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REGIODIVERGENT RING OPENING REACTIONS OF 2-ARYLATED 3-NITROCYCLOPROPANE-1,1-DICARBOXYLATES LEADING TO POLYFUNCTIONALIZED DIPOLES

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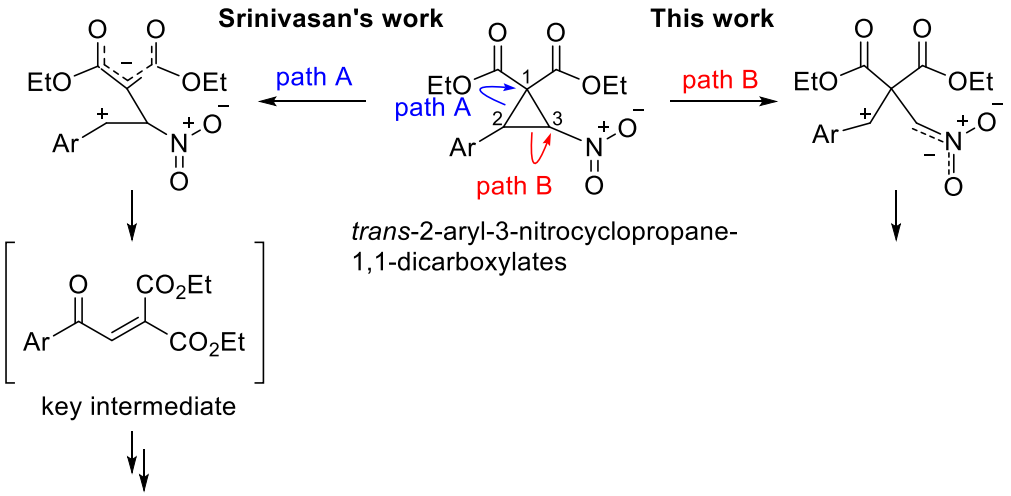
Abstract – Two kinds of Lewis acid induced ring-opening reactions of 2-aryl-3-nitrocyclopropane-1,1-dicarboxylates proceeded to afford 5-aryl-2-isoxazolines and γ-keto acid derivatives, respectively. Different ring-opening modes could be controlled by choosing the ligand or solvent.

INTRODUCTION

Donor−acceptor (D−A) cyclopropanes have recently attracted widespread attention because of their synthetic utility for a variety of carbocyclic[1] and heterocyclic[2] frameworks. They have 1,3-dipole character due to the stabilization of the cation and anion by the donor and the acceptor substituents, respectively.[3] Therefore, D−A cyclopropanes serve as C3 building blocks upon cleavage of C–C bond induced by Lewis acid, Brønsted acid or base. Recently, nitro substituted D–A cyclopropanes has been intensively studied due to the versatile reactivity and wide transformability of nitro groups.[4] Indeed, Srinivasan *et al*. successfully synthesized imidazoles, quinoxalines, benzo[1,4]thiazines,[5] oxazoles,[6] thiophenes,[7] and pyrido[1,2-*a*]pyrimidin-4-one derivatives[8] via Lewis acid promoted ring opening rearrangement of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates. In these cases, only C1–C2 bond cleavage selectively occurred to yield (aroylmethylidene)malonates as a key intermediate (Scheme 1, path A) although formation of two dipolar structures is possible. To the best of our knowledge, no reaction is

This paper is dedicated to Professor Yasuyuki Kita on his 77th birthday.



Scheme 1. Possible ring opening pattern of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates

known which includes C2–C3 bond cleavage between aryl substituted and nitro substituted carbons (path B). Thus, the seeking for novel reactivity of nitrocyclopropanes is of great interest.

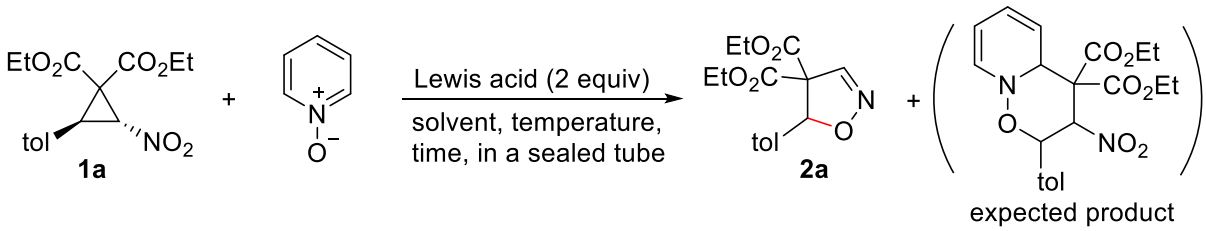
Under these circumstances, we explored Lewis acid promoted ring-opening reaction of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates **1**, and subsequent formal [3+3] cycloaddition of the resultant dipole with pyridine *N*-oxide (PNO). During the studies, formation of 2-isoxazoline *via* unexpected ring opening mode (C2–C3 bond cleavage) was observed upon treatment of nitrocyclopropane with $SnCl_2$. Only single description was found in the literature, which deals with the formation of isoxazoline framework from a nitrocyclopropane *via* iodide induced ring-opening followed by intramolecular *O*-attack of the nitro group.[9] Furthermore, the regioselective ring-opening reaction could be controlled by choosing appropriate ligand, and applied to the synthesis of multiply functionalized 2-isoxazolines under mild conditions.

