substituted 4*H*-1,4-benzoxazine derivatives were reported. The first one involves the synthesis in four steps of the 4-Boc-4*H*-1,4-benzoxazine and its regioselective substitution on C-3 following a lithiation–electrophilic substitution sequence. The second route involves palladium-catalyzed coupling reactions between organostannanes and a vinylphosphate obtained from a benzoxazin-3-one derivative.



Scheme 1.

Introduction

In the course of our studies related to the synthesis of bioactive compounds containing a 1,4-benzoxazine unit we were confronted with the lack of a general and efficient method allowing easy access to this kind of derivative. Indeed, 4*H*-1,4-benzoxazines constitute a little studied heterocyclic system and few of them have been described in the literature. For instance, to the best of our knowledge, only one example of a 3-substituted 4*H*-1,4-benzoxazine has been reported.[1] Concerning 2,3-disubstituted derivatives, except phenoxazines of course, only very particular derivatives have been prepared via cycloaddition reactions which are far from being generally applicable.[2,3] We have very recently reported two complementary methods allowing the synthesis of 3-substituted benzoxazines.[4,5] The present paper concerns the extension of this preliminary work and moreover the preparation of 2,3-disubstituted benzoxazines.

Results and Discussion

Synthesis of 3-substituted-4*H*-1,4-benzoxazines via the regioselective formation of the 3-lithio-4-Boc-4*H*-1,4-benzoxazines

The past decade has seen the growing utility of Directed

Keywords: 4*H*-1,4-benzoxazine; metallation; lithiation–electrophilic substitution.

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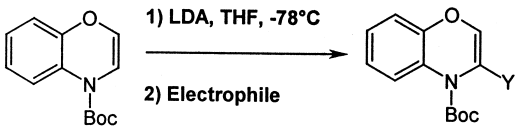
Table 1.



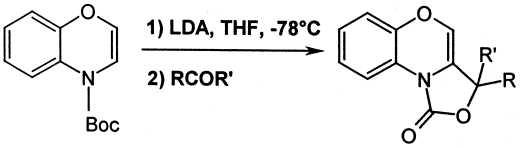
3 4 a-h

4	Electrophile	Y	Yield (%)[a]
a	MeI	Me	75
b	Me_3SiCl	Me_3Si	83
c	I_2	I	81
d	$Cl_2BrCCBrCl_2$	Br	82
e	CO_2	CO_2H	85
f	ClCOOEt	COOEt	65
g	Me_3SnCl	Me_3Sn	83
h	Bu_3SnCl	Bu_3Sn	65

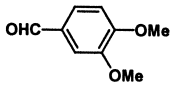
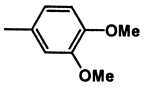
[a] Isolated yield.

Metallation Groups (DMGs) for the regiospecific construction of polysubstituted aromatic and heteroaromatic compounds. The Directed *Ortho* Metallation (DOM) reaction involves the deprotonation of a site *ortho* to a heteroatom-containing DMG by a lithiated base.[6] The *ortho*-lithiated species treated with electrophilic species lead to 1,2-disubstituted derivatives. Among numerous DMGs the *tert*-butoxycarbonyl group (Boc) has been described by Muchowski[7] and Beak[8] as an excellent directing activator for both the *ortho*-lithiation of anilines and tetrahydroquinolines as well as the α-lithiation of secondary amines. We postulated that this group could direct the metallation of the C-3 site of the unsaturated benzoxazine **3** thus allowing the regiospecific functionalisation of this position (Scheme 1).

Table 2.



3 5 a-d

5	RCOR′	R	R′	Yield (%)[a]
a	CH_3COCH_3	Me	Me	90
b		$-(CH_2)_5-$		70
c	CH_3CHO	Me	H	82
d			H	75

[a] Isolated yield.

We prepared carbamate **2** in two steps from commercially available 2-aminophenol. Treatment of 2-aminophenol with di-*tert*-butyl dicarbonate in dry tetrahydrofuran at room temperature led to *N*-Boc phenolic compounds **1** in 96% yield. The 2,3-dihydrobenzoxazine **2** was then obtained in 75% yield by heating **1** and 1,2-dibromoethane in refluxing acetone for 20 h in the presence of an excess of potassium carbonate. This reaction could be advantageously performed under microwave irradiation for 1 h in refluxing pentan-3-one (yield: 76%). The required unsaturated carbamate **3** was finally obtained in 76% yield by using a bromination–debromination sequence previously described for the synthesis of benzodioxines[9] and benzoxazines.[4] The brominated intermediate was not isolated.

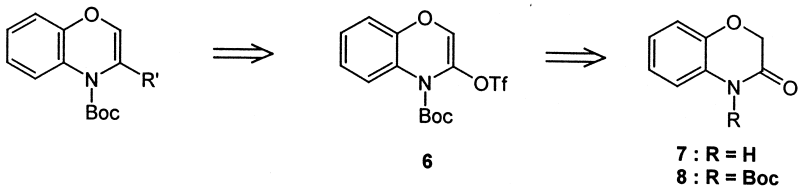
As expected, the deprotonation occurred regio-specifically on the heterocyclic ring at carbon C-3, adjacent to the *N*-Boc group, when **3** was reacted in dry tetrahydrofuran at low temperature with lithium diisopropylamide. The reaction of the 3-lithio intermediate with electrophiles led, according to the nature of the latter, to the 3-substituted benzoxazines **4** (Table 1) or **5** (Table 2). In the two cases, the required heterocyclic compounds were obtained in satisfactory yields.

It could be advantageous to use easily available vinylstannanes **4g** and **4h** or unsaturated halides **4c** and **4d** for performing palladium-catalyzed cross-coupling reactions (Stille and Suzuki reactions). Benzoxazines bearing vinyl, aryl and heteroaryl groups on C-3 could be easily obtained in this way but we developed an alternative and more convenient method.

When aldehydes or ketones were used as electrophiles, the formation in situ of an alkoxide anion induced the cleavage of the carbamic moiety and the formation of a new heterocyclic system.

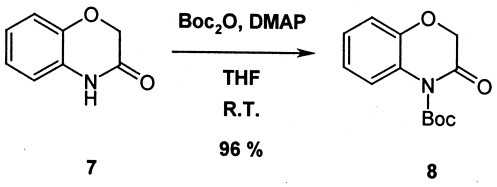
Synthesis of 3-substituted-4*H*-1,4-benzoxazines via palladium-catalyzed coupling reactions

Palladium-catalyzed coupling reactions of organostannanes with aryl and alkenyl halides or triflates, known as the Stille reaction, are powerful tools for the construction of carbon–carbon bonds. Comins[10] and more recently Hiemstra[11] prepared lactam derived enol triflates as useful building



6 7 : R = H 8 : R = Boc

Scheme 2.

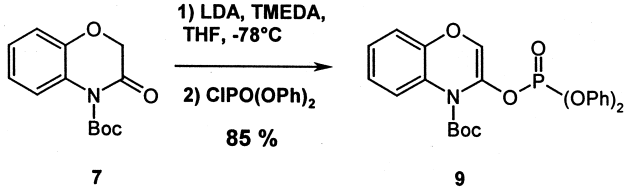


Scheme 3.

blocks in several palladium-catalyzed reactions. We postulated that we could obtain in a similar way 3-substituted benzoxazines from the benzoxazin-3-one **8** via the enol triflate **6** (Scheme 2).

Treatment of commercial 4*H*-1,4-benzoxazine-3-one **7** with di-*tert*-butyldicarbonate in dry tetrahydrofuran at room temperature in the presence of DMAP led to the *N*-Boc derivative **8** in 96% yield (Scheme 3).

