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Synthesis of 2-Phenyl-4,5-Substituted Oxazoles by Copper-Catalyzed Intramolecular Cyclization of Functionalized Enamides

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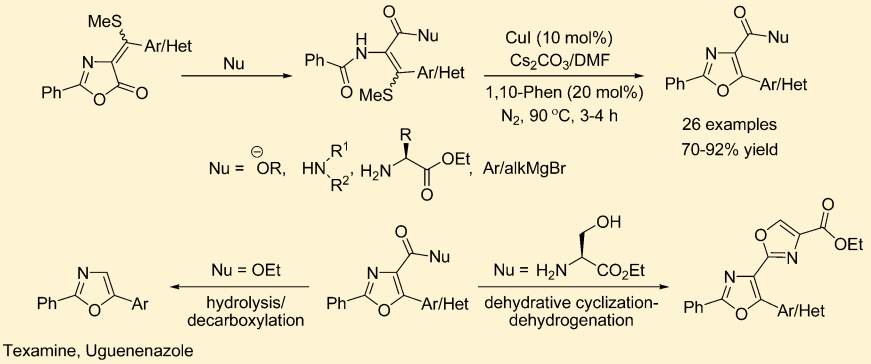
Supporting Information



ABSTRACT: An efficient two-step synthesis of 2-phenyl-4,5-substituted oxazoles involving intramolecular copper-catalyzed cyclization of highly functionalized novel *β*-(methylthio)enamides as the key step has been reported. These enamides are obtained by nucleophilic ring-opening of newly synthesized 4-[(methylthio)hetero(aryl)methylene]-2-phenyl-5-oxazolone precursors by alkoxides, amines, amino acid esters and aryl/alkyl Grignard reagents, thus leading to the introduction of an ester, N-substituted carboxamide or acyl functionalities at 4-position of the product oxazoles. Synthesis of two naturally occurring 2,5-diaryloxazoles, i.e., texamine and uguenenazole, via two-step hydrolysis−decarboxylation of the corresponding 2,5-diaryloxazole-4-carboxylates has also been described. Similarly, three of the serine-derived oxazole-4-carboxamides were elaborated to novel trisubstituted 4,2′-bisoxazoles through DAST/DBU-mediated cyclodehydration−dehydrohalogenation sequence. The present protocol is complementary and an improvement to our previously reported silver carbonate-induced cyclization of *β*-bis(methylthio)enamides to 2-phenyl-5-(methylthio)-4-substituted oxazoles.

INTRODUCTION

Oxazole structural motifs have attracted considerable attention from both synthetic and medicinal chemists because of their presence in a wide range of natural products[1] and their pivotal role as synthetic intermediates.[2] Thus, several of the complex natural products containing oxazole moiety such as Diazonamide A, Ulapualide A, Hennoxazole A, Telomestatin, Leucamide A, and Virginiamycin M1 display significant biological activity as cytotoxic, antifungal, antibacterial, antitumor and antiviral agents.[1,3,4] Also, 2,4- and 2,4,5-substituted oxazole subunits are frequently encountered in many pharmaceuticals, lead structures,[4,5] and new functional compounds with interesting photophysical properties.[6] This has stimulated renewed interest in the chemistry and synthesis of these important classes of heterocycles,[1,4,7] and many synthetic protocols have been devised to access their general structures.[8] The most important classical procedures for synthesis of oxazoles include cyclodehydration of acyclic precursors exemplified by Robinson−Gabriel synthesis and its improved versions,[4,9] biomimetic approach involving cyclization of serine derivatives,[1,4,10] transition metal-catalyzed cross-coupling,[4,11] direct C−H arylation/alkenylation of prefunctionalized oxazoles[12a−e] and metalation reactions.[4,12f−m] The other newly developed methods include copper-catalyzed cycloamidation of vinyl halides,[13] catalyzed cycloisomerization of propargylamides,[4,14] Rh-catalyzed amidation of *α*-diazo-*β*-keto carboxylate,[4,8c,15] iodine/copper-catalyzed tandem oxidative cyclization,[8b,16] cycloaddition of activated methylene isonitriles,[4,17] and miscellaneous approaches.[18] Despite the availability of these elegant methods, only a few reports deal with efficient and regioselective synthesis of 2,4,5-trisubstituted oxazoles[4,8c,9,13a,b,15,16a,18] with flexible substitution pattern at all positions.

