



HAL
open science

TDAE Strategy in the Benzoxazolone Series: Synthesis and Reactivity of a New Benzoxazolinonic Anion

Aïda R. Nadji-Boukrouche, Omar Khoumeri, Thierry Terme, Messaoud Liacha, Patrice Vanelle

► **To cite this version:**

Aïda R. Nadji-Boukrouche, Omar Khoumeri, Thierry Terme, Messaoud Liacha, Patrice Vanelle. TDAE Strategy in the Benzoxazolone Series: Synthesis and Reactivity of a New Benzoxazolinonic Anion. *Molecules*, 2015, 20, pp.1262-1276. 10.3390/molecules20011262 . hal-01234886

HAL Id: hal-01234886

<https://amu.hal.science/hal-01234886>

Submitted on 1 Dec 2015

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Article

TDAE Strategy in the Benzoxazolone Series: Synthesis and Reactivity of a New Benzoxazolinonic Anion

Aïda R. Nadji-Boukrouche ^{1,2,3}, Omar Khoumeri ³, Thierry Terme ³, Messaoud Liacha ² and Patrice Vanelle ^{3,*}

¹ Département de Génie des Procédés, Université 8 mai 1945 Guelma, BP 401, Guelma 24000, Algeria; E-Mail: nadji_aida@yahoo.fr

² Laboratoire de Synthèse et de Biocatalyse Organique (LSBO), Faculté des Sciences, Université Badji Mokhtar-Annaba, BP 12 El-Hadjjar, Annaba 23000, Algeria; E-Mail: m_liacha@yahoo.fr

³ Aix-Marseille Université, CNRS, Institut de Chimie Radicalaire ICR, UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Marseille 13385, France; E-Mails: omar.khoumeri@univ-amu.fr (O.K.); thierry.termes@univ-amu.fr (T.T.)

* Author to whom correspondence should be addressed; E-Mail: patrice.vanelle@univ-amu.fr; Tel.: +33-4-9183-5580; Fax: +33-4-9179-4677.

Academic Editor: Derek J. McPhee

Received: 11 December 2014 / Accepted: 8 January 2015 / Published: 14 January 2015

Abstract: We describe an original pathway to produce new 5-substituted 3-methyl-6-nitro-benzoxazolones by the reaction of aromatic carbonyl and α -carbonyl ester derivatives with a benzoxazolinonic anion formed exclusively via the TDAE strategy.

Keywords: TDAE; benzoxazolone; benzoxazolinonic anion; benzylic alcohols; oxiranes

1. Introduction

Many benzoxazolinone derivatives have been described in therapeutics as possessing a wide variety of pharmacological activities [1–10]. Indeed, the clinical applications of this template are very broad, and range from analgesic anti-inflammatory compounds to antipsychotic and neuroprotective anticonvulsant compounds [11]. Several potentially useful drugs and pharmacological tools based on these pharmacophores have been developed in recent years [12–16].

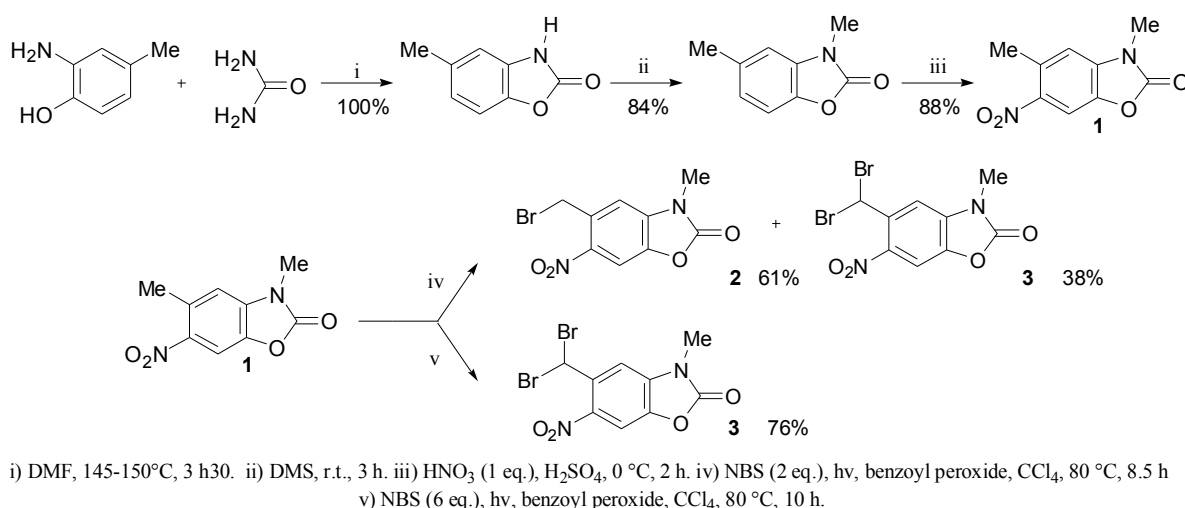
Tetrakis(dimethylamino)ethylene (TDAE) is a reducing agent which reacts with halogenated derivatives to generate an anion under mild conditions via two sequential transfers of one electron [17–19]. Through this strategy, we have developed many reactions between nitrobenzylic substrates and a series of electrophiles such as aldehydes, ketones, α -ketoesters, α -ketolactams and ketomalonates leading to corresponding alcohol adducts [20–23]. This reactivity was recently extended using original heterocyclic carbaldehydes as electrophiles. The reactions led to the expected products, while at the same time bringing to light a new and original reactivity and enabling us to define some limitations of this strategy [24]. Moreover, we reported the reactions of dihalo- and trihalomethyl heterocyclic derivatives with aromatic aldehydes in the presence of TDAE, providing a mixture of *cis/trans* isomers of oxiranes and α -haloketone derivatives, respectively [25,26]. In the same context, the expected alcohols and oxiranes were obtained in good yields in the quinonic series [27].

In continuation of our research program centered on the design and synthesis of novel bioactive molecules [28–32], we report herein the preparation of 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) and 5-(dibromomethyl)-3-methyl-6-nitrobenzoxazolone (**3**) and the study of their reactivity with various aromatic carbonyl and α -carbonyl ester derivatives using the TDAE methodology.

2. Results and Discussion

2.1. Synthesis of Mono and Dibromide Substrates

We prepared 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) and 5-(dibromomethyl)-3-methyl-6-nitrobenzoxazolone (**3**) [33] in four and five steps, respectively. The condensation of 2-amino-4-methylphenol with urea was inspired by a previously described method [34,35]. After methylation using dimethyl sulfate, the nitration of the obtained 3,5-dimethylbenzoxazolone by action of a mixture of nitric and sulfuric acids afforded 3,5-dimethyl-6-nitrobenzoxazolone (**1**) in 88% yield.



Scheme 1. Synthesis of 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) and 5-(dibromomethyl)-3-methyl-6-nitrobenzoxazolone (**3**).

The bromination of **1** with 2 equivalents of *N*-bromosuccinimide in refluxing CCl₄ for 8.5 h gave 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) in 61% yield, accompanied by 5-(dibromomethyl)-

3-methyl-6-nitrobenzoxazolone (**3**) in 38% yield. However, the preparation of this latter compound was optimized (76%) using 6 equivalents of *N*-bromosuccinimide in refluxing CCl₄ for 10 h (Scheme 1).

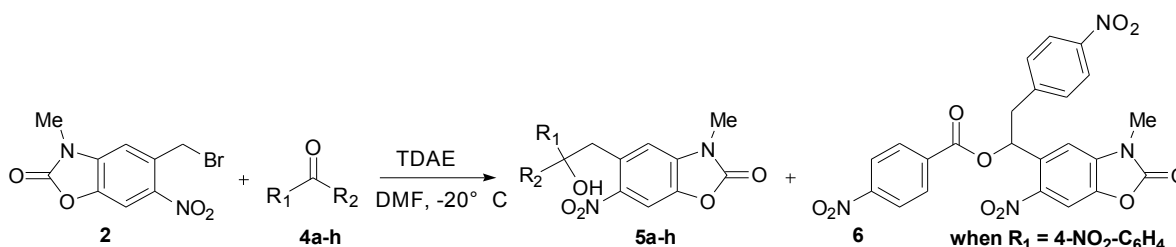
2.2. TDAE Reactivity of 5-(Bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**)

The reaction of 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) with 3 equivalents of various aromatic carbonyl and α -carbonyl ester derivatives **4a–j** in the presence of TDAE at $-20\text{ }^{\circ}\text{C}$ for 1 h, followed by 2 h at room temperature (r.t.) led to the corresponding alcohol derivatives **5a–j** in moderate to good yields (31%–72%) as shown in Table 1 and Scheme 2.

Table 1. Reaction of bromide **2** with aromatic carbonyl and α -carbonyl ester derivatives using TDAE ^a.