The corresponding lithium enolate obtained at −78°C in dry tetrahydrofuran with LDA (1.2 equiv.) and TMEDA (1.2 equiv.) was then reacted with the triflating agent *N*-phenyltrifluoromethanesulfonimide. The required enol triflate could not be isolated, as it decomposed when the temperature exceeded −50 °C. Such a lack of stability was previously observed by Nicolaou with cyclic ketene acetal triflates and the problem was overcome using cyclic ketene acetal phosphate.[12,13] We hoped that such a methodology would allow, in our case, access to the diphenyl phosphate **9** and its further use in coupling reactions. The lithium enolate of the lactam was prepared as previously described and quenched at −78°C with diphenylchlorophosphate (1.2 equiv.). The phosphate **9** proved to be stable enough at room temperature to be purified by flash chromatography on silica gel; it was eventually obtained in 85% yield (Scheme 4).



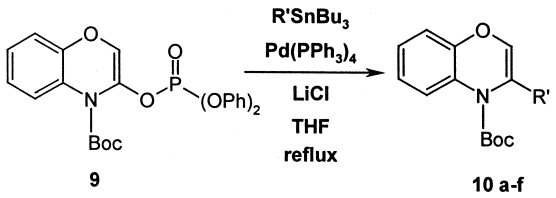
Scheme 4.

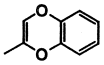
Vinyl phosphate **9** was then tested in palladium-catalyzed coupling reactions with vinyl, aryl and heteroaryl organostannanes (3 equiv.) (Table 3).

All experiments were run under an argon atmosphere, in refluxing tetrahydrofuran with a catalytic amount of $Pd(PPh_3)_4$ (0.05 equiv.) in the presence of lithium chloride (3 equiv.) according to the procedure previously described by Nicolaou.[12] Most of the organostannanes were commercially available (entries **a**–**e**); the benzodioxine derivative (entry **f**) was easily obtained by condensation of Bu_3SnCl and 2-lithio-1,4-benzodioxine.[14]

The 3-substituted benzoxazines were obtained in high yields and the procedure could be extended to many organostannanes providing easy access to a wide range of new heterocyclic systems.

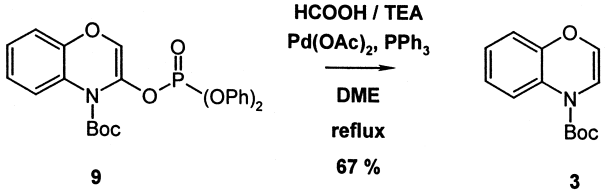
Table 3.



10	R′	Yield (%)[a]
a		87
b		82
c		91
d		96
e		84
f		93

[a] Isolated yield.

The reduction of vinyl phosphate **9** was performed in 67% yield according to the procedure described by Cacchi et al.,[15] and constitutes an attractive alternative to the method previously described for the synthesis of **3** (Scheme 5).

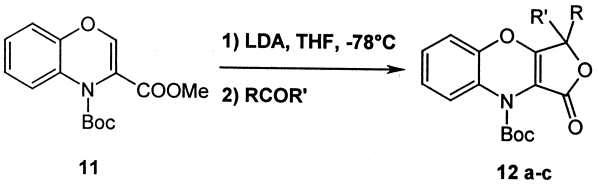


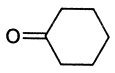
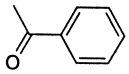
Scheme 5.

Synthesis of 2,3-disubstituted-4*H*-1,4-benzoxazines

Next, we focused our interest on the synthesis of benzoxazines bearing two distinct substituents on C-2 and C-3, with the further aim of constructing polycyclic nitrogen containing analogs of natural products. We postulated that the presence of a withdrawing group on C-3 could greatly facilitate deprotonation on the nearby atom C-2. A methyl ester group appeared as a good candidate for this purpose because it may be further easily converted to other functional groups. Treatment of benzoxazinic acid **4e** with methyl iodide in dimethylacetamide for 24 h at room temperature afforded the required methyl ester **11** in 85% yield. The lithiation of **11** with LDA (3 equiv.) at −78°C in

Table 4.



12	Electrophile	R	R′	Yield (%)[a]
a	CH_3COCH_3	Me	Me	78
b		$-(CH_2)_5-$		72
c		Me	Ph	70

[a] Isolated yield.

dry tetrahydrofuran was followed by reaction with electrophilic reagents to give disubstituted benzoxazines **12** or **13** (Tables 4 and 5).

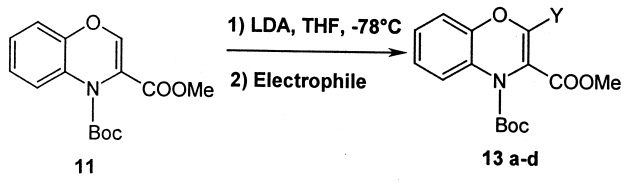
When the 2-lithio intermediate was quenched with ketones (3 equiv.), the in situ formation of alkoxy species induced an intramolecular cyclisation leading to lactone derivatives **12** (Table 4).

Other electrophiles (3 equiv.) reacted as expected with the lithiated species leading to the desired 2,3-disubstitued-4*H*-1,4-benzoxazines **13** in good yields (Table 5).

As shown in Table 6, the presence of a withdrawing group on C-3 is not essential to observe deprotonation on C-2.

The typical procedure previously used also affords 2,3-disubstituted benzoxazines **14** in high yield from the 3-phenyl substituted derivative **10e**.

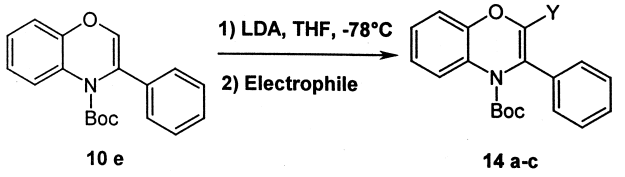
Table 5.



13	Electrophile	Y	Yield (%)[a]
a	$ClSiMe_3$	Me_3Si	72
b	I_2	I	70
c	$ClSnMe_3$	Me_3Sn	78
d	CO_2	CO_2H	82

[a] Isolated yield.

Table 6.



14	Electrophile	Y	Yield (%)[a]
a	$ClSiMe_3$	Me_3Si	80
b	$ClSnBu_3$	Bu_3Sn	83
c	CO_2	CO_2H	81

[a] Isolated yield.

Conclusion

We have developed two new versatile methods allowing easy access to a little known heterocyclic system, the 4*H*-1,4-benzoxazines. A large number of derivatives can be obtained using either procedures: the unsubstituted product or 3-substituted and 2,3-disubstituted heterocycles.

The coupling reaction involving vinyl phosphate will allow the introduction of vinyl, aryl or heteroaryl groups depending on the available organostannanes.

On the other hand, the lithiation–electrophilic substitution sequence should be preferentially used for the synthesis of derivatives bearing substituents such as iodine and bromine, alkyl, trialkylsilyl, trialkylstannyl or carboxyl groups.

Moreover these methods could probably be extended to the synthesis and functionalization of several types of nitrogen or oxygen-containing heterocycles.

Experimental

General

Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT PARAGON 1000 PC. ^1H and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometer (250.19 MHz ^1H, 62.89 MHz ^{13}C), multiplicities were determined by the DEPT 135 sequence. MS were recorded on a Perkin–Elmer SCIEX API 3000 spectrometer. For microwave heating, reactives were placed in a quartz tube introduced into the Synthewave S402 Prolabo microwave reactor (power 300 W, microwave frequency 2450 MHz). All reactions were carried out in flame-dried glassware under an argon atmosphere. Thin layer chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ precoated plates. "Usual workup" means extraction with EtOAc, drying with $MgSO_4$, filtration and evaporation.

