

Article

Synthesis of Bicyclic Isoxazoles and Isoxazolines via Intramolecular Nitrile Oxide Cycloaddition

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Abstract: An efficient and straight forward procedure for the syntheses of bicyclic isoxazole/isoxazoline derivatives from the corresponding dimethyl-2-(2-nitro-1-aryl/alkyl)-2-(prop-2-yn-1yl)malonates or dimethyl 2-allyl-2-(2-nitro-1-aryl/alkyl ethyl)malonate is described. High yields and simple operations are important features of this methodology.

Keywords: bicyclic isoxazole/isoxazolines; cycloaddition; nitrile oxide; nitroalkane; Yamaguchi reagent

1. Introduction

Isoxazole and isoxazoline derivatives are important scaffolds found in many naturally occurring and biologically active compounds [1–5]. They are considered to be important precursors for the synthesis of β -hydroxyketones or β -aminoalcohols, α,β -unsaturated ketones, and many other valuable compounds [6–10]. Isoxazole or isoxazoline motifs fused with carbocycles or heterocycles are known to possess a variety of bioactivities and are also useful surrogates for the generation of various other bioactive compounds [11–15].

Isoxazole and isoxazoline derivatives are typically synthesized through *in situ* formation of a nitrile oxide followed by an intramolecular dipolar cycloaddition [16–19]. The most common methods for generating nitrile oxides are the dehydrohalogenation of hydroximoyl chlorides [20–24], the oxidation of aldoximes [25–32], and the dehydration of nitroalkanes [33–36]. Although a wide variety of procedures are available for the synthesis of diverse isoxazole and isoxazoline derivatives, few of them address the preparation of carbocyclic fused isoxazole/isoxazoline derivatives [37–42]. The dehydration of the nitroalkanes followed by intramolecular dipolar cycloaddition is the most popular method for the construction of carbocyclic fused isoxazole/isoxazoline derivatives. The literature procedures for the generation of carbocyclic fused isoxazole/isoxazoline from various nitroalkane derivatives [43–47] involve the use of phenyl isocyanate and triethylamine, treatment of the nitronate with di-*tert*-butyl dicarbonate in the presence of catalytic amounts of dimethylaminopyridine (DMAP), the use of chloroformates in the presence of trimethylamine and trimethylsilyl chloride (TMSCl) in the presence of trimethylamine. We also reported on a different procedure for the construction of bicyclicisoxazole/isoxazoline derivatives by using trichlorotriazine (TCT), chloroformate and phenyl isocyanate as dehydrating agents. Although a few methods for the synthesis of carbocyclic fused isoxazole/isoxazoline derivatives are efficient, some of the available methods suffer from drawbacks such as low yields and selectivity and long reaction times. Hence, a simple and straightforward method for generating such derivatives in high yields and in better selectivity would be highly desirable. It is well known that the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) is a dehydrating agent used in the construction of macrolides and highly functionalized esters [48–50]. However, to our knowledge this reagent has not been utilized for the dehydration of nitroalkanes. Herein, we wish to report on the synthesis of bicyclicisoxazole/isoxazoline derivatives from the corresponding dimethyl 2-propargyl-2-(2-nitro-1-aryl/alkylethyl)malonate/dimethyl 2-allyl-2-(2-nitro-1-aryl/alkyl ethyl)malonates using the Yamaguchi reagent as a dehydrating agent.

2. Results and Discussion

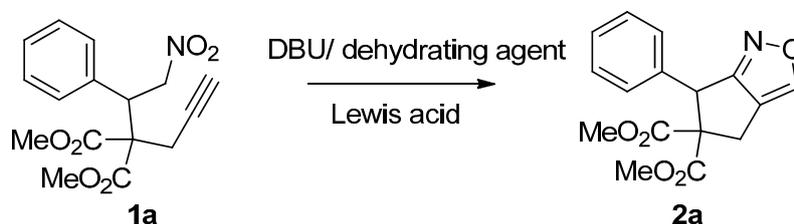
We first synthesized the starting materials, including the dimethyl 2-propargyl-2-(2-nitro-1-aryl/alkylethyl)malonates **1a–15a** or dimethyl 2-allyl-2-(2-nitro-1-aryl/alkyl ethyl)malonates **1c–6c** from the corresponding nitroalkenes and propargylmalonate/allylmalonate derivatives in the presence of potassium tertiary butoxide (*t*-BuOK) and lithium bis(trimethylsilyl)amide (LHMDS) [34,43]. We then initiated our studies of the reaction by using dimethyl-2-(2-nitro-1-phenylethyl)-2-(prop-2-yn-1-yl)malonate (**1a**) as the substrate.

To start the reaction, **1a** was treated with potassium *tert*-butoxide (2.5 equiv.) and the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) in dichloromethane at -78 °C. The corresponding bicyclic isoxazole product was produced in 65% yield after 24 h. Encouraged by this initial result, we next focused our attention on optimizing the reaction conditions for the formation of the bicyclic isoxazole product. To find a superior base for this transformation the reaction, various bases, including trimethylamine (Et_3N), 1,8-diazabicycloundec-7-ene (DBU), and dimethylaminopyridine (DMAP) were screened. Among them, DBU was found to be the most suitable one. As the Yamaguchi reagent functions as a dehydrating agent in this reaction, we were curious to examine whether other benzoyl chlorides could be used for this purpose. To check this, we reacted **1a** with various benzoyl chlorides including unsubstituted, 2-chloro-, and 3,4-dichlorobenzoyl chlorides in the presence of DBU. All of these reactions resulted in the

production of the desired product in moderate to good yields. However, the yield of the desired product was higher when the Yamaguchi reagent was used as the dehydrating agent. Although the yield of the product was satisfactory, the reaction time was longer when a base (2.5 equiv.) and a dehydrating agent (3 equiv.) was used.

On the other hand, we observed that the efficiency of the nitroalkane to nitrile oxide dehydration reaction was enhanced in the presence a catalytic amount of Lewis acid [43] and conducting the reaction in the presence of a Lewis acid produced the corresponding product in a very short time. Hence, we tested various Lewis acid catalysts, including SnCl₄, ZnCl₂ and ZrCl₄. Among the Lewis acids tested, ZrCl₄ was found to be the best choice. Further, to determine the optimum amount of base required for this reaction, we carried out the reaction using 2 equiv., 1.5 equiv., and 1.0 equiv. of DBU. The reaction was the most efficient when more than 1.5 equivalent of base was used. Moreover, the reaction resulted in excellent yields and the reaction time was shorter when a base (1.5 equiv.) and 1.5 equiv. of the Yamaguchi reagent was used. To determine the effect of temperature, we conducted the reactions at 0 °C and at room temperature. The reaction furnished the desired bicyclic isoxazole derivative in moderate yield when it was conducted at 0 °C, whereas a poor yield of the bicyclic isoxazole was obtained when the reaction was carried out at room temperature. Thus, the optimum reaction conditions for the formation of the bicyclic isoxazole were determined to be the use of 1.5 equiv. DBU, 1.5 equiv. of the Yamaguchi reagent and 10 mol % ZrCl₄ as the catalyst in DCM at −78 °C. These optimization studies are summarized in Table 1.

Table 1. Optimization studies.

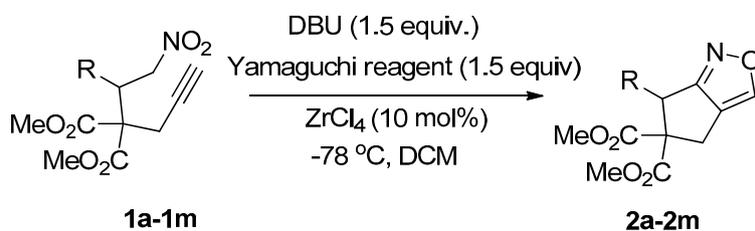


Entry	Base (equiv.)	Dehydrating Agent (equiv.)	Lewis Acid	Temp. (°C)	Time (h)	Yield ^{a, b}
1	K ^t -BuO (2.5)	2,4,6-Trichlorobenzoyl chloride (3)	—	−78	24	65
2	TEA (2.5)	2,4,6-Trichlorobenzoyl chloride (3)	—	−78	24	50
3	DMAP (2.5)	2,4,6-Trichlorobenzoyl chloride (3)	—	−78	24	67
4	DBU (2.5)	2,4,6-Trichlorobenzoyl chloride (3)	—	−78	24	73
5	DBU (2.5)	Benzoyl chloride (3)	—	−78	48	62
6	DBU (2.5)	2-Chlorobenzoyl; chloride (3)	—	−78	35	65
7	DBU (2.5)	3,4-Dichlorobenzoyl chloride (3)	—	−78	24	65
8	DBU (2.5)	2,4,6-Trichlorobenzoyl chloride (1.5)	ZnCl ₂	−78	3	82
9	DBU (2.5)	2,4,6-Trichlorobenzoyl chloride (1.5)	ZnCl ₄	−78	4	87
10	DBU (2.5)	2,4,6-Trichlorobenzoyl chloride (1.5)	SnCl ₄	−78	5	60
11	DBU (2.0)	2,4,6-Trichlorobenzoyl chloride (1.5)	ZnCl ₄	−78	4	90
12	DBU (1.5)	2,4,6-Trichlorobenzoyl chloride (1.5)	ZnCl ₄	−78	4	95
13	DBU (1.0)	2,4,6-Trichlorobenzoyl chloride (1.5)	ZnCl ₄	−78	7	85
14	DBU (1.5)	2,4,6-Trichlorobenzoyl chloride (1.5)	ZnCl ₄	0	2	40
15	DBU (1.5)	2,4,6-Trichlorobenzoyl chloride (1.5)	ZnCl ₄	25	2	20

^a NMR yields. ^b Reactions carried out in 0.5 mmol scale.