RESULTS AND DISCUSSION

Initially, we studied the reaction of *trans*-2-tolyl-3-nitrocyclopropane-1,1-dicarboxylate (**1a**) and PNO in the presence of Lewis acids with expecting the formation of formal [3+3] product (Table 1). Strong Lewis acids such as $AlCl_3$, $InCl_3$, or $BF_3{\cdot}OEt_2$[10] caused no change for the starting material, which was presumably due to the formation of complex with weakly basic PNO (entries 1–3).[11] On the other hand, $SnCl_2$, weak Lewis acid, brought about the consumption of nitrocyclopropane, in which small amount of diethyl 5-(*p*-tolyl)isoxazoline-4,4-dicarboxylate (**2a**)[12] was formed (entry 4). This structure is formed by the C2–C3 bond cleavage followed by annulation including C–O bond formation and reduction. Moreover, functionalized 2-isoxazoline derivatives consist an important class of heterocycles including a number of biologically active compounds such as Afoxolancer, Fluralaner, and VGX-1027. Hence, this

result prompted us to study short optimization of reaction time and temperature. When the reaction was conducted at 100 ºC for 14 h, **1a** was completely consumed (entry 5). Interestingly, this reaction did not proceed in the absence of PNO (entry 6). To further improve the results, we surveyed some other solvents (entries 7–12). Etheric solvents such as THF and 1,4-dioxane were found to be suitable solvents to afford 2-isoxazoline **2a** in high yields. It is surprising that benzene is also effective for this reaction despite the lower polarity.