Entry ^a	Aromatic Carbonyl	R ₁	R ₂	Product Number	Yield (%) ^b
1	4-Nitrobenzaldehyde	4-NO ₂ -C ₆ H ₄	H	5a	52
2	4-Bromobenzaldehyde	4-Br-C ₆ H ₄	H	5b	49
3	4-Cyanobenzaldehyde	4-CN-C ₆ H ₄	H	5c	31
4	2-Nitrobenzaldehyde	2-NO ₂ -C ₆ H ₄	H	5d	44
5	2-Bromobenzaldehyde	2-Br-C ₆ H ₄	H	5e	49
6	3-Bromobenzaldehyde	3-Br-C ₆ H ₄	H	5f	43
7	Ethyl glyoxylate	CO ₂ C ₂ H ₅	H	5g	72
8	Diethyl ketomalonate	CO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	5h	62

Notes: ^a All the reactions were performed using 3 equivalents of aromatic carbonyl **4a–h**, 1 equivalent of bromide **2** and 1 equivalent of TDAE in anhydrous DMF stirred at $-20\text{ }^{\circ}\text{C}$ for 1 h and then warmed to rt for 2 h; ^b % Yield relative to bromide **2**.



Scheme 2. TDAE reactivity of 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) with aromatic carbonyl and some α -keto-ester derivatives **4a–h**.

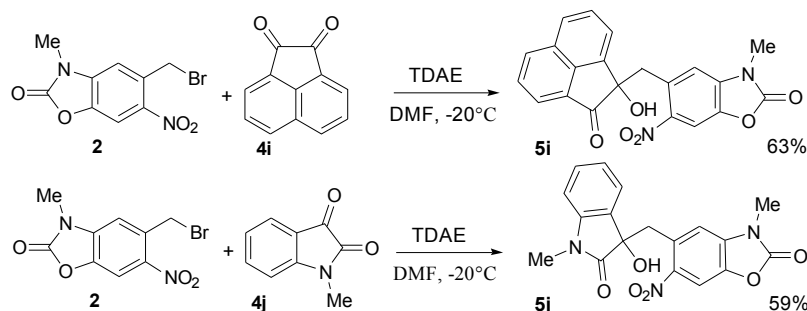
The reaction of substrate **2** with the aromatic aldehydes **4a–f** under TDAE-initiated conditions furnished the expected alcohols **5a–f** in moderate to good yields. The best yield (52%) was obtained with *p*-nitrobenzaldehyde (**4a**). Unexpectedly, *o,p*-bromobenzaldehyde (**4e,4b**) gave the same yield (49%), while *o*-nitrobenzaldehyde (**4d**) and *m*-bromobenzaldehyde (**4f**) gave approximately the same yield (44% and 43%, respectively). Notably, with *p*-nitrobenzaldehyde (**4a**) we observed 23% of the ester **6**. According to a recent mechanistic study [36], the formation of the unexpected ester derivative **6** may be explained by an electron transfer in a primary step between 4-nitrobenzaldehyde (**4a**) as acceptor and TDAE as donor.

p-Cyanobenzaldehyde (**4c**) produced a moderate yield (31%). The formation of these alcohol derivatives may be explained by nucleophilic addition of benzazolinonic carbanions formed by the

action of TDAE with 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) on the carbonyl group of the corresponding aldehyde. In summary, the difference in yields does not appear to be totally explained by electronic effects: the halogen groups furnished approximately the same yields in either position. With nitrobenzaldehydes, steric hindrance could explain the difference between *o*- and *p*-nitrobenzaldehyde yields (44% versus 52%).

It is important to note that in the reactions of substrate **2** with the electrophiles **4b–f**, we observed the unavoidable formation of the reduction product **1** [37]. Extending the reaction times to 8 h at ambient temperature increases its percentage, but decreases the yield of alcohol. On the other hand, after 4 h of reaction, the percentage of reduction product decreases at the same time as that of the alcohol: in this case we also observed traces of the dimerization of substrate **2**.

Moreover, after the reaction with aromatic aldehydes, we investigated the reaction of **2** with α -keto-ester derivatives such as ethyl glyoxylate (**4g**), diethyl ketomalonate (**4h**), acenaphthenedione (**4i**) and 1-methylisatin (**4j**) in the presence of TDAE. The reactions with these electrophiles furnished the corresponding hydroxyl derivatives **5i–j** in good yields (59%–63%), as shown in Table 1 and Scheme 3.



Scheme 3. TDAE reactivity of the 5-(bromomethyl)-3-methyl-6-nitrobenzoxazolone (**2**) and α -diketone and α -ketolactam derivatives **4i–j**.

2.3. TDAE Reactivity of 5-(Dibromomethyl)-3-methyl-6-nitrobenzoxazolone (**3**)

The optimized protocol of the dibromomethyl derivative **3**, was defined with 3 equivalents of aromatic carbonyls **4a–h**, 1 equivalent of 5-(dibromomethyl)-3-methyl-6-nitrobenzoxazolone (**3**) and 1.5 equivalents of TDAE in anhydrous DMF, for 1 h at -20 °C followed by 2 h at r.t. The reactions led to a mixture of *cis/trans* isomers of the corresponding oxiranes **7a–h** in moderate to good yields as reported in Table 2 (Scheme 4). The formation of these oxiranes may be explained by nucleophilic addition of a α -bromocarbanion, formed by the action of TDAE with 5-(dibromomethyl)-3-methyl-6-nitrobenzoxazolone (**3**), on the carbonyl group of aldehydes **4a–h** followed by an intramolecular nucleophilic substitution [26].

In the case of the nitroaromatic aldehydes, steric hindrance could explain the yield difference between *o*- and *p*-nitrobenzaldehyde (46% and 63%). However, this effect disappears in the *o*-bromo-substituted aldehyde which gave 64% of the corresponding oxirane, the *p*- and *m*- substituted aldehydes with 55 and 48% yields respectively. *p*-Cyanobenzaldehyde gave the expected oxirane in good yield (72%).

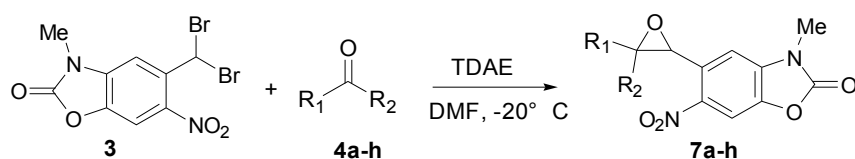
Under the same experimental conditions, we studied the reaction of derivative **3** with α -keto-ester derivatives **4g–h** as reported in Table 2 (Scheme 4). Only the *trans* isomers of the oxiranes **7g** and **7h** were obtained in 26% and 37% yields, respectively, with ethyl glyoxylate (**4g**) and diethyl ketomalonate

(4h). Otherwise, acenaphthenedione (4i) and methyl isatin (4j) furnished mixtures of *like/unlike* original stereoisomers 7i and 7j, respectively, in good yields (Scheme 5). The diastereoisomers were separable, and their configuration was identified by NMR-analysis from the γ -left effect, as previously described [26,38].

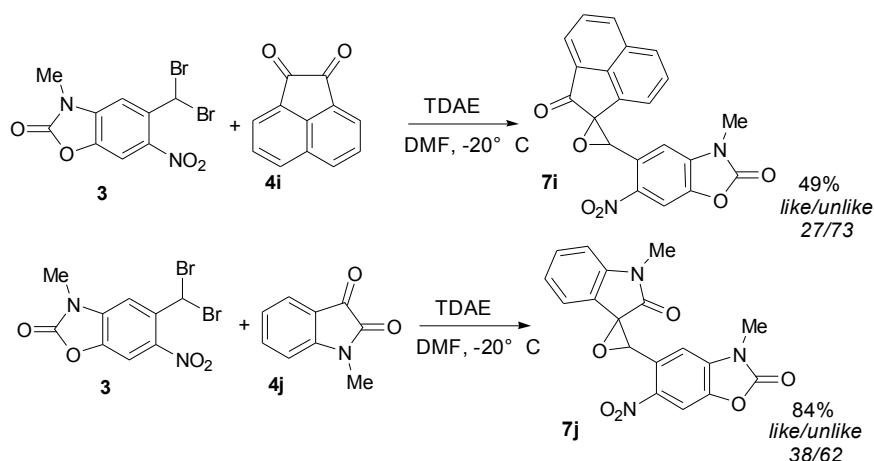
Table 2. Reaction of dibromide 3 with aromatic carbonyl and α -carbonyl ester derivatives using TDAE ^a.

