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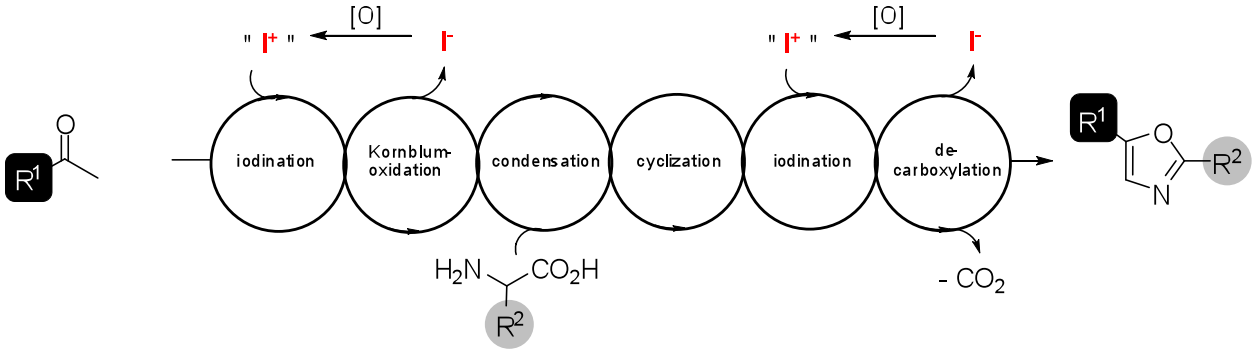


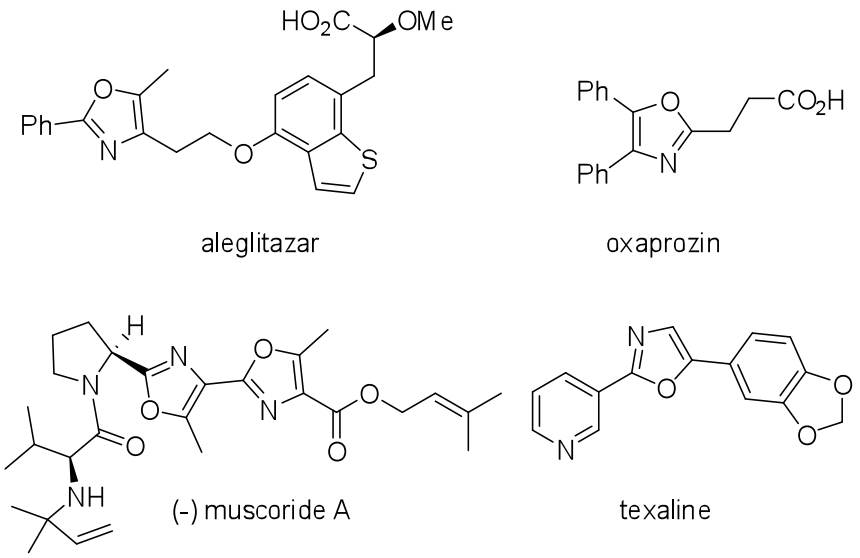
ABSTRACT: An efficient iodine-catalyzed synthesis of highly substituted oxazoles is presented. Starting from readily available aryl methyl ketones, β-keto esters or styrenes, in combination with α-amino acids as amine-containing coupling partners, the corresponding 2-alkyl-5-aryl substituted oxazoles were obtained in up to 80% yield via a decarboxylative domino reaction.

INTRODUCTION

The oxazole motif is a commonly found core structure in pharmaceuticals and natural products. Representative examples are the PPARα/γ agonist aleglitazar,[1] the non-steroidal anti-inflammatory drug oxaprozin,[2] the peptide alkaloide muscoride A[3] or the antimycobacterial natural product texaline (Figure 1).[4] As a consequence of the extraordinary abundance of oxazoles in biological

active compounds, a variety of synthetic procedures yielding highly substituted oxazoles have been developed during the last decades.

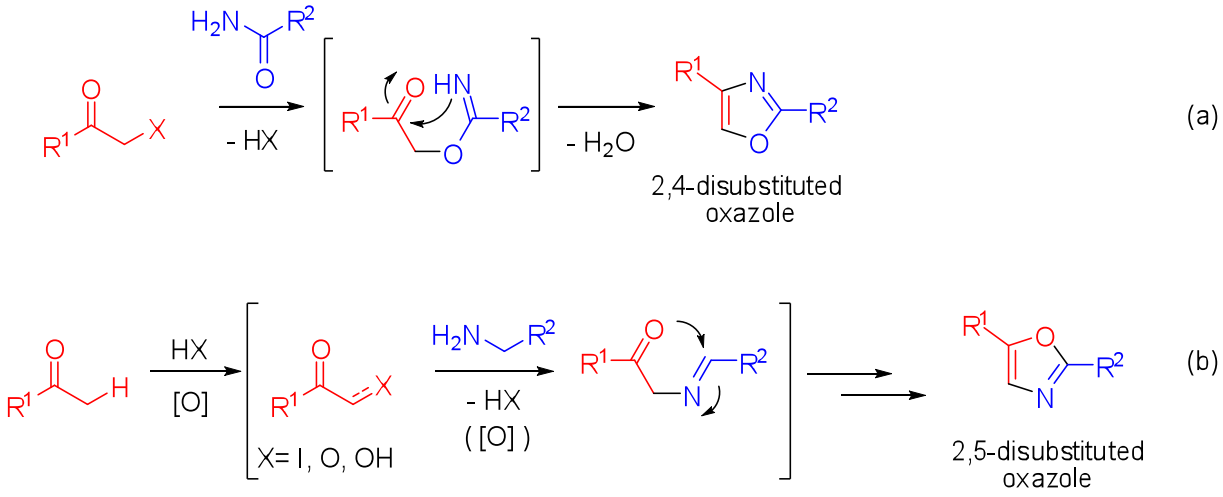
Figure 1. Representative examples of oxazoles in pharmaceuticals and other biological active compounds.



Classical routes to the oxazole motif include the cyclodehydration of (α-acylamino)ketones (Robinson-Gabriel Synthesis), the cyclodehydration of (α-acyloxy)ketones in the presence of ammonia, the condensation of cyanhydrines and aromatic aldehydes (Fischer Synthesis) and the annulation of enamides.[5-15] 2-Alkyl substituted oxazoles are accessible by reactions of aryl alkyl ketones and nitriles using hypervalent iodine reagents,[16-18] mercury-[19] and thallium-salts[20], by [3+2] cycloadditions[21-23] by the cycloisomerization of propargylamides,[24-30] or by a Ritter reaction of α-oxotosylates.[31] However, an underevaluated route to oxazoles, which primarily yields 2,4-disubstituted derivatives, is the cyclocondensation of α-halogenated ketones and carboxamides as initially described by Blümlein and Lewy in the 1880s (Scheme 1 – a).[32,33] Major drawbacks of this transformation are harsh reaction conditions and the necessity of hazardous α-halo ketones as precursors. The in situ generation of α-halo ketones or synthetic equivalents thereof from α-unsubstituted ketones by in situ halogenation or oxidation, subsequent substitution with an amine

and cyclization in a domino process would be much more efficient (Scheme 1 – b).[34] The utilization of acetophenones for the de novo synthesis of heterocycles via oxidative domino reactions has been studied intensively and resulted in the development of a variety of transformations including the synthesis of 2-acylbenzo[*d*]thiazoles,[35] isooxazoles,[36] quinazolinones,[37] imidazoles and thiazoles,[38,39] imidazo[1,2-*a*]pyridines,[40] and 1,2,3-triaroylindolizines.[41]