Table 1. Optimization of reaction conditions

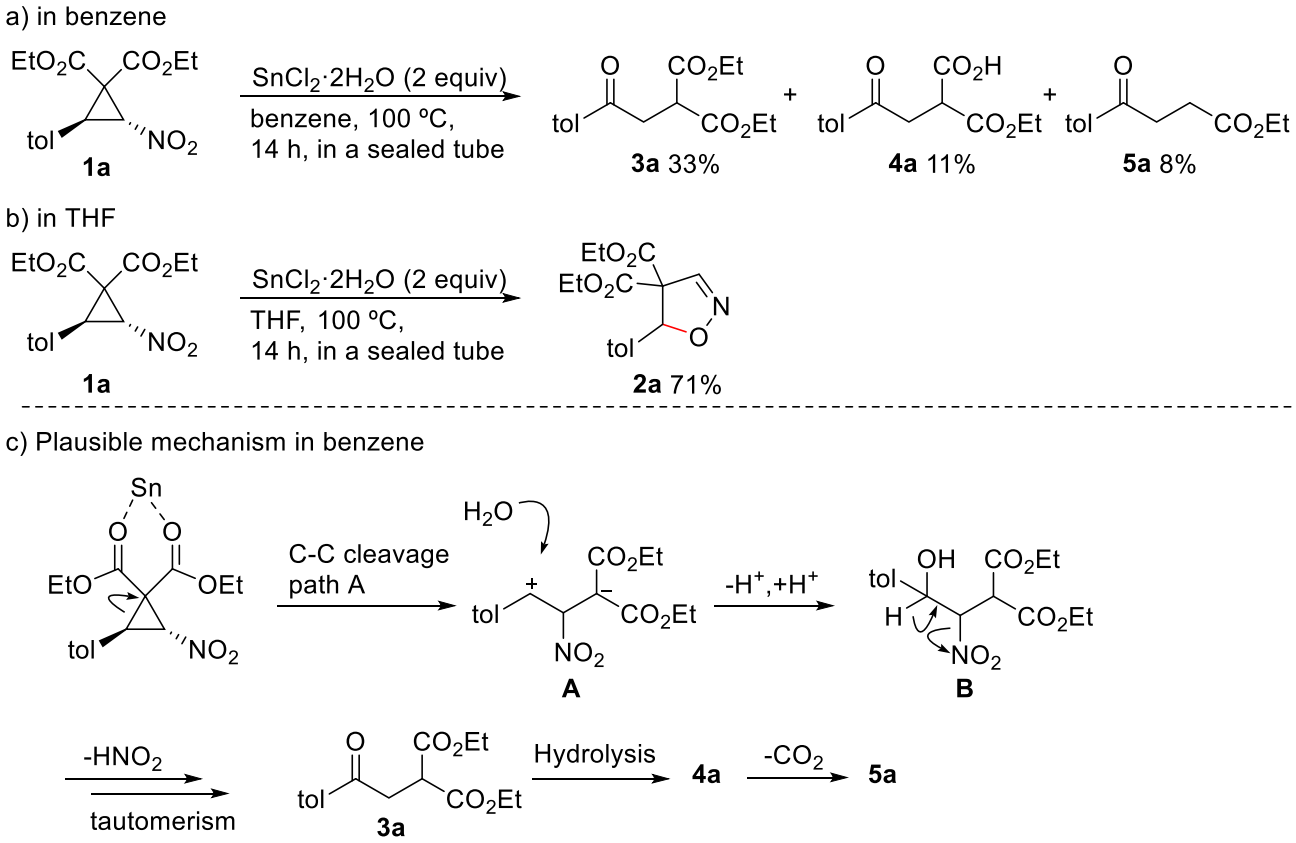


Entry	Reaction conditions				Yield (%)[a]	
	Lewis acid	Solvent	temp. (ºC)	time (h)	Recovery of **1a**	**2a**
1	$AlCl_3$	chloroform	65	6	>99	–
2	$InCl_3$	chloroform	65	6	>99	–
3	$BF_3{\cdot}OEt_2$	chloroform	65	6	>99	–
4	$SnCl_2{\cdot}2H_2O$	chloroform	65	6	61	11
5	$SnCl_2{\cdot}2H_2O$	chloroform	100	14	0	43 (37)[b]
6[c]	$SnCl_2{\cdot}2H_2O$	chloroform	100	14	0	0
7	**$SnCl_2{\cdot}2H_2O$**	**THF**	**100**	**14**	**0**	**68**
8	$SnCl_2{\cdot}2H_2O$	1,4-dioxane	100	14	trace	67
9	$SnCl_2{\cdot}2H_2O$	acetonitrile	100	14	0	24
10	**$SnCl_2{\cdot}2H_2O$**	**benzene**	**100**	**14**	**0**	**69**
11	$SnCl_2{\cdot}2H_2O$	toluene	100	14	20	46
12	$SnCl_2{\cdot}2H_2O$	hexane	100	14	14	27

[a]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [b]Isolated yield. [c]In the absence of PNO.

Next, we focused on the reaction mechanism of this ring-opening reaction and carried out several control experiments. Regarding the role of PNO, we conducted reactions in the absence of PNO, in which, to our surprise, different reactivities were observed depending on solvents (Scheme 2). When benzene was used as solvent, ring-opened products **3-5a** were obtained through different cleavage pattern (path A). On the

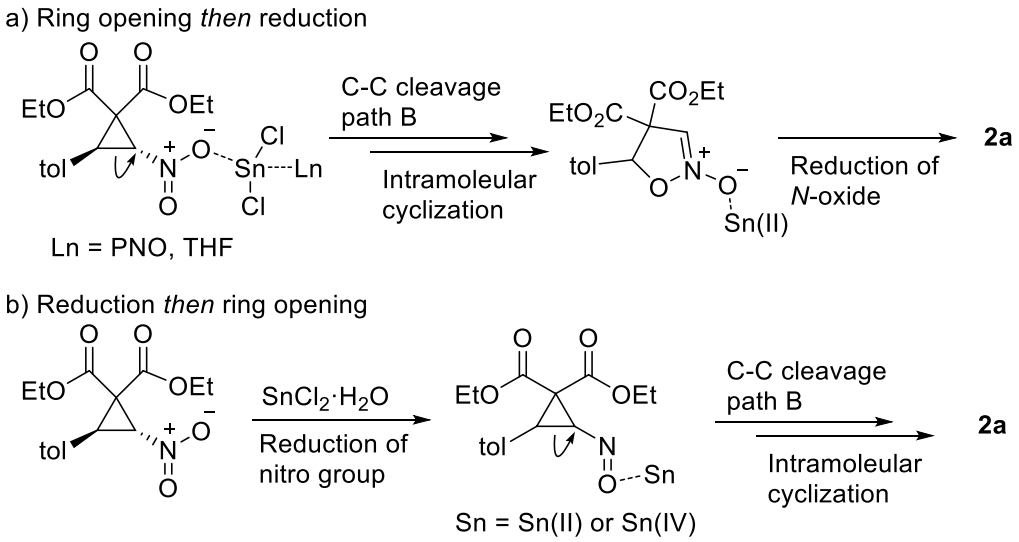
other hand, isoxazoline **2a** was obtained as a sole product when the reaction performed in THF even in the absence of PNO. In the case of benzene, the 1,3-dipolar intermediate **A** was formed through the $SnCl_2$ promoted ring cleavage at C1–C2 as shown in Scheme 2(c). After addition of water to the cationic benzyl carbon leading to intermediate **B**, **3a** was formed by elimination of HNO_2 followed by tautomerism. Meanwhile, the mono-hydrolysis of **3a** afforded **4a**, and the subsequent decarboxylation delivered compound **5a**. These facts suggested PNO or THF promote C2–C3 bond cleavage in the presence of $SnCl_2$.



Scheme 2. Control experiments and plausible reaction mechanism for the formation of **3-5a**

Although we could not obtain any direct evidence for forming the complex of $SnCl_2$ with PNO or THF under the reaction conditions employed, both stable complexes, $SnCl_2·(PNO)_2$[13] and $SnCl_2·(THF)_x$,[14] are enough stable to be detected. These complexes facilitated to coordinate with the nitro group preferentially to promote the ring-opening reaction at C2-C3 (Scheme 3a). Subsequently, the intramolecular cyclization furnishes the isoxazoline *N*-oxide, and then, reduction affords product **2a**. As an alternative route, reduction of the nitro group by $SnCl_2$ firstly occurred leading to nitroso group (Scheme 3b). The coordination of tin species (Sn(II) or Sn(IV)) to nitroso group facilitated the ring-opening reaction and the

subsequent cyclization to afford isoxazoline **2a**. In this case, ligands are considered to activate the reducing ability of tin species enough for conversion of a nitro group to a nitroso group.

