

Allylic–Allylic Alkylation with 3,5-Dimethyl-4-nitroisoxazole: A Route to Dicarboxylic Acid Derivatives

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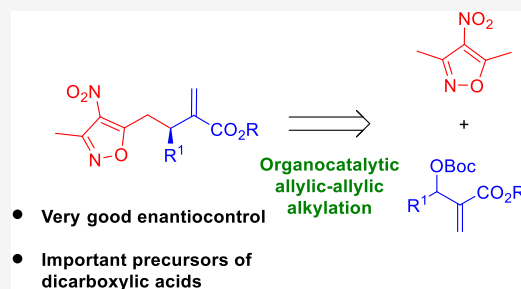


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Supporting Information

ABSTRACT: In this work, the first application of 3,5-dimethyl-4-nitroisoxazole as a vinylogous pronucleophile in the allylic–allylic alkylation of Morita–Baylis–Hillman (MBH) carbonates is described. The reaction has been realized under nucleophilic catalysis conditions with dimeric cinchona alkaloids, providing excellent enantiocontrol of the process. The usefulness of the products thus obtained has been confirmed in selected chemoselective reactions. The most important one involves the transformation of the isoxazole moiety into a carboxylic acid group, thus opening access to dicarboxylic acid derivatives.



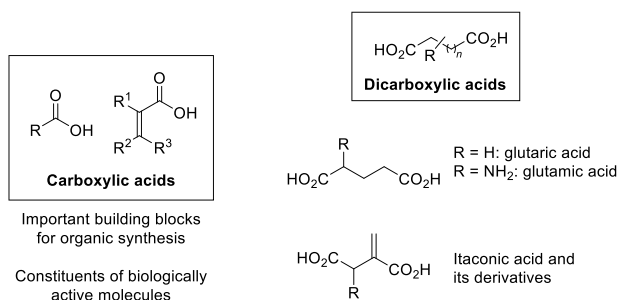
INTRODUCTION

The asymmetric synthesis of simple, chiral building blocks possessing important functional groups (that can be subsequently utilized for their further chemical and stereochemical diversifications) constitutes an important task in the contemporary organic synthesis.¹ Carboxylic acids and their α,β -unsaturated derivatives belong to such a category of compounds with widespread applications in organic and polymer sciences (Scheme 1).² Dicarboxylic acids bearing

employing various vinylogous pronucleophiles in this reaction.⁵ In such a manner, allylic–allylic alkylations have been introduced, leading to various synthetically relevant products bearing two allylic moieties connected through the C–C bond in a stereocontrolled manner.

In continuation of our studies related to the development of novel vinylogous reactivities,^{6,7} we became particularly interested in 3,5-dimethyl-4-nitroisoxazole (**1**, Scheme 2). This compound and its alkylidene derivatives have recently emerged as a useful class of compounds capable of participating in various C–C bond forming reactions.⁸ One relevant feature of this group of reactants is the possibility to transform the isoxazole ring system to the carboxylic acid group. As a consequence, they are considered as carboxylic acid surrogates. To our surprise, such pronucleophiles have never before been explored in the allylic–allylic alkylation with MBH-carbonates **2** realized under nucleophilic catalysis conditions (Scheme 2, top). It was anticipated that the initially obtained product **3** could be utilized as a direct precursor of dicarboxylate **4**. Notably, an alternative strategy for the preparation of **4** can be based on the allylic alkylation of MBH-carbonates with malonates or related systems, followed by the hydrolysis and monocarboxylation. While the first step of the sequence is known in the literature, the development of the enantioselective protocol remains a challenge or requires a specific substitution pattern.⁹ Therefore, the development of an alternative strategy is highly appealing.

Scheme 1. Importance of Carboxylic Acids and Their Derivatives



two carboxylic moieties in their structure are an interesting group of carboxylic acid derivatives with molecules containing such a structural motif being exploited in target-oriented synthesis.³