***N*-(*tert*-butoxycarbonyl)-2-aminophenol (1).** A mixture of 2-aminophenol (4.91 g, 45 mmol) and di-*tert*-butyldicarbonate (19.64 g, 90 mmol) in THF (70 mL) was stirred at room

temperature for 2 h. After concentration and hydrolysis, the reaction mixture was treated according to usual workup and gave colorless crystals that were washed with carbon tetrachloride, filtered and dried in vacuo (9.2 g, 96%). Mp: 140–141°C. IR (KBr): ν cm^{-1} 3426 (OH), 3292 (NH), 1691 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.53 (s, 9H), 6.66 (bs, 1H), 6.81–7.08 (m, 4H), 8.12 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 28.2 ($3CH_3$), 82.1 (C), 118.9 (CH), 120.7 (CH), 121.4 (CH), 125.5 (CH), 125.6 (C), 147.5 (C), 155.0 (C). MS: *m*/*z*=210 (M+1). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14, H, 7.23, N, 6.69. Found C, 63.19, H, 7.26, N, 6.72.

4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine (2). *Oil bath heating*: A solution of **1** (2.09 g, 10 mmol), dibromoethane (15.03 g, 80 mmol) and potassium carbonate (27.64 g, 200 mmol) in acetone (200 mL) were refluxed for 18 h. The reaction mixture was cooled, then filtered through Celite. After the usual workup and chromatography with petroleum ether/EtOAc (95/5), **2** was obtained as a white solid (1.76 g, 75%). *Microwave heating*: A solution of **1** (2.09 g, 10 mmol), dibromoethane (15.03 g, 80 mmol) and potassium carbonate (27.64 g, 200 mmol) in pentan-3-one (100 mL) were refluxed under microwave irradiation for 1 h. The reaction mixture was cooled, then filtered through Celite. After the usual workup and chromatography with petroleum ether/EtOAc (95/5), **2** was obtained as a white solid (1.79 g, 76%): mp: 78–79°C. IR (KBr): ν cm^{-1} 1722 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.54 (s, 9H), 3.83–3.88 (m, 2H), 4.22–4.27 (m, 2H), 6.80–7.01 (m, 3H), 7.76 (d, 1H, *J*=7.8 Hz). ^{13}C NMR ($CDCl_3$): δ ppm 28.3 ($3CH_3$), 42.1 (CH_2), 65.6 (CH_2), 81.6 (C), 116.9 (CH), 120.2 (CH), 123.5 (CH), 124.3 (CH), 126.2 (C), 145.9 (C), 152.6 (C). MS: *m*/*z*=236 (M+1). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36, H, 7.28, N, 5.95. Found C, 66.15, H, 7.43, N, 5.90.

4-(*tert*-Butoxycarbonyl)-4*H*-1,4-benzoxazine (3). *Method A*: To a solution of compound **2** (940 mg, 4 mmol) in dry carbon tetrachloride (50 mL) was added *N*-bromosuccinimide (1.56 g, 8.8 mmol) and a catalytic amount of benzoyl peroxide. The resulting mixture was stirred and heated with a bulb lamp (60 W) at reflux for 45 min. The mixture was allowed to cool and the succinimide was filtered off. The filtrate was evaporated to yield an oil sufficiently pure to be used directly in the next step of the reaction. The crude product was stirred in acetone (50 mL) at room temperature for 2 h with sodium iodide (2.99 g, 20 mmol). The acetone was removed from the greenish slurry under reduced pressure then water, EtOAC and 1 M sodium thiosulfate solution were added to the resulting brown residue. After the usual workup and chromatography with petroleum ether/EtOAc (95/5), **3** was obtained as a colorless oil (1.88 g, 86%). *Method B*: A solution of formic acid (184 mg, 4 mmol) and triethylamine (607 mg, 6 mmol) in DME (3 mL) was stirred for 5 min at room temperature and a solution of triphenylphosphine (42 mg, 0.16 mmol), palladium(II) acetate (19 mg, 0.08 mmol) and compound **9** (963 mg, 2 mmol) in DME (3 mL) was added. The mixture was stirred at reflux for 1 h. After the usual workup and chromatography on silica gel of the residue with petroleum ether/EtOAc (95/5), **3** was obtained as a colorless oil (312 mg, 67%). IR (neat): ν cm^{-1} 1712 (C=O), 1587 and 1495 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.54 (s, 9H), 5.97 (d, 1H, *J*=4.4 Hz), 6.18 (d, 1H, *J*=4.4 Hz), 6.70–6.77 (m, 1H), 6.89–7.01 (m, 2H), 7.78 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 28.2 ($3CH_3$), 82.1 (C), 110.4 (CH), 116.3 (CH), 121.4 (CH), 123.5 (CH), 125.5 (CH), 127.7 (C), 130.9 (CH), 147.3 (C), 150.1 (C). MS: *m*/*z*=234 (M+1). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94, H, 6.48, N, 6.00. Found C, 67.05, H, 6.57 N, 6.15.

4-(*tert*-Butoxycarbonyl)-3-methyl-4*H*-1,4-benzoxazine (4a). To a cold (−78°C) solution of **3** (466 mg, 2 mmol) in dry THF (15 mL) was added a solution of LDA 2 M in heptane/THF (1.2 mL, 2.4 mmol). The reaction solution was stirred at −78°C for 35 min and iodomethane (851 mg, 6 mmol) was added, then the mixture was treated with a solution of saturated ammonium chloride solution, and allowed to warm to room temperature. After usual workup and chromatography with petroleum ether/EtOAc (95/5), **4a** was obtained as a white solid (371 mg, 75%). Mp: <25°C. IR (KBr): ν cm^{-1} 1724 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.53 (s, 9H), 2.01 (d, 3H, *J*=1 Hz), 6.22 (d, 1H, *J*=1 Hz), 6.83–6.89 (m, 1H), 7.00–7.08 (m, 2H), 7.43–7.49 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 15.6 (CH_3), 29.7 ($3CH_3$), 81.9 (C), 116.3 (CH), 121.8 (C), 122.8 (CH), 124.6 (CH), 125.6 (CH), 129.1 (C), 134.9 (CH), 150.9 (C), 152.3 (C). MS: *m*/*z*=248 (M+1). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00, H, 6.93, N, 5.66. Found C, 68.15, H, 7.12, N, 5.75.

4-(*tert*-Butoxycarbonyl)-3-trimethylsilyl-4*H*-1,4-benzoxazine (4b). The reaction was carried out as described above for the synthesis of compound **4a** with chlorotrimethylsilane (652 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **4b** (507 mg, 83%) as a white solid. Mp: 71–72°C. IR (KBr): ν cm^{-1} 1695 (C=O). ^1H-NMR ($CDCl_3$): δ ppm 0.23 (s, 9H), 1.53 (s, 9H), 6.23 (s, 1H), 6.83–6.88 (m, 1H), 6.96–7.09 (m, 2H), 7.36–7.41 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 0.3 ($3CH_3$), 28.3 ($3CH_3$), 82.1 (C), 116.3 (CH), 123.5 (CH), 123.7 (CH), 125.7 (CH), 125.5 (C), 129.1 (C), 143.0 (CH), 149.9 (C), 151.8 (C). MS: *m*/*z*=306 (M+1). Anal. Calcd for $C_{16}H_{23}NO_3Si$: C, 62.92, H, 7.59, N, 4.59. Found C, 63.11, H, 7.68, N, 4.71.

