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Metal-free Insertion Reactions of Diazo carbonyls to Azlactones

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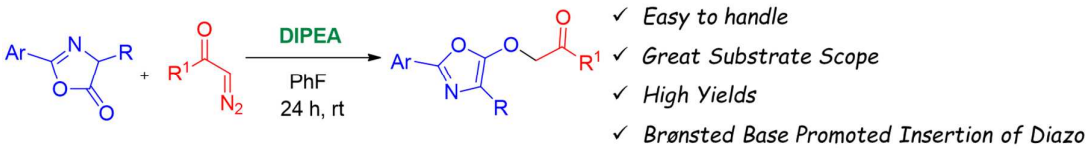
TOC Graphic



ABSTRACT

Insertion reactions of diazo carbonyls to azlactones in basic conditions have been performed. The developed method allows the preparation of a wide range of oxazole derivatives in yields ranging from 74 to 98%. Different substituents on both azlactone rings and diazo carbonyls do not compromise the methodology, even those containing stereogenic centers. Isotopic labelling experiments revealed the mechanism may proceed through a rare diazo carbonyl activation by an ammonium salt derivative.

Keywords: diazo carbonyls; insertion reactions; azlactones; tertiary amines.

Since the synthesis of the first diazo compound by Theodor Curtius in 1883[1], the chemistry involving substances containing a diazo group has been investigated and explored extensively[2–7]. They are a remarkable class of compounds due to the range of different transformations they can perform. Moreover, they are a powerful tool in bond-forming reactions[8–10]. Typically, the reactivity of diazo compounds is associated with metal catalysis[11–14] and, among others, great advances in insertion reactions have been reported with rhodium and copper complexes catalysts[15–20].

Recently, some studies brought new approaches in insertion reactions of diazo carbonyl compounds in the absence of metal catalysts. To this end, different types of hydrogen bonding donor derivatives were explored to the diazo compound protonation step[21,22], including the use of strong Brønsted acid catalysts[23].

In the present study, an innovative metal-free methodology for insertion reaction in basic conditions is described. In addition, the use of azlactones[24-26] lead us to oxazole derivatives, which can present biological activity. It is important to mention that this heterocycle moiety has been observed in different classes of pharmaceutical agents[27–29] (Figure 1).

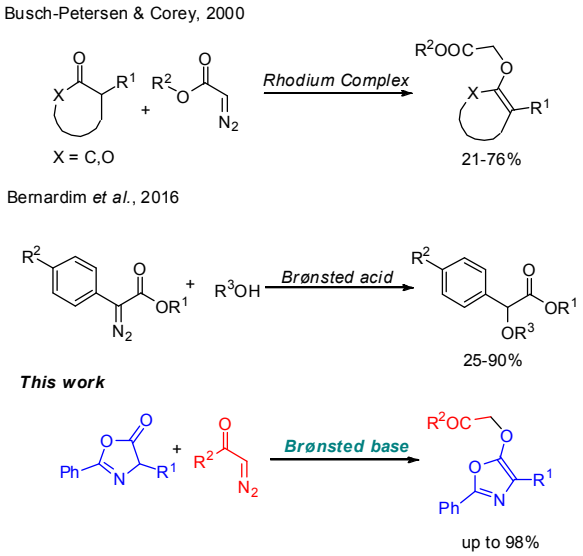
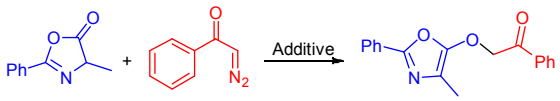


Figure 1. Selective examples of diazo carbonyls insertion reactions.

The studies began using CSA as a Brønsted acid catalyst in diazo insertion reactions. However, this catalyst afforded traces of the desired product. Phenol has also been tried, but failed. Notably, the use of triethylamine (1 equiv) in toluene, at room temperature, 24 h reaction, led to the desired product in good yield (Table 1, entry 2). Nevertheless, to achieve higher yields, several attempts varying the tertiary amine, solvents, reaction time, temperature, concentration were carried out (Table 1). Further improvement was observed when the reaction was carried out using 1 equiv of DIPEA in fluorobenzene (Table 1, entry 11). Longer reaction time gives lower yield (Table 1, entry 12). Perhaps, after 24 h, the product is unstable in the crude reaction mixture or becomes a little bit more soluble. It is important to mention, the product is filtered off from the crude reaction mixture. Concentration at 0.3 mol L^{-1} gave the best yield (Table 1, entry 18). Note that the reaction does not occur in the absence of the base.

Table 1. Optimization of the insertion reaction conditions[a].