Entry ^a	Aromatic Carbonyl	R ₁	R ₂	Oxirane	Cis/Trans Isomers % ^b	Yield (%) ^c
1	4-Nitrobenzaldehyde	4-NO ₂ -C ₆ H ₄	H	7a	15/85	63
2	4-Bromobenzaldehyde	4-Br-C ₆ H ₄	H	7b	7/93	55
3	4-Cyanobenzaldehyde	4-CN-C ₆ H ₄	H	7c	15/85	72
4	2-Nitrobenzaldehyde	2-NO ₂ -C ₆ H ₄	H	7d	32/68	46
5	2-Bromobenzaldehyde	2-Br-C ₆ H ₄	H	7e	19/81	64
6	3-Bromobenzaldehyde	3-Br-C ₆ H ₄	H	7f	7/93	48
7	Ethyl glyoxylate	CO ₂ C ₂ H ₅	H	7g	0/100	26
8	Diethyl ketomalonate	CO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	7h	0/100	37

Notes: ^a All the reactions were performed using 3 equivalents of aromatic carbonyl 4a–h, 1 equivalent of dibromide 3 and 1.5 equivalent of TDAE in anhydrous DMF stirred at –20 °C for 1 h and then warmed to r.t for 2 h; ^b % isomers determined on ¹H-NMR measurements from the crude product; ^c % yield relative to dibromide 3.



Scheme 4. TDAE reactivity of 5-(dibromomethyl)-3-methyl-6-nitrobenzoxazolone (3) with aromatic carbonyl and some α -keto-ester derivatives 4a–h.



Scheme 5. TDAE reactivity of 5-(dibromomethyl)-3-methyl-6-nitrobenzoxazolone (3) and α -keto-ester derivatives 4i–j.

The relative *cis/trans* percentages of oxirane isomers reported in Table 2 showed that the stereoselectivity of these reactions is not only sensitive to steric hindrance, but it also depends on the nature of the electrophile substituents. The reactions with bromo-substituted aldehydes in either position were more

selective than with nitro-substituted aldehydes. The same percentages of *cis/trans* isomers were previously reported with *p*-nitro- and cyanobenzaldehyde. However, the reactions with ethyl glyoxylate and diethyl ketomalonate were the most selective. Moreover, stereoselectivity was recorded in the mixtures of *like/unlike* original stereoisomers with methyl isatin and acenaphthenedione.

3. Experimental Section

3.1. General Information

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille. Both ^1H - (200 MHz) and ^{13}C -NMR (50 MHz) spectra were determined on a Bruker AC 200 spectrometer. The ^1H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvent peaks: CDCl_3 (76.9 ppm) or $\text{Me}_2\text{SO}-d_6$ (39.6 ppm). Absorptions are reported using the following notation: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets. The following adsorbents were used for column chromatography: silica gel 60 (Merck, Darmstadt, Germany, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm \times 10 cm aluminium plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent. 3,5-Dimethyl-6-nitrobenzoxazolone (**1**) was synthesized in three steps: condensation of 2-amino-4-methylphenol with urea [34], methylation using dimethyl sulfate and nitration by action of a mixture of nitric and sulfuric acids.

3.2. Synthesis of Substrates 1–3

3,5-Dimethyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (**1**): yellow solid; mp 159 °C (EtOH); ^1H -NMR (CDCl_3): δ 2.70 (s, 3H, CH_3), 3.45 (s, 3H, NCH_3), 6.87 (s, 1H, CH), 7.95 (s, 1H, CH). ^{13}C -NMR (CDCl_3): δ 21.6 (CH_3), 28.5 (NCH_3), 107.3 (CH), 110.7 (CH), 132.2 (C), 135.7 (C), 140.2 (C), 143.5 (CNO_2), 154.3 (CO). Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_4$ (208.17): C, 51.93; H, 3.87; N, 13.46. Found: C, 52.34; H, 3.95; N, 13.40.

5-(Bromomethyl)-3-methyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (**2**) and 5-(dibromomethyl)-3-methyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (**3**) were prepared according to a previously described method [27].

5-(Bromomethyl)-3-methyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (**2**): yellow solid (EtOH); mp 120 °C; ^1H -NMR (CDCl_3): δ 3.49 (s, 3H, CH_3), 4.91 (s, 2H, CH_2Br), 7.14 (s, 1H, CH), 7.99 (s, 1H, CH). ^{13}C -NMR (CDCl_3): δ 28.7 (NCH_3), 29.3 (CH_2Br), 108.0 (CH), 110.6 (CH), 131.1 (C), 136.1 (C), 141.7 (C), 142.6 (CNO_2), 153.9 (CO). Anal. Calcd for $\text{C}_9\text{H}_7\text{BrN}_2\text{O}_4$ (287.07): C, 37.66; H, 2.46; N, 9.76. Found: C, 38.48; H, 2.58; N, 9.88.

5-(Dibromomethyl)-3-methyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (**3**): yellow solid (EtOH); mp 134 °C; ^1H -NMR (CDCl_3): δ 3.55 (s, 3H, NCH_3), 7.55 (s, 1H, CHBr_2), 7.75 (s, 1H, CH), 7.78 (s, 1H, CH). ^{13}C -NMR (CDCl_3): δ 29.0 (NCH_3), 34.4 (CHBr_2), 106.2 (CH), 110.7 (CH), 134.3 (C), 136.5 (C), 139.0 (C), 142.0 (CNO_2), 153.6 (CO). Anal. Calcd for $\text{C}_9\text{H}_7\text{Br}_2\text{N}_2\text{O}_4$ (365.96): C, 29.54; H, 1.65; N, 7.65. Found: C, 29.59; H, 1.67; N, 7.69.

3.3. General Procedure for the Reaction of **2** and Aromatic Carbonyl Derivatives **4a–f**, α -Carbonyl Ester **4g**, Ketomalonate **4h**, Acenaphthenedione **4i** and Ketolactam **4j** Using TDAE

A solution of **2** (0.5, 1.74 mmol) in anhydrous DMF (10 mL) and the corresponding carbonyl derivative **4a–j** (5.22 mmol, 3 equivalents) were placed under nitrogen at $-20\text{ }^{\circ}\text{C}$ in a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet. The solution was stirred and maintained at this temperature for 30 min and then the TDAE (0.41 mL, 1.74 mmol, 1 equivalent) was added dropwise via a syringe. A red color immediately developed with the formation of a fine white precipitate. The solution was vigorously stirred at $-20\text{ }^{\circ}\text{C}$ for 1 h and then warmed to r.t. for 2 h. After this time TLC analysis (dichloromethane) clearly showed that **2** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethylxamidinium dibromide) and hydrolyzed with 80 mL of H_2O . The aqueous solution was extracted with toluene ($3 \times 40\text{ mL}$), the combined organic layers washed with H_2O ($3 \times 40\text{ mL}$) and dried over MgSO_4 . Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography and recrystallization in ethyl alcohol gave the corresponding products.

5-(2-Hydroxy-2-(4-nitrophenyl)ethyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (5a): Brown solid; mp $233\text{ }^{\circ}\text{C}$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): δ 3.37 (s, 3H, NCH_3), 3.17–3.33 (m, 2H, $2 \times \text{CH}$), 4.92–5.01 (m, 1H, 1H, CH), 5.67 (bs, 1H, OH), 7.33 (s, 1H, CH), 7.61 (d, $J = 8.5\text{ Hz}$, 2H, $2 \times \text{CH}$), 8.00 (s, 1H, CH), 8.21 (d, $J = 8.5\text{ Hz}$, 2H, $2 \times \text{CH}$). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$): δ 28.9 (NCH_3), 42.2 (CH_2), 72.1 (CH), 106.7 (CH), 112.5 (CH), 123.6 ($2 \times \text{CH}$), 127.0 ($2 \times \text{CH}$), 131.2 (C), 135.8 (C), 140.2 (C), 144.1 (C), 146.7 (C), 153.2 (C), 154.3 (CO). HRMS (EI): calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_7$ (M^+) 337.1092, found 337.1092.

5-(2-(4-Bromophenyl)-2-hydroxyethyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (5b): Brown solid; mp $213\text{ }^{\circ}\text{C}$; $^1\text{H-NMR}$ (CDCl_3): δ 2.13 (d, $J = 3.2\text{ Hz}$, 1H, OH), 3.13 (dd, $J = 13.7\text{ Hz}$, $J = 9.1\text{ Hz}$, 1H, CH), 3.43 (s, 3H, NCH_3), 3.50 (dd, $J = 13.7\text{ Hz}$, $J = 3.7\text{ Hz}$, 1H, CH), 5.06 (dd, $J = 9.1\text{ Hz}$, $J = 3.7\text{ Hz}$, 1H, CH), 6.85 (s, 1H, CH), 7.33 (d, $J = 8.4\text{ Hz}$, 2H, $2 \times \text{CH}$), 7.52 (d, $J = 8.4\text{ Hz}$, 2H, $2 \times \text{CH}$), 7.94 (s, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 28.6 (NCH_3), 43.7 (CH_2), 73.5 (CH), 107.5 (CH), 111.9 (CH), 121.7 (C), 127.3 ($2 \times \text{CH}$), 131.7 ($2 \times \text{CH}$), 135.6 (C), 140.8 (C), 142.7 (CH), 144.0 (C), 154.3 (CO). C- NO_2 was not observed under these experimental conditions. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{O}_5$ (393.19) C, 48.88; H, 3.33; N, 7.12. Found: C, 48.91; H, 3.39; N, 7.19.