4-(*tert*-Butoxycarbonyl)-3-iodo-4*H*-1,4-benzoxazine (4c). To a cold (−78°C) solution of **3** (466 mg, 2 mmol) in dry THF (15 mL) was added a solution of LDA 2 M in heptane/THF (1.2 mL, 2.4 mmol). The reaction solution was stirred at −78°C for 35 min and iodine (1.01 g, 4 mmol) in cold (−78°C) THF (5 mL) was added, then the mixture was treated with a solution of sodium thiosulfate 1 M, allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with EtOAc (3×10 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated. Chromatography with toluene gave **4c** (582 mg, 81%) as a colorless oil. IR (neat): ν cm^{-1} 1721 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.55 (s, 9H), 6.57 (s, 1H), 6.86–6.91 (m, 1H), 7.07–7.11 (m, 2H), 7.40–7.44 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 28.1 ($3CH_3$), 70.3 (C), 83.5 (C), 115.9 (CH), 123.8 (CH), 124.7 (CH), 126.7 (CH), 128.0 (C), 143.7 (CH), 150.6 (C), 151.4 (C). MS: *m*/*z*=360 (M+1). Anal. Calcd for $C_{13}H_{14}INO_3$: C, 43.47, H, 3.93, N, 3.90. Found C, 43.50, H, 3.99, N, 4.01.

3-Bromo-4-(*tert*-butoxycarbonyl)-4*H*-1,4-benzoxazine (4d). The reaction was carried out as described above for the

synthesis of compound **4a** with 1,2-dibromotetrachloroethane (1.95 g, 6 mmol) in solution in THF (5 mL) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **4d** (624 mg, 82%) as a colorless oil. IR (neat): ν cm^{-1} 1732 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.55 (s, 9H), 6.61 (s, 1H), 6.91–6.95 (m, 1H), 7.07–7.16 (m, 2H), 7.44–7.48 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 28.1 ($3CH_3$), 83.5 (C), 87.8 (C), 115.9 (CH), 123.8 (CH), 124.9 (CH), 126.7 (CH), 128.7 (C), 138.2 (C), 138.9 (CH), 150.7 (C). MS: *m*/*z*=312 (^{79}Br) (M+1), 314 (^{81}Br) (M+1). Anal. Calcd for $C_{13}H_{14}BrNO_3$: C, 50.02, H, 4.52, N, 4.49. Found C, 50.11, H, 4.60, N, 4.53.

4-(*tert*-Butoxycarbonyl)-4*H*-1,4-benzoxazine-3-carboxylic acid (4e). To a cold (−78°C) solution of **3** (466 mg, 2 mmol) in dry THF (15 mL) was added a solution of LDA 2 M in heptane/THF (1.2 mL, 2.4 mmol). The reaction solution was stirred at −78°C for 35 min then carbon dioxide from dry ice, dried over sulfuric acid, was introduced above the surface of the rapidly stirred solution during 10 min, then the mixture was treated with a sodium hydroxide solution (20%) and allowed to warm to room temperature. The mixture was extracted with dichloromethane (2×10 mL), the aqueous phase was acidified with hydrochloric acid solution (10%) and extracted with dichloromethane (3×10 mL). The organic phases were dried over $MgSO_4$, concentrated and **4e** (471 mg, 85%) was obtained as a crude product. Mp: 154–155°C. IR (KBr): ν cm^{-1} 3400–2600 (OH), 1726 (C=O), 1702 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.49 (s, 9H), 6.92–6.96 (m, 1H), 7.06–7.16 (m, 2H), 7.40 (s, 1H), 7.61–7.65 (m, 1H), 10.03 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.9 ($3CH_3$), 83.2 (C), 116.1 (CH), 116.8 (C), 124.7 (CH), 126.3 (2CH), 127.9 (C), 147.2 (CH), 148.6 (C), 151.5 (C), 168.7 (C). MS: *m*/*z*=278 (M+1). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65, H, 5.45, N, 5.05. Found C, 60.68, H, 5.50, N, 5.07.

4-(*tert*-Butoxycarbonyl)-3-ethyl-4*H*-1,4-benzoxazine-3-carboxylate (4f). The reaction was carried out as described above for the synthesis of compound **4a** with ethyl chloroformate (651 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (80/20) gave **4f** (397 mg, 65%) as a colorless oil. IR (neat): ν cm^{-1} 1725, 1665 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.33 (t, 3H, *J*=7.2 Hz), 1.49 (s, 9H), 4.28 (q, 2H, *J*=7.2 Hz), 6.90–6.93 (m, 1H), 7.07–7.20 (m, 2H), 7.26 (s, 1H), 7.62–7.66 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 15.1 (CH_3), 28.3 ($3CH_3$), 61.9 (CH_2), 83.1 (C), 116.3 (CH), 118.2 (C), 124.5 (CH), 124.8 (CH), 126.6 (CH), 128.4 (C), 139.1 (CH), 150.3 (C), 153.6 (C), 163.4 (C). MS: *m*/*z*=306 (M+1). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94, H, 6.27, N, 4.59. Found C, 63.06, H, 6.33, N, 4.69.

4-(*tert*-Butoxycarbonyl)-3-trimethyltin-4*H*-1,4-benzoxazine (4g). The reaction was carried out as described above for the synthesis of the compound **4a** with trimethyltin chloride (797 mg, 4 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (99/1) gave **4g** (657 mg, 83%) as white crystals. Mp: 78–79°C. IR (KBr): ν cm^{-1} 1676 (C=O), 1583, 1497 (C=C). ^1H NMR ($CDCl_3$): δ ppm 0.25 (s, 9H, *J* (^{119}Sn,CH_3)=57 Hz, *J* (^{117}Sn,CH_3)=54 Hz), 1.58 (s, 9H), 5.94 (s, 1H, *J* (^{119}Sn,H_2)=19 Hz, *J* (^{117}Sn,H_2)=18 Hz), 6.80–6.84 (m, 1H), 6.94–7.06 (m, 2H), 7.42–7.46 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm −6.3 ($3CH_3$), 28.2 ($3CH_3$), 82.2 (C), 116.3 (CH), 122.3 (CH), 122.9 (CH), 125.3 (CH), 123.5 (C), 128.6 (C), 138.3 (CH), 148.9 (C), 152.1 (C). MS: *m*/*z*=394 (M+1) (^{116}Sn), 396 (M+1) (^{118}Sn), 398 (M+1) (^{120}Sn). Anal. Calcd for $C_{16}H_{23}NO_3Sn$: C, 48.52, H, 5.85, N, 3,54. Found C, 48.48, H, 5.89, N, 3.51.

4-(*tert*-Butoxycarbonyl)-3-tributyltin-4*H*-1,4-benzoxazine (4h). The reaction was carried out as described above for the synthesis of the compound **4a** with tributyltin chloride (1.30 g, 4 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (98/2) gave **4g** (679 mg, 65%) as a colorless oil. IR (neat): ν cm^{-1} 1675 (C=O). ^1H NMR ($CDCl_3$): δ ppm 0.84–1.55 (m, 36H), 5.86 (s, 1H), 6.75–6.79 (m, 1H), 6.90–7.01 (m, 2H), 7.32–7.36 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 12.2 ($3CH_2$), 13.7 ($3CH_3$), 27.3 ($3CH_2$), 28.2 ($3CH_3$), 28.9 ($3CH_2$), 82.0 (C), 116.2 (CH), 122.4 (CH), 122.8 (CH), 123.2 (C), 125.2 (CH), 128.7 (C), 138.4 (CH), 149.2 (C), 152.0 (C). MS: *m*/*z*=520 (M+1) (^{116}Sn), 522 (M+1) (^{118}Sn), 524 (M+1) (^{120}Sn). Anal. Calcd for $C_{25}H_{41}NO_3Sn$: C, 57.49, H, 7.91, N, 22.68. Found C, 57.62, H, 8.05, N, 22.85.