Our own contribution in this regard centered on a substrate controlled protocol, in which highly functionalized *N*-benzoyl-*β*-bis(methylthio)enamide precursors **2** were generated by nucleophilic ring-opening of a common 4-bis(methylthio)-methylene-2-phenyloxazole-5-one template **1** by various oxygen, nitrogen and carbon nucleophiles.[4,19] These enamide

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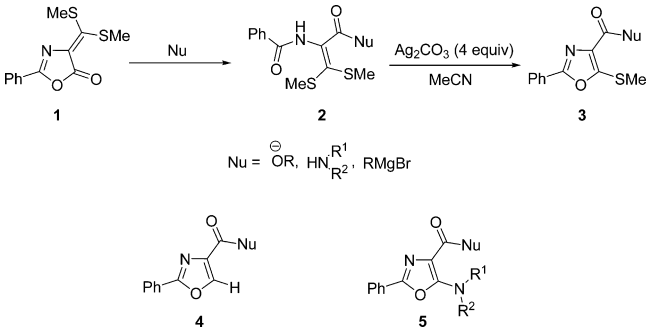
intermediates were subsequently transformed into 2-phenyl-5-(methylthio)-4-alkoxycarbonyl/amido/acyloxazoles **3** by silver carbonate (4 equiv) induced 5-*endo* cyclization (Scheme 1).

Scheme 1. Synthesis of 2-Phenyl-4,5-Substituted Oxazoles via Silver Carbonate-Induced Intramolecular Cyclization of Enamide Precursors



The 5-(methylthio)oxazoles were either dethiomethylated with Raney Ni to 5-unsubstituted oxazoles **4** or transformed into 5-alkyl/arylaminooxazoles **5** in two steps involving peracid oxidation and replacement of 5-methylsulfonyl group by primary and secondary amines (Scheme 1). It should be noted that despite broad scope and versatile applications of Robinson−Gabriel and related oxazole synthesis involving cyclodehydration of α-acylaminoketones, only a limited number of examples deal with intramolecular cyclization of enamides precursors.[13,20] In continuation of this work, along with our ongoing interest in design and development of new general efficient methods for novel five- and six-membered heterocycles,[21] we sought to explore possible utilization of this strategy for the synthesis of 4-substituted 2,5-di(hetero)-aryloxazoles by installation of a (hetero)aryl group at 5-position of oxazoles. The 2,5-diaryloxazoles comprising of annuloline **6**,[22] balsoxine **7a**,[23a] texamine **7b**,[23b,d] texaline **7c**[23c,d] and halfordinol **8a**[23e] are among the first relatively simple naturally occurring oxazoles to be isolated (Figure 1).