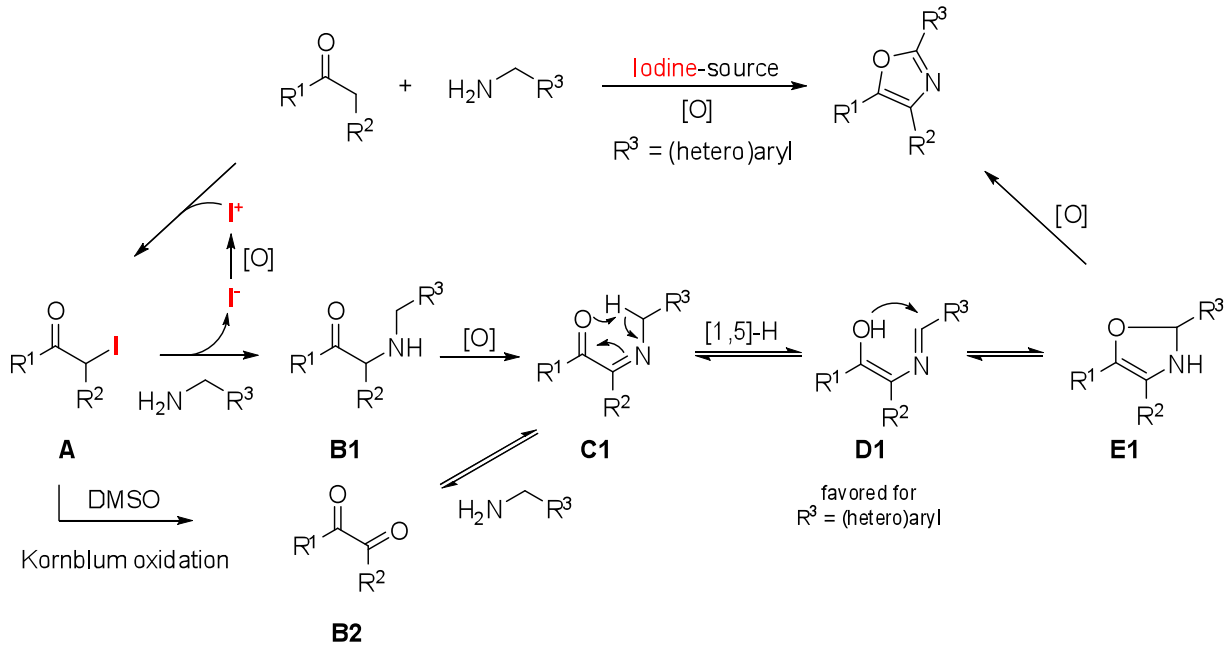
Scheme 1. Synthesis of oxazoles starting from α-halo ketones and carboxamides (a) or ketones and amines (b)



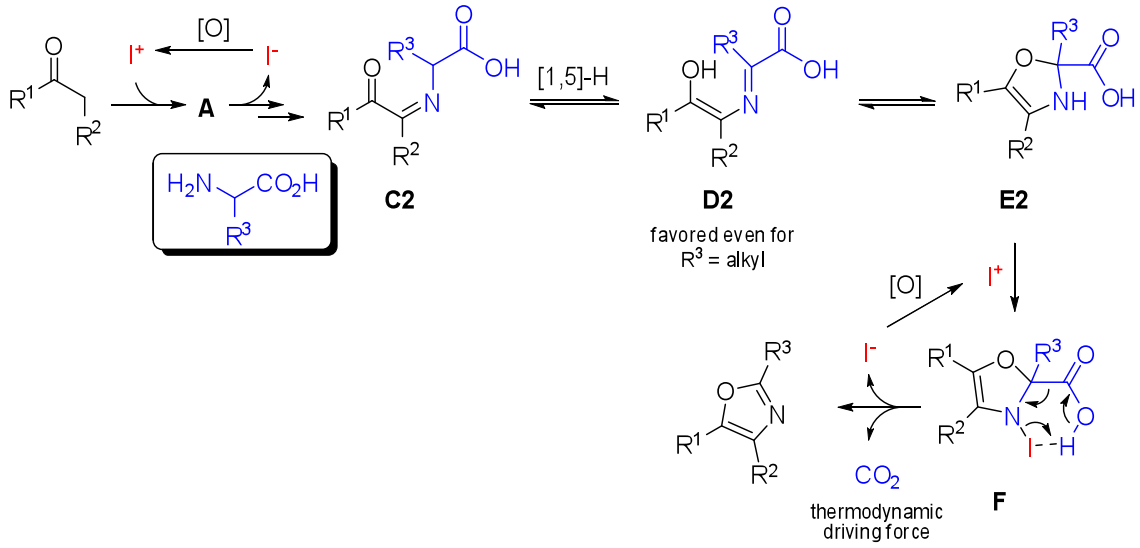
However, the synthesis of oxazoles via oxidative domino reactions is less common.[21,22,42,43] For example, Wang and co-workers developed an efficient synthesis of 2,5-disubstituted oxazoles starting from α-amino ketones and aromatic carboxaldehydes.[44] Jiang and co-workers reported an oxidative domino reaction yielding 2,5- or 2,4,5-substituted oxazoles starting from styrenes and benzyl amines. Here, α-halo ketones, as key intermediates, are formed in situ from styrenes by combining molecular iodine and *tert*-butyl hydroperoxide as co-oxidant.[45] The same authors described an efficient iodine-mediated synthesis of polysubstituted imidazoles.[46] 2-aryl-4-acyl-substituted oxazoles can be generated by an iodine-catalyzed cascade sp^3 C-H activation starting from alkyl acetoacetates and benzyl amines.[47]

Scheme 2. Mechanistic proposal for (a) the known oxidative domino synthesis of 2-aryl-5-aryl-disubstituted oxazoles from aryl methyl ketones and benzyl amines and (b) a decarboxylative domino reaction based on α-amino acids.

(a) previous work: synthesis of 2-aryl-5-aryl-substituted oxazoles



(b) working hypothesis - a decarboxylative domino process yielding 2-alkyl-5-aryl-substituted oxazoles



Wu and co-workers presented an iodine-mediated synthesis of oxazoles based on benzoins, aryl methyl ketones and ammonium acetate by the convergent integration of two self-labor domino sequences.[48]

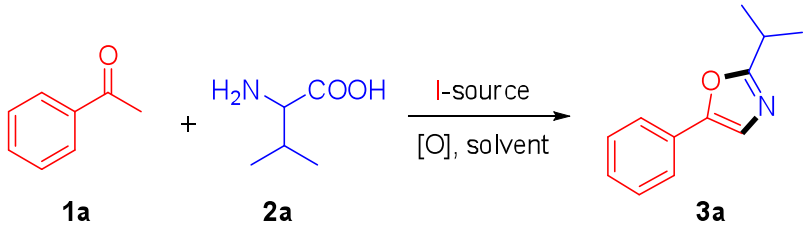
Very recently, the same group developed an iodine-mediated and peroxide-free oxidative domino synthesis of 2-aryl-5-aryl-disubstituted oxazoles utilizing aryl methyl ketones and benzyl amines as substrates.[49] However, all oxidative domino sequences described above give 2-aryl-substituted oxazoles exclusively. The complementary 2-alkyl-substituted derivatives are not accessible via these iodine-mediated oxidative domino sequences.[21,25,50,51] An efficient synthetic approach towards 2-alkyl substituted oxazoles was reported by Martínez-Alvarez and co-workers through the reaction of 1-(methylthio)acetone with nitriles in the presence of triflic acid.[52] However, an explanation for the preferred 2-aryl substituent in iodine-mediated oxidative domino sequences for the synthesis of oxazoles is given in Scheme 2 (a). In either case, the α-iodinated ketone **A** is generated by in situ iodination. **A** reacts with the corresponding amine to the aza enone **C1** either by a substitution/oxidation mechanism through the α-amino ketone **B1** or, depending on the reaction conditions, via a Kornblum oxidation through 1,2-dicarbonyl intermediate **B2**. However, for the key cyclization step, **C1** must isomerize via a [1,5]-H-shift to compound **D1**, which after cyclization to **E1** and subsequent oxidation gives the desired oxazole. Looking at this cascade reaction it seems obvious that formation of **D1** is highly favored for R^3 being an (hetero)aromatic residue due to the generation of a highly conjugated π-system explaining the high preference for benzyl amines in this transformation. Inspired by the mechanism shown in Scheme 2 (a) we were intended to introduce aliphatic residues in 2-position of the oxazole by using α-amino acids in a decarboxylative process (Scheme 2 – b). The carboxylic acid would act as a directing group that has two positive effects on this domino process: (1) intermediate **C2** would be favored, even for an aliphatic residue at R^3 due to a conjugation with the carboxylic acid and (2) an iodine mediated oxidative decarboxylation can be formulated (**F**) generating the oxazole directly through the oxidative loss of CO_2. Our working hypothesis was strongly supported by two recently published articles describing iodine mediated decarboxylative domino reactions based on α-amino acids for the construction of highly substituted

pyridines and quinazolines by Wang and co-workers.[53,54] Based on this proposal and on recent results of our group and others in iodine-mediated oxidative couplings, halogenations and domino reactions,[55-63] we herein report the first iodine-catalyzed synthesis of 2-alkyl-substituted oxazoles by a decarboxylative domino reaction starting from aryl methyl ketones or styrenes and α-amino acids.