After determining the optimum conditions for the formation of bicyclic isoxazoles, we then utilized these conditions for investigating the scope and limitations of the methodology with various dimethyl-2-(2-nitro-1-aryl/alkyl)-2-(prop-2-yn-1-yl)malonates derived from the corresponding nitroalkenes and dimethylpropargylmalonate (Table 2).

Table 2. Synthesis of bicyclic isoxazole derivatives.



Entry	Substrate	Product	Time (h)	Yield% ^{a,b}
1			4	95
	1a	2a		
2			2	86
	1b	2b		
3			3	89
	1c	2c		
4			3	92
	1d	2d		
5			5	90
	1e	2e		
6			5	87
	1f	2f		

Table 2. Cont.

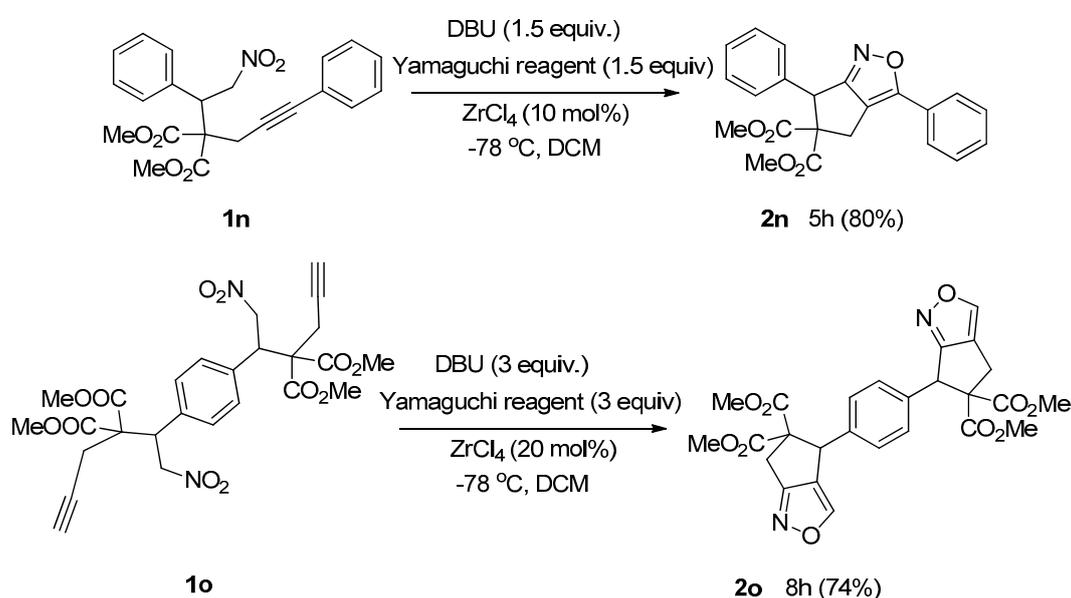
Entry	Substrate	Product	Time (h)	Yield% ^{a,b}
7	 1g	 2g	3	84
8	 1h	 2h	3	86
9	 1i	 2i	3	84
10	 1j	 2j	15	79
11	 1k	 2k	7	92
12	 1l	 2l	12	80
13	 1m	 2m	5	87

^a Isolated yields. ^b Reactions performed in 0.5 mmol scale.

Under the optimized conditions, the substrate containing an unsubstituted phenyl group (compound **1a**) gave the corresponding bicyclic isoxazole derivative in excellent yield. The reactions of substrates possessing an electron withdrawing group such as a bromo group (compound **1b**) and substrates containing an electron donating group such as methyl (compound **1c**) and methoxy (compound **1d**) groups at the *ortho* position of the phenyl group reacted smoothly to yield the corresponding bicyclic isoxazole derivatives in excellent yields. On the other hand, substrates containing an electron withdrawing group at the *para* position of the phenyl group such as **1e** and **1f**, provided the corresponding bicycloisoxazole derivatives

2e and **2f**, respectively, in excellent yields. In addition, substrates possessing electron donating groups (OMe and Me) and an electron neutral group (SMe) at the *para* position of the phenyl group reacted with equal ease to provide the desired products **2g**, **2h** and **2i** in good yields. Further, substrates containing thiophene (compound **1j**), and methyleneoxy groups (compound **1k**) reacted smoothly and provided the corresponding bicyclicisoxazole derivatives **2j** and **2k**, respectively, in good to excellent yields. Substrates containing a naphthalene moiety (compound **2l**) and an alkyl group (compound **2m**) also produced the corresponding products in high yields under the present reaction conditions.

To extend the scope of this reaction, we examined the reactions of dimethyl 2-(2-nitro-1-phenylethyl)-2-(3-phenylprop-2-yn-1-yl)malonate (**1n**) and tetramethyl 2,2'-(1,4-phenylenebis(2-nitroethane-1,1-diyl))bis(2-(prop-2-yn-1-yl)malonate) (**1o**). To our delight, both reactions provided the corresponding bicyclic isoxazole derivatives (**2n** and **2o**) in good yields (Scheme 1).



Scheme 1. Synthesis of bicyclic isoxazole derivatives.

We also investigated the reactions of 2-allyl-2-(2-nitro-1-aryl/alkyl ethyl)malonate derivatives under the present reaction conditions and the results are listed in Table 3. As shown in Table 3, the reactions of substrates containing both electron withdrawing as well as electron donating groups exhibited a similar reactivity under the reaction conditions. However, when substrates containing thienyl and naphthyl moieties were used a slightly longer reaction time was needed to produce good yield of the corresponding bicyclic isoxazoline derivatives (Table 3).

It is important to note that the reactions of all 2-allyl-2-(2-nitro-1-aryl/alkylethyl)malonate derivatives resulted in the production of mixture of diastereomers and among the diastereomers, the *cis* isomer was the major component and the *trans* isomer was the minor one. The NMR signal for the methine proton at the bridgehead carbon in the *trans* isomer appears at 4.62 ppm, compared to 3.82 ppm for the *cis* isomer, which permits *trans* and *cis* isomers to be identified. The diastereoselectivity (*cis:trans*) ranged from 5.6:1 to 3.6:1. The diastereoselectivity for this reaction slightly better than in our previous report [43]. These results were consistent with the our previous results as well as other literature reports [43,51,52].

Table 3. Synthesis of bicyclic isoxazoline derivatives.