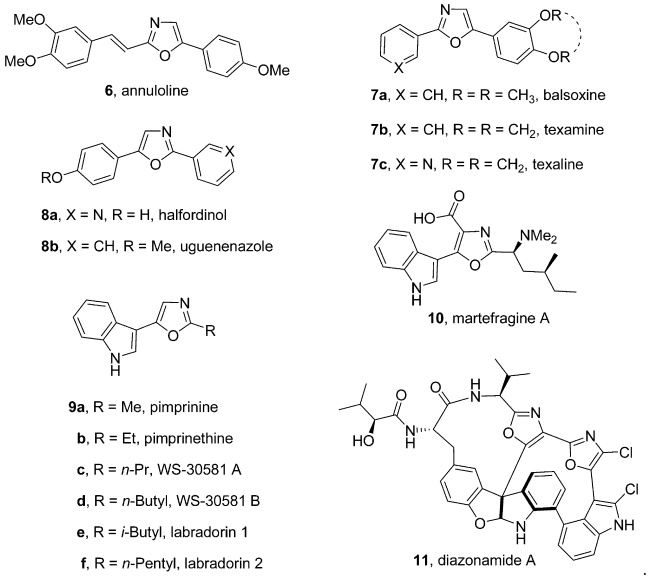
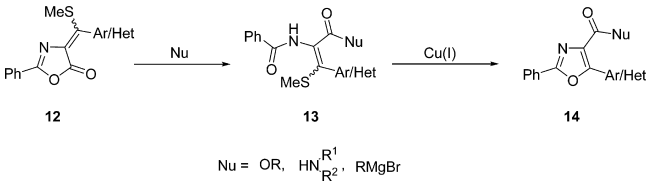


Figure 1. Selected examples of natural products containing 2,5-di(hetero)aryl/alkylloxazole moiety.

The 2,5-diaryloxazoles are also of considerable interest due to their ability to scintillate light in presence of ionizing radiation.[24] Similarly 2-substituted-5-(3-indolyl)oxazole ring system occurs in several natural products ranging from simple pimprinine alkaloids,[25] pimprinine **9a**, pimprinethine **9b**, WS-30581A, WS-30581B **9c,d**, labradorin 1 and labrodorin 2 **9e,f**,[25] through trisubstituted martefragin A **10**[26a,b] to complex marine natural product diazonamide A **11**[26c] displaying a range of biological activity (Figure 1).[25c,e,26a,c]

We therefore envisaged a related transformation as depicted in Scheme 2 and successfully executed it to develop a general

Scheme 2. Proposed Strategy for the Synthesis of 2-Phenyl-5-(hetero)aryl-4-Functionalized Oxazoles



protocol for diversity oriented synthesis of 2-phenyl-5-(hetero)aryl-4-substituted oxazoles **14** by a sequential nucleophilic ring-opening of newly synthesized 4-[methylthio(aryl/heteroaryl)methylene]-2-phenyl-5-oxazolone precursors **12** followed by copper-catalyzed intramolecular cyclization of the resulting highly functionalized enamide intermediates **13** (Scheme 2). The results of these studies have been reported in this paper along with the synthesis of two naturally occurring 2,5-diaryloxazoles, i.e., texamine and uguenenazole, following this protocol.

RESULTS AND DISCUSSION

The desired 2-phenyl-4-[(methylthio)(aryl/heteroaryl)-methylene]-5-oxazolones **12a−i** were synthesized in good yields by reacting 2-phenyl-5-oxazolone **15** with appropriate (hetero)aryl dithioesters **16** in the presence of sodium hydride in DMF followed by alkylation of the resulting thiolate salts with methyl iodide (Scheme 3). The structures of all these newly synthesized 4-arylidene oxazolone precursors **12a−i** were established with the help of spectral and analytical data. The ^{1}H and ^{13}C NMR spectra of **12a−i** revealed that these compounds exist as mixture of *E*/*Z* stereoisomers (Scheme 3). The oxazolone precursors **12a−i** were next subjected to nucleophilic ring-opening in the presence of various alkoxides (Scheme 4). Thus **12a** was allowed to react with sodium ethoxide in ethanol at room temperature for 2−3 h furnishing exclusively α-[(methylthio)(4-methoxyphenyl)methylene]-*N*-benzoylglycinate **17a** (Ar = 4-MeOC$_6$H$_4$, R^1 = Et) in 88% yield. Similarly the other substituted open chain ethyl- (**17b−f**), *n*-butyl-, benzyl- and *t*-butyl esters (**17g−i**) were obtained in high yields on treatment of the corresponding oxazolones **12** with either sodium ethoxide, *n*-butoxide, benzyloxide or *tert*-butoxide under identical conditions (Scheme 4).[27]