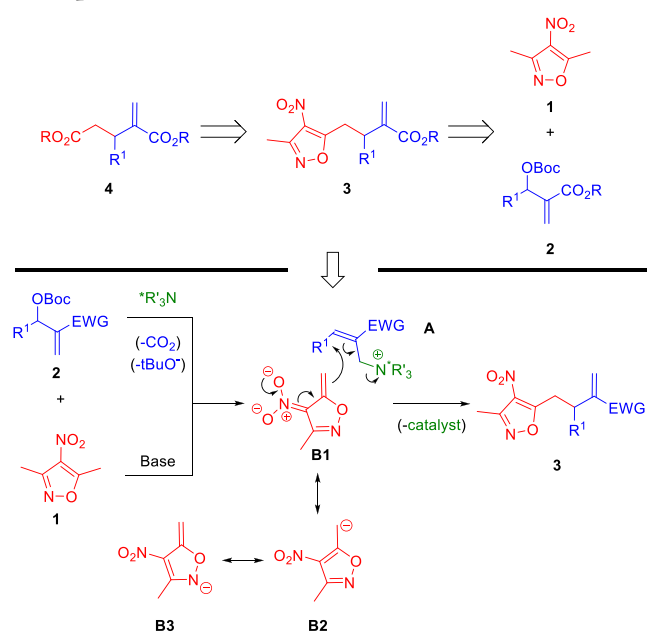
Allylic alkylation with the participation of Morita–Baylis–Hillman (MBH) carbonates realized under nucleophilic catalysis constitutes a facile route for the synthesis of acrylic acid derivatives bearing a chiral substituent in the α -position.⁴ The synthetic potential of allylic alkylations realized with MBH-carbonates has been recently significantly expanded by

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Scheme 2. Synthetic Objectives of Our Study and the Anticipated Mechanistic Scenario



Herein, we present our studies on the development of the first allylic–allylic alkylation using 3,5-dimethyl-4-nitroisoxazole (**1**) as a vinylogous pronucleophile and the application of the products **3** obtained for the synthesis of enantiomerically enriched dicarboxylates **4**. The anticipated mechanistic scenario for the key step of the devised strategy should be initiated through two independent activation processes (Scheme 2, bottom). The first one involving the corresponding MBH-carbonate **2** relies on the S_N2' reaction of **2** with a nucleophilic catalyst to give intermediate **A**. The reaction proceeds with the concomitant release of carbon dioxide and *tert*-butoxide anion. In a parallel transformation 3,5-dimethyl-4-nitroisoxazole (**1**) is deprotonated to give anion **B** that is stabilized through mesomeric effect. A subsequent second S_N2' reaction between **A** and **B** yields target product **3** and releases the nucleophilic catalyst that can re-enter the catalytic cycle.

RESULTS AND DISCUSSION

The optimization studies were performed using isoxazole **1** and MBH-carbonate **2a** as model reactants (Table 1 and Supporting Information). Initially, quinine **5a** was used as a catalyst, and to our delight, the formation of the desired product **3a** was observed (Table 1, entry 1). However, both the yield and enantioselectivity of the reaction were low. Therefore, a catalyst screening was performed employing various cinchona-alkaloids-derived systems **5b–g**. While cupreine derivative **5b** catalyzed the reaction with similar efficiency (Table 1, entry 2), the thiourea derivative **5c** failed to induce any reactivity (Table 1, entry 3). Therefore, we turned our attention to dimeric catalysts **5d–g** (Table 1, entries 4–7) as their ability to act as nucleophilic catalysts in allylic alkylation reactions is well recognized. We were pleased to observe that the use of **5f** led to an increase in enantioselectivity of the developed reaction (Table 1, entry 6). In order to further improve the results, the solvent screening was initiated (Table 1, entries 6, 8–12). Among solvents tested, chloroform proved the best reaction medium that enabled to increase the yield of the reaction significantly

Table 1. Enantioselective Allylic–allylic Alkylation Using 3,5-Dimethyl-4-nitroisoxazole **1** as a Vinylogous Pronucleophile: Optimization Studies^a

entry	solvent (catalyst)	T [°C]	yield [%] ^b	er ^c
1	CH ₂ Cl ₂ (5a)	rt	26	60:40
2	CH ₂ Cl ₂ (5b)	rt	22	81:19
3	CH ₂ Cl ₂ (5c)	rt	<5	nd
4	CH ₂ Cl ₂ (5d)	rt	22	79:21
5	CH ₂ Cl ₂ (5e)	rt	41	88:12
6	CH ₂ Cl ₂ (5f)	rt	43	90:10
7	CH ₂ Cl ₂ (5g)	rt	38	76:24
8	CHCl ₃ (5f)	rt	69	91:9
9	ClCH ₂ CH ₂ Cl (5f)	rt	40	86:14
10	toluene (5f)	rt	19	89:11
11	THF (5f)	rt	36	87:13
12	CH ₃ CN (5f)	rt	80	89:11
13 ^d	CHCl ₃ (5f)	rt	41	89:11
14 ^e	CHCl ₃ (5f)	rt	66	90:10
15	CHCl ₃ (5f)	10	20	92:8
16	CHCl ₃ (5f)	40	84	96:4
17	CHCl ₃ (5f)	60	78	90:10
18 ^f	CHCl ₃ (5f)	40	81	91:9
19 ^g	CHCl ₃ (5f)	40	79	93:7

^aReactions performed on a 0.1 mmol scale using **1** (1 equiv) and **2a** (1 equiv) in 0.4 mL of the solvent. ^bIsolated yields are given. ^cDetermined by a chiral stationary phase HPLC. ^dReaction was performed in 0.8 mL of CH₂Cl₂. ^eReaction was performed in 0.2 mL of CH₂Cl₂. ^fReaction was performed using **1** (1.5 equiv). ^gReaction was performed using **2a** (1.5 equiv).