RESULTS AND DISCUSSION

In initial experiments we investigated the reaction between acetophenone **1a** and (DL)-valine **2a** in the presence of an iodine-source and a co-oxidant. Since it is well known, that the combination of I_2 and the co-oxidant TBHP (*tert*-butyl hydroperoxide) gives undesired α-ketoamides from acetophenones and amines,[64] it was not surprising to us, that initial experiments using the common co-oxidant TBHP gave the desired oxazole **3a** in only low yields of 27% (Table 1, entry 1). Other oxidants such as NaOCl or H_2O_2 did not yield **3a** at all (Table 1, entries 2 and 3). To our great delight, the co-oxidant Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) gave **3a** in a promising isolated yield of 53% (Table 1, entry 4). Switching the iodine-source from molecular iodine to tetrabutylammonium iodide (TBAI) resulted in an almost complete loss of reactivity (Table 1, entry 5). For a mechanistic discussion it is important to note that the reaction can be exclusively performed in DMSO. Other polar aprotic solvents such as DMF and CH_3CN gave the desired product only in trace amounts (Table 1, entries 6 and 7). The reason for this solvent dependency is most likely a Kornblum oxidation giving 1,2-diketone of type **B2** as discussed in Scheme 2. Addition of base additives such as K_2CO_3 or Na_2CO_3 as well as acid additives such as acetic acid did not improve yields significantly (Table 1, entries 8-10). However, when the amount of co-oxidant was increased from 2.5 to 3 equivalents the isolated yield of **3a** could be increased from 53 to 80% (Table 1, entry 11).

Table 1. Optimization studies.[a]



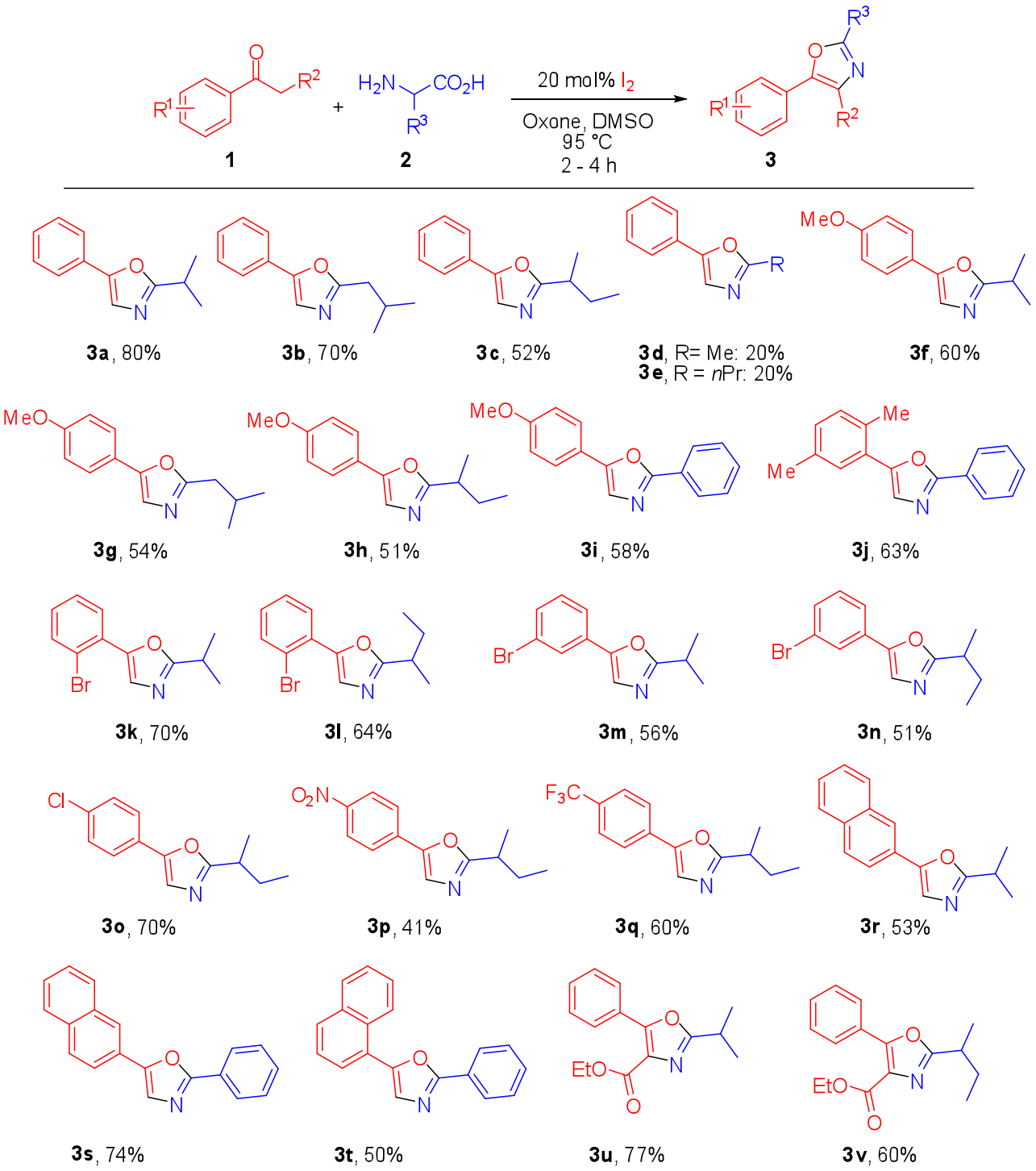
1a **2a** **3a**

entry	cat (mol%)	oxidant (equiv.)	solvent	T [°C]	t [h]	yield 3a [%][a,b]
1	I_2 (20)	TBHP (2.5)[c]	DMSO	95	2	27
2	I_2 (20)	NaOCl (2.5)[d]	DMSO	95	2	0
3	I_2 (20)	H_2O_2 (2.5)[e]	DMSO	95	2	0
4	I_2 (20)	Oxone (2.5)	DMSO	95	2	53
5	TBAI (20)	Oxone (2.5)	DMSO	95	2	traces
6	I_2 (20)	Oxone (2.5)	DMF	95	2	traces
7	I_2 (20)	Oxone (2.5)	CH_3CN	95	2	traces
8[f]	I_2 (20)[c]	Oxone (2.5)	DMSO	95	2	53
9[g]	I_2 (20)[d]	Oxone (2.5)	DMSO	95	2	53
10[h]	I_2 (20)[e]	Oxone (2.5)	DMSO	95	2	57
11	**I_2 (20)**	**Oxone (3.0)**	**DMSO**	**95**	**2**	**80**
12	I_2 (20)	Oxone (3.5)	DMSO	95	2	74
13	I_2 (20)	Oxone (3.0)	DMSO	75	2	60
14	I_2 (20)	Oxone (3.0)	DMSO	115	2	67

[a]General reaction conditions: 0.4 mmol (1 equiv) acetophenone **1a**, 1.2 mmol (3 equiv) DL-valine **2a** and catalyst in 3 mL of solvent [b]Isolated yield after flash column chromatography. [c]70% aq. solution. [d]30% aq. solution. [e]5% aq. solution. [f]2 equiv. of K_2CO_3 were added. [g]2 equiv. of Na_2CO_3 were added. [h]2 equiv. of AcOH were added.

When 3.5 equivalents of Oxone were used, yields dropped again (Table 1, entry 12). The initially chosen 95 °C seemed to be the ideal reaction temperature since increasing or lowering the reaction temperature resulted in a significant drop in yields (Table 1, entries 13 and 14). Having these optimized reaction conditions in hand, we tested the reactivity of a variety of aryl methyl ketones and α-amino acids in this novel domino reaction (Scheme 3). Besides valine, other aliphatic amino acids, in particular leucine and isoleucine reacted smoothly to give the desired oxazoles **3b** and **3c** in 70% and 52% yield respectively.