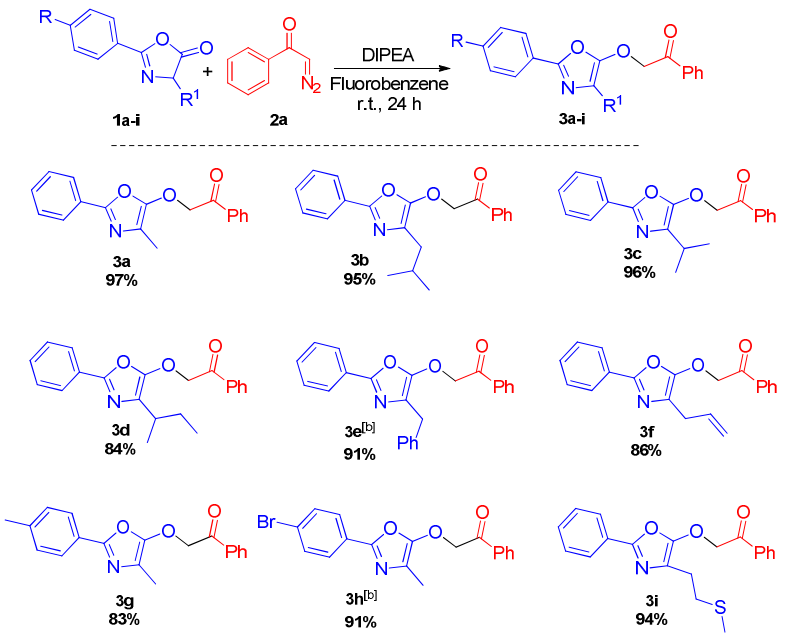


Entry	additive (equiv)	Solvent	conc (mol L^{-1})	temp (◦C)	time (hour)	yield (%)
1	CSA (10 mol%)	Toluene	0.2	r.t.	24	Traces
2	TEA (1.0)	Toluene	0.2	r.t.	24	79
3	DABCO (1.0)	Toluene	0.2	r.t.	24	48
4	-	Toluene	0.2	r.t.	24	-
5	DMOA (1.0)	Toluene	0.2	r.t.	24	71
6	DMAP (1.0)	Toluene	0.2	r.t.	24	66
7	Pyridine (1.0)	Toluene	0.2	r.t.	24	17
8	DIPEA (1.0)	Toluene	0.2	r.t.	24	82
9	DIPEA (1.0)	Benzene	0.2	r.t.	24	53
10	DIPEA (1.0)	Nitromethane	0.2	r.t.	24	37
11	DIPEA (1.0)	Fluorobenzene	0.2	r.t.	24	87
12	DIPEA (1.0)	Fluorobenzene	0.2	r.t.	48	73
13	DIPEA (1.0)	Fluorobenzene	0.2	r.t.	8	49
14	DIPEA (1.0)	Fluorobenzene	0.2	0	8	73
15	DIPEA (1.0)	Fluorobenzene	0.2	0	24	77
16	DIPEA (0.5)	Fluorobenzene	0.2	r.t.	24	69
17	DIPEA (0.75)	Fluorobenzene	0.2	r.t.	24	71
18	DIPEA (1.0)	Fluorobenzene	0.3	r.t.	24	97
19	DIPEA (1.0)	Fluorobenzene	0.4	r.t.	24	87

[a] Reactions were carried out using 1 equiv. of azlactone and 1.1 equiv. of diazo carbonyl derivative.

In order to study the substrate scope of the methodology, a series of functionalized azlactones were tested (Table 2). The reaction was found to tolerate different azlactones, for example, the sterically bulky azlactones **1b** and **1d** provided the desired products **3b** and **3d** in 95% and 84% yield. Besides, substitution on the aromatic ring does not adversely influence the reaction outcome, e.g., products **3g** and **3h**. Unfortunately, the use of alkyl group at C2-position on azlactone ring gave no product. Instead, basically azlactone decomposition was observed.

Table 2. Scope of insertion reactions of azlactones[a].

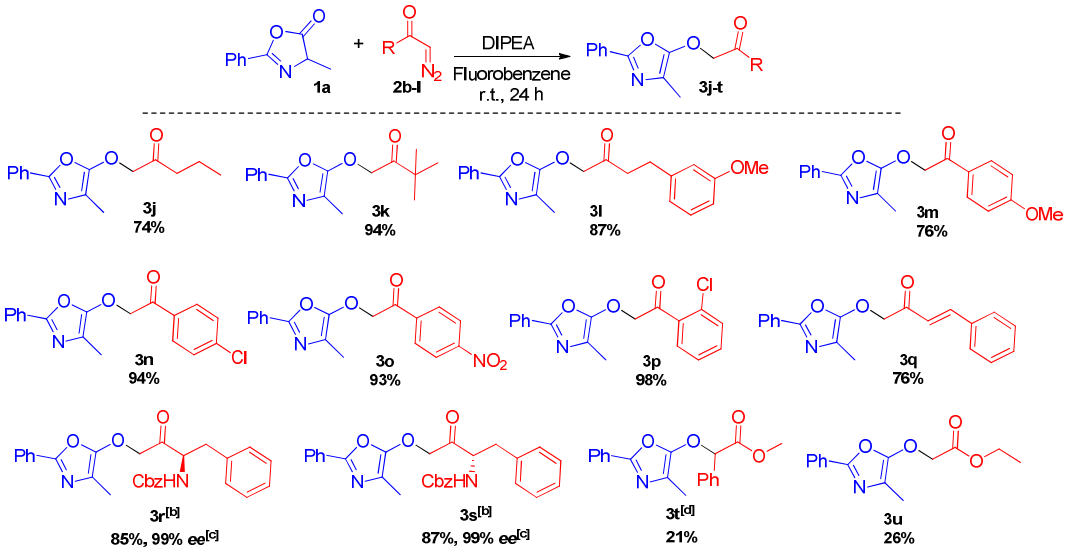


[a] Reactions were carried out using a 0.3 mol L^{-1} solution of **1a–i** in fluorobenzene, 1.1 equiv of **2** and 1 equiv of DIPEA. [b] Concentration of 0.2 mol L^{-1}.

The power of this method could be also demonstrated concerning different diazo compounds (Table 3). Electron-withdrawing functionalities on the aromatic rings in both the *para* and *ortho* positions gave the corresponding products **3n**, **3o** and **3p** in high yields. Electron-donating group well tolerated the reaction conditions, affording products **3l** and **3m** with 87% and 76% yield, respectively. Diazo carbonyls bearing both aliphatic and unsaturated groups were used to obtain the corresponding products in high yields. Although the isolated yield was low, the current method was also applied to a secondary diazo compound, leading to the corresponding product **3t** with 21% yield.

It is important to mention that carbamate derivatives **3r** and **3s** were obtained in good yields. Moreover, these compounds were submitted for enantiopurity determination, where chiral HPLC analyses revealed the methodology preserved the chirality (see Supporting Information). No racemization was observed up to 8 h of reaction.

Table 3. Scope of insertion reactions in the presence of diazo carbonyls[a].