(Table 1, entry 8). In the course of further studies, various experiments aiming at fine-tuning of the reaction conditions were performed (Table 1, entries 13–19). It was found that neither dilution of the reaction mixture (Table 1, entry 13) nor an increase in concentration (Table 1, entry 14) had a beneficial effect on its outcome. Subsequently, the temperature effect was checked (Table 1, entries 8, 15–17). Interestingly, while the decrease in temperature resulted in sluggish conversion (Table 1, entry 15), its increase led to an

improvement of reactivity (Table 1, entries 16 and 17) with 40 °C, providing also a better outcome in terms of enantioselectivity of the process (Table 1, entry 16). Finally, the influence of the relative reactant ratios was checked; however, it resulted in deteriorated results (Table 1, entries 18 and 19).

With the optimization studies accomplished (Table 1, entry 16), the scope of the developed methodology was studied (Table 2). It was found that the presence of electron-

Table 2. Enantioselective Allylic–Allylic Alkylation Using 3,5-Dimethyl-4-nitrosoxazole 1 as a Vinylogous Pronucleophile: Scope Studies^a

entry	R ¹	R ²	yield [%] ^b	er ^c
1	Ph (3a)	Me	84	96:4
2	4-CF ₃ C ₆ H ₄ (3b)	Me	82	90:10
3	4-BrC ₆ H ₄ (3c)	Me	86	97:3
4	4-ClC ₆ H ₄ (3d)	Me	90	98:2
5	3-ClC ₆ H ₄ (3e)	Me	89	96:4
6	2-ClC ₆ H ₄ (3f)	Me	83	94:6
7	4-CH ₃ C ₆ H ₄ (3g)	Me	92	97:3
8	4-CH ₃ OC ₆ H ₄ (3h)	Me	90	96:4
9	3,4-(OCH ₂ O)C ₆ H ₃ (3i)	Me	89	96:4
10	2-furyl (3j)	Me	84	98:2
11	<i>E</i> -Prop-1-enyl (3k)	Me	84	95:5
12	Ph (3l)	Et	85	98:2
13	Ph (3m)	<i>t</i> Bu	90	99:1
14 ^d	Ph (3a)	Me	58	96:4

^aReactions performed on a 0.1 mmol scale using 1 (1 equiv) and 2a (1 equiv) in 0.4 mL of the solvent. ^bIsolated yields are given. ^cDetermined by a chiral stationary phase HPLC. ^dReaction was performed on a 5 mmol scale.

withdrawing groups on the aromatic ring in 2 did not significantly influence the reaction outcome (Table 2, entries 2–6). In all of the cases, high yields and enantioselectivities were obtained. Similarly, the reaction proved unbiased toward the position of substituent with *para*-, *meta*- and *ortho*-substitution being well-tolerated (Table 2, entries 4–6). Furthermore, it was found that the introduction of electron-donating groups had no deteriorative effect on the reaction (Table 2, entries 7 and 8). The disubstituted aromatic ring, heteroaromatic group, and alkenyl moiety were also able to be present in 2 as demonstrated in the synthesis of 3i–k (Table 2, entries 9–11). Finally, the possibility to modify the ester group in 2 was checked (Table 2, entries 12 and 13) with excellent enantiocontrol achieved when *tert*-butyl ester was employed (Table 2, entry 13). The reaction also proved possible to scale up (5 mmol, Table 1, entry 14) with 3a obtained in lower yield (54%) (for information on additional scope experiments, see Supporting Information).

The absolute configuration of the representative products 3a,g was established by comparison of their experimental

electronic circular dichroism (ECD) spectrum with the calculated ones (for details, see Supporting Information).¹⁰ A perfect consistency between experimental and theoretical data (see Figure 1) unambiguously confirmed the *R* absolute configuration of the model compounds tested. The absolute stereochemistry of the products 3b–f,h–m was assigned through analogy.