Scheme 3. Reaction of various aryl methyl ketones with α-amino acids.[a,b]

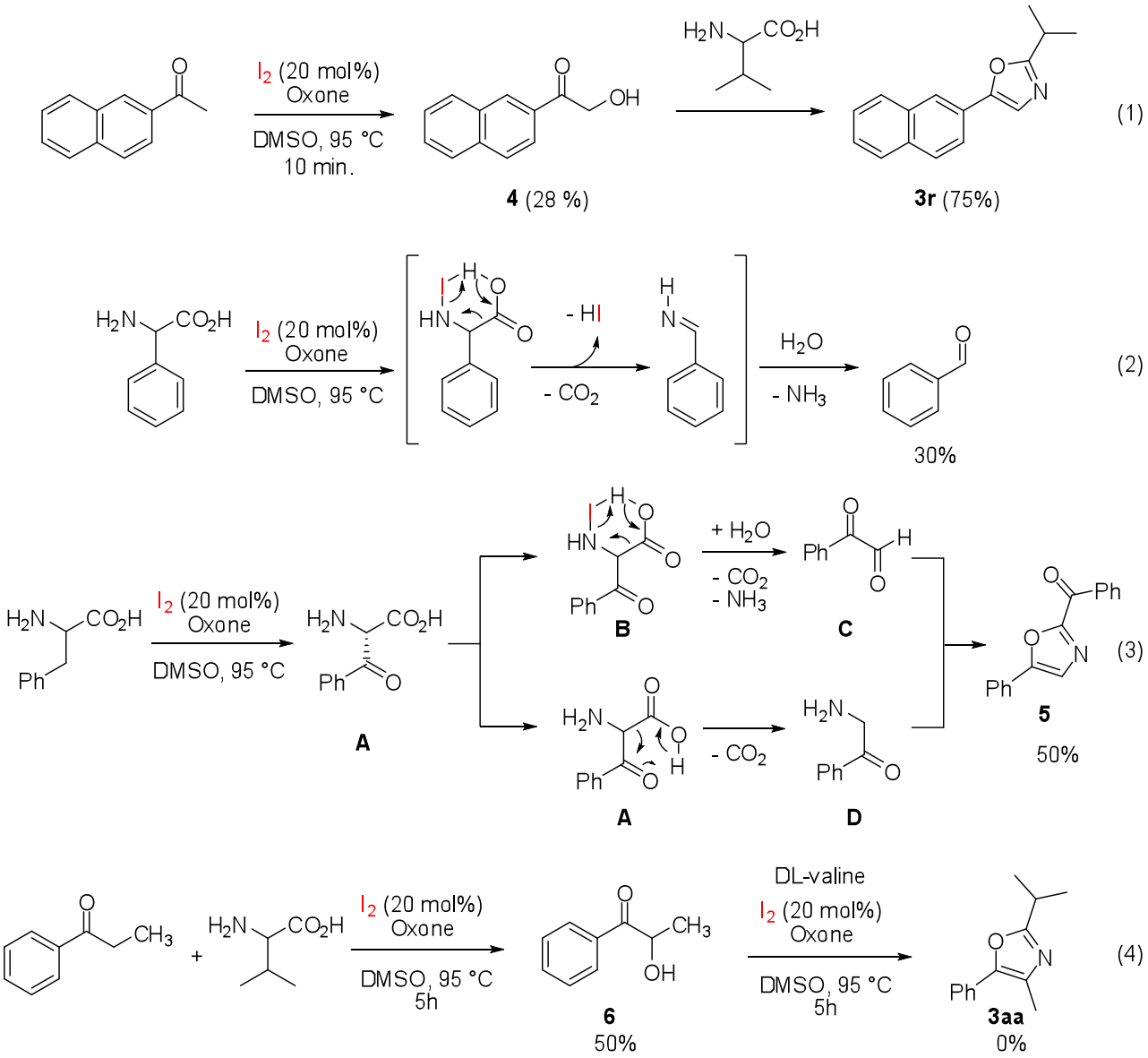


[a]General reaction conditions: 0.4 mmol (1 equiv) **1**, 1.2 mmol **2** (3 equiv), 0.08 mmol (20 mol%) I_2, 1.2 mmol (3 equiv) Oxone, 3 ml DMSO. [b]Isolated yield after flash column chromatography.

To our surprise yields dropped significantly to 20% when unbranched aliphatic α-amino acids such as alanine or norvaline were used as substrates (**3d** and **3e**). Furthermore, it is worth mentioning that enantiopure (2S,3S)-isoleucine gave the corresponding oxazole **3c** as a racemic mixture. Electron rich aryl methyl ketones such as 4-methoxy acetophenone or 2',5'-dimethylacetophenone gave oxazoles **3f-3j** in good yields of up to 63%. Here, α-aryl substituted amino acids such as phenyl glycine could be used as substrates as well. A variety of ortho-, meta- and para-halogenated acetophenones could be utilized giving **3k-3o** in up to 70% yield. 4-Nitro and 4-CF_3-substituted acetophenones yielded oxazoles **3p** and **3q** in 41% and 60% yield respectively. 1- and 2-naphthalenones resulted in formation of 5-(1-naphthyl) and 5-(2-naphthyl)-substituted oxazoles **3r-3t** in 53-74% yield. Finally, the 1,3-dicarbonyl compound ethyl benzoyl acetate was tested in this domino process. Reaction with valine and isoleucine gave the 2,4,5-trisubstituted oxazoles **3u** and **3v** in 77% and 60% yield. However, it is worth mentioning that other, higher substituted, aryl alkyl ketones such as propiophenone which would give an access to 2,4,5-trisubstuted oxazoles cannot be used under our optimized reaction conditions. Aliphatic ketones such as cyclopentanone or butan-2-one also showed no reactivity. To gain detailed insides into the mechanism of our newly developed domino reaction, we were intended to isolate side products and reaction intermediates formed during the reaction cascade (Scheme 4). First, we could isolate the α-hydroxylated 1-naphthalenone **4** (Scheme 4 – 1) which is formed by hydrolysis of the α-iodoketone. Subsequently, **4** was shown to react with valine to the desired oxazole **3r** in 75% yield under the same optimized reaction conditions previously found in Table 1. Thus **4** can be seen as an intermediate which is formed in a constructive side pathway coexistent to the Kornblum oxidation pathway. Since an excess of the corresponding amino acid (relative to the ketone) is needed, an undesired decomposition of the

amino acid was expected. As a control experiment, phenylglycine was treated with molecular iodine in the presence of Oxone, without the addition of the corresponding ketone.

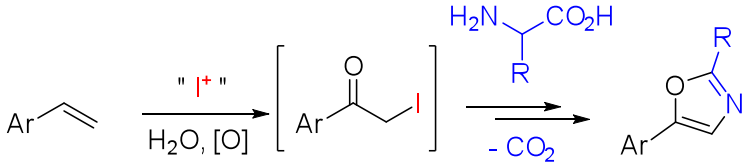
Scheme 4. Decomposition pathways.