DBU (1.5 equiv.)
Yamaguchi reagent (1.5 equiv.)
ZrCl₄ (10 mol%)
-78 °C, DCM

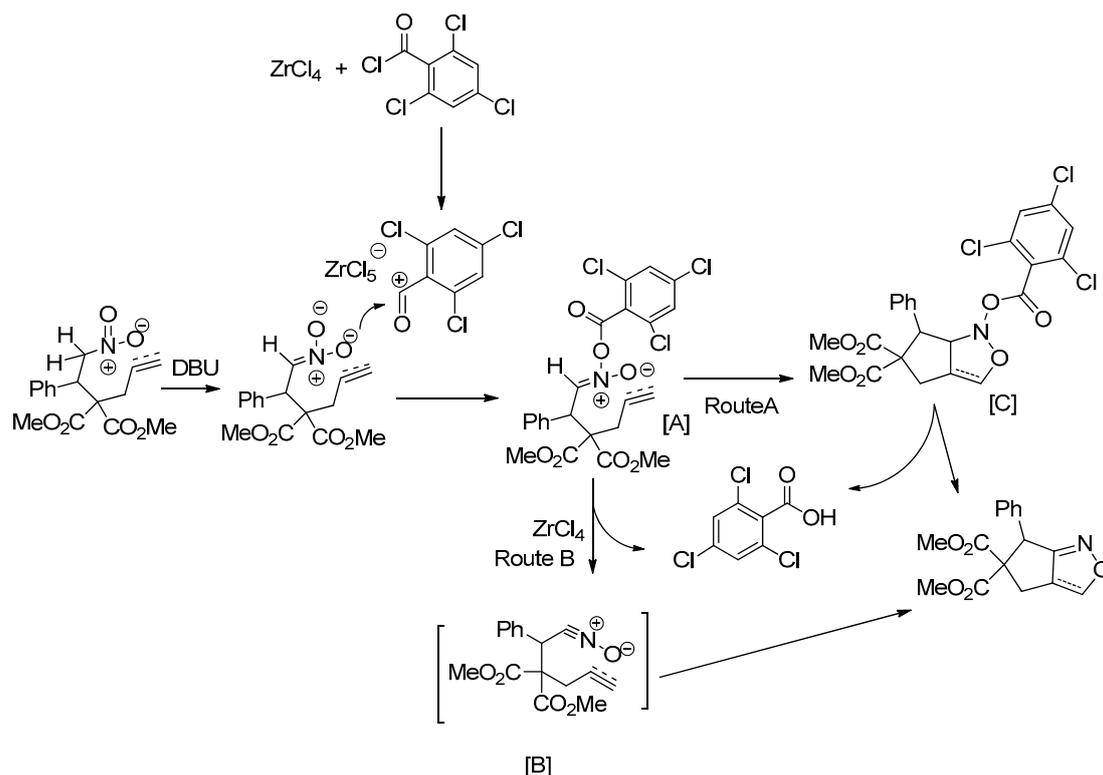
3a-3f → **4a-4f**

Entry	Substrate	Product	Time (h)	Yield% ^{a,b}	<i>cis:trans</i> ^c
1			3	88	5.3:1
2			4	83	4.6:1
3			5	81	3.6:1
4			5	85	5.4:1
5			12	78	4.8:1
6			7	84	5.6:1

^a Isolated yields. ^b Reactions performed in 0.5 mmol scale. ^c *cis:trans* isomers were determined from ¹H-NMR.

Based on our experience with nitroalkanes and the literature reports related to the Yamaguchi reagent, the formation of bicyclic isoxazole/isoxazolines from dimethyl 2-propargyl-2-(2-nitro-1-aryl/alkylethyl)malonates or dimethyl 2-allyl-2-(2-nitro-1-aryl/alkylethyl)malonates with a base and the Yamaguchi reagent in the presence of an acidic catalyst could be explained by two mechanistic pathways shown in Scheme 2. The reaction of the nitroalkane in the presence a base could result in the production

of a nitronate ion, which could be further converted into a benzoylnitronate [A] by reaction with the Yamaguchi reagent and zirconium chloride. This benzoylnitronate [A] could then be converted into the corresponding nitrile oxide [B] intermediate in the presence of zirconium chloride, which would further undergo intramolecular nitrile oxide cycloaddition (INOC) to afford the desired carbocycle fused isoxazole/isoxazoline (Scheme 2, Route B). Another possibility is that the benzoylnitronate might act as a 1,3-dipole [53] to undergo INOC to obtain intermediate [C], which upon losing trichlorobenzoic acid, would produce the desired bicyclic compound (Scheme 2, Route A).



Scheme 2. Plausible mechanistic pathways.

3. Experimental Section

3.1. General Information

All chemicals were purchased from various commercial sources and used directly without further purification. Analytical thin-layer chromatography was performed using E. Merck (New York, NY, USA) silica gel 60F glass plates and E. Merck silica gel 60 (230–400 mesh) was used in flash chromatography separations. MS were measured by a JMS-HX110 spectrometer (JEOL, Hsinchu, Japan). HRMS spectra were recorded using ESI-TOF or EI⁺ mode or FAB⁺. ¹H- (400 MHz) and ¹³C-NMR (100 MHz) spectra were recorded with an Advance EX 400 MHz spectrometer (Bruker, San Francisco, CA, USA). Chemical shifts are reported in parts per million (δ) using TMS as an internal standard and coupling constant were expressed in hertz. IR spectra were performed on a 100 series FT-IR instrument (Perkin Elmer, Waltham, MA, USA). Melting points were recorded using an capillary melting point apparatus (Electrothermal, Staffordshire, UK) and are uncorrected. All substrates were prepared using literature procedures.

3.2. General Procedure for the Preparation of **1a–1o**

Potassium *tert*-butoxide (3 mmol) was added to a solution of dimethyl propargylmalonate (2.4 mmol) in anhydrous THF (15 mL) at room temperature under nitrogen atmosphere. The reaction mixture was then cooled to -78 °C and a solution of the nitroalkene (2 mmol) in anhydrous THF (5 mL) was added dropwise over a period of five minutes. The reaction mixture was then stirred at -78 °C until the reaction was complete, which was monitored by TLC. A saturated aqueous NH_4Cl was then added and the resulting mixture extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over MgSO_4 and the solvent removed *in vacuo*. The residue was purified by flash column chromatography over silica (ethyl acetate and hexane).

Dimethyl 2-(1-(2-bromophenyl)-2-nitroethyl)-2-(prop-2-yn-1-yl)malonate (1b): Colorless solid; Yield: 67% (5 h); m.p. 100–101 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.60 (d, $J = 8.0$ Hz, 1H), 7.30 (t, $J = 7.6$ Hz, 1H), 7.20–7.14 (m, 2H), 5.22 (d, $J = 8.0$ Hz, 1H), 5.16–5.03 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.76 (m, 2H), 2.15 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.2, 169.1, 134.8, 134.2, 130.1, 128.4, 128.2, 127.3, 78.8, 78.0, 72.8, 60.8, 53.6, 53.3, 44.8, 23.8; HRMS (EI) m/z calc. for $\text{C}_{16}\text{H}_{16}\text{NO}_6^{79}\text{Br}$ (M^+) 397.0161, found 397.0156.

*Dimethyl 2-(2-nitro-1-(*o*-tolyl)ethyl)-2-(prop-2-yn-1-yl)malonate (1c)*: Colorless solid; Yield: 75% (4 h); m.p. 98–99 °C. $^1\text{H-NMR}$ (CDCl_3) δ 7.17–7.12 (m, 3H), 6.92–6.90 (m, 1H), 5.32 (dd, $J = 6.7$, 3.1 Hz, 1H), 4.96 (dd, $J = 11.6$ Hz, 6.6 Hz, 1H), 4.81 (dd, $J = 5.6$ Hz, 2.9 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.85 (dd, $J = 8.7$ Hz, 2.8 Hz, 1H), 2.51 (s, 3H), 2.41 (dd, $J = 8.7$ Hz, 2.6 Hz, 1H), 2.15 (t, $J = 2.7$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.5, 169.4, 139.2, 133.7, 131.7, 128.5, 126.6, 126.4, 79.2, 79.0, 73.2, 60.8, 53.4, 53.3, 40.8, 23.7, 20.1; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{19}\text{NO}_6$ (M^+) 372.1059, found 372.1069.

Dimethyl 2-(2-nitro-1-(2-methoxyphenyl)ethyl)-2-(prop-2-yn-1-yl)malonate (1d): Colorless solid; Yield: 72% (4 h); m.p. 141–142 °C. $^1\text{H-NMR}$ (CDCl_3) δ 7.26–7.22 (m, 2H), 6.88–6.81 (m, 2H), 5.17 (d, $J = 5.8$ Hz, 2H), 4.65 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 2.80 (d, $J = 17.1$ Hz, 1H), 2.30 (d, $J = 16.3$ Hz, 1H), 2.11 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.5, 169.1, 157.6, 133.0, 130.0, 122.3, 120.9, 111.2, 78.6, 76.4, 72.6, 59.0, 55.3, 53.2, 52.7, 44.0, 24.3.

Dimethyl 2-(1-(4-fluorophenyl)-2-nitroethyl)-2-(prop-2-yn-1-yl)malonate (1e): Colorless solid; Yield: 84% (3 h); m.p. 89–90 °C. $^1\text{H-NMR}$ (CDCl_3) δ 7.18 (dd, $J = 8.4$, 5.3 Hz, 2H), 7.00 (t, $J = 8.5$ Hz, 2H), 5.28 (dd, $J = 13.6$, 3.0 Hz, 1H), 4.96 (dd, $J = 13.5$, 11.6 Hz, 1H), 4.50 (dd, $J = 11.7$, 2.9 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.79 (dd, $J = 17.5$ Hz, 2.5 Hz, 1H), 2.37 (dd, $J = 17.5$ Hz, 2.5 Hz, 1H), 2.23 (t, $J = 2.3$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.1, 169.0, 164.0 (d, $J_{\text{C-F}} = 245.0$), 130.7 (d, $J_{\text{C-F}} = 8.0$), 130.6 (d, $J_{\text{C-F}} = 4.0$), 116.3 (d, $J_{\text{C-F}} = 21.0$), 78.0, 76.9, 73.8, 59.7, 53.6, 53.4, 44.9, 24.1; HRMS (EI) m/z calc. for $\text{C}_{16}\text{H}_{16}\text{NO}_6\text{F}$ (M^+) 337.0963, found 337.0969.

Dimethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)-2-(prop-2-yn-1-yl)malonate (1f): Colorless solid; Yield: 98% (5 h); m.p. 123–124 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.30 (d, $J = 8.3$ Hz, 2H), 7.15 (d, $J = 8.3$ Hz, 2H), 5.30 (dd, $J = 13.8$, 2.9 Hz, 1H), 4.97 (dd, $J = 13.8$, 11.7 Hz, 1H), 4.51 (dd, $J = 11.7$, 2.9 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.81 (dd, $J = 17.5$ Hz, 2.2 Hz, 1H), 2.37 (dd, $J = 17.5$ Hz, 2.2 Hz, 1H), 2.25 (s, 1H);

^{13}C -NMR (CDCl_3) δ 168.9, 168.8, 134.8, 133.2, 130.2, 129.3, 77.9, 77.5, 73.9, 59.5, 53.6, 53.4, 44.9, 24.1; HRMS (EI) m/z calc. for $\text{C}_{16}\text{H}_{16}\text{NO}_6^{35}\text{Cl}$ (M^+) 353.0666, found 353.0661.

Dimethyl 2-(1-(4-methoxyphenyl)-2-nitroethyl)-2-(prop-2-yn-1-yl)malonate (1g): Colorless solid; Yield: 81% (2 h); m.p. 111–112 °C; ^1H -NMR (CDCl_3) δ 7.11 (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 5.27 (dd, $J = 13.5, 2.9$ Hz, 1H), 4.98 (dd, $J = 13.5, 11.4$ Hz, 1H), 4.46 (dd, $J = 11.4, 2.9$ Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.79 (dd, $J = 17.4$ Hz, 2.2 Hz, 1H), 2.42 (dd, $J = 17.4$ Hz, 2.2 Hz, 1H), 2.22 (s, 1H); ^{13}C -NMR (CDCl_3) δ 169.2, 169.1, 159.9, 130.0, 126.4, 114.5, 78.3, 77.9, 73.5, 59.9, 55.4, 53.4, 53.3, 45.0, 24.1; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{19}\text{NO}_7$ (M^+) 349.1162, found 349.1156.

Dimethyl 2-(2-nitro-1-(p-tolyl)ethyl)-2-(prop-2-yn-1-yl)malonate (1h): Colorless solid; Yield: 92% (2 h); m.p. 91–92 °C; ^1H -NMR (CDCl_3) δ 7.15 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 8.0$ Hz, 2H), 5.28 (dd, $J = 13.6, 3.0$ Hz, 1H), 5.00 (dd, $J = 13.6, 11.6$ Hz, 1H), 4.47 (dd, $J = 11.6, 2.9$ Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.78 (dd, $J = 17.4$ Hz, 2.4 Hz, 1H), 2.41 (dd, $J = 17.4$ Hz, 2.4 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 1H); ^{13}C -NMR (CDCl_3) δ 169.2, 169.1, 138.7, 131.5, 129.8, 128.6, 78.3, 77.8, 73.5, 59.7, 53.4, 53.3, 45.2, 24.1, 21.2; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{19}\text{NO}_6$ (M^+) 333.1212, found 333.1207.

Dimethyl 2-(2-nitro-1-(4-methylthiophenyl)ethyl)-2-(prop-2-yn-1-yl)malonate (1i): Yellow oil; Yield: 88% (2 h); ^1H -NMR (CDCl_3) δ 7.16 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 5.26 (dd, $J = 13.7, 3.1$ Hz, 1H), 4.97 (dd, $J = 13.7, 11.4$ Hz, 1H), 4.46 (dd, $J = 11.4, 3.1$ Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.78 (dd, $J = 17.4$ Hz, 2.6 Hz, 1H), 2.43 (s, 3H), 2.39 (dd, $J = 17.4, 2.4$ Hz, 1H), 2.22 (t, $J = 2.6$ Hz, 1H); ^{13}C -NMR (CDCl_3) δ 169.1, 169.0, 139.6, 131.1, 129.2, 126.6, 78.2, 77.7, 73.6, 59.7, 53.4, 53.3, 45.1, 24.1, 15.4; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{19}\text{NO}_6\text{S}$ (M^+) 365.0933, found 365.0928.

Dimethyl 2-(2-nitro-1-(thiophen-2-yl)ethyl)-2-(prop-2-yn-1-yl)malonate (1j): Colorless solid; Yield: 90% (2.5 h); m.p. 101–102 °C; ^1H -NMR (CDCl_3) δ 7.25 (d, $J = 5.0$ Hz, 1H), 7.00 (d, $J = 3.6$ Hz, 1H), 6.95 (dd, $J = 5.0, 3.6$ Hz, 1H), 5.26 (dd, $J = 13.4, 2.6$ Hz, 1H), 4.97 (dd, $J = 13.4, 11.1$ Hz, 1H), 4.86 (d, $J = 11.1$ Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.89 (dd, $J = 17.5, 2.7$ Hz, 1H), 2.61 (dd, $J = 17.4, 2.7$ Hz, 1H); 2.23 (t, $J = 2.7$ Hz, 1H); ^{13}C -NMR (CDCl_3) δ 168.8, 168.7, 136.8, 128.6, 127.2, 126.3, 79.1, 78.0, 73.6, 60.1, 53.6, 53.5, 41.8, 24.1; HRMS (EI) m/z calc. for $\text{C}_{14}\text{H}_{15}\text{NO}_6\text{S}$ (M^+) 325.0620, found 325.0615.

Dimethyl 2-(1-benzo[d][1,3]dioxol-5yl)-2-nitroethyl)-2-(prop-2-yn-1-yl)malonate (1k): Colorless solid; Yield: 95% (4 h); m.p. 169–170 °C. ^1H -NMR (CDCl_3) δ 6.73 (d, $J = 8.4$ Hz, 1H), 6.67–6.65 (m, 2H), 5.95 (s, 2H), 5.24 (dd, $J = 13.6, 3.1$ Hz, 1H), 4.94 (dd, $J = 13.6, 11.4$ Hz, 1H), 4.42 (dd, $J = 11.1, 3.1$ Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.81 (dd, $J = 17.4, 2.6$ Hz, 1H), 2.46 (dd, $J = 17.4, 2.6$ Hz, 1H); 2.17 (t, $J = 2.6$ Hz, 1H); ^{13}C -NMR (CDCl_3) δ 169.1, 169.0, 148.2, 148.1, 128.1, 122.6, 109.0, 108.8, 101.5, 78.2, 77.9, 73.6, 59.9, 53.5, 53.4, 45.4, 25.2; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_8$ (M^+) 363.0954, found 363.0949.

Dimethyl 2-(1-(naphthalen-1-yl)-2-nitroethyl)-2-(prop-2-yn-1-yl)malonate (1l): Colorless solid; Yield: 77% (2 h); m.p. 145–146 °C; ^1H -NMR (CDCl_3) δ 8.45 (d, $J = 8.6$ Hz, 1H), 7.80 (t, $J = 9.4$ Hz, 2H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.24 (d, $J = 7.2$ Hz, 1H), 5.56–5.48 (m, 2H), 5.22 (dd, $J = 13.5, 10.9$ Hz, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 2.78 (dd, $J = 17.5, 2.6$ Hz, 1H),

2.36 (dd, $J = 17.5, 2.6$ Hz, 1H); 2.21 (t, $J = 2.6$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.4, 169.2, 134.1, 132.8, 131.9, 129.5, 128.8, 126.7, 126.3, 125.0, 124.8, 123.8, 79.1, 78.7, 73.3, 60.9, 53.4, 53.3, 39.2, 23.6; HRMS (EI) m/z calc. for $\text{C}_{20}\text{H}_{19}\text{NO}_6$ (M^+) 369.1212, found 369.1207.

Dimethyl 2-(4-methyl-1-nitropentan-2-yl)-2-(prop-2-yn-1-yl)malonate (1m): Pale yellow oil; Yield: 82% (3 h); $^1\text{H-NMR}$ (CDCl_3) δ 4.98 (dd, $J = 14.5, 3.9$ Hz, 1H), 4.30 (dd, $J = 14.5, 5.7$ Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.36–3.31 (m, 1H), 2.93 (dd, $J = 17.6, 2.7$ Hz, 1H), 2.84 (dd, $J = 17.6, 2.6$ Hz, 1H); 2.11 (t, $J = 2.7$ Hz, 1H), 1.58–1.51 (m, 1H), 1.31–1.18 (m, 2H), 0.93 (d, $J = 6.4$ Hz, 3H), 0.90 (d, $J = 6.4$ Hz, 3H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.7, 169.4, 78.5, 78.3, 72.9, 60.0, 53.2, 53.1, 39.7, 37.9, 25.7, 23.9, 23.3, 21.4; HRMS (EI) m/z calc. for $\text{C}_{14}\text{H}_{21}\text{NO}_6$ (M^+) 300.1448, found 300.1444.