3,3-Dimethyl-3*H*-benzo [*b*][1,3]oxazolo [3,4-*d*][1,4]oxazin-1-one (5a). The reaction was carried out as described above for the synthesis of compound **4a** with acetone (348 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **5a** (391 mg, 90%) as white crystals. Mp: 125–126°C. IR (KBr): ν cm^{-1} 1757 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.59 (s, 6H), 5.78 (s, 1H), 6.66–6.71 (m, 1H), 6.89–6.98 (m, 2H), 7.89–7.95 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.8 ($2CH_3$), 79.4 (C), 116.1 (CH), 116.5 (CH), 119.7 (CH), 124.1 (CH), 124.4 (CH), 126.5 (C) 126.3 (C), 143.3 (C), 151.5 (C). MS: *m*/*z*=218 (M+1). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35, H, 5.10, N, 6.45. Found C, 66.24, H, 5.21, N, 6.45.

3-Spiro [4,5]-3*H*-benzo[*b*][1,3]oxazolo[3,4-*d*][1,4]oxazin-1-one (5b). The reaction was carried out as described above for the synthesis of compound **4a** with cyclohexanone (589 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **5b** (360 mg, 70%) as white crystals. Mp: 152–153°C. IR (KBr): ν cm^{-1} 1749 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.42–2.09 (m, 10H), 5.72 (s, 1H), 6.58–6.66 (m, 1H), 6.85–6.94 (m, 2H), 7.88–7.96 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 21.4 ($2CH_2$), 24.4 (CH_2), 36.8 ($2CH_2$), 81.3 (C), 116.0 (CH), 116.5 (CH), 120.4 (CH), 124.1 (CH), 124.5 (C), 126.4 (CH), 129.9 (C), 143.5 (C), 150.4 (C). MS: *m*/*z*=258 (M+1). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02, H, 5.88, N, 5.44. Found C, 69.99, H, 5.91, N, 5.39.

3-Methyl-3*H*-benzo [*b*][1,3]oxazolo [3,4-*d*][1,4]oxazin-1-one (5c). The reaction was carried out as described above for the synthesis of compound **4a** with acetaldehyde (264 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **5c** (333 mg, 82%) as white crystals. Mp: 90–91°C. IR (KBr): ν cm^{-1} 1755 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.58 (d, 3H, *J*=6.3 Hz), 5.10–5.18 (qd, 1H, *J*=6.3 Hz, *J*=2.2 Hz), 5.74 (d, 1H, *J*=2.2 Hz), 6.63–6.66 (m, 1H), 6.86–6.96 (m, 2H), 7.86–7.90 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 21.8 (CH_3),

71.3 (CH), 116.1 (CH), 116.4 (CH), 120.4 (CH), 124.2 (CH), 122.4 (C), 124.1 (C), 126.6 (CH), 143.4 (C), 151.5 (C). MS: *m*/*z*=204 (M+1). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02, H, 4.46, N, 6.89. Found C, 64.99, H, 4.50, N, 6.78.

3-(3,4-Dimethoxyphenyl)-3*H*-benzo [*b*][1,3]oxazolo [3,4-*d*]-[1,4]oxazin-1-one (5d). The reaction was carried out as described above for the synthesis of compound **4a** with 3,4-dimethoxybenzaldehyde (997 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (80/20) gave **5d** (488 mg, 75%) as yellow crystals. Mp: 120–121°C. IR (KBr): ν cm^{-1} 1762 (C=O). ^1H NMR ($CDCl_3$): δ ppm 3.91 (s, 3H), 3.93 (s, 3H), 5.63 (d, 1H, *J*=2 Hz), 5.93 (d, 1H, *J*=2 Hz), 6.66–6.70 (m, 1H), 6.87–7.03 (m, 5H), 7.92–7.97 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 56.4 (CH_3), 56.5 (CH_3), 77.1 (CH), 110.4 (CH), 111.4 (CH), 116.6 (CH), 116.9 (CH), 120.7 (CH), 121.1 (C), 122.9 (CH), 124.7 (CH), 124.1 (C), 127.1 (CH), 128.1 (C), 143.8 (C), 149.9 (C), 150.8 (C), 150.9 (C). MS: *m*/*z*=326 (M+1). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 66.46, H, 4.65, N, 4.31. Found C, 66.52, H, 4.67, N, 4.41.

4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (8). To a solution of **7** (1.49 g, 10 mmol) in THF (20 mL) were added di-*tert*-butyldicarbonate (2.62 g, 12 mmol) and 4-dimethylaminopyridine (1.46 g, 12 mmol). The mixture was stirred at room temperature for 3 h. After concentration, the residue was diluted with EtOAc and washed with a solution of hydrochloric acid 3 M (2×10 mL). After the usual workup and chromatography with petroleum ether/EtOAc (95/5), **8** was obtained as white crystals (2.39 g, 96%). Mp: 72–73°C. IR (KBr): ν cm^{-1} 1779–1702 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.62 (s, 9H), 4.56 (s, 2H), 7.03–7.17 (m, 4H). ^{13}C NMR ($CDCl_3$): δ ppm 27.6 ($3CH_3$), 68.3 (CH_2), 85.6 (C), 117.3 (CH), 118.4 (CH), 122.8 (CH), 125.3 (CH), 126.2 (C), 145.4 (C), 149.5 (C), 164.2 (C). MS=250 (M+1). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64, H, 6.07, N, 5.62. Found C, 62.71, H, 6.18, N, 5.73.

4-(*tert*-Butoxycarbonyl)-3-[(diphenoxyphosphoryl)oxo]-4*H*-1,4-benzoxazine (9). To a cold (−78°C) solution of **8** (2.49 g, 10 mmol) in dry THF (50 mL) and *N*,*N*,*N*′,*N*′-tetramethylenediamine (1.28 g, 11 mmol) was added a solution of LDA 2 M in heptane/THF (6 mL, 12 mmol). The reaction mixture was stirred at −78°C for 1 h and 30 min and freshly distilled diphenyl chlorophosphate (3.22 mL, 12 mmol) was added, then the mixture was stirred for 20 min, and allowed to warm to room temperature. The volatiles were removed and the residue was hydrolyzed. After the usual workup and chromatography on silica gel with petroleum ether/EtOAc (90/10), **9** was obtained as white crystals (4.09 g, 85%). Mp: 64–65°C. IR (KBr): ν cm^{-1} 1732 (C=O), 1591, 1489 (C=C), 1315 (P=O). ^1H NMR ($CDCl_3$): δ ppm 1.46 (s, 9H), 6.70 (d, 1H, $J_{H,P}$=4 Hz), 6.91–7.41 (m, 14H). ^{13}C NMR ($CDCl_3$): δ ppm 27.9 ($3CH_3$), 83.2 (C), 115.9 (CH), 119.8 (4CH, $J_{C,P}$=4.6 Hz), 123.5 (CH), 124.9 (CH), 125.6 (2CH), 126.6 (CH), 128.4 (CH, $J_{C,P}$=3.2 Hz), 128.5 (C), 129.8 (4CH), 132.4 (C, $J_{C,P}$=10.7 Hz), 150.2 (2C, $J_{C,P}$=7.7 Hz), 150.9 (C), 151.7 (C). MS: *m*/*z*=482 (M+1). Anal. Calcd for $C_{25}H_{24}NO_7P$: C, 62.37, H, 5.02, N, 2.91. Found C, 62.46, H, 5.05, N, 2.88.