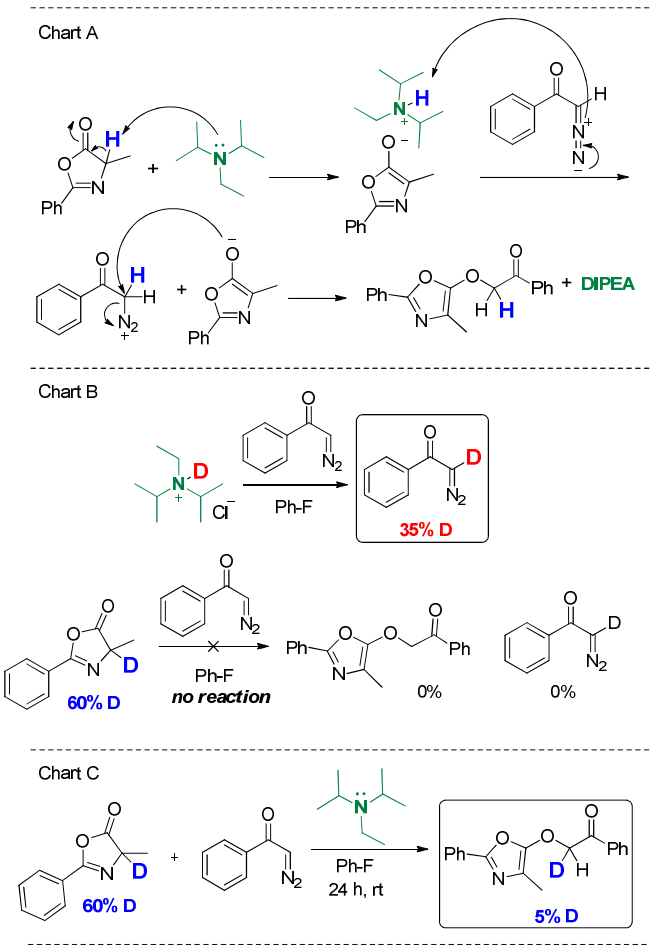


[a] Reactions were carried out using a 0.3 mol L^{-1} solution of **1a–i** in fluorobenzene, 1.1 equiv of **2** and 1 equiv of DIPEA. [b] Reaction time was 8 h. [Caution: after this period, significant racemization process]. [c] Measured by HPLC with enantiodiscriminating stationary phase. [d] Reaction in toluene at 90 °C.

A plausible mechanism is also proposed. The presence of an acidic hydrogen (pKa ≈ 9) in azlactone ring suggests that DIPEA initially deprotonates it, leading to its conjugated acid and the enolate form of the azlactone[30] (Scheme 1, Chart A). Next, the forming Brønsted acid (ammonium salt of DIPEA) protonates the diazo carbonyl derivative to give a diazonium ion. Finally, nucleophilic displacement by the enolate leads to the product and releases molecular nitrogen. To confirm if the ammonium salt of DIPEA could, in fact, protonate the diazo carbonyl compound and activate it, deuterium studies were carried-out. First, an ammonium salt of DIPEA, prepared by the reaction between DIPEA and DCl, was stirred in the presence of diazo compound **2a** in fluorobenzene. The analysis of the product revealed a 35% incorporation of deuterium on diazo **2a** (Scheme 1, Chart B). This indicates that, even being a weak Brønsted acid, the ammonium salt of DIPEA can in fact protonate the diazo compound. It is worth-mentioning that stirring the deuterated azlactone of **1a** (60% deuterium) with diazo **2a** did not furnished any of the desired product **3a** nor deuterated **2a**, showing that the presence of the base DIPEA is crucial for the reaction to proceed. Finally, performing the reaction with the same best condition depicted in Table 1

(entry 18), using deuterated **1a** (60% deuterium), led to the product **3a** with 5% of deuterium incorporation (of a maximum of 30%) (Scheme 1, Chart C).

Scheme 1. Mechanistical investigations



In summary, an insertion reaction of diazo carbonyls to widely available azlactones has been described. The metal-free methodology was optimized and led to oxazole derivatives in good to excellent yields. It is worth highlighting the great substrate scope, even diazo carbonyls bearing stereogenic centers could be used (99% e.e. preserved). To the best of our knowledge, for the first time, the use of basic conditions in an insertion reaction involving diazo compounds and azlactones was demonstrated. Finally, isotopic labelling experiments suggested a mechanism trough a rare DIPEA's conjugated acid as responsible for the diazo carbonyl protonation step, following by nucleophilic displacement.

EXPERIMENTAL SECTION

1. General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Unless otherwise noted, all reaction mixtures were carried out in a flame-dried vial under a positive pressure of dry nitrogen. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed TLC plates (silica gel 60 F254) and visualized by a UV lamp (254 nm). Yields refer to chromatographically purified and spectroscopically pure compounds, unless stated otherwise. ^{1}H and ^{13}C spectra were recorded on a 300 MHz, 400 MHz and 500 MHz spectrometer. Chemical shifts are reported in ppm. ^{1}H NMR spectra are referenced to $CDCl_3$ (7.26 ppm), and ^{13}C NMR spectra are referenced to $CDCl_3$ (77.0 ppm). All ^{13}C spectra were measured with complete proton decoupling. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dq, doublet of quartets; ddt, doublet of doublet of triplets; q, quartet; t, triplet; sex, sextet; sept, septet; m, multiplet; br, broad; and J, coupling constants in hertz. High resolution mass spectra were acquired in the positive-ion mode using a mass spectrometer equipped with an electrospray ionization source HRMS (ESI-QTOF). Chiral HPLC analysis was carried out using instrument fitted with a plate autosampler and a Chiralpak IA column.

2. General Procedure and Characterization Data for azlactones. Azlactones **1a-j** were prepared according to the literature method[31,32]. To a suspension of *N*-benzoyl amino acid (1 equiv) in dry CH_2Cl_2 (0.1 mol L^{-1}) under N_2 at 0 °C was added EDC.HCl (1.3 equiv). The crude was stirred for 1 h. The reaction mixture was diluted with an equal volume of CH_2Cl_2, and washed successively with cold water (6x, 5 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. In all cases, corresponding products were obtained in a pure form and use without further purification.

4-methyl-2-phenyloxazol-5(4H)-one. The product **1a** was obtained as a white solid (226.2 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 4.45 (q, J = 7.6 Hz, 1H), 1.59 (d, J = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.0, 161.5, 132.7, 128.7, 127.8, 125.8, 61.0, 16.8.