Intramolecular 5-*endo* cyclization of the open-chain esters **17a−i** to the desired 2-phenyl-4-carboalkoxy-5-(hetero)-aryloxazoles **18** was next examined under the influence of various cyclizing agents reported earlier.[4] Thus **17a** underwent facile cyclization in the presence of excess of silver carbonate (4 equiv) in refluxing acetonitrile yielding the corresponding ethyl 2-phenyl-5-(4-methoxyphenyl)oxazole-4-carboxylate **18a** in 85% yield (Table 1, entry 1). On the other hand, the yield of

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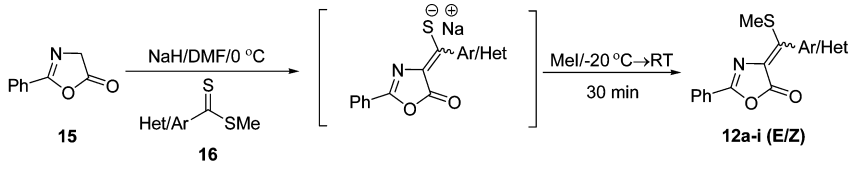
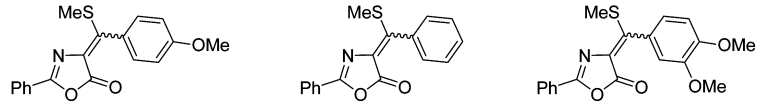
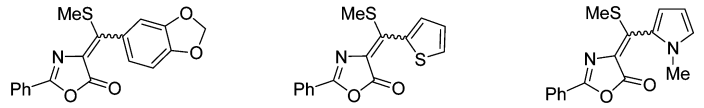
Scheme 3. Synthesis of Novel 2-Phenyl-4-[methylthio(aryl/heteroaryl)methylene]-5-oxazolone Precursors 12a–i[a]



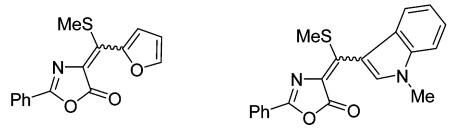
15 16 12a-i (E/Z)



12a, 80%, *E/Z* = 60:40 **12b**, 75%, *E/Z* = 55:45 **12c**, 78%, *E/Z* = 63:37



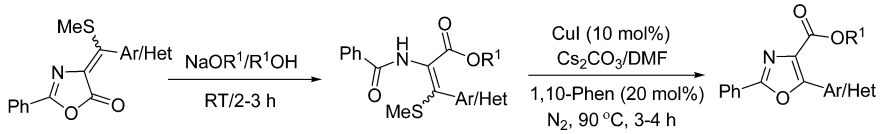
12d, 72%, *E/Z* =52:48 **12e**, 70%, *E/Z* = 55:45 **12f**, 75%, *E/Z* =75:25



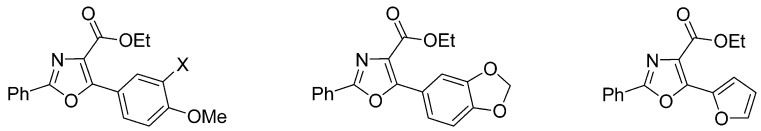
12g, 70%, *E/Z* = 55:45 **12h**, 78%, *E/Z* = 64:36 **12i**, 60%, *E/Z* = 57:43

[a]Reaction conditions: **15** (1.0 mmol), **16** (1.0 mmol), NaH (2 equiv) in DMF at 0 °C for 1 h, and then MeI (1.0–1.5 equiv) at −20 °C for 30 min. All products **12a–i** were obtained as a mixture of *E*/*Z* isomers.