4-(1-Hydroxy-2-(3-methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)ethyl)benzotrile (5c): Yellow solid; mp $213\text{ }^{\circ}\text{C}$; $^1\text{H-NMR}$ (CDCl_3): δ 2.27 (d, $J = 3.0\text{ Hz}$, 1H, OH), 3.05 (dd, $J = 13.5\text{ Hz}$, $J = 9.4\text{ Hz}$, 1H, CH), 3.46 (s, 3H, NCH_3), 3.57 (dd, $J = 13.5\text{ Hz}$, $J = 2.6\text{ Hz}$, 1H, CH), 5.15 (dd, $J = 9.4\text{ Hz}$, $J = 2.6\text{ Hz}$, 1H, CH), 6.93 (s, 1H, CH), 7.61 (d, $J = 8.3\text{ Hz}$, 2H, $2 \times \text{CH}$), 7.70 (d, $J = 8.3\text{ Hz}$, 2H, $2 \times \text{CH}$); 7.98 (s, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 28.6 (NCH_3), 43.8 (CH_2), 73.3 (CH), 107.6 (CH), 111.7 (C), 112.0 (CH), 118.7 (C), 126.3 ($2 \times \text{CH}$), 131.5 (C), 132.5 ($2 \times \text{CH}$), 135.7 (C), 140.9 (C), 149.0 (C), 154.2 (CO). C- NO_2 was not observed under these experimental conditions. HRMS (EI): calcd for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_5$ (M^+) 357.1193, found 357.1194.

5-(2-Hydroxy-2-(2-nitrophenyl)ethyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (5d): Brown solid; mp $130\text{ }^{\circ}\text{C}$; $^1\text{H-NMR}$ (CDCl_3): δ 3.36 (dd, $J = 13.8\text{ Hz}$, $J = 8.8\text{ Hz}$, 1H, CH), 3.41 (s, 3H, NCH_3), 3.56 (dd,

$J = 13.8$ Hz, $J = 3.2$ Hz, 1H, CH), 5.47 (dd, $J = 8.8$ Hz, $J = 3.2$ Hz, 1H, CH), 7.05 (s, 1H, CH), 7.44 (t, $J = 7.0$ Hz, 1H, CH), 7.65 (t, $J = 7.6$ Hz, 1H, CH), 7.73 (s, 1H, CH), 7.80 (d, $J = 7.0$ Hz, 1H, CH), 7.89 (d, $J = 7.6$ Hz, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 28.5 (NCH₃), 40.6 (CH₂), 70.4 (CH), 107.1 (CH), 111.0 (CH), 124.5 (CH), 128.4 (CH), 128.6 (CH), 131.1 (C), 133.9 (CH), 135.5 (C), 139.1 (C), 140.5 (C), 144.8 (C), 147.4 (C), 154.3 (CO). HRMS (EI): calcd for C₁₆H₁₃N₃O₇ (M⁺) 337.1092, found 337.1092.

5-(2-(2-Bromophenyl)-2-hydroxyethyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (5e): Yellow solid; mp 159 °C; $^1\text{H-NMR}$ (DMSO-*d*₆): δ 3.29 (s, 3H, NCH₃), 3.30–3.33 (m, 2H, CH₂), 5.51 (bs, 1H, CH), 7.15 (s, 1H, CH), 7.21 (d, $J = 7.3$ Hz, 1H, CH), 7.40 (t, $J = 7.7$ Hz, 1H, CH), 7.51–7.54 (m, 2H, 2 × CH), 7.95 (s, 1H, CH). $^{13}\text{C-NMR}$ (DMSO-*d*₆): δ 28.6 (NCH₃), 40.5 (CH₂), 71.35 (CH), 106.6 (CH), 111.9 (CH), 121.4 (C), 128.1 (CH), 128.3 (CH), 129.3 (C), 130.5 (CH), 132.3 (CH), 135.4 (C), 140.1 (C), 143.8 (C), 144.7 (C), 154.3 (CO). HRMS (EI): calcd for C₁₆H₁₃BrN₂O₅ (M⁺) 410.0346, found 410.0347.

5-(2-(3-Bromophenyl)-2-hydroxyethyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (5f): Yellow solid; mp 154 °C; $^1\text{H-NMR}$ (CDCl_3): δ 2.15 (d, $J = 2.9$ Hz, 1H, OH), 3.13 (dd, $J = 13.6$ Hz, $J = 9.0$ Hz, 1H, CH), 3.44 (s, 3H, NCH₃), 3.53 (dd, $J = 13.6$ Hz, $J = 3.4$ Hz, 1H, CH), 5.08 (dd, $J = 9.0$ Hz, $J = 3.4$ Hz, 1H, CH), 6.87 (s, 1H, CH), 7.29 (s, 1H, CH), 7.35–7.48 (m, 2H, 2 × CH), 7.61–7.63 (m, 1H, CH), 7.95 (s, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 28.5 (NCH₃), 43.7 (CH₂), 73.4 (CH), 107.5 (CH), 111.9 (CH), 122.8 (C), 124.3 (CH), 128.7 (CH), 130.2 (CH), 131.0 (CH), 131.7 (C), 135.6 (C), 140.8 (C), 144.0 (C), 146.1 (C), 154.3 (CO). Anal. Calcd for C₁₆H₁₃BrN₂O₅ (393.19) C, 48.88; H, 3.33; N, 7.12. Found: C, 49.11; H, 3.46; N, 7.28.

Ethyl 2-hydroxy-3-(3-methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)propanoate (5g): Yellow solid; mp 136 °C; $^1\text{H-NMR}$ (CDCl_3): δ 1.32 (t, $J = 7.1$ Hz, 3H, CH₃), 2.99 (d, $J = 5.3$ Hz, 1H, OH), 3.17 (dd, $J = 13.9$ Hz, $J = 8.8$ Hz, 1H, CH), 3.46 (s, 3H, NCH₃), 3.68 (dd, $J = 13.9$ Hz, $J = 3.7$ Hz, 1H, CH), 4.28 (q, $J = 7.1$ Hz, 2H, CH₂), 4.50–4.55 (m, 1H, CH), 7.02 (s, 1H, CH), 7.91 (s, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 14.1 (CH₃), 28.6 (NCH₃), 37.9 (CH₂), 62.4 (CH₂), 70.1 (CH), 107.4 (CH), 111.6 (CH), 130.3 (CH), 135.5 (CH), 140.8 (CH), 144.2 (CH), 154.2 (CO), 173.9 (CO). Anal. Calcd for C₁₃H₁₄N₂O₇ (310.26) C, 50.33; H, 4.55; N, 9.03. Found: C, 50.28; H, 4.54; N, 8.91

Diethyl 2-hydroxy-2-((3-methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)methyl)malonate (5h): Yellow solid; mp 111 °C; $^1\text{H-NMR}$ (CDCl_3): δ 1.27 (t, $J = 7.1$ Hz, 6H, 2xCH₃), 3.43 (s, 3H, NCH₃), 3.85 (bs, 1H, OH), 3.88 (s, 2H, CH₂), 4.11–4.34 (m, 4H, CH₂), 7.14 (s, 1H, CH), 7.75 (s, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 13.9 (2 × CH₃), 28.5 (NCH₃), 35.5 (2 × CH₂), 63.1 (CH₂), 78.4 (C-OH), 107.2 (CH), 111.8 (CH), 127.1 (C), 134.8 (C), 140.8 (C), 145.6 (C), 154.2 (CO), 169.4 (2 × CO). Anal. Calcd for C₁₆H₁₈N₂O₉ (382.32) C, 50.26; H, 4.75; N, 7.33. Found: C, 50.25; H, 4.83; N, 7.18.