In this experiment we observed benzaldehyde as the only side product in 30% yield, most likely due to an iodine-mediated decarboxylation and subsequent hydrolysis of the emerging imine (Scheme 4 – 2). During our investigations towards the substrate scope we already recognized, that phenyl alanine was a surprisingly poor substrate for our domino reaction. A remarkable side reaction was

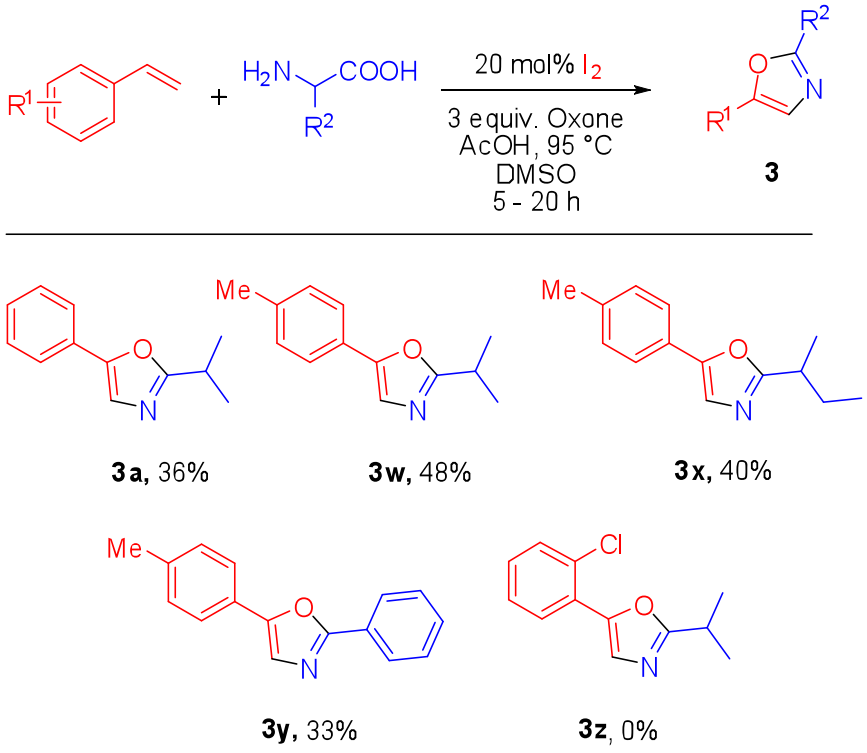
observed when phenyl alanine was reacted with Oxone in the presence of iodine. As the only product, the unexpected 2-acyl oxazole **5** was isolated in 50% yield (Scheme 4 – 3). Here, a benzylic oxidation of phenyl alanine to its β-oxo derivative **A** is proposed. **A** must be prone to two convergent decomposition processes yielding 1,2-diketone **C** via an iodine-mediated oxidative decarboxylation. Simultaneously, decarboxylation of the β-keto acid **A** gives α-amino acetophenone **D**. Condensation of both substrates finally yields 2-acyl-5-aryl oxazole **5**. Finally, we tried to elucidate the poor reactivity of higher substituted aryl alkyl ketones. When propiophenone was reacted under our optimized reaction conditions no oxazole formation was observed. Instead, we could only isolate the corresponding α-hydroxlated derivative **6** in 50 % yield upon reaction with valine. In contrast to the primary alcohol **4**, this secondary hydroxyl group can obviously not be further oxidized to the corresponding 1,2-diketone since further reaction of isolated **6** with valine under the same reaction conditions did also not result in the formation of desired 2,4,5-trisubstituted oxazole **3aa**. Next, we investigated an even more ambitious domino reaction. The conversion of styrenes into the corresponding α-iodo ketones with electrophilic iodine reagents is well known.[35,38,39,65-71] Thus, a direct conversion of styrenes to oxazoles with I_2 and a co-oxidant should be possible as well. One example for such a reaction was reported in 2010 by Jiang and co-workers.[45] However, stoichiometric amounts of molecular iodine were necessary and again only 2-aryl substituted oxazoles are accessible via this method. Therefore, we wondered whether we could extend the substrate scope of our decarboxylative domino reaction sequence to styrenes as well (Scheme 5). Initial optimization studies for the reaction between styrene and valine revealed that this reaction can be performed under similar reaction conditions as described in Table 1 (data not shown). The only significant difference is a previously not observed positive effect of acetic acid as an additive.

Scheme 5. Reaction of styrene with an α- amino acid to give 2-alkyl-5-aryl oxazoles via a decarboxylative domino reaction.



Finally, oxazole **3a** could be isolated in only moderate yield of 36% (Scheme 6), which was significantly lower in comparison with the same reaction based on acetophenone as substrate (80%). However, we observed, that the reaction with styrenes are in general significantly slower leading to a substantial negative influence of the amino acid decomposition pathways as described in Scheme 4, which explains the significant drop in yield. Furthermore, undesired side reaction of the styrene such as epoxidations and/or iodohydroxylations cannot be ruled out.

Scheme 6. Reaction of styrenes with α-amino acids.[a,b]



[a]General reaction conditions: 0.3 mmol **1** 0.6 mmol (2 equiv) styrene, 0.06 mmol I_2 (20 mol%), 0.9 mmol AcOH (3 equiv) and 0.75 mmol (2.5 equiv) Oxone in 2 mL of DMSO. [b]Isolated yield after flash column chromatography.

Even dropwise addition of the amino acid and/or styrene did not improve product yields. Electron poor styrenes such as 2-chloro styrene reacted messy and the desired oxazole **3z** could not be isolated in significant amounts. However, moderately electron rich styrenes, such as *p*-methyl styrene, yielded the desired oxazoles **3w-3y** in up to 48% yield.

In summary we have developed an efficient synthesis of 2-alkyl-5-aryl oxazoles starting from acetophenones and α-amino acids based on an iodine-catalyzed decarboxylative domino reaction. The reaction must be conducted in DMSO which strongly supports an initial Kornblum oxidation pathway. With only 20 mol% of molecular iodine and Oxone as cheap and readily available co-oxidant, a variety of 2-alkyl-5-aryl-substituted oxazoles could be isolated in excellent yields of up to 80% using a variety of alkyl-substituted amino acids. Finally, this domino reaction could be extended to styrenes as substrates as well, however with significantly lower yields.

EXPERIMENTAL SECTION

1H NMR spectra were recorded on a 400 MHz instrument. Chemical shifts for 1H NMR were reported as δ (parts per million) relative to the signal of $CHCl_3$ at 7.26(s) ppm. Chemical shifts for 13C NMR were reported as δ (parts per million) relative to the $CDCl_3$ triplet at 77.0 ppm. The following abbreviations were used to describe splitting patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet. Coupling constants *J* are given in Hz. Mass spectra were recorded using EI ionization method with a quadrupole mass analyzer. High resolution mass spectra were recorded using ESI ionization method with a FT-ICR mass analyzer.

Unless otherwise stated, all chemicals were either used as received from their commercial supplier or purified according to *Purification of Common Laboratory Chemicals*.[72] Solvents for flash column and thin layer chromatography including cyclohexane, ethyl acetate, toluene, and diethyl ether were distilled prior to use. DMSO was 99.5% pure and used without further drying or purification. Thin layer chromatography was performed on fluorescence indicator marked precoated silica gel 60 plates and visualized either by UV light (254 nm/366 nm). Flash column chromatography was performed on silica gel (0.040 – 0.063 mm). Melting points are uncorrected.

General experimental procedure 1 for preparation of 2-alkyl-5-aryl oxazoles from aryl ketones. A solution of the corresponding acetophenone **1** (0.40 mmol, 1 equiv.), the α-amino acid (1.2 mmol, 3 equiv.), Oxone (1.2 mmol, 3 equiv.) and iodine (0.08 mmol, 0.2 equiv.) in DMSO (3 mL) was heated to 95 °C. The resulting mixture was stirred at 95 °C until the starting material was completely converted. The reaction mixture was allowed to cool to rt and then treated with saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford **3a-v**.

General experimental procedure 2 for preparation of 2-alkyl-5-aryl oxazoles from styrenes. A solution of the corresponding styrene (0.30 mmol, 1 equiv.), the α-amino acid (0.90 mmol, 3 equiv.), Oxone (0.75 mmol, 2.5 equiv.), iodine (0.06 mmol, 0.2 equiv.) and acetic acid (0.90 mmol, 3 equiv.) in DMSO (2 mL) was heated to 95 °C. The resulting mixture was stirred at 95 °C until the starting material was completely converted. The reaction mixture was allowed to cool to rt and then treated with saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$. The aqueous phase was extracted

with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford **3a,3w-3z**.