4-(*tert*-Butoxycarbonyl)-3-vinyl-4*H*-1,4-benzoxazine (10a). Phosphate **9** (481 mg, 1 mmol) and tributyl(vinyl)tin (634 mg, 2 mmol) were dissolved in THF (3 mL). Tetrakis-(triphenylphosphine)palladium (0) (58 mg, 0.05 mmol) and lithium chloride (127 mg, 3 mmol) were added and the reaction was refluxed for 2 h. After usual workup, extraction with acetonitrile/pentane and chromatography with petroleum ether/EtOAc (95/5), **10a** was obtained as a colorless oil (225 mg, 87%). IR (neat): ν cm^{-1} 1716 (C=O), 1662 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.47 (s, 9H), 5.06 (d, 1H, *J*=10.9 Hz), 5.25 (d, 1H, *J*=17.2 Hz), 6.18 (dd, 1H, *J*=10.9 Hz, *J*=17.2 Hz), 6.65 (s, 1H), 6.90–6.96 (m, 1H), 7.07–7.12 (m, 2H), 7.46–7.53 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.9 ($3CH_3$), 81.9 (C), 115.7 (CH_2), 118.8 (CH), 123.2 (CH), 125.2 (C), 125.3 (CH), 125.8 (CH), 128.1 (CH), 128.8 (C), 138.8 (CH), 150.6 (C), 152.2 (C). MS: *m*/*z*=260 (M+1). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48, H, 6.61, N, 5.40. Found C, 69.45, H, 6.68, N, 5.34.

4-(*tert*-Butoxycarbonyl)-3-(1-ethoxyvinyl)-4*H*-1,4-benzoxazine (10b). The reaction was carried out as described above for the synthesis of compound **10a** with tributyl(1-ethoxyvinyl)tin (722 mg, 2 mmol). Chromatography with petroleum ether/EtOAc (95/5) gave **10b** (249 mg, 82%) as a colorless oil. IR (neat): ν cm^{-1} 1715 (C=O), 1587, 1492 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.34 (t, 3H, *J*=7 Hz), 1.47 (s, 9H), 3.84 (q, 2H, *J*=7 Hz), 4.07 (d, 1H, *J*=2.5 Hz), 4.31 (d, 1H, *J*=2.5 Hz), 6.86 (s, 1H), 6.88–6.92 (m, 1H), 7.04–7.09 (m, 2H), 7.53–7.57 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 14.4 (CH_3), 28.0 ($3CH_3$), 63.2 (CH_2), 81.5 (CH_2), 82.1 (C), 115.8 (CH), 123.0 (C), 123.3 (CH), 125.0 (CH), 125.9 (CH), 129.1 (C), 137.9 (CH), 150.9 (C), 152.2 (C), 154.8 (C). MS: *m*/*z*=304 (M+1). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31, H, 6.98, N, 4.62. Found C, 67.39, H, 7.02, N, 4.52.

4-(*tert*-Butoxycarbonyl)-3-(2-thienyl)-4*H*-1,4-benzoxazine (10c). The reaction was carried out as described above for the synthesis of compound **10a** with 2-(tributylstannyl)-thiophene (746 mg, 2 mmol). Chromatography with petroleum ether/EtOAc (95/5) gave **10c** (287 mg, 91%) as a colorless oil. IR (neat): ν cm^{-1} 1712 (C=O), 1588, 1491 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.35 (s, 9H), 6.73 (s, 1H), 6.95–6.99 (m, 2H), 7.04–7.06 (m, 1H), 7.09–7.13 (m, 2H), 7.18 (dd, 1H, *J*=1.2 Hz, *J*=5 Hz), 7.61–7.69 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.7 ($3CH_3$), 82.2 (C), 115.8 (CH), 121.8 (C), 123.2 (CH), 123.4 (CH), 123.5 (CH), 125.0 (CH), 125.8 (C), 126.1 (CH), 126.2 (CH), 128.9 (C), 135.5 (CH), 151.0 (C), 152.2 (C). MS: *m*/*z*=316 (M+1). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74, H, 5.43, N, 4.44. Found C, 64.86, H, 5.49, N, 4.40.

4-(*tert*-Butoxycarbonyl)-3-(2-furyl)-4*H*-1,4-benzoxazine (10d). The reaction was carried out as described above for the synthesis of compound **10a** with 2-(tributylstannyl)furan (714 mg, 2 mmol). Chromatography with petroleum ether/EtOAc (95/5) gave **10d** (287 mg, 96%) as a colorless oil. IR (neat): ν cm^{-1} 1726 (C=O), 1589, 1491 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.35 (s, 9H), 6.30 (dd, 1H, *J*=0.6 Hz, *J*=3.2 Hz), 6.39 (dd, 1H, *J*=1.7 Hz, *J*=3.2 Hz), 6.86 (s, 1H), 6.92–6.95 (m, 1H), 7.07–7.11 (m, 2H), 7.35 (dd, 1H, *J*=0.6 Hz, *J*=1.7 Hz), 7.61–7.65 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.7 ($3CH_3$), 82.0 (C), 105.6 (CH), 110.9 (CH), 115.8 (CH), 118.7 (C), 123.4 (CH), 125.0 (CH), 126.1

(CH), 128.7 (C), 136.2 (CH), 140.8 (CH), 147.9 (C), 150.8 (C), 152.1 (C). MS: *m*/*z*=300 (M+1). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22, H, 5.72, N, 4.68. Found C, 68.26, H, 5.77, N, 4.63.

4-(*tert*-Butoxycarbonyl)-3-phenyl-4*H*-1,4-benzoxazine (10e). The reaction was carried out as described above for the synthesis of compound **10a** with tributylphenyltin (734 mg, 2 mmol). Chromatography with petroleum ether/EtOAc (95/5) gave **10e** (260 mg, 84%) as white crystals. Mp: 115–116°C. IR (KBr): ν cm^{-1} 1710 (C=O), 1588, 1493 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.15 (s, 9H), 6.59 (s, 1H), 6.90–6.96 (m, 1H), 7.08–7.12 (m, 2H), 7.24–7.37 (m, 5H), 7.69–7.71 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.6 ($3CH_3$), 81.9 (C), 115.8 (CH), 123.4 (CH), 124.5 (CH), 124.6 (CH), 125.8 (CH), 126.0 (CH), 126.7 (C), 127.2 (CH), 128.3 (2CH), 129.0 (C), 135.4 (CH), 135.5 (C), 151.0 (C), 152.0 (C). MS: *m*/*z*=310 (M+1). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77, H, 6.19, N, 4.53. Found C, 73.79, H, 6.18, N, 4.50.

3-[2-(1,4-Benzodioxino)]-4-(*tert*-butoxycarbonyl)-4*H*-1,4-benzoxazine (10f). The reaction was carried out as described above for the synthesis of the compound **10a** with 2-trimethyltin-1,4-benzodioxine (846 mg, 2 mmol). Chromatography with petroleum ether/EtOAc (95/5) gave **10f** (340 mg, 93%) as a colorless oil. IR (neat): ν cm^{-1} 1722 (C=O), 1491 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.48 (s, 9H), 6.11 (s, 1H), 6.70–6.75 (m, 3H), 6.83–6.93 (m, 3H,), 7.07–7.11 (m, 2H), 7.55–7.59 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 28.2 ($3CH_3$), 83.8 (C), 116.1 (CH), 116.3 (CH), 116.4 (CH), 118.9 (C), 123.5 (CH), 123.7 (CH), 124.3 (2CH), 125.3 (CH), 126.4 (CH), 128.7 (C), 132.3 (C), 136.6 (CH), 142.3 (C), 142.5 (C), 151.0 (C), 152.2 (C). MS: *m*/*z*=366 (M+1). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 69.03, H, 5.24, N, 3.83. Found C, 69.09, H, 5.28, N, 3.79.