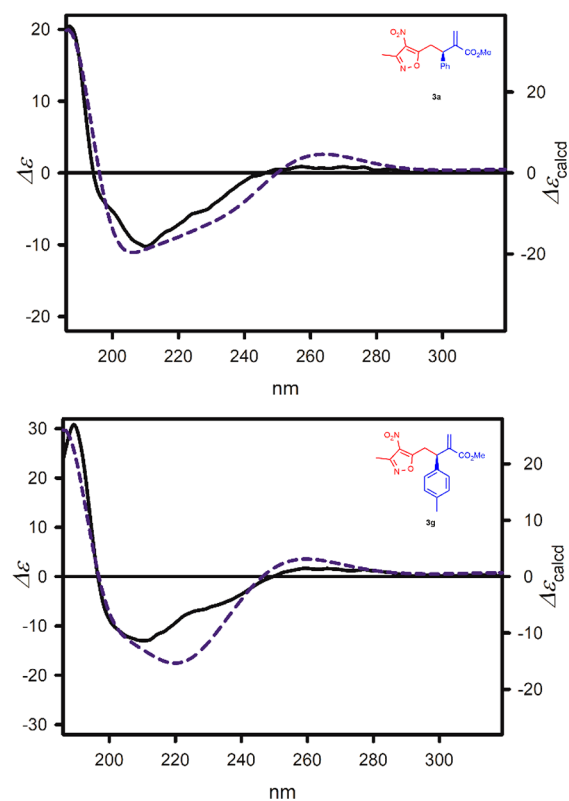
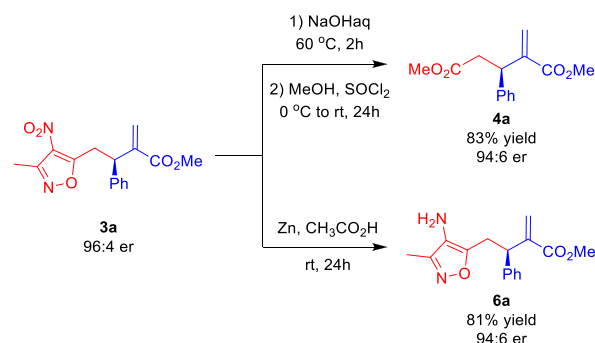


Figure 1. ECD spectra of 3a and 3g, measured in cyclohexane (solid black lines) and calculated at the TD-CAM-B3LYP/6-311++G-(2d,2p) level and $\Delta\Delta G$ -based Boltzmann average (dashed blue lines). Wavelengths were corrected to match the experimental UV maximum.

In order to demonstrate the synthetic usefulness of the allylic–allylic alkylation products 3, acrylate 3a was subjected to selected transformations (Scheme 3). Initially, the possibility to transform the 4-nitrosoxazole moiety in 3a into the carboxylic group was attempted (Scheme 3, top). It

Scheme 3. Enantioselective Allylic–Allylic Alkylation Using 3,5-Dimethyl-4-nitrosoxazole 1 as a Vinylogous Pronucleophile: Synthetic Applications



proved possible employing sodium hydroxide aqueous solution. The dicarboxylic acid initially obtained was directly subjected to esterification to afford dimethyl ester **4a** in an 83% yield. Importantly, the optical purity introduced in the organocatalytic step was almost entirely maintained despite basic reaction conditions. In the course of further studies, it was found that the reduction of the nitro group in **3a** was possible to be conducted chemoselectively when Zn in acetic acid was used as a reducing agent (Scheme 3, bottom). The reaction again occurred with the preservation of the optical purity of **3a**.

CONCLUSIONS

In conclusion, we have demonstrated that 3,5-dimethyl-4-nitroisoxazole **1** serves as a new vinylogous pronucleophile in the allylic–allylic alkylation reaction. The reaction proceeded efficiently in the presence of dimeric cinchona alkaloid derivative **5f** as the nucleophilic catalyst initiating the reaction sequence. Target products bearing an interesting functionalization potential were obtained with high yields and with excellent enantiocontrol. The possibility to transform the 4-nitroisoxazole moiety into the carboxylic group was demonstrated.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^1H and 176 MHz for ^{13}C , respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CDCl_3 : 7.26 ppm for ^1H NMR, 77.16 ppm for ^{13}C NMR). Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species). Analytical thin-layer chromatography (TLC) was performed using precoated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation. Silica gel (Silica gel 60, 230–400 mesh, Fluka) was used for flash chromatography (FC). MBH carbonates **2** were prepared according to literature procedures.¹¹ Cinchona-alkaloid-derived catalyst **5c** was synthesized following the literature procedure.¹²

General Procedure for the Synthesis of Compounds 3a–m. An ordinary screw-cap vial was charged with a magnetic stir bar, the corresponding 3,5-dimethyl-4-nitroisoxazole **1** (0.1 mmol, 1 equiv), the corresponding MBH carbonate **2** (0.1 mmol, 1 equiv), catalyst **5f** (0.01 mmol, 0.1 equiv), and CHCl_3 (0.4 mL). The reaction mixture was stirred at 40 °C in an aluminum heating block and monitored by ^1H NMR spectroscopy. After 24 h, the mixture was directly purified by FC on silica gel to afford a target product **3**.