4-isobutyl-2-phenyloxazol-5(4H)-one. The product **1b** was obtained as a white solid (82.1 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.5 Hz, 2H), 7.60 – 7.46 (m, 3H), 4.42 (dd, J = 9.0, 5.7 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.89 – 1.80 (m, 1H), 1.73 - 1.64 (m, 1H), 1.05 – 1.03 (m, 6H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 179.1, 161.7, 133.0, 129.0, 128.8, 128.2, 127.3, 126.2, 64.1, 41.0, 25.4, 23.0, 22.3.

4-isopropyl-2-phenyloxazol-5(4H)-one. The product **1c** was obtained as a white solid (86.3 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01-7.99 (m, 2H), 7.56 (dt, 1H, J = 6.7 Hz, J = 1.2 Hz), 7.48-7.45 (m, 2H), 4.27 (d, 1H, J = 4.6 Hz), 2.37 (sept, 1H, J = 6.9 Hz, J = 4.6 Hz), 1.14 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.9 Hz). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.9, 161.7, 132.7, 128.8, 128.0, 126.0, 70.8, 31.3, 18.8, 17.6.

4-(sec-butyl)-2-phenyloxazol-5(4H)-one. The product **1d** was obtained as a yellow oil (186.0 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (appeared as a mixture of diastereomers)

8.02 - 7.99 (m, 2H), 7.58 – 7.55 (m, 1H), 7.50 – 7.46 (m, 2H), 4.39 (d, J = 4.5 Hz, 1H), 2.17 – 2.12 (m, 1H), 1.73 - 1.53 (m, 1H), 1.49 - 1.36 (m, 1H), 1.07 – 0.90 (m, 6H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ (appeared as a mixture of diastereomers) 178.7, 177.9, 161.8, 161.7, 132.8, 130.7, 129.0, 128.9, 128.0, 126.1, 69.9, 69.3, 37.9, 26.4, 25.1, 15.6, 14.6, 11.9, 11.8.

4-benzyl-2-phenyloxazol-5(4H)-one. The product **1e** was obtained as a white solid (89.4 mg, 89%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 4.0 Hz, 2H), 7.55 – 7.50 (m, 1H), 7.49 – 7.40 (m, 2H), 7.28 – 7.19 (m, 5H), 4.67 (dd, J = 6.6, 5.0 Hz, 1H), 3.36 (dd, J = 14.0, 4.8, 1H), 3.17 (dd, J = 14.0, 6.6 Hz, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 177.7, 161.9, 135.5, 132.6, 129.7, 128.9, 128.6, 128.0, 127.3, 126.0, 66.7, 37.5.

4-allyl-2-phenyloxazol-5(4H)-one. The product **1f** was obtained as a yellow oil (67.3 mg, 93%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.1 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H) 7.51 (t, J = 7.7 Hz, 2H), 5.82 (ddt, J = 17.4, 10.2, 6.9 Hz, 1H), 5.27 (dq, J = 17.1, 1.4 Hz, 1H), 5.19 (dd, J = 10.2, 1.4 Hz, 1H), 4.52 (dd, J = 7.5, 5.5 Hz, 1H), 2.84 (ddd, J = 14.1, 6.7, 5.5 Hz, 1H), 2.67 (ddd, J = 14.2, 7.5, 6.5 Hz, 1H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.7, 161.9, 132.8, 132.6, 131.4, 128.8, 128.0, 119.8, 65.4, 35.4.

4-methyl-2-(p-tolyl)oxazol-5(4H)-one. The product **1g** was obtained as a white solid (74.0 mg, 98%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.46 (q, J = 7.5 Hz, 1H), 2.45 (s, 3H), 1.61 (d, J = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.1, 161.6, 143.5, 129.6, 127.9, 123.1, 61.0, 21.7, 17.0.

2-(4-bromophenyl)-4-methyloxazol-5(4H)-one. The product **1h** was obtained as a white solid (70.9 mg, 93%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 4.44 (q, J = 7.6 Hz, 1H), 1.59 (d, J = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 178.6, 160.9, 132.2, 129.3, 127.7, 124.8, 61.2, 16.8.

4-(2-(methylthio)ethyl)-2-phenyloxazol-5(4H)-one. The product **1f** was obtained as a colorless oil (77.2 mg, 82%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H) 7.48 (t, J = 7.6 Hz, 2H), 4.60 (t, J = 6.5 Hz, 1H), 2.73 (t, J = 7.1 Hz, 2H), 2.34 – 2.27 (m, 1H), 2.18 – 2.09 (m, 4H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 178.6, 160.9, 132.2, 129.3, 127.7, 124.8, 61.2, 16.8.

3. General Procedure and Characterization Data for α-diazoketones. α-diazoketones were prepared according to the literature method[33-42]. The corresponding acyl halides (8 mmol, 1 equiv) were added dropwise to ethereal solution of diazomethane (0.4 M, 20 mmol, 2.5 equiv, 50 mL) at 0 °C and the crude reaction mixture was warmed to room temperature and stirred for 2 h. After that, the solvent was removed under vacuum and the residue purified by flash column chromatography (hexane/EtOAC 9:1) to afford diazoketones **2a-h**. Diazoketones **2j** and **2k** were prepared via mixed anhydrides. To that, *N*-Cbz phenylalanine (10 mmol, 3.2 g) in dry Et_2O (22 mL) and THF (22 mL) was stirred at -20 °C under argon atmosphere. Then, triethylamine (10 mmol, 1 equiv, 1.4 mL) was added followed by isobutyl chloroformate (10 mmol, 1 equiv, 1.3 mL). The solution was stirred for 30 min and subsequently warmed to -10 °C. Then, an ethereal solution of

diazomethane (0.4 M, 23 mmol, 2.3 equiv, 58 mL) was added via syringe pump for 30 min and the reactional mixture was stirred for 3 h while it was warmed to room temperature. The solvent was removed under reduced pressure and the crude product was diluted with Et_2O (25 mL) and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 ml), and brine (25 ml). The organic phase was dried with Na_2SO_4 and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–hexane 2:8–1:1).