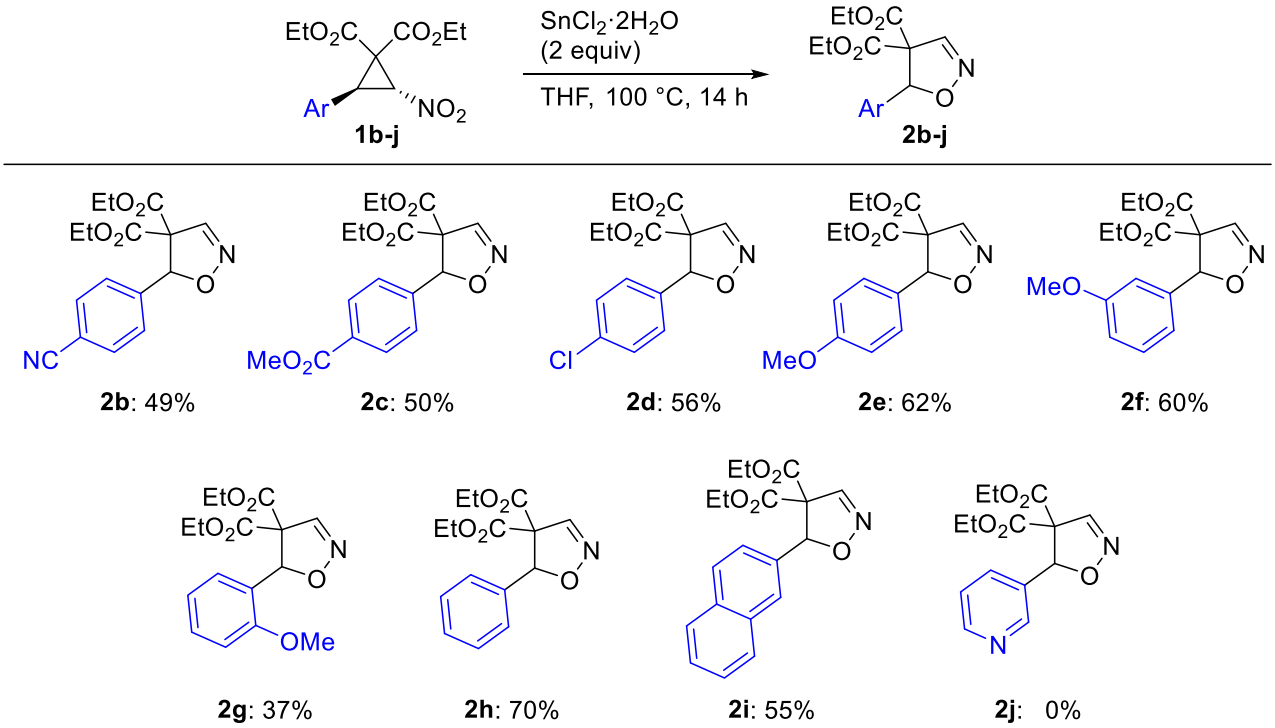


Scheme 3. Plausible role of tin in the presence of PNO or THF in the reaction

To obtain deep insight into the reaction mechanism, ^{119}Sn NMR studies were also performed to know the change in valence of tin species during the reaction. The standard products, tin(II) chloride dehydrate and tin(IV) chloride pentahydrate, show signals at -370 ppm and -625 ppm, respectively. After the reaction was conducted in benzene, the solvent was evaporated, and the residue was subjected to the ^{119}Sn NMR measurement using DMSO-d_6 as a solvent with Me_4Sn as an internal standard. A sharp singlet signal was observed at -625 ppm corresponding to the Sn(IV), which indicates tin is oxidized during the reaction. Based on these results, tin species is considered to serve not only as a Lewis acid to promote the ring opening but also as a reductant, although a possibility serving as an initiator of radical reaction cannot be excluded.

Next, the scope and limitations of this reaction were studied using various nitrocyclopropanes **1b–j** (Table 2). Several nitrocyclopropanes **1b–e** possessing a *para*-substituted aryl group were subjected to this reaction. This reaction was not considerably influenced by either electron-withdrawing group (-CN, -CO_2Me, -Cl) or electron-donating group (-OMe) to give the corresponding isoxazolines in moderate to good yields. Although a similar reactivity was observed for the *meta*-OMe derivative **1f**, the yield of **2g** was decreased by the steric hindrance of the *ortho*-OMe substituent. While the reaction proceeded smoothly with phenyl or naphthyl substituted cyclopropanes **1h-i** giving the corresponding 2-isoxazoline in good yield, 3-pyridyl substituted cyclopropane **1j** did not undergo the reaction, which might be due to the formation of the salt of $SnCl_2$ with the pyridyl group.

Table 2. Synthesis of 5-arylated 2-isoxazoline dicarboxyrates



In conclusion, we have demonstrated the generation of two types of 1,3-dipole intermediates *via* different ring-opening mode of *trans*-2-aryl-3-nitrocyclopropnae-1,1-dicarboxylates **1**. 5-Aryl-2-isoxazolines **2** were obtained by $SnCl_2$ induced C–C bond cleavage in the presence of ligand such as PNO and THF. In the absence of ligands, γ-keto esters were obtained through the ring-opening caused by coordination of $SnCl_2$ on malonate moiety and the subsequent elimination of HNO_2.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 spectrometer (400 MHz and 100 MHz, respectively) in $CDCl_3$ using TMS as an internal standard. The assignments of the ^{13}C NMR were performed by DEPT experiments. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer equipped with an ATR detector. High-resolution mass spectra were obtained on an AB SCIEX Triplet TOF 4600 mass spectrometer. Melting points were recorded on an SRS-Optimelt automated melting point system and were uncorrected.