Dimethyl 2-(2-nitro-1-phenylethyl)-2-(3-phenylprop-2-yn-1-yl)malonate (1n): Pale yellow oil; Yield: 98% (3 h); $^1\text{H-NMR}$ (CDCl_3) δ 7.46–7.45 (m, 2H), 7.35–7.31 (m, 6H), 7.24–7.23 (m, 2H), 5.35 (dd, $J = 13.7, 3.0$ Hz, 1H), 5.06 (dd, $J = 13.7, 11.3$ Hz, 1H), 4.61 (dd, $J = 11.2, 3.0$ Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.02 (d, $J = 17.5$ Hz, 1H), 2.63 (d, $J = 17.5$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.2, 169.1, 134.8, 131.7, 129.0, 128.8, 128.7, 128.5, 128.4, 122.8, 85.5, 83.5, 77.0, 60.1, 53.3, 53.2, 45.7, 24.9; HRMS (EI) m/z calc. for $\text{C}_{22}\text{H}_{21}\text{NO}_6$ (M^+) 395.1369, found 395.1366.

Tetramethyl 2,2'-(1,4-phenylenebis(2-nitroethane-1,1-diyl))bis(2-(prop-2-yn-1-yl)malonate) (1o): Colorless solid; Yield: 60% (2 h); m.p. 180–182 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.18 (s, 4H), 5.29 (dd, $J = 13.9, 3.0$ Hz, 2H), 5.00 (ddd, $J = 13.9, 11.1, 3.1$ Hz, 2H), 4.48 (d, $J = 9.9$ Hz, 2H), 3.76 (s, 6H), 3.75 (s, 6H), 2.78 (dd, $J = 17.4, 2.4$ Hz, 2H), 2.34 (dt, $J = 17.4, 3.5$ Hz, 2H); 2.20 (s, 2H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.2, 169.1, 169.0, 135.7, 135.6, 129.5, 78.2, 78.1, 73.8, 73.7, 59.9, 53.5, 53.4, 45.4, 24.2, 24.1; HRMS (ESI) m/z calc. for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_{12}$ (M^+) 560.1642, found 560.1642.

3.3. General Procedure for the Synthesis of 3a–3f

LHMDS (1.5 mmol) was added to a solution of dimethyl propargylmalonate (1.2 mmol) in anhydrous THF (5 mL) at 0 °C under a nitrogen atmosphere, followed by stirring for 1 h. A solution of nitroalkene (1 mmol) in anhydrous THF (5 mL) was then added drop wise over a period of five minutes at 0 °C. The reaction mixture was then stirred at the same temperature until the reaction was complete, which was monitored by TLC. After the completion of the reaction, a saturated aqueous NH_4Cl was added and the resulting mixture extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over MgSO_4 and the solvent removed *in vacuo*. The residue was purified by flash column chromatography over silica (ethyl acetate and hexane).

Dimethyl 2-allyl-2-(1-(4-chlorophenyl)-2-nitroethyl)malonate (3b): Colorless solid; Yield: 98% (2.5 h); m.p. 98–99 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.29 (d, $J = 8.4$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 2H), 5.75–5.65 (m, 1H), 5.15–4.91 (m, 4H), 4.18 (dd, $J = 11.1, 3.1$ Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.58 (dd, $J = 14.5, 6.4$ Hz, 1H), 2.27 (dd, $J = 14.5, 8.1$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 170.0, 169.9, 134.7, 133.6, 131.7, 130.4, 129.2, 120.2, 78.2, 60.7, 53.0, 52.9, 46.3, 38.5; HRMS (EI) m/z calc. for $\text{C}_{16}\text{H}_{18}\text{NO}_6^{35}\text{Cl}$ (M^+) 355.0823, found 355.0817.

Dimethyl 2-allyl-2-(2-nitro-1-(p-tolyl)ethyl)malonate (3c): Colorless solid; Yield: 97% (4 h); m.p. 88–89 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.10 (d, $J = 7.9$ Hz, 2H), 6.98 (d, $J = 7.9$ Hz, 2H), 5.78–5.68 (m, 1H), 5.14–4.93 (m, 4H), 4.16 (dd, $J = 10.8, 3.4$ Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 2.56 (dd, $J = 14.4, 6.5$ Hz, 1H), 2.30 (s, 3H) 2.29–2.25 (m, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 170.4, 170.2, 138.6, 132.1, 131.8, 129.7, 128.8, 120.0, 78.6, 61.1, 53.0 52.9, 46.7, 38.7, 21.2; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{21}\text{NO}_6$ (M^+) 335.1369, found 335.1363.

Dimethyl 2-allyl-2-(1-(4-methoxyphenyl)-2-nitroethyl)malonate (3d): Yellow oil; Yield: 80% (7 h); $^1\text{H-NMR}$ (CDCl_3) δ 7.02 (d, $J = 8.7$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 5.76–5.67 (m, 1H), 5.15–4.92 (m, 4H), 4.14 (dd, $J = 11.0, 3.4$ Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 2.57 (dd, $J = 14.4, 8.0$ Hz, 1H), 2.29 (dd, $J = 14.4, 8.0$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 170.4, 170.2, 159.9, 132.1, 130.1, 126.7, 120.0, 114.4, 78.6, 61.2, 55.4, 53.0, 52.9, 46.4, 38.7; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{21}\text{NO}_7$ (M^+) 351.1318, found 349.1313.

Dimethyl 2-allyl-2-(2-nitro-1-(thiophen-2-yl)ethyl)malonate (3e): Yellow oil; Yield: 95% (4 h); $^1\text{H-NMR}$ (CDCl_3) δ 7.24 (d, $J = 5.0$ Hz, 1H), 6.93–6.90 (m, 1H), 6.89 (d, $J = 5.0$ Hz, 1H), 5.79–5.72 (m, 1H), 5.17–4.92 (m, 4H), 4.52 (dd, $J = 10.5, 3.1$ Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 2.69 (dd, $J = 14.5, 6.5$ Hz, 1H), 2.43 (dd, $J = 14.5, 8.1$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 169.8, 169.7, 137.1, 131.8, 128.4, 127.0, 126.1, 120.2, 79.6, 61.2, 53.0, 42.7, 38.6; HRMS (EI) m/z calc. for $\text{C}_{14}\text{H}_{17}\text{NO}_6\text{S}$ (M^+) 327.0777, found 327.0771.

Dimethyl 2-allyl-2-(1-(naphthalen-1-yl)-2-nitroethyl)malonate (3f): Yellow oil; Yield 98% (3.5 h); $^1\text{H-NMR}$ (CDCl_3) δ 8.31 (d, $J = 8.6$ Hz, 1H), 7.82 (dd, $J = 13.7, 8.2$ Hz, 1H), 7.59 (td, $J = 7.4, 0.8$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 7.2$ Hz, 1H), 5.75–5.65 (m, 1H), 5.35 (t, $J = 7.0$ Hz, 1H), 5.16 (d, $J = 7.1$ Hz, 2H), 5.00 (d, $J = 10.1$ Hz, 1H), 4.90 (d, $J = 17.0$ Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 2.38 (dd, $J = 14.2, 6.6$ Hz, 1H), 2.23 (dd, $J = 14.2, 7.9$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 170.6, 170.4, 134.2, 133.1, 132.7, 132.2, 129.4, 129.1, 127.0, 126.3, 125.2, 124.6, 123.5, 119.6, 79.4, 62.8, 52.9, 40.6, 39.1; HRMS (EI) m/z calc. for $\text{C}_{20}\text{H}_{21}\text{NO}_6$ (M^+) 371.1369, found 371.1363.

3.4. General Procedure for the Preparation of 2a–2o and 4a–4f

A mixture of allyl or propargyl dimethyl malonate (1 mmol) and DBU (1.5 equiv.) in anhydrous dichloromethane (3 mL) was stirred at -78 °C for 20 min under nitrogen. To this mixture, the Yamaguchi reagent (1.5 equiv.) and ZrCl_4 (10 mol %) were added. The reaction mixture was then stirred at the same temperature for 10 min. then stopped the cooler and continued until the reaction was complete, as indicated by TLC. After the completion of the reaction, the reaction mixture was washed with water, and extracted with CH_2Cl_2 , washed the organic layer with brine solution. The organic layers were collected, combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was then purified by column chromatography using EtOAc-hexane to give the desired product. **2a**, **2j**, **2k**, **4a–4f** are known compounds [43].