5-((1-Hydroxy-2-oxo-1,2-dihydroacenaphthyl-1-yl)methyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (5i): Green solid; mp 204 °C; $^1\text{H-NMR}$ (CDCl_3): δ 3.45 (s, 3H, NCH₃), 3.64 (d, $J = 14.0$ Hz, 1H, CH), 3.84 (d, $J = 14.0$ Hz, 1H, CH), 7.12 (s, 1H, CH), 7.27 (d, $J = 7.3$ Hz, 1H, CH), 7.61 (dd, $J = 8.0$ Hz, $J = 7.3$ Hz, 1H, CH), 7.77 (dd, $J = 7.8$ Hz, $J = 7.3$ Hz, 1H, CH), 7.88 (s, 1H, CH), 7.89–7.98 (m, 2H, 2 × CH), 8.15 (d, $J = 8.0$ Hz, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 28.6 (NCH₃), 40.9 (CH₂), 79.8 (C-OH), 107.5 (CH), 112.4 (CH), 120.3 (CH), 122.7 (CH), 125.9 (CH), 128.6 (CH), 128.7 (CH+C), 130.1 (C),

130.7 (C), 132.4 (CH), 135.3 (C), 138.7 (C), 140.7 (C), 141.0 (C), 144.5 (C), 154.3 (CO); 203.8 (CO). Anal. Calcd for C₂₁H₁₄N₂O₆ (390.35) C, 64.62, H, 3.62, N, 7.18. Found: C, 64.15, H, 3.72, N, 7.05.

5-((3-Hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (**5j**): Yellow solid; mp 253 °C; ¹H-NMR (DMSO-*d*₆): δ 3.03 (s, 3H, NCH₃), 3.31 (s, 3H, NCH₃), 3.36 (d, *J* = 13.7 Hz, 1H, CH), 3.66 (d, *J* = 13.7 Hz, 1H, CH), 6.19 (s, 1H, CH), 6.78 (d, *J* = 6.8 Hz, 1H, CH), 6.91–6.95 (m, 2H, 2 × CH), 7.13 (s, 1H, CH), 7.24–7.31 (m, 1H, CH). ¹³C-NMR (DMSO-*d*₆): δ 26.0 (NCH₃); 28.5 (NCH₃), 75.4 (C-OH), 106.7 (CH), 108.6 (CH), 112.9 (CH), 122.3 (CH), 123.9 (CH), 127.6 (C), 129.4 (CH), 130.5 (C), 135.0 (C), 140.3 (C), 142.8 (C), 144.7 (C), 154.3 (CO), 176.8 (CO). C-NO₂ was not observed under these experimental conditions. Anal. Calcd for C₁₈H₁₅N₃O₆ (369.33) C, 58.54, H, 4.09, N, 11.38. Found: C, 58.26, H, 4.25, N, 11.01.

1-(3-Methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)-2-(4-nitrophenyl)ethyl 4-nitrobenzoate (**6**): Yellow solid; mp 305 °C; ¹H-NMR (CDCl₃): δ 3.35 (s, 3H, NCH₃), 3.73 (d, *J* = 6.2 Hz, 2H, CH₂), 6.44 (t, *J* = 6.2 Hz, 1H, CH), 6.84 (s, 1H, CH), 7.68 (d, *J* = 8.5 Hz, 2H, 2 × CH), 7.97 (s, 1H, CH), 8.17 (d, *J* = 8.8 Hz, 2H, 2 × CH), 8.28 (d, *J* = 8.5 Hz, 1H, 2 × CH), 8.32 (d, *J* = 8.5 Hz, 1H, 2 × CH). ¹³C-NMR (CDCl₃): δ 28.5 (NCH₃), 40.8 (CH₂), 76.4 (CH), 108.1 (CH), 110.7 (CH), 114.1 (C), 123.8 (2 × CH), 124.3 (2 × CH), 127.1 (2 × CH), 129.6 (C), 130.7 (2 × CH), 134.4 (C), 135.9 (C), 141.2 (C), 145.9 (C), 148.1 (C), 150.9 (C), 153.8 (CO). HRMS (EI): calcd for C₂₃H₁₆N₄O₁₀ (M⁺) 526.1205, found 526.1209.

3.4. General Procedure for the Reaction of **3** and Aromatic Carbonyl Derivatives **4a–f**, α -Carbonyl Ester **4g**, Ketomalonate **4h**, Acenaphthenedione **4i** and Keto-lactam **4j** Using TDAE

A solution of **3** (0.5 g, 1.36 mmol) in anhydrous DMF (10 mL) and the corresponding carbonyl derivative **4a–j** (4.098 mmol, 3 equivalents) were placed under nitrogen at –20 °C in a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet. The solution was stirred and maintained at this temperature for 30 min and then the TDAE (0.48 mL, 2.049 mmol, 1.5 equivalent) was added dropwise via a syringe. A red color immediately developed with the formation of a fine white precipitate. The solution was vigorously stirred at –20 °C for 1 h and then warmed to rt for 2 h. After this time TLC analysis (dichloromethane) clearly showed that **3** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethylloxamidinium dibromide) and hydrolyzed with 80 mL of H₂O. The aqueous solution was extracted with toluene (3 × 40 mL), the combined organic layers washed with H₂O (3 × 40 mL) and dried over MgSO₄. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography and recrystallization in ethyl alcohol solvent gave the corresponding oxiranes **7a–j**.

3-Methyl-6-nitro-5-(3-(4-nitrophenyl)oxiran-2-yl)benzo[d]oxazol-2(3H)-one (**7a**) *trans*-isomer: Yellow solid; mp 224 °C; ¹H-NMR (CDCl₃): δ 3.52 (s, 3H, NCH₃), 3.92 (d, *J* = 1.9 Hz, 1H, CH), 4.54 (d, *J* = 1.9 Hz, 1H, CH), 7.33 (s, H, CH), 7.60 (d, *J* = 8.7 Hz, 2H, 2 × CH), 8.13 (s, 1H, CH), 8.30 (d, *J* = 8.7 Hz, 2H, 2 × CH). ¹³C-NMR (CDCl₃): δ 28.8 (NCH₃), 61.0 (CH), 61.1 (CH), 105.7 (CH), 107.4 (CH), 124.0 (2 × CH), 126.6 (2 × CH), 131.8 (C), 137.28 (C), 141.6 (C), 142.1 (C), 143.0 (C), 148.2 (CO). C-NO₂ was not observed under these experimental conditions. HRMS (EI): calcd for C₁₆H₁₁N₃O₇ (M⁺) 375.0935, found 375.0943.

5-(3-(4-Bromophenyl)oxiran-2-yl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (**7b**) *trans*-isomer: Yellow solid; mp 209 °C; ¹H-NMR (CDCl₃): δ 3.51 (s, 3H, NCH₃), 3.77 (d, *J* = 1.9 Hz, 1H, CH), 3.54 (d, *J* = 1.9 Hz, 1H, CH), 7.28 (d, *J* = 8.4 Hz, 2H, 2 × CH), 7.31 (s, 1H, CH), 7.54 (d, *J* = 8.4 Hz, 2H, 2 × CH), 8.11 (s, 1H, CH). ¹³C-NMR (CDCl₃): δ 28.7 (NCH₃), 60.5 (CH), 61.7 (CH), 105.6 (CH), 107.3 (CH), 122.8 (C), 127.5 (2 × CH), 131.9 (2 × CH), 132.5 (C), 134.8 (C), 137.0 (C), 141.3 (C), 154.1 (CO). Anal. Calcd for C₁₆H₁₁BrN₂O₅ (391.17) C, 49.13; H, 2.83; N, 7.16. Found: C, 49.27; H, 2.92; N, 7.85.

4-(3-(3-Methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)oxiran-2-yl)benzotrile (**7c**) *trans*-isomer: Yellow solid; mp 213 °C; ¹H-NMR (CDCl₃): δ 3.51 (s, 3H, NCH₃), 3.86 (d, *J* = 1.8 Hz, H, CH), 4.52 (d, *J* = 1.8 Hz, H, CH), 7.32 (s, 1H, CH), 7.53 (d, *J* = 8.3 Hz, 2H, 2 × CH), 7.72 (d, *J* = 8.3 Hz, 2H, 2 × CH), 8.12 (s, 1H, CH). ¹³C-NMR (CDCl₃): δ 28.7(NCH₃), 61.0 (CH), 61.2 (CH), 105.7 (CH), 107.3 (CH), 112.6 (C), 118.5 (C), 126.5 (2 × CH), 131.9 (C), 132.5 (2 × CH), 137.1(C), 141.1 (C), 141.5 (C), 142.1(C); 154.1 (CO). HRMS (EI): calcd for C₁₇H₁₁N₃O₅ (M⁺) 355.1037, found 355.1036.

3-Methyl-6-nitro-5-(3-(2-nitrophenyl)oxiran-2-yl)benzo[d]oxazol-2(3H)-one (**7d**) *trans*-isomer: yellow solid; mp 215 °C; ¹H-NMR (CDCl₃): δ 3.52 (s, 3H, NCH₃), 4.54 (d, *J* = 2.0 Hz, 1H, CH), 4.60 (d, *J* = 2.0 Hz, 1H, CH), 7.36 (s, 1H, CH), 7.52–7.61 (m, 1H, CH), 7.75–7.77 (m, 2H, 2 × CH), 8.14 (s, 1H, CH), 8.23 (d, *J* = 8.0 Hz, 1H, CH). ¹³C-NMR (CDCl₃): δ 28.7 (NCH₃), 59.9 (CH), 60.0 (CH), 105.5 (CH), 107.6 (CH), 125.2 (CH), 126.9 (CH), 129.2 (C), 131.8 (CH), 132.5 (C), 134.4 (CH), 137.0 (C), 141.5 (C), 142.6 (C), 147.9 (C), 154.2 (CO). HRMS (EI): calcd for C₁₆H₁₁N₃O₇ (M⁺) 375.0935, found 375.0940.