General procedures for the preparation of 2-aryl-3-nitrocyclopropane-1,1-dicarboxylate

Nitrocyclopropanes **1** were synthesized according to a reported procedure.[5] A solution of nitrostyrene (6 mmol) and diethyl 2-bromomalonate (8 mmol) in DMF (20 mL) was stirred for 5 min at room temperature. After addition of triethylamine (14 mmol), the reaction mixture was stirred at room

temperature overnight, and quenched with NH_4Cl aq. (50 mL). The resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (30 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated. The crude product was purified by silica gel column chromatography to give the product.

Diethyl 2-(4-methylphenyl)-3-nitrocyclopropane-1,1-dicarboxylate (1a)[5]

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.31 (dd, *J* = 7.1, 7.1 Hz, 3H), 2.32 (s, 3H), 3.99 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.08 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.15 (d, *J* = 5.9 Hz, 1H), 4.28 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.33 (dq , *J* = 7.1, 10.8 Hz, 1H), 5.37 (d, *J* = 5.9 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.9 (CH_3), 21.1 (CH_3), 37.4 (CH), 46.3 (C), 62.6 (CH_2), 62.9 (CH_2), 66.3 (CH), 127.2 (C), 128.1 (CH), 129.4 (CH), 138.4 (C), 163.2 (C), 163.3 (C).

Diethyl 2-(4-cyanophenyl)-3-nitrocyclopropane-1,1-dicarboxylate (1b)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.31 (dd, *J* = 7.2, 7.2 Hz, 3H), 4.01 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.06 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.21 (d, *J* = 6.0 Hz, 2H), 4.30 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.34 (dq, *J* = 7.2, 10.8 Hz, 1H), 5.40 (d, d, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 13.8 (CH_3), 36.8 (CH), 46.1 (C), 63.1 (CH_2), 63.3 (CH_2), 65.8 (CH), 112.7 (C), 118.0 (C), 129.3 (CH), 132.5 (CH), 135.5 (C), 162.7 (C), 162.8 (C); IR (ATR) 1364, 1560, 1734, 2343 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{16}N_2O_6Na$: 355.0901, found: 355.0901.

Diethyl 2-[(4-methoxycarbonyl)phenyl]-3-nitrocyclopropane-1,1-dicarboxylate (1c)

White powder; Mp 98.0–99.0 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.29 (dd, *J* = 7.1, 7.1 Hz, 3H), 3.89 (s, 3H), 3.96 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.00 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.20 (d, *J* = 6.0 Hz, 1H), 4.27 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.32 (dq, *J* = 7.2, 10.8 Hz, 1H), 5.41 (d, *J* = 6.0 Hz, 1H), 7.34 (d, *J* = 8.2, 2H), 7.98 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.8 (CH_3), 37.0 (CH_3), 46.1 (C), 52.2 (CH), 62.8 (CH_2), 63.1 (CH_2), 66.0 (CH), 128.5 (CH), 129.9 (CH), 130.4 (C), 135.2 (C), 162.9 (C), 163.0 (C), 166.3 (C); IR (ATR) 1371, 1557, 1731, 1732, 1748 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{17}H_{19}NO_8Na$: 388.1003, found: 388.1005.

Diethyl 2-(4-chlorophenyl)-3-nitrocyclopropane-1,1-dicarboxylate (1d)[5]

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.30 (dd, *J* = 7.1, 7.1 Hz, 3H), 4.00 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.05 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 4.28 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.33 (dq, *J* = 7.1, 10.8 Hz, 1H), 5.37 (d, *J* = 6.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 13.8 (CH_3), 36.7 (CH), 46.1 (C), 62.8 (CH_2), 63.1 (CH_2), 66.1 (CH), 128.8 (C), 129.0 (CH), 129.7 (CH), 134.6 (C), 163.0 (C), 163.0 (C).

Diethyl 2-(4-methoxyphenyl)-3-nitrocyclopropane-1,1-dicarboxylate (1e)[5]

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.30 (dd, *J* = 7.2, 7.2 Hz, 3H), 3.79 (s, 3H), 4.00 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.04 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.13 (d, *J* = 6.0 Hz, 1H), 4.28 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.32 (dq, *J* = 7.2, 10.8 Hz, 1H), 5.60 (d, *J* = 6.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 13.8 (CH_3), 37.1 (CH), 46.4 (C), 55.3 (CH_3), 62.6 (CH_2), 66.5 (CH_2), 114.1 (CH), 122.1 (C), 129.5 (CH), 159.7 (C), 163.2 (C), 163.3 (C); HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{19}NO_7$: 360.1053, found: 360.1037.

Diethyl 2-(3-methoxyphenyl)-3-nitrocyclopropane-1,1-dicarboxylate (1f)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 4.00 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.04 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.17 (d, *J* = 6.0 Hz, 1H), 4.29 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.33 (dq, *J* = 7.2, 10.8 Hz, 1H), 5.38 (d, *J* = 6.0 Hz, 1H), 6.80 (br s, 1H), 6.86–6.83 (m, 2H), 7.23 (dd, *J* = 6.4, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.8 (CH_3), 37.4 (CH), 46.2 (C), 55.3 (CH_3), 62.6 (CH_2), 63.0 (CH_2), 66.3 (CH), 113.4 (CH), 114.1 (CH), 120.5 (CH), 129.8 (CH), 131.7 (C), 159.8 (C), 163.1 (C), 163.2 (C); IR (ATR) 1366, 1557, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{19}NO_7Na$: 360.1054, found: 360.1038.