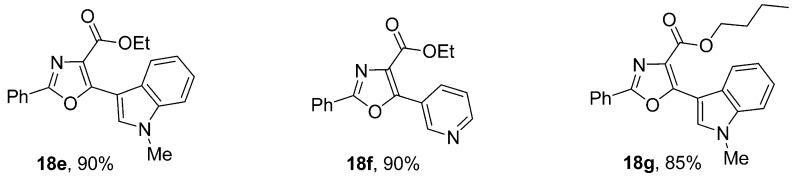
Scheme 4. Synthesis of Novel 2-Phenyl-5-(hetero)aryloxazole-4-carboxylates



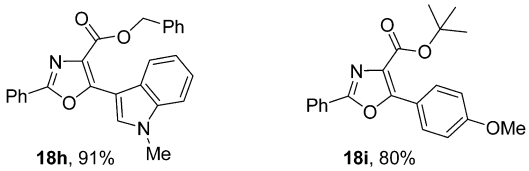
12 17a-i 18a-i



18a, X=H 92%
18b, X=OMe 88%
18c, 90% **18d**, 92%



18e, 90% **18f**, 90% **18g**, 85%



18h, 91% **18i**, 80%

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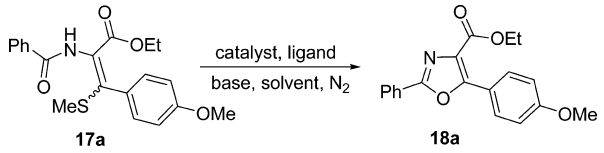
Table 1. Optimization of Reaction Conditions for Cyclization of Enamide 17a to Oxazole 18a[a]



17a 18a

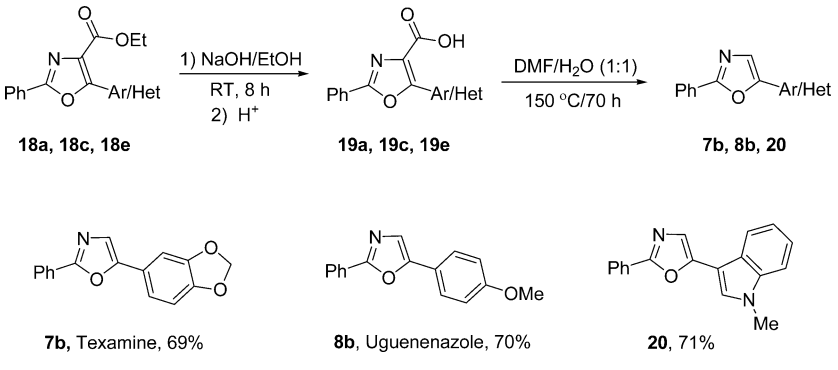
entry	reagent/catalyst	base	solvent	time (h)	% yield **18a**
1	Ag_2CO_3 (4 equiv)	–	CH_3CN	4	85
2	Ag_2CO_3 (2 equiv)	–	CH_3CN	12	58
3	Cu_2O	–	DMF	15	63
4	CuCl	–	DMF	15	62
5	CuI	–	DMF	15	65
6	CuCl	Cs_2CO_3	DMF	12	70
7	CuBr	Cs_2CO_3	DMF	12	71
8	CuI	Cs_2CO_3	DMF	7	79
9	Cu powder	Cs_2CO_3	DMF	12	69
10	CuI/L-proline	Cs_2CO_3	DMF	8	81
11	CuI/TMEDA	Cs_2CO_3	DMF	10	75
12	CuI/Py	Cs_2CO_3	DMF	10	78
13	**CuI/Phen**	**Cs_2CO_3**	**DMF**	**3**	**92**
14	CuI/Phen	K_2CO_3	DMF	10	79
15	CuI/Phen	*t*BuOK	DMF	10	81
16	CuI/Phen	*t*BuOLi	DMF	10	80
17	CuI/Phen	Cs_2CO_3	toluene	10	71
18	CuI/Phen	Cs_2CO_3	DMA	10	70
19	CuI/Phen	Cs_2CO_3	DMSO	10	72
20	CuI (5 mol %)/Phen	Cs_2CO_3	DMF	10	85

[a]Reactions were performed using **17a** (1 mmol) in 3 mL of solvents with 10 mol % of Cu catalyst, 20 mol % of ligand and 1 equiv of base at 90 °C.