3-Methyl-6-nitro-5-(3-(2-nitrophenyl)oxiran-2-yl)benzo[d]oxazol-2(3H)-one (**7d**) *cis*-isomer: Beige solid; mp 166 °C; ¹H-NMR (CDCl₃): δ 3.38 (s, 3H, NCH₃), 5.14 (d, *J* = 4.9 Hz, 1H, CH), 5.17 (d, *J* = 4.9 Hz, 1H, CH), 7.03 (s, 1H, CH), 7.30–7.40 (m, 1H, CH), 7.44–7.46 (m, 2H, 2 × CH), 7.86–7.90 (m, 2H, 2 × CH). ¹³C-NMR (CDCl₃): δ 28.6 (NCH₃), 59.0 (2 × CH), 107.3 (CH), 107.4 (CH), 124.7 (CH), 128.8 (CH), 128.9 (C), 129.2 (CH), 129.4 (C), 132.7 (CH), 135.9 (C), 141.2 (C), 148.5 (C), 153.9 (CO). Anal. Calcd for C₁₆H₁₁N₃O₇ (357.27) C, 53.79; H, 3.10; N, 11.76. Found: C, 53.48; H, 3.30; N, 11.44.

5-(3-(2-Bromophenyl)oxiran-2-yl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (**7e**) *trans*-isomer: Green solid; mp 203 °C; ¹H-NMR (CDCl₃): δ 3.52 (s, 3H, NCH₃), 4.09 (d, *J* = 1.9 Hz, 1H, CH), 4.57 (d, *J* = 1.9 Hz, 1H, CH), 7.20–7.29 (m, 1H, CH), 7.36 (s, 1H, CH), 7.38–7.47 (m, 2H, 2 × CH), 7.60 (d, *J* = 7.5 Hz, 1H, CH), 8.12 (s, 1H, CH). ¹³C-NMR (CDCl₃): δ 28.7 (NCH₃), 60.1 (CH), 62.0 (CH), 105.6 (CH), 107.4 (CH), 123.1 (C), 126.1 (CH), 127.8 (CH), 130.0 (CH), 132.2 (C), 132.7 (CH), 135.2 (C), 137.0 (C), 141.4 (C), 142.4 (C), 154.2 (CO). Anal. Calcd for C₁₆H₁₁BrN₂O₅ (391.17) C, 49.13; H, 2.83; N, 7.16. Found: C, 49.27; H, 2.93; N, 7.17.

5-(3-(2-Bromophenyl)oxiran-2-yl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (**7e**) *cis*-isomer: Green solid; mp 151 °C; ¹H-NMR (CDCl₃): δ 3.42 (s, 3H, NCH₃), 4.71 (d, *J* = 4.4 Hz, 1H, CH), 5.17 (d, *J* = 4.4 Hz, 1H, CH), 6.98–7.14 (m, 3H, 3 × CH), 7.16 (s, 1H, CH), 7.36–7.42 (m, 1H, CH), 7.93 (s, 1H, CH). ¹³C-NMR (CDCl₃): δ 28.6 (NCH₃), 59.3 (CH), 61.0 (CH), 107.3 (CH), 107.9 (CH), 122.5 (C), 126.4 (CH), 128.0 (CH), 129.4 (C), 129.6 (CH), 132.7 (CH), 132.9 (C), 135.8 (C), 141.1 (C), 142.5 (C), 154.0 (CO). Anal. Calcd for C₁₆H₁₁BrN₂O₅ (391.17) C, 49.13; H, 2.83; N, 7.16. Found: C, 49.42; H, 3.02; N, 7.28.

5-(3-(3-Bromophenyl)oxiran-2-yl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (**7f**) *trans*-isomer: Beige solid; mp 165 °C; ¹H-NMR (CDCl₃): δ 3.51 (s, 3H, 3H, NCH₃), 3.77 (d, *J* = 1.9 Hz, 1H, CH), 4.55 (d, *J* = 1.9 Hz, 1H, CH), 7.24–7.28 (m, 1H, CH), 7.32 (s, 1H, CH), 7.33–7.38 (m, 1H, CH), 7.49–7.54 (m, 2H, 2 × CH), 8.11 (s, 1H, CH). ¹³C-NMR (CDCl₃): δ 28.7 (NCH₃), 60.6 (CH), 61.4 (CH), 105.7 (CH), 107.3 (CH), 122.8 (C), 124.6 (CH), 128.7 (CH), 130.2 (CH), 131.9 (CH), 132.3 (C), 137.0 (C), 138.1 (C), 141.4 (C), 142.1 (C), 154.1 (CO). Anal. Calcd for C₁₆H₁₁BrN₂O₅ (391.17) C, 49.13; H, 2.83; N, 7.16. Found: C, 49.30; H, 2.97; N, 7.10.

Ethyl 3-(3-methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)oxirane-2-carboxylate (**7g**) *trans*-isomer: Light yellow needles; mp 199 °C; ¹H-NMR (CDCl₃): δ 1.36 (t, *J* = 7.2 Hz, H, CH); 3.38 (d, *J* = 1.9 Hz, 3H, CH); 3.48 (s, 3H, NCH₃); 4.35 (q, *J* = 7.2 Hz, 2H, CH₂); 4.75 (d, *J* = 1.9 Hz, 1H, CH); 7.19 (s, 1H, CH); 8.12 (s, 1H, CH). ¹³C-NMR (CDCl₃): δ 14.1 (CH₃), 28.8 (NCH₃), 56.0 (CH), 56.6 (CH), 62.2 (CH₂), 105.8 (CH), 107.4 (CH), 130.9 (C), 137.0 (C), 141.6 (C), 142.2 (C), 154.0 (CO), 167.2 (CO). HRMS (EI): calcd for C₁₃H₁₂N₂O₇ (M⁺) 309.0717, found 309.0713.

Diethyl 3-(3-methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)oxirane-2,2-dicarboxylate (**7h**) *trans*-isomer: Dark brown; mp 118 °C; ¹H-NMR (CDCl₃): δ 0.98 (t, *J* = 7.2 Hz, 3H, CH₃), 1.37 (t, *J* = 7.2 Hz, 3H, CH₃), 3.48 (s, 3H, NCH₃), 3.98 (q, *J* = 7.2 Hz, 2H, CH₂), 4.39 (q, *J* = 7.2 Hz, 2H, CH₂), 5.14 (s, 1H, CH), 7.24 (s, 1H, CH), 8.12 (s, 1H, CH). ¹³C-NMR (CDCl₃): δ 13.8 (CH₃), 14.0 (CH₃), 28.9 (NCH₃), 61.2 (CH), 62.2 (CH₂), 63.3 (CH₂), 107.2 (CH), 107.4 (CH), 127.9 (C), 136.7 (C), 141.9 (C), 142.3 (C), 153.9 (C), 163.3 (CO), 164.6 (CO). Anal. Calcd for C₁₆H₁₆N₂O₉ (380.31) C, 50.53; H, 4.24; N, 7.37. Found: C, 50.96; H, 4.54; N, 7.25.

3-Methyl-6-nitro-5-(2-oxo-2H-spiro[acenaphthylene-1,2'-oxiran]-3'-yl)benzo[d]oxazol-2(3H)-one (**7i**) *like*-isomer: Yellow solid; mp 235 °C; ¹H-NMR (CDCl₃): δ 3.59 (s, 3H, NCH₃), 5.29 (s, 1H, CH), 7.62 (d, *J* = 6.8 Hz, 1H, CH₂), 7.74 (s, 2H, 2 × CH); 7.77–7.80 (m, 1H, CH), 7.85 (d, *J* = 6.7 Hz, 1H, CH₂), 8.01 (d, *J* = 8.4 Hz, 1H, CH₂), 8.06 (s, 1H, CH), 8.19 (d, *J* = 8.1 Hz, 1H, CH). ¹³C-NMR (CDCl₃): δ 28.9 (NCH₃), 65.8 (CH), 67.1 (C), 106.8 (CH), 108.9 (CH), 118.9 (CH), 122.1 (CH), 126.5 (CH), 128.3 (CH), 128.7 (CH), 129.2 (C), 130.4 (C), 131.2 (C), 132.1 (C), 132.3 (CH), 136.5 (C), 141.4 (C), 141.7 (C), 142.5 (C), 154.2 (CO), 196.0 (CO). Anal. Calcd for C₂₁H₁₂N₂O₆ (388.33) C, 64.95; H, 3.11; N, 7.21. Found: C, 64.08; H, 3.26; N, 6.85.