Dimethyl-6-(2-bromophenyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2b): Brown solid; m.p. 127–129 °C; $^1\text{H-NMR}$ (CDCl_3) δ 8.10 (s, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.16 (t, $J = 7.4$ Hz, 1H),

7.08 (td, $J = 7.7, 1.3$ Hz, 1H), 6.73 (d, $J = 7.6$ Hz, 1H), 5.97 (s, 1H), 3.88 (d, $J = 17.2$ Hz, 1H), 3.80 (s, 3H), 3.29 (s, 3H), 3.25 (d, $J = 17.2$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 172.8, 170.9, 168.2, 150.8, 137.1, 133.2, 129.8, 129.5, 127.8, 125.5, 121.3, 72.6, 53.7, 52.5, 46.9, 29.9; HRMS (EI) m/z calc. for $\text{C}_{16}\text{H}_{14}^{79}\text{BrNO}_5$ (M^+) 379.0055, found 379.0050.

Dimethyl-6-(o-tolyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2c): White solid; m.p. 117–118 °C; $^1\text{H-NMR}$ (CDCl_3) δ 8.08 (s, 1H), 7.16–7.08 (m, 2H), 7.03 (t, $J = 7.4$ Hz, 1H), 6.97 (d, $J = 7.4$ Hz, 1H), 5.63 (s, 1H), 3.63 (d, $J = 17.4, 1.5$ Hz, 1H), 3.79 (s, 3H), 3.25 (d, $J = 17.4, 1.4$ Hz, 1H), 3.19 (s, 3H), 2.49 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3) δ 173.5, 171.5, 168.5, 150.5, 137.1, 135.8, 130.6, 128.3, 127.9, 126.3, 121.4, 72.9, 53.6, 52.4, 44.0, 29.8, 20.2. HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_5\text{Na}$ ($\text{M}^+ + \text{Na}$) 338.1005, found 338.1015.

Dimethyl-6-(2-methoxyphenyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2d): Pale yellow oil; $^1\text{H-NMR}$ (CDCl_3) δ 8.02 (s, 1H), 7.21 (td, $J = 7.8, 1.5$ Hz, 1H), 6.97 (d, $J = 6.8$ Hz, 1H), 6.86–6.81 (m, 2H), 5.63 (s, 1H), 3.88 (dd, $J = 16.7, 1.2$ Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.22 (s, 3H), 3.16 (d, $J = 16.7$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 172.9, 171.6, 168.7, 157.4, 149.8, 130.5, 129.4, 125.8, 121.6, 120.7, 111.1, 72.3, 55.6, 53.5, 52.4, 43.5, 30.4; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_6$ (M^+) 331.1056, found 331.1064.

Dimethyl-6-(4-fluorophenyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2e): Pale yellow oil; $^1\text{H-NMR}$ (CDCl_3) δ 8.10 (s, 1H), 7.21 (dd, $J = 8.0, 3.9$ Hz, 1H), 6.97 (t, $J = 8.4$ Hz, 3H), 5.31 (s, 1H), 3.80 (s, 3H), 3.67 (d, $J = 16.4$ Hz, 1H), 3.24 (s, 3H), 3.11 (d, $J = 16.8$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 171.8, 171.0, 168.9, 162.6 (d, $J = 245$ Hz), 150.6, 131.8 (d, $J = 3$ Hz), 130.5 (d, $J = 8$ Hz), 121.6, 115.5 (d, $J = 21$ Hz), 72.9, 53.5, 48.0, 29.7; HRMS (EI) m/z calc. for $\text{C}_{16}\text{H}_{14}\text{FNO}_5$ (M^+) 319.0856, found 319.0851.

Dimethyl-6-(4-chlorophenyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2f): Pale yellow solid; m.p. 124–125 °C; $^1\text{H-NMR}$ (CDCl_3) δ 8.11 (s, 1H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.17 (d, $J = 8.1$ Hz, 2H), 5.30 (s, 1H), 3.81 (s, 3H), 3.68 (d, $J = 16.6$ Hz, 1H), 3.25 (s, 3H), 3.13 (d, $J = 16.6$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 171.5, 170.9, 168.8, 150.6, 134.6, 134.2, 130.5, 128.7, 121.4, 72.9, 53.6, 52.7, 48.1, 29.7; HRMS (EI) m/z calc. for $\text{C}_{16}\text{H}_{14}^{35}\text{ClNO}_5$ (M^+) 335.056, found 335.0555.

Dimethyl-6-(4-methoxyphenyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2g): White solid; m.p. 111–110 °C; $^1\text{H-NMR}$ (CDCl_3) δ 8.06 (s, 1H), 7.09 (d, $J = 8.6$ Hz, 2H), 6.78 (d, $J = 8.64$ Hz, 2H), 5.24 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.66 (d, $J = 16.5$ Hz, 1H), 3.23 (s, 3H), 3.10 (d, $J = 16.5$ Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 172.2, 171.1, 168.9, 159.4, 150.3, 130.1, 128.0, 121.2, 113.9, 72.8, 55.3, 53.4, 52.5, 48.0, 29.5; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_6$ (M^+) 331.1056, found 331.1050.

Dimethyl-6-(p-tolyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2h): White solid; m.p. 102–103 °C; $^1\text{H-NMR}$ (CDCl_3) δ 8.00 (s, 1H), 7.01 (d, $J = 8.2$ Hz, 2H), 6.98 (d, $J = 8.2$ Hz, 2H), 5.19 (s, 1H), 3.72 (s, 3H), 3.63 (d, $J = 16.6$ Hz, 1H), 3.17 (s, 3H), 3.06 (d, $J = 16.6$ Hz, 1H), 2.22 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3) δ 171.9, 170.9, 168.5, 150.1, 137.6, 132.8, 128.9, 128.6, 121.1, 72.7, 53.2, 52.3, 48.1, 29.4, 21.0; HRMS (EI) m/z calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_5$ (M^+) 315.1107, found 315.1101.

Dimethyl-6-(4-(methylthio)phenyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2i): Orange solid; m.p. 114–116 °C; ¹H-NMR (CDCl₃) δ 8.09 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 5.27 (s, 1H), 3.79 (s, 3H), 3.69 (dd, *J* = 16.0, 1.0 Hz, 1H), 3.25 (s, 3H), 3.12 (dd, *J* = 16.0, 1.0 Hz, 1H), 2.44 (s, 3H); ¹³C-NMR (CDCl₃) δ 171.9, 171.1, 168.8, 150.5, 138.7, 132.8, 129.5, 126.6, 121.3, 72.9, 53.5, 52.6, 48.3, 29.7, 15.9; HRMS (EI) *m/z* calc. for C₁₇H₁₇NO₅S (M⁺) 347.0827, found 347.0822.

Dimethyl-6-(thiophen-2-yl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2j): White solid; m.p. 129–130 °C; ¹H-NMR (CDCl₃) δ 8.08 (s, 1H), 7.23–7.21 (m, 1H), 6.94–6.91 (m, 2H), 5.53 (s, 1H), 3.81 (s, 3H), 3.68 (dd, *J* = 16.5, 1.2 Hz, 1H), 3.41 (s, 3H), 3.14 (dd, *J* = 16.5, 1.2 Hz, 1H); ¹³C-NMR (CDCl₃) δ 171.5, 170.7, 168.5, 150.6, 137.4, 127.5, 126.8, 125.9, 120.6, 72.9, 53.5, 52.8, 44.1, 29.3; HRMS (EI) *m/z* calc. for C₁₄H₁₃NO₅S (M⁺) 307.0514, found 307.0513.

Dimethyl-6-(benzo[d][1,3]dioxol-5-yl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2k): White solid; m.p. 93–94 °C; ¹H-NMR (CDCl₃) δ 8.08 (s, 1H), 6.72–6.66 (m, 3H), 5.91–5.90 (m, 2H), 5.23 (s, 1H), 3.79 (s, 3H), 3.66 (d, *J* = 16.5 Hz, 1H), 3.33 (s, 3H), 3.11 (d, *J* = 16.5 Hz, 1H); ¹³C-NMR (CDCl₃) δ 171.9, 171.0, 168.7, 150.4, 147.7, 129.5, 122.5, 121.2, 109.4, 108.1, 101.2, 72.7, 53.4, 52.6, 48.3, 29.5; HRMS (EI) *m/z* calc. for C₁₇H₁₅NO₇ (M⁺) 345.0849, found 345.0847.

Dimethyl-6-(naphthalen-1-yl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2l): White solid; m.p. 131–133 °C; ¹H-NMR (CDCl₃) δ 8.39 (d, *J* = 5.4 Hz, 1H), 8.15 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.58 (t, *J* = 6.8 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.31 (s, 1H), 3.91 (d, *J* = 16.9 Hz, 1H), 3.83 (s, 3H), 3.31 (d, *J* = 16.9 Hz, 1H), 2.71 (s, 3H); ¹³C-NMR (CDCl₃) δ 173.3, 171.4, 168.2, 150.6, 133.9, 133.5, 131.9, 128.8, 128.7, 126.6, 126.3, 125.9, 125.3, 124.2, 121.6, 73.0, 53.7, 52.0, 43.2, 29.8; HRMS (EI) *m/z* calc. for C₂₀H₁₇NO₅ (M⁺) 351.1106, found 351.1101.