(R)-Methyl 4-(3-Methyl-4-nitroisoxazol-5-yl)-2-methylene-3-phenylbutanoate (3a). Following the general procedure, **3a** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 84% yield (28.5 mg) as a pale-yellow oil (910.4 mg, 58% yield of **3a** was obtained when the reaction was performed on a 5 mmol scale). ^1H NMR (700 MHz, CDCl_3): δ 7.32–7.28 (m, 2H), 7.27–7.22 (m, 3H), 6.41 (s, 1H), 5.79 (d, $J = 1.4$ Hz, 1H), 4.60 (t, $J = 8.1$ Hz, 1H), 3.80–3.77 (m, 2H), 3.71 (s, 3H), 2.52 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.8, 166.5, 155.6, 141.5, 139.9, 129.6, 128.9 (2C), 127.8 (2C), 127.6, 125.8, 52.2, 44.1, 32.4, 11.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$, 339.0952; found, 339.0951. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 11.6$ min, $\tau_{\text{minor}} = 10.5$ min (96:4 er). $[\alpha]_{\text{D}}^{20} = -173.1$ ($c = 0.8$, CHCl_3).

(R)-Methyl 4-(3-Methyl-4-nitroisoxazol-5-yl)-2-methylene-3-(4-(trifluoromethyl)phenyl)butanoate (3b). Following the general procedure, **3b** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 82% yield (33.4 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.41 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H),

6.40 (s, 1H), 5.77 (d, $J = 1.2$ Hz, 1H), 4.54 (td, $J = 8.2$, 1.2 Hz, 1H), 3.74 (d, $J = 8.1$ Hz, 2H), 3.69 (s, 3H), 2.51 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.2, 166.1, 155.8, 144.1, 140.1, 130.2 (q, $J = 30.7$ Hz), 128.2 (2C), 128.0, 126.4, 125.9 (q, $J = 3.7$ Hz, 2C), 125.5, 124.1 (q, $J = 272.1$ Hz), 52.4, 43.9, 32.1, 11.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_5\text{Na}$, 407.0826; found, 407.0828. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 8.8$ min, $\tau_{\text{minor}} = 11.5$ min (90:10 er). $[\alpha]_{\text{D}}^{20} = -146.8$ ($c = 0.7$, CHCl_3).

(R)-Methyl 3-(4-Bromophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2-methylenebutanoate (3c). Following the general procedure, **3c** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 86% yield (35.9 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.41 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.40 (s, 1H), 5.77 (d, $J = 1.3$ Hz, 1H), 4.55–4.53 (m, 1H), 3.74 (d, $J = 8.1$ Hz, 2H), 3.69 (s, 3H), 2.51 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.4, 166.3, 155.7, 141.1, 139.0, 132.0 (2C), 129.6 (2C), 126.0 (2C), 121.6, 52.3, 43.6, 32.2, 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{O}_5\text{Na}$, 417.0057/419.0037; found, 417.0069/419.0044. The er was determined by HPLC using a Chiralpak IF column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 18.0$ min, $\tau_{\text{minor}} = 15.9$ min (97:3 er). $[\alpha]_{\text{D}}^{20} = -151.2$ ($c = 0.9$, CHCl_3).

(R)-Methyl 3-(4-Chlorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2-methylenebutanoate (3d). Following the general procedure, **3d** was isolated by FC on silica (hexane/ethyl acetate 96:4) in a 90% yield (33.6 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.26–7.25 (m, 2H), 7.18 (d, $J = 8.5$ Hz, 2H), 6.40 (s, 1H), 5.77 (d, $J = 1.2$ Hz, 1H), 4.61–4.47 (m, 1H), 3.74 (d, $J = 8.1$ Hz, 2H), 3.69 (s, 3H), 2.51 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.4, 166.3, 155.7, 141.2, 138.5, 133.5, 129.2 (2C), 129.1 (2C), 126.0 (2C), 52.3, 43.6, 32.3, 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_5\text{Na}$, 373.0562; found, 373.0570. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 14.6$ min, $\tau_{\text{minor}} = 11.8$ min (98:2 er). $[\alpha]_{\text{D}}^{20} = -132.1$ ($c = 0.8$, CHCl_3).