Diethyl 2-(2-methoxyphenyl)-3-nitrocyclopropane-1,1-dicarboxylate (1g)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.31 (dd, *J* = 7.2, 7.2 Hz, 3H), 3.84 (s, 3H), 4.01 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.04 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.08 (d, *J* = 6.0 Hz, 1H), 4.29 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.32 (dq, *J* = 7.2, 10.8 Hz, 1H), 5.29 (d, *J* = 6.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.90 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.28 (dd, *J* = 8.4, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.9 (CH_3), 33.9 (CH), 45.5 (C), 55.5 (CH_3), 62.4 (CH_2), 62.7 (CH_2), 67.0 (CH), 110.6 (CH), 118.9 (C), 120.3 (CH), 129.1 (CH), 129.8 (CH), 158.3 (C), 163.5 (C), 163.8 (C); IR (ATR) 1364, 1559, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{19}NO_7Na$: 360.1054, found: 360.1054.

Diethyl 3-nitro-2-phenylcyclopropane-1,1-dicarboxylate (1h)[5]

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.30 (dd, *J* = 7.1, 7.1 Hz, 3H), 3.97 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.01 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.19 (d, *J* = 5.9 Hz, 1H), 4.29 (dq , *J* = 7.2, 10.8 Hz, 1H), 4.33 (dq, *J* = 7.2, 10.8 Hz, 1H), 5.40 (d, *J* = 5.9 Hz, 1H), 7.35–7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.8 (CH_3), 37.5 (CH), 46.2 (C), 62.6 (CH_2), 63.0 (CH_2), 66.2 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 130.3 (C), 163.1 (C), 163.3 (C).

Diethyl 2-(2-naphtyl)-3-nitrocyclopropane-1,1-dicarboxylate (1i)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.33 (dd, *J* = 7.1, 7.1 Hz, 3H), 3.93 (dq , *J* = 7.1, 10.8 Hz, 1H), 3.97 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.32 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.35 (d, *J* = 5.9 Hz, 1H), 4.36 (dq, *J* = 7.2, 10.8 Hz, 1H), 5.52 (d, *J* = 5.9 Hz, 1H), 7.37 (dd, *J* = 8.5, 1.8 Hz, 1H),

7.53-7.47 (m, 2H), 7.74 (br s, 1H), 7.82–7.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.9 (CH_3), 37.7 (CH), 46.4 (C), 62.7 (CH_2), 63.1 (CH_2), 66.4 (CH), 125.7 (CH), 126.6 (CH), 126.7 (CH), 127.6 (CH), 127.6 (C), 127.6 (C), 127.7 (CH), 127.8 (CH), 128.6 (CH), 133.0 (C), 163.2 (C), 163.3 (C), IR (ATR) 1371, 1555, 1730, 1744 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calculated for $C_{19}H_{20}NO_6$: 356.1140, found: 356.1146.

Diethyl 3-nitro-2-(3-pyridyl)cyclopropane-1,1-dicarboxylate (1j)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.31 (dd, *J* = 7.2, 7.2 Hz, 3H), 4.01 (dq, *J* = 7.2, 10.4 Hz, 1H), 4.07 (dq, *J* = 7.2, 10.4 Hz, 1H), 4.17 (d, *J* = 6.0 Hz, 1H), 4.30 (dq, *J* = 7.2, 10.4 Hz, 1H), 4.34 (dq, *J* = 7.2, 10.4 Hz, 1H), 5.42 (d, *J* = 6.0 Hz, 1H), 7.28 (dd, *J* = 4.4, 8.0 Hz, 1H), 7.60 (ddd, *J* = 0.8, 4.4, 8.0 Hz, 1H), 8.57–8.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.8 (CH_3), 34.8 (CH), 45.8 (C), 63.0 (CH_2), 63.2 (CH_2), 65.6 (CH), 123.3 (CH), 126.4 (C), 149.8 (CH), 149.8 (CH), 162.8 (C), 162.9 (C); IR (ATR) 1288, 1367, 1559, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calculated for $C_{14}H_{17}N_2O_6$: 309.1081, found: 309.1081.

General procedures for the synthesis of 2-isoxazoline 2 (in THF)

To the solution of $SnCl_2$•$2H_2O$ (0.6 mmol) in THF (1 mL) in a sealed tube, the solution of nitrocyclopropane **1** (0.3 mmol) in THF (1 mL) was added. The resultant mixture was heated at 100 ºC for 14 h, and the solvent was removed in vacuo. The residue was extracted by Et_2O and then evaporated. The crude product was purified by silica gel column chromatography to give the product.

Measurement of ^{119}Sn NMR spectra

To know the valence change of tin species after the reaction, ^{119}Sn NMR spectra was measured. To a solution of $SnCl_2$•$2H_2O$ (0.6 mmol) in benzene (1 mL) in a sealed tube, was added the solution of nitrocyclopropane **1** (0.3 mmol) in benzene (1 mL), and the resultant mixture was heated at 100 ºC for 14 h. After removal of the solvent in vacuo, the residue was dissolved in DMSO-d_6, and subjected to the measurement of ^{119}Sn NMR using Me_4Sn as an internal standard.