2-diazo-1-phenylethan-1-one. The product **2a** was obtained as a yellow solid (1.0 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2H), 7.58 – 7.51 (m, 1H), 7.45 (m, 2H), 5.91 (s, 1H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 186.3, 136.7, 132.7, 128.7, 126.7, 126.7, 54.2.

1-diazopentan-2-one. The product **2b** was obtained as a yellow oil (0.69 g, 77%). ^{1}H NMR (400 MHz, Benzene-*d6*) δ 4.41 (s, 1H), 1.85 (t, *J* = 7.3 Hz, 2H), 1.53 – 1.41 (m, 2H), 0.75 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Benzene-*d6*) δ 193.3, 52.8, 42.7, 18.6, 13.8.

1-diazo-3,3-dimethylbutan-2-one. The product **2c** was obtained as a yellow oil (0.87 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (s, 1H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 201.3, 42.6, 27.1.

1-diazo-4-(3-methoxyphenyl)butan-2-one. The product **2d** was obtained as a yellow oil (1.4 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 1H), 6.80 – 6.70 (m, 3H), 5.22 (s, 1H), 3.76 (s, 3H), 2.94 – 2.87 (m, 2H), 2.67-2.53 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.9, 159.7, 142.2, 129.5, 120.6, 114.1, 111.5, 55.1, 54.6, 42.2, 30.9.

2-diazo-1-(4-methoxyphenyl)ethenone. The product **2e** was obtained as a yellow solid (0.82 g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 6.95 – 6.90 (m, 2H), 5.85 (s, 1H), 3.86 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 185.2, 163.2, 132.2, 129.5, 128.7, 113.8, 55.4, 53.4.

1-(4-chlorophenyl)-2-diazoethanone. The product **2f** was obtained as a yellow solid (1.1 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 2H), 7.45 – 7.39 (m, 2H), 5.87 (s, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 184.9, 139.0, 135.0, 129.0, 128.1, 54.4.

2-diazo-1-(4-nitrophenyl)ethanone. The product **2g** was obtained as a yellow solid (1.0 g, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 – 8.28 (m, 2H), 7.95 – 7.91 (m, 2H), 5.99 (s, 1H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 184.0, 150.2, 141.4, 127.8, 123.9, 55.7.

1-(2-chlorophenyl)-2-diazoethanone. The product **2h** was obtained as a yellow solid (1.4 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.48 (m, 1H), 7.44 – 7.30 (m, 3H), 5.81 (s, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 186.6, 137.4, 131.8, 131.1, 130.5, 129.3, 127.0, 57.8.

Benzyl (S)-(4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate. The product **2j** was obtained as a pale yellow solid (1.8 g, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.09 (m, 10H), 5.39 (br s, 1H), 5.20 (s, 1H), 5.08 (s, 2H), 4.55 – 4.41 (m, 1H), 3.04 (d, *J* = 6.8 Hz, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 192.7, 155.7, 136.2, 136.0, 129.3, 128.7, 128.5, 128.2, 128.1, 127.1, 67.0, 58.9, 54.6, 38.5.

Benzyl (R)-(4-diazo-3-oxo-1-phenylbutan-2-yl)carbamate. The product **2k** was obtained as a pale yellow solid (1.6 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.05 (m, 10H), 5.48 – 5.38 (m, 1H), 5.21 (s, 1H), 5.07 (s, 2H), 4.54 – 4.42 (m, 1H), 3.03 (d, *J* = 6.7 Hz, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 192.7, 155.7, 136.1, 136.0, 129.3, 128.7, 128.5, 128.2, 128.0, 127.1, 67.0, 58.9, 54.6, 38.5.

4. General Procedure and Characterization Data for (*E*)-1-diazo-4-phenylbut-3-en-2-one. *(E)-1-diazo-4-phenylbut-3-en-2-one* was prepared according to the literature method[43]. To a solution of diethyl 3-diazo-2-oxopropylphosphonate (400 mg, 1.81 mmol, 1 equiv.) and benzaldehyde (185 µL, 1.81 mmol, 1 equiv.) in EtOH (5 mL) at room temperature was added 3.6 mL of 0.5 mol L^{-1} of NaOH solution (water:EtOH, 1:1) via syringe pump during a period of 1 h. The mixture was stirred for further 30 min and then the reaction was quenched by the addition of saturated NaCl (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and dried over $MgSO_4$. The crude product was purified by flash column chromatography (EtOAc/hexane 1:9) to afford unsaturated diazoketone **2i** (233.7 mg, 75%) as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 15.8 Hz, 1H), 7.55-7.51 (m, 2H), 7.39-7.37 (m, 3H), 6.60 (d, *J* = 15.8 Hz, 1H), 5.45 (s, 1H). ^{13}C{1H} NMR (125 MHz, CDCl3) δ 184.3, 140.7, 134.4, 130.3,128.9, 128.2, 123.7, 56.2.

5. General Procedure and Characterization Data for Preparation of methyl 2-diazo-2-phenylacetate. *Methyl 2-diazo-2-phenylacetate* was prepared according to the literature method[44]. To a solution of methyl 2-phenylacetate (1.50 g, 10 mmol, 1 equiv.) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (2.88 g, 12 mmol, 1.2 equiv.) in anhydrous CH_3CN (30 mL) 2.10 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (14 mmol, 1.4 equiv.) was added. The reaction mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was diluted with distilled water (20 mL) followed by extraction with diethyl ether (3 × 10 mL). The organic phase was washed with 10% NH_4Cl solution (3 x 10 mL) and brine (3 x 10 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford **2l** (1.4 g, 81%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.42 – 7.35 (m, 2H), 7.22 – 7.15 (m, 1H), 3.87 (s, 3H). ^{13}C{1H} NMR (125 MHz, CDCl3) δ 165.6, 129.0, 125.8, 125.5, 124.0, 52.0.