(R)-Methyl 3-(3-Chlorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2-methylenebutanoate (3e). Following the general procedure, **3e** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 89% yield (33.2 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.24–7.20 (m, 3H), 7.14 (dt, $J = 7.3$, 1.8 Hz, 1H), 6.42 (s, 1H), 5.79 (d, $J = 1.2$ Hz, 1H), 4.55 (td, $J = 8.2$, 1.1 Hz, 1H), 3.77 (dd, $J = 15.1$, 8.1 Hz, 1H), 3.73 (dd, $J = 15.1$, 8.2 Hz, 1H), 3.70 (s, 3H), 2.52 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.3, 166.2, 155.7, 142.1, 140.8, 134.7, 130.2, 129.6, 128.0, 127.9, 126.3, 126.1, 52.4, 43.8, 32.3, 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_5\text{Na}$, 373.0562; found, 373.0566. The er was determined by HPLC using a Chiralpak IF column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 7.6$ min, $\tau_{\text{minor}} = 6.8$ min (96:4 er). $[\alpha]_{\text{D}}^{20} = -142.3$ ($c = 0.7$, CHCl_3).

(S)-Methyl 3-(2-Chlorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2-methylenebutanoate (3f). Following the general procedure, **3f** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 83% yield (30.1 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.34 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.30 (dd, $J = 7.8$, 1.7 Hz, 1H), 7.24 (td, $J = 7.6$, 1.4 Hz, 1H), 7.18 (td, $J = 7.6$, 1.7 Hz, 1H), 6.45 (s, 1H), 5.71 (d, $J = 1.4$ Hz, 1H), 5.17–5.03 (m, 1H), 3.82 (dd, $J = 15.1$, 7.7 Hz, 1H), 3.69 (s, 3H), 3.67 (dd, $J = 15.1$, 8.3 Hz, 1H), 2.52 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.3, 166.3, 155.7, 140.6, 137.5, 134.3, 130.2, 129.6, 128.8, 128.4, 127.3, 126.8, 52.3, 40.4, 31.7, 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_5\text{Na}$, 373.0562; found, 373.0569. The er was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 11.0$ min, $\tau_{\text{minor}} = 10.3$ min (94:6 er). $[\alpha]_{\text{D}}^{20} = -129.5$ ($c = 0.8$, CHCl_3).

(R)-Methyl 4-(3-Methyl-4-nitroisoxazol-5-yl)-2-methylene-3-(*p*-tolyl)butanoate (3g). Following the general procedure, **3g** was isolated by FC on silica (hexane/ethyl acetate 96:4) in a 92% yield (32.5 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.12 (d, $J = 8.1$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.36 (s, 1H), 5.75 (d, $J = 1.2$ Hz, 1H), 4.54 (t, $J = 8.1$ Hz, 1H), 3.74 (dd, $J = 8.1$, 1.5 Hz, 2H),

3.69 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 173.0, 166.6, 155.6, 141.7, 137.2, 136.9, 129.6, 129.5, 127.7, 127.6, 125.8, 125.5, 52.3, 43.7, 32.5, 21.3, 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$, 353.1108; found, 353.1112. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 12.8$ min, $\tau_{\text{minor}} = 11.2$ min (97:3 er). $[\alpha]_{\text{D}}^{20} -186.8$ ($c = 0.8$, CHCl_3).

(R)-Methyl 3-(4-Methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2-methylenebutanoate (3h). Following the general procedure, **3h** was isolated by FC on silica (hexane/ethyl acetate 96:4) in a 90% yield (33.2 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.14 (d, $J = 8.7$ Hz, 2H), 6.81 (d, $J = 8.7$ Hz, 2H), 6.35 (s, 1H), 5.74 (d, $J = 1.2$ Hz, 1H), 4.53 (td, $J = 8.2, 1.2$ Hz, 1H), 3.77 (s, 3H), 3.73 (dd, $J = 8.1, 2.5$ Hz, 2H), 3.69 (s, 3H), 2.50 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 173.1, 166.7, 159.0, 155.7, 141.9, 132.0, 129.0 (2C), 125.5 (2C), 114.3 (2C), 55.5, 52.3, 43.5, 32.7, 11.9. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_6\text{Na}$, 369.1057; found, 369.1054. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 20.3$ min, $\tau_{\text{minor}} = 18.9$ min (96:4 er). $[\alpha]_{\text{D}}^{20} -172.6$ ($c = 0.7$, CHCl_3).