Diethyl 5-(4-methylphenyl)isoxazoline-4,4(5*H*)-dicarboxylate (2a)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.31 (dd, *J* = 7.1, 7.1 Hz, 3H), 2.32 (s, 3H), 3.67 (dq , *J* = 7.2, 10.7 Hz, 1H), 3.73 (dq , *J* = 7.2, 10.7 Hz, 1H), 4.30 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.36 (dq , *J* = 7.1, 10.8 Hz, 1H), 6.18 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4, 2H), 7.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (CH_3), 14.0 (CH_3), 21.2 (CH_3), 62.4 (CH_2), 63.1 (CH_2), 75.3 (C), 85.7 (CH), 126.9 (CH), 128.9 (CH), 131.7 (C), 138.7 (C), 143.0 (CH), 164.9 (C), 165.5 (C); IR (ATR) 1746, 1732 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calculated for $C_{16}H_{20}NO_5$: 306.1336, found: 306.1336.

Diethyl 5-[(4-methoycarbonyl)phenyl]isoxazoline-4,4(5*H*)-dicarboxylate (2b)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.33 (dd, *J* = 7.1, 7.1 Hz, 3H),

3.64 (dq, *J* = 7.1, 10.8 Hz, 1H), 3.72 (dq , *J* = 7.1, 10.8 Hz, 1H), 3.92 (s, 3H), 4.32 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.39 (dq , *J* = 7.1, 10.8 Hz, 1H), 6.24 (s, 1H), 7.30 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 14.0 (CH_3), 52.2 (CH_3), 62.6 (CH_2), 63.3 (CH_2), 75.5 (C), 85.1 (CH), 127.0 (CH), 129.4 (CH), 130.7 (C), 139.8 (C), 143.1 (CH), 164.5 (C), 165.3 (C), 166.6 (C); IR (ATR) 1715, 1730, 1748 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calculated for $C_{17}H_{20}NO_7$: 350.1234, found: 350.1233.

Diethyl 5-(4-chlorophenyl)isoxazoline-4,4(5*H*)-dicarboxylate (2c)

Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.32 (dd, *J* = 7.2 Hz, 3H), 3.70 (dq , *J* = 7.2, 10.8 Hz, 1H), 3.77 (dq , *J* = 7.2, 10.8 Hz, 1H), 4.30 (dq , *J* = 7.2, 10.8 Hz, 1H), 4.38 (dq , *J* = 7.2, 10.8 Hz, 1H), 6.17 (s, 1H), 7.27–7.32 (m, 4H), 7.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 14.0 (CH_3), 62.6 (CH_2), 63.3 (CH_2), 75.3 (C), 85.0 (CH), 128.4 (CH), 128.4 (CH), 133.8 (C), 134.9 (C), 143.1 (CH), 164.6 (C), 165.3 (C); IR (ATR) 1092, 1730, 1746 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calculated for $C_{15}H_{17}ClNO_5$: 326.0790, found: 326.0800.

Diethyl 5-(4-cyanophenyl)isoxazoline-4,4(5*H*)-dicarboxylate (2d)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.33 (dd, *J* = 7.2, 7.2 Hz, 3H), 3.68 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.75 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.32 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.39 (dq, *J* = 7.2, 10.8 Hz, 1H), 6.21 (s, 1H), 7.30 (s, 1H), 7.51 (d, *J* = 6.8 Hz, 2H), 7.64 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 13.9 (CH_3), 62.8 (CH_2), 63.5 (CH_2), 75.6 (C), 84.6 (CH), 112.9 (C), 118.3 (C), 127.8 (CH), 132.0 (CH), 140.0 (C), 143.1 (CH), 164.3 (C), 165.1 (C); IR (ATR) 1263, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{16}N_2O_5Na$: 339.0951, found:339.0941.

Diethyl 5-(4-methoxyphenyl)isoxazoline-4,4(5*H*)-dicarboxylate (2e)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, *J* = 6.8, 6.8 Hz, 3H), 1.31 (dd, *J* = 6.8, 6.8 Hz, 3H), 3.69 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.74 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.30 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.36 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.79 (s, 3H), 6.17 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 14.0 (CH_3), 55.3 (CH_3), 62.4 (CH_2), 63.1 (CH_2), 75.1 (C), 85.6 (CH), 113.6 (CH), 126.7 (C), 128.4 (CH), 143.0 (CH), 164.9 (C), 165.5 (C); IR (ATR) 1516, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{19}NO_6Na$: 344.1105, found: 344.1094.

Diethyl 5-(3-methoxyphenyl)isoxazoline-4,4(5*H*)-dicarboxylate (2f)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.25 (dd, *J* = 7.2, 7.2 Hz, 3H), 3.62 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.68 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.71 (s, 3H), 4.23 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.30 (*J* = 7.2, 10.8 Hz, 1H), 6.11 (s, 1H), 6.77 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.82 (s, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 7.6, 8.4 Hz, 1H), 7.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3 (CH_3), 13.0 (CH_3), 54.3 (CH_3), 61.4 (CH_2), 62.1(CH_2), 74.4 (C), 84.6 (CH), 111.1 (CH), 114.0 (CH), 118.3 (CH), 128.3 (CH), 135.2 (C), 142.1 (CH), 158.5 (C), 163.8 (C), 164.5 (C); IR (ATR) 1263, 1735, 1740 cm^{-1};

HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{19}NO_6Na$: 344.1105, found: 344.1089.