6. General Procedure and Characterization Data for the insertion products. To a solution of azlactone (0.1 mmol) and diazo compound (0.11 mmol, 1.1 equiv) in fluorobenzene (0.33 mL, 0.3 mol L^{-1}) was added the DIPEA (0.1 mmol, 1 equiv) at room temperature for 24 h. After reaction completion, the precipitate formed was filtered off under reduced pressure.

2-((4-methyl-2-phenyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3a** was obtained as a white solid (28.6 mg, 97%), m.p. 96.8-98.7 °C .IR (ZnSe, cm^{-1}): 3419, 3357, 3242, 2996, 2949, 1686, 1521, 1442, 1349, 1229, 838, 726, 688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 6.8 Hz, 2H), 8.00 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.43 – 7.36 (m, 3H), 5.60 (s, 2H), 2.45 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.6, 161.1, 154.6, 134.4, 134.1, 130.9, 129.1, 129.1, 128.5, 128.2, 126.2, 54.5, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{15}NO_3Na$ 316.0944, found 316.0926.

2-((4-isobutyl-2-phenyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3b** was obtained as a white solid (31.8 mg, 95%), m.p. 71.2-72.6 °C. IR (ZnSe, cm^{-1}): 3060, 2960, 2929, 2873, 1693, 1596, 1481, 1445, 1349, 1226, 984, 751, 718, 689, 844. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.0 Hz, 2H), 8.02 (d, *J* = 7.9 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.44 – 7.36 (m, 3H), 5.61 (s, 2H), 2.57 (d, *J* = 7.3 Hz, 2H), 2.29 – 2.20 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 6H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.8, 161.3, 157.6, 134.4, 134.2, 131.1, 129.1, 129.0, 128.4, 128.2, 126.4, 54.3, 34.9, 27.9, 22.4. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{21}NO_3Na$ 358.1419, found 358.1415.

2-((4-isopropyl-2-phenyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3c** was obtained as a white solid (30.8 mg, 96%), m.p. 145.6-148.2 °C. IR (ZnSe, cm^{-1}): 3063, 2972, 2936, 2863, 1688, 1596, 1496, 1453, 1348, 1223, 838, 748, 680. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 6.9 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 2H), 7.44 – 7.33 (m, 3H), 5.62 (s, 2H), 2.90 (sept, *J* = 6.8 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 6H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 191.0, 162.8, 161.3, 134.3, 134.2, 131.3, 129.1, 128.9, 128.4, 128.1, 126.4, 54.2, 26.0, 21.4. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{19}NO_3Na$ 344.1257, found 344.1247.

2-((4-(sec-butyl)-2-phenyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3d** was obtained as a white solid (28.2 mg, 84%), m.p. 88.8-91.9 °C. IR (ZnSe, cm^{-1}): 3063, 2962, 2924, 2870, 1690, 1595, 1479, 1448, 1346, 1222, 986, 746, 684. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.2 Hz, 2H), 8.02 (d, *J* = 7.6 Hz, 2H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.36 (m, 3H), 5.67 (d, *J* = 17.8 Hz, 1H), 5.58 (d, *J* = 17.8 Hz, 1H), 2.70 – 2.60 (sex, *J* = 6.9 Hz,1H), 1.96 – 1.87 (m, 1H), 1.75 – 1.67 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 191.0, 162.2, 161.4, 134.3, 134.3, 131.3, 129.1, 128.9, 128.4, 128.2, 126.2, 54.2, 33.1, 28.9, 19.3, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{21}NO_3Na$ 358.1419, found 358.1406.

2-((4-benzyl-2-phenyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3e** was obtained as a white solid (33.5 mg, 91%) using the general procedure with concentration of 0.2 mol L^{-1} of azlactone in fluorobenzene, m.p. 159.7-161.2 °C. IR (ZnSe, cm^{-1}): 3080, 3059, 3026, 2977, 2936, 1692, 1596, 1479, 1438, 1348, 1226, 841, 761, 716, 691. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.0 Hz, 2H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.46 – 7.36 (m, 3H), 7.30 – 7.16 (m, 5H), 5.37 (s, 2H), 4.22 (s, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.7, 161.2, 156.2, 135.0, 134.3, 134.1, 130.9, 129.1, 129.0, 128.9, 128.6, 128.5, 128.0, 127.2, 126.3, 54.8, 32.7. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{19}NO_3Na$ 392.1257, found 392.1261.

2-((4-allyl-2-phenyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3f** was obtained as a light orange solid (27.3 mg, 86%), m.p. 126.7-128.0 °C. IR (ZnSe, cm^{-1}): 3067, 2982, 2922, 1696, 1592, 1475, 1446, 1345, 1221, 922, 724, 684. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.45 – 7.35 (m, 3H), 6.01 – 5.94 (m, 1H), 5.62 (s, 2H), 5.17 (d, *J* =10.1 Hz, 1H), 5.13 (d, *J* =17.21 Hz, 1H), 3.58 (d, *J* = 5.8 Hz, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.8, 161.3, 155.5, 134.4, 134.2, 131.7, 130.9, 129.1, 128.5, 128.1, 126.3, 118.3, 54.6, 30.9. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{17}NO_3Na$ 342.1101, found 342.1084.

2-((4-methyl-2-(p-tolyl)oxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3g** was obtained as a white solid (25.5 mg, 83%), m.p. 156.4-157.6 °C. IR (ZnSe, cm^{-1}): 3064, 3037, 2934, 1695, 1592, 1492, 1452, 1338, 1222, 748, 688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 6.8 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 7.4, 2H), 5.59 (s, 2H), 2.44 (s, 3H), 2.38 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.7, 161.2, 154.4, 139.0, 134.4, 134.1, 129.2, 129.1, 128.1, 126.1, 54.5, 21.3, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{17}NO_3Na$ 330.1101, found 330.1086.