(R)-Methyl 3-(Benzo[d][1,3]dioxol-5-yl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2-methylenebutanoate (3i). Following the general procedure, **3i** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 89% yield (34.1 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 6.72–6.69 (m, 2H), 6.68 (dd, $J = 8.0, 1.7$ Hz, 1H), 6.37 (s, 1H), 5.92 (s, 2H), 5.75 (d, $J = 1.3$ Hz, 1H), 4.50 (td, $J = 8.2, 1.4$ Hz, 1H), 3.71 (d, $J = 1.2$ Hz, 1H), 3.70 (s, 3H), 3.70 (d, $J = 1.6$ Hz, 1H), 2.51 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.8, 166.5, 155.7, 148.0, 147.0, 141.6, 133.7, 129.6, 125.4, 121.1, 108.5, 108.2, 101.3, 52.3, 43.7, 32.6, 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_6\text{Na}$, 383.0850; found, 383.0855. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 14.6$ min, $\tau_{\text{minor}} = 17.0$ min (96:4 er). $[\alpha]_{\text{D}}^{20} -146.3$ ($c = 0.7$, CHCl_3).

(S)-Methyl 3-(Furan-2-yl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2-methylenebutanoate (3j). Following the general procedure, **3j** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 84% yield (27.6 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.32 (dd, $J = 1.8, 0.8$ Hz, 1H), 6.39 (s, 1H), 6.28 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.13 (dt, $J = 3.1, 0.8$ Hz, 1H), 5.74 (d, $J = 1.0$ Hz, 1H), 4.72–4.61 (m, 1H), 3.83 (dd, $J = 15.0, 8.5$ Hz, 1H), 3.76 (s, 3H), 3.73 (dd, $J = 15.0, 7.3$ Hz, 1H), 2.53 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.3, 166.3, 155.7, 153.0, 142.4, 139.3, 127.7, 110.6 (2C), 107.1, 52.4, 38.2, 31.1, 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_6\text{Na}$, 329.0745; found, 329.0748. The er was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 19:5$ min, $\tau_{\text{minor}} = 18.1$ min (98:2 er). $[\alpha]_{\text{D}}^{20} -151.2$ ($c = 0.9$, CHCl_3).

(R,E)-Methyl 3-((3-Methyl-4-nitroisoxazol-5-yl)methyl)-2-methylenehex-4-enoate (3k). Following the general procedure, **3k** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 84% yield (25.5 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 6.23 (d, $J = 0.7$ Hz, 1H), 5.64 (t, $J = 0.8$ Hz, 1H), 5.57–5.46 (m, 2H), 3.80–3.77 (m, 1H), 3.77 (s, 3H), 3.49 (dd, $J = 7.6, 2.6$ Hz, 2H), 2.54 (s, 3H), 1.63 (d, 3H, $J = 4.5$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.4, 166.4, 155.8, 153.1, 142.5, 139.4, 127.8, 110.7, 107.2, 52.5, 38.3, 31.2, 11.9. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$, 303.0952; found, 303.0947. The er was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 6.7$ min, $\tau_{\text{minor}} = 7.6$ min (95:5 er). $[\alpha]_{\text{D}}^{20} -152.6$ ($c = 0.8$, CHCl_3).

(R)-Ethyl 4-(3-Methyl-4-nitroisoxazol-5-yl)-2-methylene-3-phenylbutanoate (3l). Following the general procedure, **3l** was isolated by FC on silica (hexane/ethyl acetate 96:4) in an 85% yield (30.0 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.29–7.26 (m, 2H), 7.23–7.21 (m, 3H), 6.39 (s, 1H), 5.74 (d, $J = 1.2$ Hz, 1H), 4.59–4.56 (m, 1H), 4.16–4.10 (m, 2H), 3.77 (d, $J = 8.1$ Hz, 2H), 2.50 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.9, 166.1, 155.6, 141.8, 140.1, 129.6, 128.8 (2C), 127.8 (2C), 127.5, 125.5, 61.2, 44.1, 32.4, 32.1, 14.2. HRMS (ESI-TOF) $m/$

z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$, 353.1108; found, 353.1112. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 6.7$ min, $\tau_{\text{minor}} = 7.5$ min (98:2 er). $[\alpha]_{\text{D}}^{20} -186.1$ ($c = 0.8$, CHCl_3).