*2-Isopropyl-5-phenyloxazole (**3a**):* Prepared from acetophenone and valine following general experimental procedure 1; Yield: 60 mg (80%). Prepared from styrene and valine following general experimental procedure 2; Yield 20 mg (36 %) yellow liquid; eluent: petroleum ether/ethyl acetate (7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 8.1, 1.6 Hz, 2H), 7.34 – 7.31 (m, 2H), 7.24 – 7.20 (m, 1H), 7.15 (s, 1H), 3.08 (hept, *J* = 7.0 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 150.6, 128.7, 128.2, 128.0, 123.9, 121.5, 28.4, 20.4; IR (neat): 2974, 1691, 1552, 1489, 1363, 1273, 1203, 1139, 943, 823, 762, 712, 657, 613 (cm^{-1}); MS (EI) m/z: 187.1 (100) $[M]^+$, 172.1 (87) $[M\text{-}CH_3]^{+\cdot}$, 105.1 (9) $[M\text{-}C_5H_8N]^{+\cdot}$, 82.2 (12) $[M\text{-}C_7H_5O]^{+\cdot}$, 77.1 (16) $[M\text{-}C_6H_8NO]^{+\cdot}$ The spectral data were in good agreement with the literature.[17]

*2-Isobutyl-5-phenyloxazole (**3b**):* Prepared from acetophenone and leucine following general experimental procedure 1; Yield: 42 mg (70%), yellow liquid; eluent: petroleum ether/ethyl acetate (8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.7 Hz, 2H), 7.49 – 7.44 (m, 1H), 7.40 (s, 1H), 2.88 (d, J = 7.1 Hz, 2H), 2.43 – 2.33 (m, 1H), 1.19 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 150.8, 128.8, 128.3, 128.0, 123.9 , 121.7, 37.1, 27.6, 22.3; IR (neat): 2958, 1554, 1137, 1082, 940, 822, 759, 690, 671 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{13}H_{15}NO$ $[M+H]^+$: 202.1226, found: 202.1225.

*2-(1-Methylpropyl)-5-phenyloxazole (**3c**):* Prepared from acetophenone and isoleucine following general experimental procedure 1; Yield: 42 mg (52%), yellow liquid; eluent: petroleum ether/ethyl acetate (8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.32 – 7.27 (m, 1H), 7.22 (s, 1H), 2.97 (h, *J* = 7.0 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.74 – 1.69 (m,

1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 150.6, 128.8, 128.3, 128.0, 123.9, 121.5, 35.3, 28.2, 18.0, 11.6; IR (neat): 2967, 1552, 1449, 1138, 1055, 955, 822, 761, 742, 689 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{13}H_{15}NO$ $[M+H]^+$: 202.1226, found: 202.1226.

*2-Methyl-5-phenyloxazole (**3d**):* Prepared from acetophenone and alanine following general experimental procedure 1; Yield: 13 mg (20%), yellow solid; eluent: petroleum ether/ethyl acetate (8:1); mp.: 56.0 – 58.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.59 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.30 (tt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.21 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 151.1, 128.8, 128.1, 128.1, 123.9, 121.6, 14.1; IR (neat): 3119, 1754, 1668, 1558, 1484, 1304, 1214, 1130, 1061, 942, 834, 760, 692 (cm^{-1}); MS (EI) m/z: 159.1. (100) $[M]^+$**,** 130.1 (50) $[M-C2H5]^+$**,** 104.2 (28) $[M-C2H1NO]^+$**.** The spectral data were in good agreement with the literature.[21]

*2-Propyl-5-phenyloxazole (**3e**):*Prepared from acetophenone and norvaline following general experimental procedure 1; Yield: 15 mg (20%), pale yellow liquid; eluent: petroleum ether/ethyl acetate (7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.54 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.17 (s, 1H), 2.77 (t, *J* = 7.5 Hz, 2H), 1.84 – 1.75 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 130.84, 128.8, 128.2, 128.0, 123.9, 121.7, 30.1, 20.5, 13.7; IR (neat): 2964, 1556, 1448, 1133, 1026, 941, 760, 709, 690, 665 (cm^{-1}); MS (EI) m/z : 187.2 (36) $[M]^+$, 172.1 (13) $[M-CH_3]^{+\cdot}$, 159.1 (100) $[M-C_2H_6]^{+\cdot}$, 105.1 (6) $[M- C_5H_8N]^{+\cdot}$, 77.1 (7) $[M-C_6H_8NO]^{+\cdot}$, The spectral data were in good agreement with the literature.[17]

*2-Isopropyl-5-(4-methoxyphenyl)oxazole (**3f**):* Prepared from 4-methoxyacetophenone and valine following general experimental procedure 1; Yield: 52 mg (60%), yellow liquid; eluent: petroleum ether/ethyl acetate (8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.07 (s, 1H), 6.94 – 6.90 (m, 2H), 3.82 (s, 3H), 3.12 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101

MHz, $CDCl_3$) δ 167.9, 159.4, 150.6, 125.4, 121.2, 120.0, 114.2, 55.3, 28.4, 20.4; IR (neat): 2970, 1557, 1503, 1304, 1248, 115, 1137, 1029, 960, 831, 737, 685, 604 (cm^{-1}); HRMS (ESI) m/z calcd.. for $C_{13}H_{15}NO_2$ $[M+H]^+$: 218.1176, found: 218.1175.

*2- Isobutyl -5-(4-methoxyphenyl)oxazole (**3g**):* Prepared from 4-methoxyacetophenone and leucine following general experimental procedure 1; Yield: 50 mg (54%), yellow liquid; eluent: petroleum ether/ethyl acetate (8:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.03 (s, 1H), 6.87 – 6.84 (m, 2H), 3.76 (s, 3H), 2.62 (d, *J* = 7.1 Hz, 2H), 2.13 (dp, *J* = 13.6, 6.8 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 159.4, 150.8, 125.4, 121.2, 120.1, 114.2, 55.3, 37.1, 27.5, 22.3; IR (neat): 2957, 1620, 1558, 1503, 1463, 1295, 1250, 1174, 1028, 831, 796, 681, 608 (cm^{-1}); HRMS (ESI) m/z calcd.. for $C_{14}H_{17}NO_2$ $[M+H]^+$: 232.1332, found: 232.1332.

*2-(1-Methylpropyl)-5-(4-methoxyphenyl)oxazole (**3h**):* Prepared from 4-methoxyacetophenone and isoleucine following general experimental procedure 1; Yield: 47 mg (51%), yellow liquid; eluent: petroleum ether/ethyl acetate (8:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H), 7.08 (s, 1H), 6.93 – 6.90 (m, 2H), 3.81 (s, 3H), 2.93 (h, *J* = 7.0 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.71 – 1.66 (m, 1H), 1.36 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 159.4, 150.5, 125.4, 121.2, 119.9, 114.2, 55.2, 35.2, 28.2, 17.9, 11.5; IR (neat): 2967, 1556, 1503, 1460, 1291, 1246, 1175, 1028, 831, 799, 742, 610 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{14}H_{17}NO_2$ $[M+H]^+$: 232.1332, found: 232.1333.

*2-Phenyl-5-(4-methoxyl)oxazole (**3i**):* Prepared from 4-methoxyacetophenone and phenylglycine following general experimental procedure 1; Yield: 58 mg (58%), pale yellow solid; eluent: petroleum ether/ethyl acetate (8:1); mp.: 77.0 – 78.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (dt, *J* = 8.3, 2.2 Hz, 2H), 7.65 – 7.63 (m, 2H), 7.48 – 7.46 (m, 3H), 7.32 (s, 1H), 6.98 – 6.95 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 159.7, 151.2, 130.0, 128.7, 127.5, 126.1, 125.7,

121.8, 120.8, 114.3, 55.3; IR (neat): 2973, 1498, 1300, 1250, 1021, 951, 823, 772, 705, 614 (cm^{-1}); MS (ESI) m/z $[M]^+$: 251.1. The spectral data were in good agreement with the literature.[73]

*2-Phenyl-5-(2,5-dimethylphenyl)oxazole (**3j**):* Prepared from 2,5-dimethylacetophenone and phenylglycine following general experimental procedure 1; Yield: 62 mg (63%), white solid; eluent: petroleum ether/ethyl acetate (15:1); mp.: 79.0 – 80.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.59 (s, 1H), 7.52 – 7.46 (m, 3H), 7.34 (s, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.09 (dd, *J* = 7.7, 1.3 Hz, 1H), 2.50 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 150.9, 135.7, 131.8, 131.2, 130.2, 129.2 128.8 , 127.4, 127.2, 127.0, 126.2, 126.0, 21.4, 21.0; IR (neat): 2921, 1538, 1494, 1445, 1066, 963, 811, 772, 704, 687 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{17}H_{15}NO$ $[M+H]^+$: 250.1226, found: 250.1225.