Dimethyl-6-isobutyl-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2m): White solid; m.p. 101–102 °C; ¹H-NMR (CDCl₃) δ 7.93 (s, 1H), 3.95 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.46 (dd, *J* = 16.4, 1.5 Hz, 1H), 3.08 (dd, *J* = 16.4, 1.5 Hz, 1H), 2.03–1.96 (m, 1H), 1.41 (td, *J* = 12.9, 3.7 Hz, 1H), 1.33–1.26 (m, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H); ¹³C-NMR (CDCl₃) δ 172.4, 171.2, 169.7, 149.5, 120.1, 70.4, 53.3, 52.9, 41.7, 38.0, 29.4, 25.8, 24.0, 21.2; HRMS (EI) *m/z* calc. for C₂₀H₁₇NO₅ (M⁺) 281.1263, found 281.1258.

Dimethyl-6-(2-bromophenyl)-4H-cyclopenta[c]isoxazole-5,5(6H)-dicarboxylate (2n): White solid; m.p. 209–211 °C; ¹H-NMR (CDCl₃) δ 7.76–7.74 (m, 2H), 7.51–7.41 (m, 3H), 7.31–7.22 (m, 5H), 5.35 (s, 1H), 3.94 (d, *J* = 16.7 Hz, 1H), 3.81 (s, 3H), 3.24 (d, *J* = 16.7 Hz, 1H), 3.22 (s, 3H); ¹³C-NMR (CDCl₃) δ 173.5, 171.2, 168.8, 161.3, 136.3, 130.1, 129.3, 129.2, 128.2, 127.8, 126.3, 116.9, 73.3, 53.6, 52.6, 49.0, 31.1; HRMS (EI) *m/z* calc. for C₂₂H₁₉NO₅ (M⁺) 377.1263, found 377.1265.

4. Conclusions

In summary we report on a practical and efficient regioselective synthesis of bicyclic isoxazole/isoxazoline derivatives via intramolecular nitrile oxide cycloaddition reactions using the Yamaguchi reagent and DBU in the presence of ZrCl₄. The process is straightforward, easy to perform

and does not involve the use of costly reagents or catalysts. A wide variety of carbocyclic fused isoxazole and isoxazoline derivatives were synthesized in good to moderate yields.

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Author Contributions

Ching-Fa Yao, Wen-Chang Chen, Veerababurao Kavala, conceived and designed the experiments; Wen-Chang Chen, Yu-Hsuan Shih, Yu-Hsuan Wang, Chun-Wei Kuo, Tang-Hao Yang and Chia-Yu Huang, performed the experiments; Chia-Yu Huang, Hao-Hsiang Chiu analyzed the data; Veerababurao Kavala and Ching-Fa Yao wrote the paper.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Kamal, A.; Bharathi, E.V.; Reddy, J.S.; Ramaiah, M.J.; Dastagiri, D.; Reddy, M.K.; Viswanath, A.; Reddy T.L.; Shaik, T.B.; Pushpavalli, S.N.; *et al.* Synthesis and biological evaluation of 3,5-diaryl isoxazoline/isoxazole linked 2,3-dihydroquinazolinone hybrids as anticancer agents. *Eur. J. Med. Chem.* **2011**, *46*, 691–703.
2. Sperry J.B.; Wright, D. Furans, thiophenes and related heterocycles in drug discovery. *Curr. Opin. Drug Discov. Dev.* **2005**, *8*, 723–740.
3. Sammelson, R.E.; Ma, T.; Galietta, L.J.V.; Verkman, A.S.; Kurth M.J. 3-(2-Benzyloxyphenyl)isoxazoles and isoxazolines: Synthesis and evaluation as CFTR activators. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2509–2512.
4. Kozikowski, A.P. The isoxazoline route to the molecules of nature. *Acc. Chem. Res.* **1984**, *17*, 410–416.
5. Torssell, K.B.G. Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis; VCH Publishers: New York, NY, USA, 1988.
6. Tang, S.; He, J.; Sun, Y.; He, L.; She, X. Efficient and regioselective synthesis of 5-hydroxy-2-isoxazolines: Versatile synthons for isoxazoles, β -lactams, and γ -amino alcohols. *J. Org. Chem.* **2010**, *75*, 1961–1966.
7. Kleinbeck, F.; Carreira, E.M. Total Synthesis of Bafilomycin A₁. *Angew. Chem. Int. Ed.* **2009**, *48*, 578–581.
8. Fuller, A.A.; Chen, B.; Minter A.R.; Mapp, A.K. Succinct synthesis of β -amino acids via chiral isoxazolines. *J. Am. Chem. Soc.* **2005**, *127*, 5376–5383.

9. Namboothiri, I.N.N.; Rastogi, N. Synthesis of Heterocycles via Cycloadditions I. In *Topics in Heterocyclic Chemistry*; Hassner, A., Ed.; Springer: Berlin, Germany, 2008; volume 12, p. 1.
10. Bode J.W.; Carreira, E.M. A Mild and Chemoselective Method for the Reduction of Conjugated Isoxazolines to β -Hydroxy Ketones. *Org. Lett.* **2001**, *3*, 1587–1590.
11. Yermolina, M.V.; Wang, J.; Caffrey, M.; Rong, L.L.; Wardrop, D.J. Discovery, synthesis, and biological evaluation of a novel group of selective inhibitors of filoviral entry. *J. Med. Chem.* **2011**, *54*, 765–781.
12. Conti, P.; Amici, M.D.; di Ventimiglia, S.J.; Stensbøl, T.B.; Madsen, U.; Bräuner-Osborne, H.; Russo, E.; Sarro, G.D.; Bruno, G.; Micheli, C.D. Synthesis and anticonvulsant activity of novel bicyclic acidic amino acids. *J. Med. Chem.* **2003**, *46*, 3102–3108.
13. Kozikowski, A.P.; Park, P.U. Synthesis of streptazolin: Use of the aza-Ferrier reaction in conjunction with the INOC process to deliver a unique but sensitive natural product. *J. Org. Chem.* **1990**, *55*, 4668–4682.
14. Kozikowski, A.P.; Stein, P.D. The INOC route to carbocyclics: A formal total synthesis of (+)-sarkomycin. *J. Am. Chem. Soc.* **1982**, *104*, 4023–4024.
15. Okamoto, S.; Kobayashi, Y.; Kato, H.; Hotri, K.; Takahashi, T.; Tsuji, J.; Sato, F. Prostaglandin synthesis via two-component coupling. Highly efficient synthesis of chiral prostaglandin intermediates 4-alkoxy-2-alkyl-2-cyclopenten-1-one and 4-alkoxy-3-alkenyl-2-methylenecyclopentan-1-one. *J. Org. Chem.* **1988**, *53*, 5590–5592.
16. Trogu, E.; Vinattieri, C.; de Sarlo F.; Machetti, F. Acid-Base-Catalysed Condensation Reaction in Water: Isoxazolines and Isoxazoles from Nitroacetates and Dipolarophiles. *Chem. Eur. J.* **2012**, *18*, 2081–2093.
17. Raihan M.J.; Kavala, V.; Kuo, C.W.; Raju, B.R.; Yao, C.F. “On-water” synthesis of chromeno-isoxazoles mediated by [hydroxy (tosyloxy) iodo] benzene (HTIB). *Green Chem.* **2010**, *12*, 1090–1096.
18. Cecchi, L.; de Sarlo, F.; Machetti, F. Synthesis of 4,5-Dihydroisoxazoles by Condensation of Primary Nitro Compounds with Alkenes by Using a Copper/Base Catalytic System. *Chem. Eur. J.* **2008**, *14*, 7903–7912.
19. Belenkii, L.D.; Zelinsky, N.D. Nitrile Oxides. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, second edition; Feuer, H., Ed.; John Wiley and Sons: Hoboken, NJ, USA, 2008; p. 1.
20. Kankala, S.; Kankala, R.K.; Gundepaka, P.; Thota, N.; Nerella, S.; Gangula, M.R.; Guguloth, H.; Kagga, M.; Vadde, R.; Vasam, C.S. Regioselective synthesis of isoxazole-mercaptobenzimidazole hybrids and their *in vivo* analgesic and anti-inflammatory activity studies. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1306–1309.
21. Vitale, P.; Nunno, L.D. A novel synthesis of *N*-unsubstituted β -enamino thioesters from 3-arylisoxazoles and 3-aryl-5-phenylthio-2-isoxazolines. *Synthesis* **2010**, 3195–3203, doi:10.1055/s-0030-1258186.
22. Domingo, L.R.; Chamorro E.; Perez, P. An Analysis of the Regioselectivity of 1,3-Dipolar Cycloaddition Reactions of Benzonitrile N-Oxides Based on Global and Local Electrophilicity and Nucleophilicity Indices. *Eur. J. Org. Chem.* **2009**, *2009*, 3036–3044.
23. Grecian, S.; Fokin, V.V. Ruthenium-Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles. *Angew. Chem. Int. Ed.* **2008**, *47*, 8285–8287.