4-(*tert*-Butoxycarbonyl)-3-methyl-4*H*-1,4-benzoxazine-3-carboxylate (11). To a solution of **4e** (2.7 g, 10 mmol) in *N*,*N*-dimethylacetamide (50 mL) was added iodomethane (4.48 g, 33 mmol) and sodium hydrogencarbonate (4.2 g, 50 mmol). The resulting mixture was stirred at room temperature for 24 h. After usual workup and chromatography on silica gel with petroleum ether/EtOAc (90/10), **11** was obtained as an inert solid (2.47 g, 85%). IR (KBr): ν cm^{-1} 1742, 1707 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.49 (s, 9H), 3.84 (s, 3H), 6.84–6.94 (m, 1H), 7.08–7.12 (m, 2H), 7.24 (s, 1H), 7.62–7.66 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 28.9 ($3CH_3$), 51.9 (CH_3), 82.8 (C), 116.0 (CH), 117.6 (C), 124.5 (CH), 124.7 (CH), 126.2 (CH), 128.1 (C), 145.0 (CH), 148.8 (C), 151.5 (C), 163.6 (C). MS: *m*/*z*=292 (M+1). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85, H, 5.88, N, 4.81. Found C, 61.91, H, 5.93, N, 4.83.

9-(*tert*-Butoxycarbonyl)-3,3-dimethyl-3,9-dihydro-1*H*-benzo[*b*]furo[3,4-*e*][1,4]oxazin-1-one (12a). A solution of **11** (582 mg, 2 mmol) in dry THF (15 mL) was cooled at −78°C and LDA 2 M in solution in THF/heptane (3 mL, 6 mmol) was added slowly by syringe. The solution was stirred for 35 min at −78°C and acetone (348 mg, 6 mmol) was added. The mixture was stirred at −78°C for 10 min and the reaction was quenched by the addition of water and allowed to warm to room temperature. After the usual workup and chromatography with petroleum ether/EtOAc (95/5), **12a** was obtained as white crystals (494 mg, 78%). Mp: 120–121°C. IR (KBr): ν cm^{-1} 1780, 1724 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.53 (s, 9H), 1.59 (s, 6H), 6.91–6.99 (m, 1H), 7.05–7.19 (m, 2H), 7.73–7.81 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 24.3 ($2CH_3$), 27.9 ($3CH_3$), 78.7 (C), 83.7 (C), 108.9 (C), 116.7 (CH), 124.8 (CH), 125.5 (CH), 126.4 (CH), 127.5 (C), 147.8 (C), 151.3 (C), 163.1 (C), 168.3 (C). MS: *m*/*z*=318 (M+1). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34, H, 6.03, N, 4.41. Found C, 64.37, H, 6.07, N, 4.39.

9-(*tert*-Butoxycarbonyl)-3-spiro[4,5]-3,9-dihydro-1*H*-benzo[*b*]furo[3,4-*e*][1,4]oxazin-1-one (12b). The reaction was carried out as described above for the synthesis of compound **12a** with cyclohexanone (589 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **12b** (514 mg, 72%) as white crystals. Mp: 145–146°C. IR (KBr): ν cm^{-1} 1780, 1725 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.52 (s, 9H), 1.54–1.89 (m, 10H), 6.90–6.96 (m, 1H), 7.02–7.13 (m, 2H), 7.71–7.80 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 21.6 ($2CH_2$), 24.3 (CH_2), 27.9 ($3CH_3$), 33.2 ($2CH_2$), 80.3 (C), 83.6 (C), 109.2 (C), 116.7 (CH), 124.8 (CH), 125.5 (CH), 126.4 (CH), 127.6 (C), 147.8 (C), 151.3 (C), 163.5 (C), 168.9 (C). MS: *m*/*z*=358 (M+1). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21, H, 6.49, N, 3.92. Found C, 67.37, H, 6.44, N, 3.82.

9-(*tert*-Butoxycarbonyl)-3-methyl-3-phenyl-3,9-dihydro-1*H*-benzo[*b*]furo[3,4-*e*][1,4]oxazin-1-one (12c). The reaction was carried out as described above for the synthesis of compound **12a** with acetophenone (721 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **12c** (514 mg, 72%) as white crystals. Mp: 145–146°C. IR (KBr): ν cm^{-1} 1785, 1725 (C=O), 1488 (C=C). ^1H NMR ($CDCl_3$): δ ppm 1.54 (s, 9H), 1.95 (s, 3H), 6.96–7.14 (m, 3H), 7.36–7.54 (m, 5H), 7.77–7.80 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 24.7 (CH_3), 27.8 ($3CH_3$), 81.0 (C), 83.8 (C), 109.0 (C), 116.8 (CH), 124.7 (CH), 124.8 (2CH), 125.6 (CH), 126.4 (CH), 127.4 (C), 128.8 (3CH), 137.6 (C), 147.7 (C), 151.1 (C), 163.2 (C), 167.2 (C). MS: *m*/*z*=380 (M+1). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.65, H, 5.58, N, 3.69. Found C, 69.78, H, 5.67, N, 3.80.

4-(*tert*-Butoxycarbonyl)-2-trimethylsilyl-3-methyl-4*H*-1,4-benzoxazine-3-carboxylate (13a). The reaction was carried out as described above for the synthesis of compound **12a** with chlorotrimethylsilane (652 mg, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **13a** (523 mg, 72%) as a white solid. Mp: 62–63°C. IR (KBr): ν cm^{-1} 1724 (C=O). ^1H NMR ($CDCl_3$): δ ppm 0.29 (s, 9H), 1.51 (s, 9H), 3.78 (s, 3H), 6.85–6.91 (m, 1H), 7.01–7.11 (m, 2H), 7.50–7.59 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm −1.5 ($3CH_3$), 27.9 ($3CH_3$), 51.5 (CH_3), 82.3 (C), 115.7 (CH), 123.7 (CH), 123.8 (CH), 125.0 (CH), 125.8 (C), 128.7 (C), 150.1 (C), 151.0 (C), 163.5 (C), 164.7 (C). MS: *m*/*z*=364 (M+1). Anal. Calcd for $C_{18}H_{25}NO_5Si$: C, 59.48, H, 6.93, N, 3.85. Found C, 59.50, H, 6.93, N, 3.76.

4-(*tert*-Butoxycarbonyl)-2-iodo-3-methyl-4*H*-1,4-benzoxazine-3-carboxylate (13b). The reaction was carried out as described above for the synthesis of compound **12a** with

iodine (1,52 mg, 6 mmol) as an electrophile. After hydrolysis and warming to room temperature, the organic layer was washed with a sodium thiosulfate solution (1 M) then dried over $MgSO_4$ and concentrated. Chromatography with toluene/EtOAc (95/5) gave **13b** (584 mg, 70%) as a white solid. Mp 99–100°C. IR (KBr): ν cm^{-1} 1742, 1730 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.49 (s, 9H), 3.84 (s, 3H), 6.96–7.03 (m, 1H), 7.08–7.22 (m, 2H), 7.59–7.67 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.9 ($3CH_3$), 52.2 (CH_3), 83.4 (C), 105.5 (C), 116.0 (CH), 120.7 (C), 124.5 (CH), 125.1 (CH), 126.2 (CH), 128.1 (C), 149.9 (C), 150.3 (C), 163.4 (C). MS: *m*/*z*=418 (M+1). Anal. Calcd for $C_{15}H_{16}INO_5$: C, 43.18, H, 3.87, N, 3.36. Found C, 43.25, H, 3.99, N, 3.49.