*2-Isopropyl-5-(2-bromophenyl)oxazole (**3k**):* Prepared from 2-bromoacetophenone and valine following general experimental procedure 1; Yield: 74 mg (70%), pale yellow liquid; eluent: petroleum ether/ethyl acetate (10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.70 (m, 2H), 7.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 (td, *J* = 7.7, 1.2 Hz, 1H), 7.15 – 7.11 (m, 1H), 3.15 (hept, *J* = 7.0 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 148.1, 134.0, 128.9, 128,9, 128.3, 127.4, 126.3 119.7, 28.4, 20.4; IR (neat): 2972, 1562, 1469, 1146, 1021, 939, 833, 756, 710, 638 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{12}H_{12}BrNO$ $[M+H]^+$: 266.0175, found: 266.0175.

*2-(1-Methylpropyl)-5-(2-bromophenyl)oxazole (**3l**):* Prepared from 2-bromoacetophenone and isoleucine following general experimental procedure 1; Yield: 71 mg (64%), yellow liquid; eluent: petroleum ether/ethyl acetate (6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.70 (m, 2H), 7.64 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.14 (td, *J* = 7.8, 1.6 Hz, 1H), 2.97 (h, *J* = 7.0 Hz, 1H), 1.91 – 1.84 (m, 1H), 1.69 (dt, *J* = 14.0, 7.3 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 148.0, 134.0, 129.0, 128.9, 128.3, 127.4, 126.3, 119.7, 35.3,

28.2, 17.9, 11.6; IR (neat): 2967, 1562, 1548, 1469, 1146, 1021, 939, 833, 756, 711, 640 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{13}H_{14}BrNO$ $[M+H]^+$: 280.0332, found: 280.0334.

*2-Isopropyl-5-(3-bromophenyl)oxazole (**3m**):* Prepared from 3-bromoacetophenone and valine following general experimental procedure 1; Yield: 59 mg (56%), yellow liquid; eluent: petroleum ether/ethyl acetate (8:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 1.7 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.41 (m, 1H), 7.27 – 7.25 (m, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 3.14 (hept, *J* = 7.0 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 149.2, 130.9, 130.3, 130.2, 126.8, 122.9, 122.6, 122.4, 28.5, 20.4; IR (neat): 2974, 1582, 1549, 1472, 1281, 1139, 1074, 963, 825, 781, 684, 612 (cm^{-1});. HRMS (ESI) m/z calcd. for for $C_{12}H_{12}BrNO$ $[M+H]^+$: 266.0175, found: 266.0174.

*2-(1-Methylpropyl)-5-(3-bromophenyl)oxazole (**3n**):* Prepared from 3-bromoacetophenone and isoleucine following general experimental procedure 1; Yield: 57 mg (51%), colorless liquid; eluent: petroleum ether/ethyl acetate (7:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (t, *J* = 1.7 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.42 – 7.39 (m, 1H), 7.27 – 7.23 (m, 2H), 2.96 (h, *J* = 7.0 Hz, 1H), 1.93 – 1.80 (m, 1H), 1.73 – 1.68 (m, 1H), 1.37 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 149.1, 130.8, 130.3, 130.2, 126.8, 122.9, 122.5, 122.4, 35.3, 28.2, 17.9, 11.6; IR (neat): 2967, 1697, 1547, 1472, 1211, 1138, 1075, 958, 782, 737, 684 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{13}H_{14}BrNO$ $[M+H]^+$: 280.0332, found: 280.0332.

*2-(1-Methylpropyl)-5-(4-chlorophenyl)oxazole (**3o**):* Prepared from 4-chloroacetophenone isoleucine following general experimental procedure 1; Yield: 66 mg (70%), pale yellow liquid; eluent: petroleum ether/ethyl acetate (7:1)^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.20 (s, 1H), 2.99 – 2.90 (m, 1H), 1.91 – 1.80 (m, 1H), 1.74 – 1.64 (m, 1H), 1.36 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.2, 149.6, 133.7, 129.0, 126.8, 125.1, 121.9, 35.3, 28.1, 17.9, 11.5; IR (neat): 2967, 1549, 1485, 1139, 1092,

1012, 820, 737 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{13}H_{14}ClNO$ $[M+H]^+$: 236.0837, found: 236.0836.

*2-(1-Methylpropyl)-5-(4-nitrylphenyl)oxazole (**3p**):* Prepared from 4-nitroacetophenone and isoleucine following general experimental procedure 1; Yield: 40 mg (41%), yellow liquid; eluent: petroleum ether/ethyl acetate (6:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.24 (m, 2H), 7.75 – 7.73 (m, 2H), 7.43 (s, 1H), 2.99 (h, *J* = 7.0 Hz, 1H), 1.91 – 1.84 (m, 1H), 1.75 – 1.70 (m, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 148.6, 146.8, 134.0, 125.1, 124.4, 124.2, 35.4, 28.1, 17.8, 11.5; IR (neat): 2968, 1607, 1548, 1514, 1457, 1332, 1108, 1073, 956, 851, 752, 691 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{13}H_{14}N_2O_3$ $[M+H]^+$: 247.1077, found: 247.1078.

*2-(1-Methylpropyl)-5-(4-trifluoromethyl)oxazole (**3q**):* Prepared from 4-(trifluoromethyl)acetophenone and isoleucine following general experimental procedure 1; Yield: 64 mg (60%),pale yellow liquid; eluent: petroleum ether/ethyl acetate (8:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.31 (s, 1H), 2.97 (h, *J* = 7.0 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.74 – 1.69 (m, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 149.3, 131.4 (q, *J* = 32.3 Hz), 129.3, 129.1, 126.9, 145.5 (q, *J* = 4.0 Hz), 123.8 (q, *J* = 272.7 Hz), 122.8, 120.6 (q, *J* = 4.0 Hz), 35.4, 28.2, 17.9, 11.5; IR (neat): 2971, 1553, 1454, 1334, 1266, 1166, 1123, 1096, 960, 897, 829, 799, 745, 696, 651 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{14}H_{14}F_3NO$ $[M+H]^+$: 270.1100, found: 270.1099.

*2-Isopropyl-5-(2-naphthyl)oxazole (**3r**):* Prepared from 2-acetylnaphthalene and valine following general experimental procedure 1; Yield: 50 mg (53%), pale yellow solid; eluent: petroleum ether/ethyl acetate (10:1); mp.: 59.0 – 61.0 °C**;** ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.79 – 7.72 (m, 3H), 7.60 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.24 (s, 1H), 3.11 (hept, *J* = 6.9

Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 150.8, 133.4, 132.9, 128.6, 128.1, 127.8, 126.7, 126.3, 125.6, 122.5, 122.1, 122.0, 28.6, 20.5; IR (neat): 2967, 1570, 1508, 1129,1104, 1049, 897, 865, 818, 752, 737, 675 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{16}H_{15}NO$ $[M+H]^+$: 238.1226, found: 238.1227.

*2-Phenyl-5-(2-naphthyl)oxazole (**3s**):* Prepared from 2-acetylnaphthalene and phenylglycine following general experimental procedure 1; Yield: 80 mg (74%), pale yellow solid; eluent: petroleum ether/ethyl acetate (8:1); mp.: 100.0 – 102.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.16 (m, 3H), 7.91 – 7.83 (m, 3H), 7.76 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.55 – 7.47 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 151.3, 133.3, 133.0, 130.3, 128.8, 128.7, 128.2, 127.8, 127.4, 126.7, 126.4, 126.3, 125.2, 123.9, 122.8, 122.0; IR (neat): 3091, 1562, 1485, 1137, 973, 891, 857, 819, 744 706, 618 (cm^{-1}); MS (EI) m/z: 271.1 (100) $[M]^+$, 243.2 (22) $[M\text{-}CH_2N]^{+\cdot}$, 127.1 (12) $[M\text{-}C_9H_6NO]^{+\cdot}$ The spectral data were in good agreement with the literature.[45]