3-Methyl-6-nitro-5-(2-oxo-2H-spiro[acenaphthylene-1,2'-oxiran]-3'-yl)benzo[d]oxazol-2(3H)-one (**7i**) *unlike*-isomer: Beige solid; mp 201 °C; ¹H-NMR (CDCl₃): δ 3.63 (s, 3H, NCH₃), 5.30 (s, 1H, CH), 6.34 (d, *J* = 6.8 Hz, 1H, CH₂), 7.32 (d, *J* = 6.7 Hz, 1H, CH), 7.67 (s, 1H, CH), 7.77–7.88 (m, 2H, 2 × CH), 8.07 (s, 1H, CH), 8.12 (d, *J* = 1.7 Hz, 1H, CH), 8.16 (d, *J* = 3.2 Hz, 1H, CH). ¹³C-NMR (CDCl₃): δ 29.0 (NCH₃), 64.7 (CH), 66.5 (C); 107.3 (CH), 107.7 (CH), 119.1 (CH), 122.7 (CH), 126.8 (CH), 127.8 (CH), 128.5 (CH), 129.7 (C), 130.2 (C), 130.5 (C), 130.6 (C), 132.3 (CH), 136.9 (C), 141.9 (C), 143.2 (C), 154.0 (C), 196.3 (CO). C-NO₂ was not observed under these experimental conditions. HRMS (EI): calcd for C₂₁H₁₂N₂O₆ (M⁺) 389.0768, found 389.0768.

1-Methyl-3'-(3-methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)spiro[indoline-3,2'-oxiran]-2-one (**7j**) *like*-isomer: Beige solid; mp 190 °C; ¹H-NMR (CDCl₃): δ 3.13 (s, 3H, NCH₃), 3.54 (s, 3H, NCH₃),

5.15 (s, 1H, CH), 6.93 (dd, $J = 7.8$ Hz, $J = 0.7$ Hz, 1H, CH), 7.17 (td, $J = 7.5$ Hz, $J = 0.7$ Hz, 1H, CH), 7.32 (dd, $J = 7.3$ Hz, $J = 0.7$ Hz, 1H, CH), 7.44 (td, $J = 7.3$ Hz, $J = 1.4$ Hz, 1H, CH), 7.62 (s, 1H, CH), 8.08 (s, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 26.5 (NCH₃), 28.8(NCH₃), 62.7 (CH), 65.0 (C), 106.8 (CH), 108.9 (CH), 109.0 (CH), 122.2 (CH), 122.3 (C), 123.2 (CH), 128.8 (C), 130.8 (CH), 136.4 (C), 141.5 (C), 141.7 (C), 144.8 (CH), 154.2 (CO), 169.6 (CO). Anal. Calcd for C₁₈H₁₃N₃O₆ (367.31) C, 58.86; H, 3.57; N, 11.44. Found: C, 58.85; H, 3.71; N, 11.31.

1-Methyl-3'-(3-methyl-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)spiro[indoline-3,2'-oxiran]-2-one (7j) unlike-isomer: Beige solid; mp 211 °C; $^1\text{H-NMR}$ (CDCl_3): δ 3.33 (s, 3H, NCH₃), 3.59 (s, 3H, NCH₃), 5.18 (s, 1H, CH), 6.01 (d, $J = 7.5$ Hz, 1H, CH), 6.71 (t, $J = 7.5$ Hz, 1H, CH), 6.88 (d, $J = 7.7$ Hz, 1H, CH), 7.32 (d, $J = 7.7$ Hz, 1H, CH), 7.57 (s, 1H, CH), 8.08 (s, 1H, CH). $^{13}\text{C-NMR}$ (CDCl_3): δ 26.8 (NCH₃), 29.0 (NCH₃), 62.2 (CH), 64.4 (C), 107.3 (CH), 107.8 (CH), 109.2 (CH), 119.8 (C), 122.0 (CH), 122.4 (CH), 129.4 (C), 130.9 (CH), 137.0 (C), 141.8 (C), 141.9 (C), 145.6 (C), 154.0 (CO), 170.6 (CO). HRMS (EI): calcd for C₁₈H₁₃N₃O₆ (M⁺) 368.0877, found 368.0876.

4. Conclusions

In conclusion, we have investigated the reactivity of some new benzoxazolone derivatives formed via the TDAE strategy. This is the first example of the use of the TDAE strategy to generate a benzoxazolinonic anion, which cannot be formed via the standard organometallic strategy. This study brought to light a new and original reactivity and we have defined some limitations of the TDAE strategy. We show that 5-(bromomethyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3*H*)-one (**2**), in addition to providing the expected alcohols **5a–i** in moderate to good yields, furnished an unexpected ester **6** formed in 23% yield, particularly with the *p*-nitrobenzaldehyde. The reactions of 5-(dibromomethyl)-3-methyl-6-nitro-benzo[d]oxazol-2(3*H*)-one (**3**) led to the expected oxiranes **7a–j** and mixtures of original stereoisomers **7i–j** in good yields. All these synthesized products are currently undergoing pharmacological evaluation.

Acknowledgments

This work was supported by the Centre National de la Recherche Scientifique. We express our thanks to V. Remusat for ^1H - and ^{13}C -NMR spectra recording. A. R. Nadji Boukrouche thanks the Ministère de l'Enseignement Supérieur et de la Recherche for financial support.

Author Contributions

A.R.N.B., M.L., O.K., T.T. and P.V. conceived of and designed the study. A.R.N.B. and O.K. designed the experiments and interpreted the results.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Lesieur, D.; Carato, P.; Bonte, J.-P.; Depreux, P.; Caignard, D.-H.; Millan, M.; Newman-Tancredi, A.; Renard, P.; Rettori, M.-C. Preparation of Piperazinylmethylbenzothiazolinones, -Benzoxazolinones, -Benzoxazinones, and Related Compounds as Central Nervous System Agents. EP 841330, 13 May 1998.
2. Fukaya, T.; Ishiyama, T.; Baba, S.; Masumoto, S. Identification of a novel benzoxazolone derivative as a selective, orally active 18 kDa translocator protein (TSPO) ligand. *J. Med. Chem.* **2013**, *56*, 8191–8195.
3. Aichaoui, H.; Poupaert, J.H.; Lesieur, D.; Henichart, J.-P. Regioselectivity in the C-acylation of 2(3H)-benzoxazolones. *Tetrahedron* **1991**, *47*, 6649–6654.
4. Moussavi, Z.; Depreux, P.; Lesieur, D.; Cotelle, N.; Sauzies, J.; Plancke, M.O.; Fruchart, J.C. Pharmacomodulation of 7-(2-methylenebutyryl)-2,3-dihydrobenzoxazin-[1,4]-3-one structure and normolipemic activity. *Farmaco* **1991**, *46*, 339–355.
5. Ucar, H.; van derpoorten, K.; Cacciaguerra, S.; Spampinato, S.; Stables, J.P.; Depovere, P.; Isa, M.; Masereel, B.; Delarge, J.; Poupaert, J.H. Synthesis and anticonvulsant activity of 2(3H)-benzoxazolone and 2(3H)-benzothiazolone derivatives. *J. Med. Chem.* **1998**, *41*, 1138–1145.
6. Courtois, M.; Mincheva, Z.; Andreu, F.; Rideau, M.; Viaud-Massuard, M.C. Synthesis and biological evaluation with plant cells of new fosmidomycin analogues containing a benzoxazolone or oxazolopyridinone ring. *J. Enzym. Inhib. Med. Chem.* **2004**, *19*, 559–565.
7. Raju, B.G.; Ciabatti, R.; Maffioli, S.I.; Singh, U.; Romano, G.; Michelucci, E.; Tiseni, P.S.; Candiani, G.; Kim, B.; O'Dowd, H. Ramoplanin Derivatives Possessing Antibacterial Activity. US 0211603, 21 September 2006.
8. Jadhav, J.S.; Chatpalliwar, V.A.; Khadse, S.C.; Patil, R.R. Synthesis and screening of some new 2-(3H)-benzoxazolone derivatives for analgesic, antiinflammatory, and skeletal muscle relaxant activity. *Indian J. Heterocycl. Chem.* **2008**, *17*, 343–346.
9. Köksal, M.; Kelekci, N.G.; Mercanoglu, G.O.; Erdoğan, H. Synthesis and evaluation of analgesic, anti-inflammatory and antioxidant activities of new 6-acyl-3-alkyl-5-methyl-2(3H)-benzoxazolones. *Arzneim. Forsch.* **2008**, *58*, 398–404.
10. Mésangeau, C.; Narayanan, S.; Green, A.M.; Shaikh, J.; Kaushal, N.; Viard, E.; Xu, Y.; Fishback, J.A.; Poupaert, J.H.; Matsumoto, R.R.; *et al.* Conversion of a highly selective sigma-1 receptor-ligand to sigma-2 receptor preferring ligands with anticocaine activity. *J. Med. Chem.* **2008**, *51*, 1482–1486.
11. Poupaert, J.H.; Carato, P.; Colacino, E. 2(3H)-benzoxazolone and bioisosters as “privileged scaffold” in the design of pharmacological probes. *Curr. Med. Chem.* **2005**, *12*, 877–885.
12. Diouf, O.; Carato, P.; Depreux, P.; Bonte, J.P.; Caignard, D.H.; Guardiola-Lemaître, B.; Rettori, M.C.; Belzung, C.; Lesieur, D. 5-HT1A and 5-HT2A ligands with anxiolytic and antipanic-like properties. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2579–2584.
13. Diouf, O.; Carato, P.; Lesieur, I.; Rettori, M.C.; Caignard, D.H. Synthesis and pharmacological evaluation of novel 4-(4-fluorobenzoyl)piperidine derivatives as mixed 5-HT1A/5-HT2A/D2 receptor ligands. *Eur. J. Med. Chem.* **1999**, *34*, 69–73.