24. Barr, L.; Lincoln, S.F.; Easton, C.J. Reversal of regioselectivity and enhancement of rates of nitrile oxide cycloadditions through transient attachment of dipolarophiles to cyclodextrins. *Chem. Eur. J.* **2006**, *12*, 8571–8580.
25. Han, L.; Zhang, B.; Xiang, C.; Yan, J. One-Pot Synthesis of Isoxazolines from Aldehydes Catalyzed by Iodobenzene. *Synthesis* **2014**, *46*, 503–509.
26. Xiang, C.; Li, T.; Yan, J. Hypervalent Iodine-Catalyzed Cycloaddition of Nitrile Oxides to Alkenes. *Synth. Commun.* **2014**, *44*, 682–688.
27. Chau, J.; Xu, S.; Ciufolini, M.A. Assembly of a Key Dienic Intermediate for Tetrodotoxin via a Machetti-DeSarlo Reaction. *J. Org. Chem.* **2013**, *78*, 11901–11910.
28. Mendelsohn, B.A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V.S.; Ciufolini, M.A. Oxidation of oximes to nitrile oxides with hypervalent iodine reagents. *Org. Lett.* **2009**, *11*, 1539–1542.
29. Becker N.; Carreira, E.M. Hydroxyl-Directed Nitrile Oxide Cycloaddition Reactions with Cyclic Allylic Alcohols. *Org. Lett.* **2007**, *9*, 3857–3858.
30. Perez, L.; Khouly, M.E.E.; Cruz, P.D.L.; Araki, Y.; Ito O.; Langa, F. Comparison between the Photophysical Properties of Pyrazolo- and Isoxazolo[60]fullerenes with Dual Donors (Ferrocene, Aniline and Alkoxyphenyl). *Eur. J. Org. Chem.* **2007**, *2007*, 2175–2185.
31. Hansen, T.V.; Wu, P.; Fokin, V.V. One-pot copper (I)-catalyzed synthesis of 3,5-disubstituted isoxazoles. *J. Org. Chem.* **2005**, *70*, 7761–7764.
32. Cha, M.Y.; Choi, B.C.; Kang, K.H.; Pae, A.N.; Choi, K.I.; Cho, Y.S.; Koh, H.Y.; Lee, H.Y.; Jung, D.; Kong, J.Y. Design and synthesis of a piperazinylalkylisoxazole library for subtype selective dopamine receptor ligands. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1327–1331.
33. Nonn, M.; Kiss, L.; Forró, E.; Mucsi, Z.; Fülöp, F. Synthesis of novel isoxazoline-fused cyclic β -amino esters by regio- and stereo-selective 1,3-dipolar cycloaddition. *Tetrahedron* **2011**, *67*, 4079–4085.
34. Tu, Z.; Jang, Y.; Lin, C.; Liu, J.T.; Hsu, J.; Sastry M.N.V.; Yao, C.F. The study of reaction mechanism for the transformation of nitronate into nitrile by phosphorus trichloride. *Tetrahedron* **2005**, *61*, 10541–10551.
35. Liu, J.T.; Lin, W.W.; Jang, J.J.; Liu, J.Y.; Yan, M.C.; Hung, C.; Kao, K.H.; Wang Y.; Yao, C.F. One-pot synthesis of five- or six-membered carbocycles through intramolecular cycloadditions by the use of ethyl chloroformate. *Tetrahedron* **1999**, *55*, 7115–7128.
36. Yan, M.C.; Liu, J.Y.; Lin, W.W.; Kao, K.H.; Liu, J.T.; Jang, J.J.; Yao, C.F. One-pot synthesis of five-membered cyclic thioethers or ethers via intramolecular nitrile oxide-olefin cycloaddition (INOC) or intramolecular alkoxy-carbonyl nitronate-olefin cycloaddition (IAOC) by the use of methyl chloroformate. *Tetrahedron* **1999**, *55*, 12493–12514.
37. Butler, J.D.; Donald, M.B.; Ding, Z.; Fettingner, J.C.; Kurth, M.J. Phenylsulfonyl as a directing group for nitrile oxide cycloadditions and mCPBA epoxidations. *Tetrahedron Lett.* **2009**, *50*, 5110–5112.
38. Roda, G.; Conti, P.; Amici, M.D.; He, J.; Polavarapu, P.L.; Micheli C.D. Enantiopure stereoisomeric homologues of glutamic acid: Chemoenzymatic synthesis and assignment of their absolute configurations. *Tetrahedron Asymmetry* **2004**, *15*, 3079–3090.
39. Akritopoulou-Zanze, I.; Gracias, V.; Moore, J.D.; Djuric, S.W. Synthesis of novel fused isoxazoles and isoxazolines by sequential Ugi/INOC reactions. *Tetrahedron Lett.* **2004**, *45*, 3421–3423.

40. Giorgi, G.; Lampariello, L.R.; Minetto, G.; Paoli, M.L.; Riello, V.; Rodriguez, M.; Segà, A. Developing Molecular Diversity in the Construction of a Family of Bicyclic Isoxazolines Scaffolds: Control of Regio- and Diastereoselectivities. *Eur. J. Org. Chem.* **2003**, 4777–4785.
41. Park, K.H.; Olmstead, M.M.; Kurth, M.J. Diastereoselective synthesis of cyclopentanoids with hydantoin and isoxazoline substituents. *J. Org. Chem.* **1998**, *63*, 113–117.
42. Jung, M.E.; Vu, B.T. Substituent effects on intramolecular dipolar cycloadditions: The gem-dicarboalkoxy effect. *Tetrahedron Lett.* **1996**, *37*, 451–454.
43. Gao, S.; Tu, Z.; Kuo, C.W.; Liu, J.T.; Chu, C.M.; Yao, C.F. Efficient conversion of nitronate into nitrile oxide using cyanuric chloride. One-pot synthesis of bicyclic isoxazolines and isoxazoles from nitroalkenes. *Org. Biomol. Chem.* **2006**, *4*, 2851–2857.
44. Cheng, Q.; Oritani, T.; Horiguchi, T.; Shi, Q. High Stereoselectivity in One-Pot Intramolecular Cycloadditions of Olefinic Silyl Nitronates. *Eur. J. Org. Chem.* **1999**, *1999*, 2689–2694.
45. Namboothiri, I.N.N.; Hassner, A. A Highly Stereoselective One-Pot Tandem Consecutive 1,4-Addition-Intramolecular 1,3-Dipolar Cycloaddition Strategy for the Construction of Functionalized Five- and Six-Membered Carbocycles. *J. Org. Chem.* **1997**, *62*, 485–492.
46. Basel, Y.; Hassner, A. An improved method for preparation of nitrile oxides from nitroalkanes for *in situ* dipolar cycloadditions. *Synthesis* **1997**, *1997*, 309–312.
47. Mukaiyama, T.; Hoshino, T. The Reactions of Primary Nitroparaffins with Isocyanates I. *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342.
48. Glorius, F.; Grohmann, C.; Wang, H. Rh [III]-Catalyzed C-H Amidation Using Aroyloxycarbamates to Give N-Boc Protected Arylamines. *Org. Lett.* **2013**, *15*, 3014–3017.
49. Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.M. Macrolactonizations in the Total Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, PR1–PR40.
50. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A rapid esterification by means of mixed anhydride and its application to large-ring lactonization. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
51. Dehaen, W.; Hassner, A. Stereoselectivity in intramolecular 1,3-dipolar cycloadditions. Nitrile oxides *versus* silyl nitronates. *Tetrahedron Lett.* **1990**, *31*, 743–746.
52. Kao, K.H.; Yang, C.S.; Liu, J.T.; Lin, W.W.; Fang, H.Y.; Yao, C.F.; Chen, K. One-pot synthesis of the hydroximoyl chlorides and [3.3.0] bicyclic compounds from the reactions of β -nitrostyrenes with stabilized nucleophiles. *Tetrahedron* **1998**, *54*, 13997–14014.
53. McKillop, A.; Kobylecki, R.J. An investigation of the reaction of primary nitroalkanes with acetic anhydride/sodium acetate. *Tetrahedron* **1974**, *30*, 1365–1371.

Sample Availability: Samples of the compounds **2a–2o** and **4a–4f** are available from the authors.