2-((2-(4-bromophenyl)-4-methyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3h** was obtained as a white solid (21.2 mg, 91%) using the general procedure with concentration of 0.2 mol L^{-1} of azlactone in fluorobenzene, m.p. 166.9-169.4 °C. IR (ZnSe, cm^{-1}): 3033, 2920, 2854, 1695, 1593, 1485, 1452, 1405, 1225, 836, 685, 636. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56 – 7.53 (m, 4H), 5.60 (s, 2H), 2.45 (s, 3H). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 190.5, 160.3, 154.8, 134.5, 134.0, 131.7, 129.9, 129.1, 128.2, 127.8, 123.3, 54.5, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{14}BrNO_3Na$ 394.0049, found 394.0051.

2-((4-(2-(methylthio)ethyl)-2-phenyloxazol-5-yl)oxy)-1-phenylethan-1-one. The product **3i** was obtained as a white solid (31.5 mg, 94%), m.p. 108.7-110.3 °C. IR (ZnSe, cm^{-1}): 3059, 2942, 2914, 2836, 1682, 1593, 1481, 1448, 1351, 1226, 929, 762, 691. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 6.9 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.45 – 7.37 (m, 3H), 5.71 (s, 2H), 3.05 – 2.96 (m, 4H), 2.11 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.8, 161.3, 156.6, 134.4, 134.0, 130.9, 129.1, 128.5, 128.1, 126.3, 54.5, 32.0, 26.8, 15.9. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{19}NO_3SNa$ 376.0983, found 376.0980.

1-((4-methyl-2-phenyloxazol-5-yl)oxy)pentan-2-one. The product **3j** was obtained as a yellow solid (19.2 mg, 74%) after purification through a chromatography column (elution: hexane/ethyl acetate, 3:1), m.p. 53.7-55.2 °C. IR (ZnSe, cm^{-1}): 3347, 3063, 2962, 2929, 2874, 1722, 1668, 1519, 1442, 1356, 1112, 1036, 795, 722, 689. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.9 Hz, 2H), 7.43 – 7.37 (m, 3H), 4.90 (s, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 1.67 (sex, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 202.3, 161.2, 154.0, 130.8, 129.1, 128.5, 126.2, 57.0, 41.7, 16.7, 13.6, 11.9. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{17}NO_3Na$ 282.1101, found 282.1073.

3,3-dimethyl-1-((4-methyl-2-phenyloxazol-5-yl)oxy)butan-2-one. The product **3k** was obtained as a yellow oil (25.6 mg, 94%) after purification through a chromatography column (elution: hexane/ethyl acetate, 3:1). IR (ZnSe, cm^{-1}): 3394, 3064, 2969, 2872, 1722, 1673, 1523, 1478, 1443, 1352, 1109, 1064, 1006, 822, 725, 688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.1 Hz, 2H), 7.42 – 7.35 (m, 3H), 5.11 (s, 2H), 2.36 (s, 3H), 1.28 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 206.3, 160.9, 154.2, 130.9, 129.0, 128.4, 126.2, 52.6, 43.4, 26.1, 11.8. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{19}NO_3Na$ 296.1257, found 296.1235.

4-(3-methoxyphenyl)-1-((4-methyl-2-phenyloxazol-5-yl)oxy)butan-2-one. The product **3l** was obtained as a white solid (30.6 mg, 87%), m.p. 107.8-108.9 °C. IR (ZnSe, cm^{-1}):

3396, 3057, 2932, 2839, 2105, 1723, 1601, 1523, 1483, 1439, 1359, 1158, 1005, 786, 721, 691. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.8 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.71 (s, 1H), 4.85 (s, 2H), 3.77 (s, 3H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.33 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 201.6, 161.1, 159.8, 154.0, 141.6, 130.7, 129.7, 129.2, 128.5, 126.2, 120.6, 114.1, 111.7, 57.3, 55.1, 41.3, 29.4, 11.7. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{21}NO_4Na$ 374.1363, found 374.1361.

1-(4-methoxyphenyl)-2-((4-methyl-2-phenyloxazol-5-yl)oxy)ethan-1-one. The product **3m** was obtained as a yellow solid (24.5 mg, 76%) after purification through a chromatography column (elution: hexane/ethyl acetate, 3:1), m.p. 126.6-127.7 °C. IR (ZnSe, cm^{-1}): 3367, 3059, 2924, 2844, 1685, 1596, 1512, 1441, 1353, 1311, 1165, 1016, 984, 816, 719, 688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.3 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H), 7.42 – 7.35 (m, 3H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.52 (s, 2H), 3.87 (s, 3H), 2.43 (s, 3H).^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 189.0, 164.4, 160.9, 154.6, 130.9, 130.5, 129.0, 128.4, 127.0, 126.2, 114.2, 55.6, 54.2, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{17}NO_4Na$ 346.1050, found 346.1039.

1-(4-chlorophenyl)-2-((4-methyl-2-phenyloxazol-5-yl)oxy)ethan-1-one. The product **3n** was obtained as a white solid (30.8 mg, 94%), m.p. 137.4-139.0 °C. IR (ZnSe, cm^{-1}): 3364, 3089, 2923, 1689, 1585, 1522, 1442, 1349, 1296, 1223, 1091, 988, 835, 722, 688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 6.9 Hz, 2H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.44 – 7.36 (m, 3H), 5.55 (s, 2H), 2.44 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 189.6, 161.2, 154.6, 141.1, 132.4, 130.8, 129.6, 129.5, 129.2, 128.5, 126.2, 54.4, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{14}ClNO_3Na$ 350.0554, found 350.0545.

2-((4-methyl-2-phenyloxazol-5-yl)oxy)-1-(4-nitrophenyl)ethan-1-one. The product **3o** was obtained as a yellow solid (31.5 mg, 93%), m.p. 162.8-164.4 °C. IR (ZnSe, cm^{-1}): 3067, 2927, 2110, 1709, 1595, 1515, 1436, 1405, 1335, 1205, 1105, 984, 851, 719, 686. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 6.8 Hz, 2H), 7.44 – 7.38 (m, 3H), 5.60 (s, 2H), 2.47 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 189.6, 161.4, 154.6, 151.0, 138.4, 130.7, 129.4, 129.3, 128.6, 126.2, 124.3, 54.7, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{14}N_2O_5Na$ 361.0795, found 361.0790.