14. Carato, P.; Depreux, D.; Lesieur, D.; Millan, M.; Newman-Tancredi, A.; Rettori, M.C.; Caignard, D.H. Synthesis and binding studies on a new series of arylpiperazino benzazol-2-one and benzoxazin-3-one derivatives as selective D4 ligands. *Drug Des. Discov.* **2000**, *17*, 173–181.
15. Lesieur, D.; Delmas, E.; Yous, S.; Depreux, P.; Guillaumet, G.; Dacquet, C.; Levens, N.; Boutin, J.; Bennejean, C.; Renard, P. Preparation of Novel Heterocyclic Derivatives and Pharmaceutical Composition Containing Them as Hypoglycemic Agents. FR 2804431, 3 August 2001.
16. Lesieur, D.; Blanc-Delmas, E.; Bennejean, C.; Chavatte, P.; Guillaumet, G.; Dacquet, C.; Levens, N.; Boutin, J.; Renard, P. Preparation of Azolylalkylphenylalkylindolinones as Hypoglycemic Andhypolipidemic Agents. FR 2830012, 28 March 2003.
17. Takechi, N.; Ait-Mohand, S.; Medebielle, M.; Dolbier, W.R., Jr. Nucleophilic trifluoromethylation of acyl chlorides using the trifluoromethyl iodide/TDAE reagent. *Tetrahedron Lett.* **2002**, *43*, 4317–4319.
18. Pooput, C.; Médebielle, M.; Dolbier, W.F., Jr. A New and efficient method for the synthesis of trifluoromethylthio- and selenoethers. *Org. Lett.* **2004**, *6*, 301–303.
19. Pooput, C.; Dolbier, W.F., Jr.; Médebielle, M. Nucleophilic perfluoroalkylation of aldehydes, ketones, imines, disulfides, and diselenides. *J. Org. Chem.* **2006**, *71*, 3564–3568.
20. Giuglio-Tonolo, G.; Terme, T.; Médebielle, M.; Vanelle, P. Original reaction of *p*-nitrobenzyl chloride with aldehydes using tetrakis(dimethylamino)ethylene (TDAE). *Tetrahedron Lett.* **2003**, *44*, 6433–6435.
21. Giuglio-Tonolo, G.; Terme, T.; Médebielle, M.; Vanelle, P. Nitrobenzylation of α -carbonyl ester derivatives using TDAE approach. *Tetrahedron Lett.* **2004**, *45*, 5121–5124.
22. Amiri-Attou, O.; Terme, T.; Vanelle, P. Functionalization of 6-nitrobenzo[1,3]dioxole with carbonyl compounds via TDAE methodology. *Molecules* **2005**, *10*, 545–551.
23. Montana, M.; Crozet, M.D.; Castera-Ducros, C.; Terme, T.; Vanelle, P. Rapid synthesis of new azaheterocyclic hydroxymalonate derivatives using TDAE approach. *Heterocycles* **2008**, *75*, 925–932.
24. Nadji-Boukrouche, A.R.; Khoumeri, O.; Terme, T.; Liacha, M.; Vanelle, P. Original TDAE reactivity in benzoxa- and benzothiazolone series. *ARKIVOC* **2010**, *10*, 358–370.
25. Montana, M.; Terme, T.; Vanelle, P. Original synthesis of oxiranes via TDAE methodology: reaction of 2-(dibromomethyl)quinoxaline with aromatic aldehydes. *Tetrahedron Lett.* **2005**, *46*, 8373–8376.
26. Montana, M.; Terme, T.; Vanelle, P. Original synthesis of α -chloro ketones in aza heterocyclic series using TDAE approach. *Tetrahedron Lett.* **2006**, *47*, 6573–6576.
27. Khoumeri, O.; Montana, M.; Terme, T.; Vanelle, P. First TDAE approach in quinonic series: Synthesis of new 2-substituted 1,4-dimethoxy-9,10-anthraquinones. *Tetrahedron* **2008**, *64*, 11237–11242.
28. Vanelle, P.; Maldonado, J.; Madadi, N.; Gueiffier, A.; Chapat, J.-P.; Crozet, M.P. SRN1 reactions in imidazo[1,2-*a*]pyridine series. *Tetrahedron Lett.* **1990**, *31*, 3013–3016.
29. Delmas, F.; Gasquet, M.; Timon-David, P.; Madadi, N.; Vanelle, P.; Vaille, A.; Maldonado, J. Synthesis and *in vitro* anti-protozoan activity of new 5-nitrothiophene oxime ether derivatives. *Eur. J. Med. Chem.* **1993**, *28*, 23–27.

30. Gellis, A.; Vanelle, P.; Kaafarani, M.; Benakli, K.; Crozet, M.P. Synthesis and S_{RN}1 reactions of nitrothiazoles. *Tetrahedron* **1997**, *53*, 5471–5484.
31. Crozet, M.D.; Botta, C.; Gasquet, M.; Curti, C.; Remusat, V.; Hutter, S.; Chapelle, O.; Azas, N.; de Méo, M.; Vanelle, P. Lowering of 5-nitroimidazole's mutagenicity: Towards optimal antiparasitic pharmacophore. *Eur. J. Med. Chem.* **2009**, *44*, 653–659.
32. Dunn, L.A.; Burgess, A.G.; Krauer, K.G.; Eckmann, L.; Vanelle, P.; Crozet, M.D.; Gillin, F.D.; Upcroft, P.; Upcroft, J.A. A new-generation 5-nitroimidazole can induce highly metronidazole-resistant *Giardia lamblia* *in vitro*. *Int. J. Antimicrob. Agents* **2010**, *36*, 37–42.
33. Khoumeri, O.; Crozet, M.D.; Terme, T.; Vanelle, P. Original TDAE application: Synthesis of 2-substituted-4,11-dimethoxy-anthra[2,3-b]furan-5,10-diones via intramolecular Buchwald reaction. *Tetrahedron Lett.* **2009**, *50*, 6372–6376.
34. Suzuki, F.; Trenbeath, S.; Gleim, R.D.; Sih, C.S. Total synthesis of anthracyclines via intramolecular base-catalyzed cyclizations. *J. Org. Chem.* **1978**, *43*, 4159–4169.
35. Gökhan, N.; Köksal, M.; Küpeli, E.; Yeşilada, E.; Erdoğan, H. Some new Mannich bases of 5-methyl-2-benzoxazolinones with analgesic and anti-inflammatory activities. *Turk. J. Chem.* **2005**, *29*, 445–454.
36. Amiri-Attou, O.; Terme, T.; Médebielle M.; Vanelle, P. Original formation of benzyl benzoates by TDAE strategy. *Tetrahedron Lett.* **2008**, *49*, 1016–1020.
37. Juspin, T.; Laget, M.; Terme, T.; Azas, N.; Vanelle, P. TDAE assisted synthesis of new imidazo[2,1-*b*]thiazole derivatives as anti-infectious agents. *Eur. J. Med. Chem.* **2010**, *45*, 840–845.
38. Montana, M.; Correard, F.; Khoumeri, O.; Esteve, M.-A.; Terme, T.; Vanelle, P. Synthesis of new quinoxalines containing an oxirane ring by the TDAE strategy and *in vitro* evaluation in neuroblastoma cell lines. *Molecules* **2014**, *19*, 14987–14998.

Sample Availability: Samples of the compounds **1**, **2**, **3**, **5a–j**, **6** and **7a–j** are available from the authors.

© 2015 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/4.0/>).