(R)-tert-Butyl 4-(3-Methyl-4-nitroisoxazol-5-yl)-2-methylene-3-phenylbutanoate (3m). Following the general procedure, **3m** was isolated by FC on silica (hexane/ethyl acetate 96:4) in a 90% yield (34.3 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.29–7.26 (m, 2H), 7.22–7.19 (m, 3H), 6.30 (t, $J = 0.7$ Hz, 1H), 5.64 (dd, $J = 1.4, 0.6$ Hz, 1H), 4.51 (t, $J = 8.1$ Hz, 1H), 3.74 (dd, $J = 8.1, 0.6$ Hz, 2H), 2.50 (s, 3H), 1.35 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 173.0, 165.3, 155.6, 143.2, 140.4, 128.7 (3C), 127.8 (2C), 127.4, 124.7, 81.6, 44.2, 32.5, 28.0 (3C), 11.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5\text{Na}$, 381.1421; found, 381.1427. The er was determined by HPLC using a Chiralpak IG column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 6.0$ min, $\tau_{\text{minor}} = 7.6$ min (99:1 er). $[\alpha]_{\text{D}}^{20} -197.1$ ($c = 0.9$, CHCl_3).

Procedure for the Synthesis of Compound 4a. An ordinary screw-cap vial was charged with a magnetic stir bar and compound **3a** (0.1 mmol) and treated with a freshly made 5 M aqueous solution of NaOH (0.1 mL, 5 equiv, 0.5 mmol). The resulting solution was heated at 60 °C in an oil bath for 2 h and then allowed to reach room temperature. Isolation of free carboxylic acid involved the following: cooling the aqueous solution of compound sodium salt, adjustment of pH to 3, and extraction with EtOAc (2 × 5 mL). Combined organic layers were dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure. The crude mixture was dissolved in MeOH (3 mL) and cooled to 0 °C. Thionyl chloride (0.1 mL) was added dropwise, and the resulting solution was stirred overnight, allowing to warm gradually to room temperature. The solvent was removed under reduced pressure, and the crude mixture was diluted with EtOAc (10 mL) and washed with a saturated aqueous solution of NaHCO_3 (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried over anhydrous MgSO_4 and the solvent removed under reduced pressure.

(R)-Dimethyl 2-Methylene-3-phenylpentanedioate (4a). Following the general procedure, pure product **4a** was isolated by FC on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) in an 83% yield (22.5 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.28 (t, $J = 7.6$ Hz, 2H), 7.24–7.22 (m, 2H), 7.22–7.18 (m, 1H), 6.33 (s, 1H), 5.66 (d, $J = 1.2$ Hz, 1H), 4.45 (t, $J = 7.8$ Hz, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 2.93 (dd, $J = 15.6, 7.9$ Hz, 1H), 2.81 (dd, $J = 15.6, 7.9$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 172.0, 166.9, 142.5, 141.3, 128.6 (2C), 128.0 (2C), 127.1, 124.8, 52.1, 51.9, 42.9, 39.5. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{Na}$, 271.0941; found, 271.0949. The er was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 12.8$ min, $\tau_{\text{minor}} = 11.6$ min (94:6 er). $[\alpha]_{\text{D}}^{20} -149.4$ ($c = 0.8$, CHCl_3).

Procedure for the Synthesis of Compound 6a. To the solution of **3a** (87.6 mg, 0.1 mmol, 1.0 equiv) in acetic acid (1.6 mL) was added zinc dust (101.4 mg, 1.6 mmol, 16 equiv) slowly. After 2 h at room temperature, the mixture was filtered over Celite, diluted with ethyl acetate (5 mL), and then washed with sodium bicarbonate solution (2 × 5 mL). The combined organic phase was dried over MgSO_4 and concentrated in vacuo.

(R)-Methyl 4-(4-Amino-3-methylisoxazol-5-yl)-2-methylene-3-phenylbutanoate (6a). Following the general procedure, pure product **6a** was isolated by FC on silica gel (hexane/ethyl acetate gradient from 3:1 to 1:1) in an 81% yield (23.3 mg) as a pale-yellow oil. ^1H NMR (700 MHz, CDCl_3): δ 7.47–7.02 (m, 5H), 6.34 (s, 1H), 5.75 (s, 1H), 4.29 (t, $J = 8.0$ Hz, 1H), 3.66 (s, 3H), 3.28 (dd, $J = 14.7, 6.7$ Hz, 1H), 3.08 (dd, $J = 14.7, 9.1$ Hz, 1H), 2.12 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 167.1, 155.2, 155.0, 142.3, 141.3, 128.7 (2C), 128.0 (2C), 127.2, 125.3, 121.9, 52.1, 45.3, 30.6, 9.4. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_3$, 287.1391; found, 287.1392. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 5.2$ min, $\tau_{\text{minor}} = 4.7$ min (94:6 er). $[\alpha]_{\text{D}}^{20} -127.2$ ($c = 0.9$, CHCl_3).

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.9b02530>.

A full account of screening results, additional scope studies, details of absolute configuration assignments (computational details), copies of ^1H and ^{13}C NMR spectra, and HPLC chromatograms (PDF)

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Notes

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