4-(*tert*-Butoxycarbonyl)-2-trimethyltin-3-methyl-4*H*-1,4-benzoxazine-3-carboxylate (13c). The reaction was carried out as described above for the synthesis of compound **12a** with trimethyltin chloride (797 mg, 4 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **13c** (708 mg, 78%) as white crystals. Mp: 87–88°C. IR (KBr): ν cm^{-1} 1720, 1706 (C=O). ^1H NMR ($CDCl_3$): δ ppm 0.32 (s, 9H, $J(^{119}Sn,CH_3)$=58 Hz, $J(^{117}Sn,CH_3)$=56 Hz), 1.47 (s, 9H), 3.77 (s, 3H), 6.88–6.92 (m, 1H), 7.05–7.09 (m, 2H), 7.55–7.59 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm −7.6 ($3CH_3$), 28.0 ($3CH_3$), 51.6 (CH_3), 82.1 (C), 115.9 (CH), 123.9 (CH), 124.0 (C), 124.4 (CH), 125.8 (CH), 129.0 (C), 150.0 (C), 151.4 (C), 165.6 (C), 171.6 (C). MS: *m*/*z*=452 (M+1) (^{116}Sn), 454 (M+1) (^{118}Sn), 456 (M+1) (^{120}Sn). Anal. Calcd for $C_{18}H_{25}NO_5Sn$: C, 47.61, H, 5.55, N, 3.08. Found C, 47.70, H, 5.59, N, 3.12.

4-(*tert*-Butoxycarbonyl)-3-methoxycarbonyl-4*H*-1,4-benzoxazine-2-carboxylic acid (13d). The reaction was carried out as described above for the synthesis of compound **12a** with carbon dioxide from dry ice, (dried over sulfuric acid) as an electrophile. The mixture was treated with a sodium hydroxide solution (20%) and allowed to warm to room temperature. The mixture was extracted with dichloromethane (2×10 mL), the aqueous phase was acidified with hydrochloric acid solution (10%) and extracted with dichloromethane (3×10 mL). The organic phases were dried over $MgSO_4$, concentrated and **13d** (471 mg, 85%) was obtained as a crude product. Mp: <30°C. IR (neat): ν cm^{-1} 3704–3342 (OH), 1838–1675 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.51 (s, 9H), 3.90 (s, 3H), 7.05–7.11 (m, 3H), 7.53–7.61 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 28.0 ($3CH_3$), 53.6 (CH_3), 84.5 (C), 116.7 (CH), 123.0 (C), 123.7 (CH), 124.9 (CH), 126.9 (CH), 127.4 (C), 128.2 (C), 149.3 (C), 150.5 (C), 162.8 (C), 165.7 (C). MS: *m*/*z*=336 (M+1). Anal. Calcd for $C_{16}H_{17}NO_7$: C, 57.31, H, 5.11, N, 4.18. Found C, 57.49, H, 4.95, N, 4.12.

4-(*tert*-Butoxycarbonyl)-3-phenyl-2-trimethylsilyl-4*H*-1,4-benzoxazine (14a). A solution of **10e** (619 mg, 2 mmol) in dry THF (15 mL) was cooled at −78°C and LDA 2 M in solution in THF/heptane (3 mL, 6 mmol) was added slowly by syringe. The solution was stirred for 15 min at −78°C and chlorotrimethylsilane (348 mg, 6 mmol) was added. The mixture was stirred at −78°C for 10 min and the reaction was quenched by the addition of water and allowed to warm to room temperature. After the usual workup and chromatography on silica gel with petroleum ether/EtOAc (98/2), **14a** was obtained as white crystals (618 mg, 81%). Mp: 127–128°C. IR (KBr): ν cm^{-1} 1709 (C=O). ^1H NMR ($CDCl_3$): δ ppm −0.01 (s, 9H), 1.14 (s, 9H), 6.90–6.94 (m, 1H), 7.06–7.11 (m, 2H), 7.29–7.35 (m, 5H), 7.71–7.75 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm −0.9 ($3CH_3$), 27.7 ($3CH_3$), 81.7 (C), 115.5 (CH), 122.7 (CH), 123.5 (CH), 125.6 (CH), 127.7 (2CH), 127.9 (CH), 129.0 (2CH),130.7 (C), 136.7 (C), 137.3 (C), 150.5 (C), 151.4 (C), 152.7 (C). MS: *m*/*z*=382 (M+1). Anal. Calcd for $C_{22}H_{27}NO_3Si$: C, 69.26, H, 7.13, N, 3.67. Found C, 69.33, H, 7.08, N, 3.60.

4-(*tert*-Butoxycarbonyl)-3-phenyl-2-tributyltin-4*H*-1,4-benzoxazine (14b). The reaction was carried out as described above for the synthesis of compound **14a** with tributyltin chloride (1.95 g, 6 mmol) as an electrophile. Chromatography with petroleum ether/EtOAc (95/5) gave **13** (708 mg, 78%) as a colorless oil. IR (neat): ν cm^{-1} 1710 (C=O). ^1H NMR ($CDCl_3$): δ ppm 0.82 (t, 9H, *J*=7.2 Hz), 1.12–1.42 (m, 27H), 6.84–6.88 (m, 1H), 7.04–7.08 (m, 2H), 7.26–7.30 (m, 5H), 7.68–7.72 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 10.9 ($3CH_2$), 13.5 ($3CH_3$), 27.1 ($3CH_2$), 27.7 ($3CH_3$), 28.7 ($3CH_2$,), 81.4 (C), 115.5 (CH), 122.6 (CH), 123.7 (CH), 125.5 (CH), 127.3 (CH), 127.5 (2CH), 128.0 (2CH), 130.4 (C), 136.3 (C), 138.2 (C), 151.4 (C), 152.1 (C), 155.3 (C). MS: *m*/*z*=496 (M+1) (^{116}Sn), 498 (M+1) (^{118}Sn), 500 (M+1) (^{120}Sn). Anal. Calcd for $C_{31}H_{45}NO_3Sn$: C, 62.22, H, 7.58, N, 2.34. Found C, 62.17, H, 7.61, N, 2.30.

4-(*tert*-Butoxycarbonyl)-3-phenyl-4*H*-1,4-benzoxazine-2-carboxylic acid (14c). The reaction was carried out as described above for the synthesis of compound **14a** with carbon dioxide from dry ice (dried over sulfuric acid) as an electrophile. The mixture was treated with a sodium hydroxide solution (20%) and allowed to warm to room temperature. The mixture was extracted with dichloromethane (2×10 mL), the aqueous phase was acidified with hydrochloric acid solution (10%) and extracted with dichloromethane (3×10 mL). The organic phases were dried over $MgSO_4$, concentrated and **14c** (708 mg, 81%) was obtained as a colorless oil. IR (neat): ν cm^{-1}3400–3040 (OH), 1720, 1711 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.04 (s, 9H), 6.97–7.09 (m, 3H), 7.18–7.37 (m, 6H), 7.65–7.69 (m, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 27.5 ($3CH_3$), 83.1 (C), 116.1 (CH), 123.5 (CH), 124.0 (CH), 124.6 (C), 126.4 (CH), 127.5 (2CH), 128.3 (C), 128.9 (CH), 129.3 (2CH), 129.5 (C), 134.1 (C), 150.1 (C), 151.2 (C), 151.6 (C). MS: *m*/*z*=354 (M+1). Anal. Calcd for $C_{31}H_{45}NO_3Sn$: C, 67.98, H, 5.42, N, 3.96. Found C, 67.92, H, 5.50, N, 4.02.

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