Diethyl 5-(2-methoxyphenyl)isoxazoline-4,4(5*H*)-dicarboxylate (2g)

Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.34 (dd, *J* = 7.2, 7.2 Hz, 3H), 3.68 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.70 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.82 (s, 3H), 4.30 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.35 (*J* = 7.2, 10.8 Hz, 1H), 6.68 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.94 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.26–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (CH_3), 14.0(CH_3), 55.4 (CH_3), 62.0 (CH_2), 62.9 (CH_2), 74.7 (C), 81.3 (CH), 110.3 (CH), 120.4 (CH), 124.0 (C), 128.1 (CH), 130.0 (CH), 142.7 (CH), 157.0 (C), 165.2 (C), 165.3 (C); IR (ATR) 1252, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{19}NO_6Na$: 344.1105, found:344.1098.

Diethyl 5-phenylisoxazoline-4,4(5*H*)-dicarboxylate (2h)

Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.32 (dd, *J* = 7.1, 7.1 Hz, 3H), 3.63 (dq , *J* = 7.1, 10.7 Hz, 1H), 3.70 (dq , *J* = 7.1, 10.7 Hz, 1H), 4.31 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.37 (dq , *J* = 7.1, 10.8 Hz, 1H), 6.21 (s, 1H), 7.29 (s, 1H), 7.37–7.29(m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (CH_3), 14.0 (CH_3), 62.4 (CH_2), 63.2 (CH_2), 75.4 (C), 85.7 (CH), 127.0 (CH), 128.2 (CH), 128.9 (CH), 134.8 (C) 143.0 (CH), 164.8 (C), 165.5 (C); IR (ATR) 1732, 1738 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calculated for $C_{15}H_{18}NO_5$: 292.1179, found: 292.1174.

Diethyl 5-(2-naphthyl)isoxazoline-4,4(5*H*)-dicarboxylate (2i)

Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 (dd, *J* = 7.1, 7.1, Hz, 3H), 1.34 (dd, *J* = 7.1, 7.1 Hz, 3H), 3.51 (dq , *J* = 7.1, 10.8 Hz, 1H), 3.59 (dq , *J* = 7.1, 10.8 Hz, 1H), 4.33 (dq , *J* = 7.1, 10.7 Hz, 1H), 4.40 (dq , *J* = 7.1, 10.7 Hz, 1H), 6.38 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.49–7.46 (m, 2H), 7.86–7.79 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2 (CH_3), 14.0 (CH_3), 62.4 (CH_2), 63.2 (CH_2), 75.5 (C), 85.8 (CH), 124.3 (CH), 126.4 (CH), 126.5 (CH), 126.5 (CH), 127.6 (CH), 128.0 (CH), 128.2 (CH), 132.1 (C), 132.9 (C), 133.5 (C), 143.1 (CH), 164.8 (C), 165.5 (C); IR (ATR) 1746, 1732 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calculated for $C_{19}H_{20}NO_5$: 342.1336, found: 342.1324.

Diethyl 2-[2-oxo-2-(4-methylphenyl)ethyl]malonate (3a)[15]

Brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (dd, *J* = 7.2, 7.2 Hz, 6H), 2.41 (s, 3H), 3.60 (d, *J* = 7.2 Hz, 2H), 4.05 (t, *J* = 7.2 Hz, 1H), 4.21 (dq, *J* = 7.2, 10.8 Hz, 2H), 4.25 (dq, *J* = 7.2, 10.8 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.6 (CH_3), 37.7 (CH_2), 47.3 (CH), 61.7 (CH_2), 128.2 (CH), 129.3 (CH), 133.7 (C), 144.3 (C), 169.1 (C), 196.1 (C); IR (ATR) 1684, 1730 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{16}H_{20}O_5Na$: 315.1188, found: 315.1203.

2-Ethoxycarbonyl-4-(4-methylphenyl)-4-oxobutanoic acid (4a)

Brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.65 (dd, *J* = 6.0, 18.0 Hz, 1H), 3.76 (dd, *J* = 6.0, 18.0 Hz, 1H), 3.93 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 21.7 (CH_3), 37.6 (CH),

45.7 (CH_2), 62.5 (CH_2), 128.3 (CH), 129.4 (CH), 133.4 (C), 144.7 (C), 170.5 (C), 178.1 (C), 196.2 (C); IR (ATR) 1683, 1714, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{14}H_{16}O_5Na$: 287.0890, found:287.0882.

Ethyl 4-(4-methylphenyl)-4-oxobutanoate (5a)

Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 2.75 (t, *J* = 6.8 Hz, 2H), 3.29 (t, *J* = 6.8 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 7.26, (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 21.6 (CH_3), 28.4 (CH_2), 33.3 (CH_2), 60.6 (CH_2), 128.1 (CH), 129.3 (CH), 134.2 (C), 143.2 (C), 173.0 (C), 197.7 (C); IR (ATR) 1684, 1734 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calculated for $C_{13}H_{16}O_3Na$: 243.0992, found: 243.0983.

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