*2-Phenyl-5-(1-naphthyl)oxazole (**3t**):* Prepared from 1-acetylnaphthalene and phenylglycine following general experimental procedure 1; Yield: 54 mg (50%); pale yellow solid; eluent: petroleum ether/ethyl acetate (15:1); mp.: 113.0 – 114.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.4 Hz, 1H), 8.20 – 8.17 (m, 2H), 7.92 (t, *J* = 8.3 Hz, 2H), 7.84 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.63 – 7.49 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 150.5, 133.8, 130.4, 130.0, 129.5, 128.8, 128.7, 127.4, 127.1, 126.7, 126.4, 126.3, 126.2, 125.3, 125.3, 124.8; IR (neat): 3053, 1589, 1485, 1397, 1233, 1119, 990, 925, 839, 767, 703, 684, 655, 623, 601 (cm^{-1}); MS (EI) m/z: 271.1 (100) $[M]^+$, 243.2 (25) $[M\text{-}CH_2N]^{+\cdot}$. The spectral data were in good agreement with the literature.[45]

*2-Isopropyl-4-(carboxylic acid ethyl ester)-5-phenyloxazole (**3u**):* Prepared from ethyl benzoylacetate and valine following general experimental procedure 1; Yield: 80 mg (77%), pale yellow solid; eluent: petroleum ether/ethyl acetate (5:1); mp.: 41.0 – 42.0 °C; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.01 – 7.98 (m, 2H), 7.42 (m, 3H), 4.38 (d, *J* = 21.4 Hz, 2H), 3.18 (hept, *J* = 7.0 Hz, 1H), 1.40 – 1.34 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 162.2, 154.7, 129.9, 128.2, 128.1, 127.2, 126.6, 61.1, 28.4, 20.2, 14.2; IR (neat): 2980, 1710, 1585, 1450, 1371, 1240, 1205, 1157, 1025, 835, 768, 693 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{15}H_{17}NO_3$ $[M+H]^+$: 260.1281, found: 260.1271

*2-(1-Methylpropyl)-4-(carboxylic acid ethyl ester)-5-phenyloxazole (**3v**):* Prepared from ethyl benzoylacetate and isoleucine following general experimental procedure 1; Yield: 65 mg (60%), colorless liquid; eluent: petroleum ether/ethyl acetate (10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dt, *J* = 8.5, 2.3 Hz, 2H), 7.47 – 7.40 (m, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.01 (h, *J* = 7.0 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.74 – 1.68 (m, 1H), 1.38 (dt, *J* = 7.1, 3.6 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 162.3, 154.8, 129.9, 128.3, 128.2 , 127.3, 126.6 , 61.2, 35.3, 28.0, 17.8, 14.3, 11.7; IR (neat): 2971, 2360, 1716, 1492, 1372, 1230, 1185, 1089, 1038, 837, 766, 690 (cm^{-1}); HRMS (ESI) m/z calcd. for $C_{16}H_{19}NO_3$ $[M+Na]^+$: 296.1257, found: 296.1258.

*2-isopropyl-5-(4-methylphenyl)oxazole (**3w**):* Prepared from 4-methylstyrene and valine following general experimental procedure 2; Yield: 29 mg (48%), yellow liquid; eluent: petroleum ether/diethyl ether (10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.15 (s, 1H), 3.14 (hept, *J* = 7.0 Hz, 2H), 2.37 (m, 3H), 1.40 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 150.8, 138.0, 129.5, 125.6, 123.9, 120.9, 28.5, 21.3, 20.5; IR (neat): 2974, 1556, 1504, 1138, 1106, 1065, 1053, 940, 812, 738(cm^{-1}); HRMS (ESI/ TOF) m/z calcd. for $C_{13}H_{15}NO$ $[M+H]^+$: 202.12264, found: 202.12269.

*2-(1-Methylpropyl)-5-(4-methylphenyl)oxazole (**3x**):* Prepared from 4-methylstyrene and isoleucine following general experimental procedure 2; Yield: 26 mg (40%), yellow liquid; eluent: petroleum ether/diethyl ether (10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17 (s, 1H), 2.96 (hext, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.89 – 1.84 (m, 1H), 1.72 – 1.70 (m,

1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 150.9, 138.1, 129.5, 125.5, 124.0, 120.6, 35.3, 28.2, 21.3, 18.0, 11.6; IR (neat): 2966, 1554, 1504, 1455, 1137, 1111, 1053, 955, 812; HRMS (ESI/ TOF) m/z calcd. for $C_{14}H_{17}NO$ $[M+H]^+$: 216.13829, found: 216.13813.

*2-phenyl-5-(4-methylphenyl)oxazole (**3y**):* Prepared from 4-methylstyrene and phenylglycine following general experimental procedure 2; Yield: 23 mg (33%), yellow liquid; eluent: petroleum ether/diethyl ether (10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.10 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.40 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.25 (s, 1H), 2.40 (s, 3H)) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 151.5, 138.5, 130.2, 129.6, 128.8, 127.5, 126.2, 125.3, 124.2, 122.7, 21.4; IR (neat): 2965, 2923, 1675, 1504, 1068, 1018, 814; HRMS (ESI /TOF) m/z calcd. for $C_{16}H_{13}NO$ $[M+H]^+$: 236.10699, found: 236.10705.

*2-Hydroxy-1-naphthalen-2-yl-ethanone (**4**):* A solution 2-acetylnaphthalene (0.4 mmol, 1 equiv.), valine (1.2 mmol, 3 equiv.) iodine (0.08 mmol, 0.2 equiv.) and Oxone (1.2 mmol, 3 equiv.) in DMSO (3 mL) was heated to 95 °C for 10 minutes. The reaction mixture was allowed to cool to rt and then treated with saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford **4**. Yield: 21 mg (28%), white solid; eluent: petroleum ether/ethyl acetate (7:1); mp.: 117.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.99 – 7.88 (m, 4H), 7.66 – 7.56 (m, 2H), 5.02 (s, 2H), 3.62 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 136.1, 132.4, 130.6, 129.6, 129.5, 129.0, 128.9, 127.9, 127.1, 123.0, 65.5; IR (neat): 3422, 1678, 1406, 1245, 1185, 1100, 938, 821, 749, 603 (cm^{-1}); MS (EI) m/z: 186.1 (12) $[M]^+$, 155.1 (100) $[M\text{-}CH_3O]^{+\cdot}$, 127.1 (80) $[M\text{-}C_2H_3O_2]^{+\cdot}$. The spectral data were in good agreement with the literature.[74]

*phenyl(5-phenyloxazol-2-yl)methanone (**5**):* A solution phenylalanine (0.6 mmol, 1 equiv.) and iodine (0.06 mmol, 0.10 equiv.), Oxone® (0.75 mmol, 3 equiv.) in DMSO (3 mL) was heated to 95 °C. The resulting mixture was stirred at 95 °C until the starting material was completely converted. The reaction mixture was allowed to cool to rt and then treated with saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford **5**. Yield: 75 mg (50%), yellow solid; eluent: petroleum ether/diethyl ether (10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.48 (m, 2H), 7.84 – 7.81 (m, 2H), 7.67 – 7.63 (m, 1H), 7.61 (s, 1H), 7.56 - 7.52 (m, 2H), 7.50 – 7.42 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 157.0, 154.2, 135.3, 133.7, 130.7, 130.0, 129.1, 128.4, 126.6, 125.4, 123.9; IR (neat): 3068, 1650, 1473, 1446, 1361, 1256, 1171, 947, 904, 764, 685, 638 cm^{-1}; MS (EI) m/z: 249.1 (36) $[M]^+$, 221.1 (24) $[M\text{-}CH_2N]^{+\cdot}$, 105.1 (100) $[M\text{-}C_9H_6NO]^{+\cdot}$, 77.1 (46) $[M\text{-}C_{10}H_6NO_2]^{+\cdot}$. The spectral data were in good agreement with the literature.[75]

*2-Hydroxy-1-phenyl-1-propanone (**6**)*

Prepared from propiophenone and valine following general experimental procedure 1; Yield 50% (30 mg), pale yellow liquid; eluent: petroleum ether/ethyl acetate (7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dt, J = 8.5, 1.6 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.54 – 7.46 (m, 2H), 5.16 (q, J = 7.0 Hz, 1H), 4.17 – 3.17 (m, 1H), 1.44 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3, 133.9, 133.3, 128.8, 128.6, 69.3, 22.2. MS (EI) m/z $[M]^+$: 151.1. The spectral data were in good agreement with the following literature.[76]

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SUPPORTING INFORMATION

1H and 13C NMR spectra of oxazoles **3a**-**y** and compounds **4**, **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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