1-(2-chlorophenyl)-2-((4-methyl-2-phenyloxazol-5-yl)oxy)ethan-1-one. The product **3p** was obtained as an orange solid (32.1 mg, 98%), m.p. 103.7-105.5 °C. IR (ZnSe, cm^{-1}): 3057, 2924, 2853, 2106, 1700, 1585, 1523, 1472, 1436, 1351, 1209, 1101, 1065, 979, 834, 719, 688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.9 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 3.7 Hz, 2H), 7.43 – 7.36 (m, 4H), 5.55 (s, 2H), 2.48 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 193.5, 161.1, 154.4, 135.6, 133.3, 131.5, 130.8, 130.1, 129.1, 128.5, 127.4, 126.2, 57.4, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{14}ClNO_3Na$ 350.0554, found 350.0541.

(E)-1-((4-methyl-2-phenyloxazol-5-yl)oxy)-4-phenylbut-3-en-2-one. The product **3q** was obtained as a orange solid (24.3 mg, 76%) after purification through a chromatography column (elution: hexane/ethyl acetate, 3:1), m.p. 143.7-144.6 °C. IR (ZnSe, cm^{-1}):3357, 3024, 2923, 2853, 1783, 1665, 1622, 1523, 1491, 1442, 1352, 1311, 1193, 1101, 1071,

994, 829, 719, 685. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 16.1 Hz, 1H), 7.55 (d, *J* = 6.8 Hz, 2H), 7.45 – 7.38 (m, 6H), 6.77 (d, *J* = 16.1 Hz, 1H), 5.19 (s, 2H), 2.46 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.9, 161.2, 154.3, 145.8, 133.7, 131.4, 130.8, 129.1, 129.1, 128.7, 128.5, 126.2, 121.4, 56.2, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_3$ 320.1281, found 320.1275.

benzyl(R)-(4-((4-methyl-2-phenyloxazol-5-yl)oxy)-3-oxo-1-phenylbutan-2-yl)carbamate. The product **3r** was obtained as a white solid (40.2 mg, 85%) using the general methodology for 8 h, m.p. 123.7-124.6 °C. IR (ZnSe, cm^{-1}):3306, 3033, 2923, 2856, 1726, 1682, 1531, 1443, 1349, 1256, 1153, 1029, 979, 719, 688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.42 – 7.28 (m, 11H), 7.16 (d, *J* = 7.0 Hz, 2H), 5.38 (d, *J* = 6.5 Hz, 1H), 5.10 (s, 2H), 5.05 (d, *J* = 18.2 Hz, 1H), 4.84 (d, *J* = 18.2 Hz, 1H), 4.57 (dd, *J* = 14.1, 7.1 Hz, 1H), 3.16 (dd, *J* = 13.9, 6.3 Hz, 1H), 3.03 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.31 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 190.9, 161.2, 154.3, 145.8, 133.7, 131.4, 130.8, 129.1, 129.1, 128.7, 128.5, 126.2, 121.4, 56.2, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{26}N_2O_5Na$ 493.1734, found 493.1699.

benzyl(S)-(4-((4-methyl-2-phenyloxazol-5-yl)oxy)-3-oxo-1-phenylbutan-2-yl)carbamate. The product **3s** was obtained as a white solid (40.9 mg, 87%) using the general methodology for 8 h, m.p. 125.4-127.3 °C. IR (ZnSe, cm^{-1}):3310, 3034, 2926, 2854, 1725, 1670, 1528, 1446, 1345, 1273, 1155, 1036, 979, 721, 691. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.42 – 7.27 (m, 11H), 7.16 (d, *J* = 7.0 Hz, 2H), 5.40 (d, *J* = 6.6 Hz, 1H), 5.10 (s, 2H) 5.05 (d, *J* = 18.3 Hz, 1H), 4.84 (d, *J* = 18.2 Hz, 1H), 4.57 (dd, *J* = 13.9, 6.9 Hz, 1H), 3.15 (dd, *J* = 13.9, 6.4 Hz, 1H), 3.03 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.31 (s, 3H).^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 201.2, 161.1, 156.1, 154.6, 135.8, 135.2, 130.7, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 128.1, 127.5, 126.2, 67.4, 59.0, 55.8, 36.8, 11.6. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{26}N_2O_5Na$ 493.1734, found 493.1754.

methyl 2-((4-methyl-2-phenyloxazol-5-yl)oxy)-2-phenylacetate. The product **3t** was obtained as a yellow solid (6.8 mg, 21%) using the general procedure with toluene at 90 °C after purification through a chromatography column (elution: hexane/ethyl acetate, 3:1), m.p. 79.9-81.7 °C. IR (ZnSe, cm^{-1}): 3064, 2953, 1748, 1653, 1521, 1442, 1345, 1269, 1212, 1171, 1109, 1002, 911, 724, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.43 – 7.37 (m, 8H), 6.24 (s, 1H), 3.86 (s, 3H), 2.33 (s, 3H).^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 168.0, 160.7, 153.8, 133.1, 130.8, 129.2, 129.1, 128.9, 128.4, 128.4, 126.3, 65.2, 53.2, 12.8. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{17}NO_4Na$ 346.1050, found 346.1035.

ethyl 2-((4-methyl-2-phenyloxazol-5-yl)oxy)acetate. The product **3u** was obtained as a white solid (6.9 mg, 26%), m.p. 84-86°C . IR (ATR, cm^{-1}): 2916, 2850, 1747, 1674, 1522**,** 1483, 1444, 1376, 1350, 1242, 1206, 1113**,** 1024, 727, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.00 (m, 2H), 7.48 – 7.34 (m, 3H), 4.91 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 166.6, 161.1, 154.1, 132.0, 130.8, 129.2, 128.6, 128.5, 127.4, 126.3, 62.3, 49.8, 14.1, 12.0. HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{15}NNaO_4$ 284.0899, found 284.0876.

ASSOCIATED CONTENT

Supporting information contains ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, IR spectra, HPLC chromatograms, and mechanistic investigation. The supporting information is available free of charge on the ACS Publications website at DOI:

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Notes
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