18a was drastically reduced (58%) when the reaction was performed with 2 equiv of silver carbonate under identical conditions even for prolonged time (Table 1, entry 2). The other previously utilized cyclizing agents (Et_3N/C_6H_6, Cs_2CO_3/dioxane, $CuBr_2$/DBU, etc.)[4] were also not found to be very effective, yielding **18a** in unsatisfactory yields (with maximum yield of 67% with Et_3N/C_6H_6). Therefore, in view of the large amount and high cost of silver carbonate employed in this cyclization, we envisaged a related transformation of these highly functionalized enamides **17** to oxazoles **18** by means of copper-catalyzed cyclization reactions, which provide a promising alternative mainly due to their high efficiency, mild reaction conditions and low cost.[28] Over the past years, remarkable progress has been achieved in the synthesis of heterocycles by copper-catalyzed C–C and C–heteroatom bond formations.[29,30] A few methods relevant to the present work are mentioned here. Thus, Pattenden and co-workers have reported a cupric bromide-mediated cyclization of bromoenamides[20b] for construction of oxazole ring. Recently Stahl et al. have described intramolecular oxidative cyclization of enamides induced by cupric chloride (2 equiv) furnishing 2,5-aryl/alkyloxazoles in moderate to good yields.[31] On the other hand, Glorius and co-workers have developed a method by copper-catalyzed coupling of primary amides with 1,2-dihalogenated olefins affording a mixture of 2,4- and 2,5-substituted oxazoles via bromoenamide intermediates.[13a] Buchwald[13b] has reported a two-step one-pot methodology for substituted oxazoles involving copper-catalyzed cross coupling of primary amide with vinyl bromide followed by iodine mediated intramolecular O-vinylation of the resulting enamide intermediates. During the preparation of this manuscript, the same workers have reported an elegant synthesis of a broad range of 2,5-disubstituted oxazoles involving Cu(II)-catalyzed oxidative cyclization of enamide intermediates under ambient conditions employing potassium persulfate as promoter.[13c]

For our studies, enamide **17a** was chosen as model substrate for its cyclization to oxazole **18a** under copper catalysis (Table 1). Initial studies were performed by screening various copper catalysts (10 mol %) in the absence of base in DMF at 90 °C, affording the oxazole **18a** in maximum yield of 65% (Table 1, entries 3–5). However in the presence of Cs_2CO_3 as base (1 equiv), in the absence of any ligand, the oxazole **18a** was obtained in increased yields (Table 1, entries 6–9), and CuI proved to be best choice among catalysts investigated, yielding **18a** in 79% yield after 7 h (Table 1, entry 8). Subsequently our study focused on cyclization of **17a** by testing various ligands (entries 10–13), and it was found that use of 1,10-phenanthroline as ligand significantly improved the catalyst efficiency, affording **18a** in 92% yield within 3 h (Table 1, entry 13). Further screening of bases including K_2CO_3, *t*-BuOK or *t*-BuOLi revealed that no obvious improvement in yields was achieved and Cs_2CO_3 was the base of choice (Table 1, entries 14–16). Among solvent selection, DMF was clearly the best solvent compared to toluene, DMA or DMSO (Table 1, entries 13, 17–19). A low catalytic loading was not effective, resulting in diminished yield of **18a** with prolonged reaction time (Table 1, entry 20). Further screening of reaction temperature or reaction time did not show any improvement in yield of **18a**; therefore, CuI (10 mol %) in the presence of 1,10-phenanthroline (20 mol %) as ligand and Cs_2CO_3 (1equiv)

Scheme 5. Synthesis of 2-Phenyl-5-(hetero)aryloxazole Natural Products



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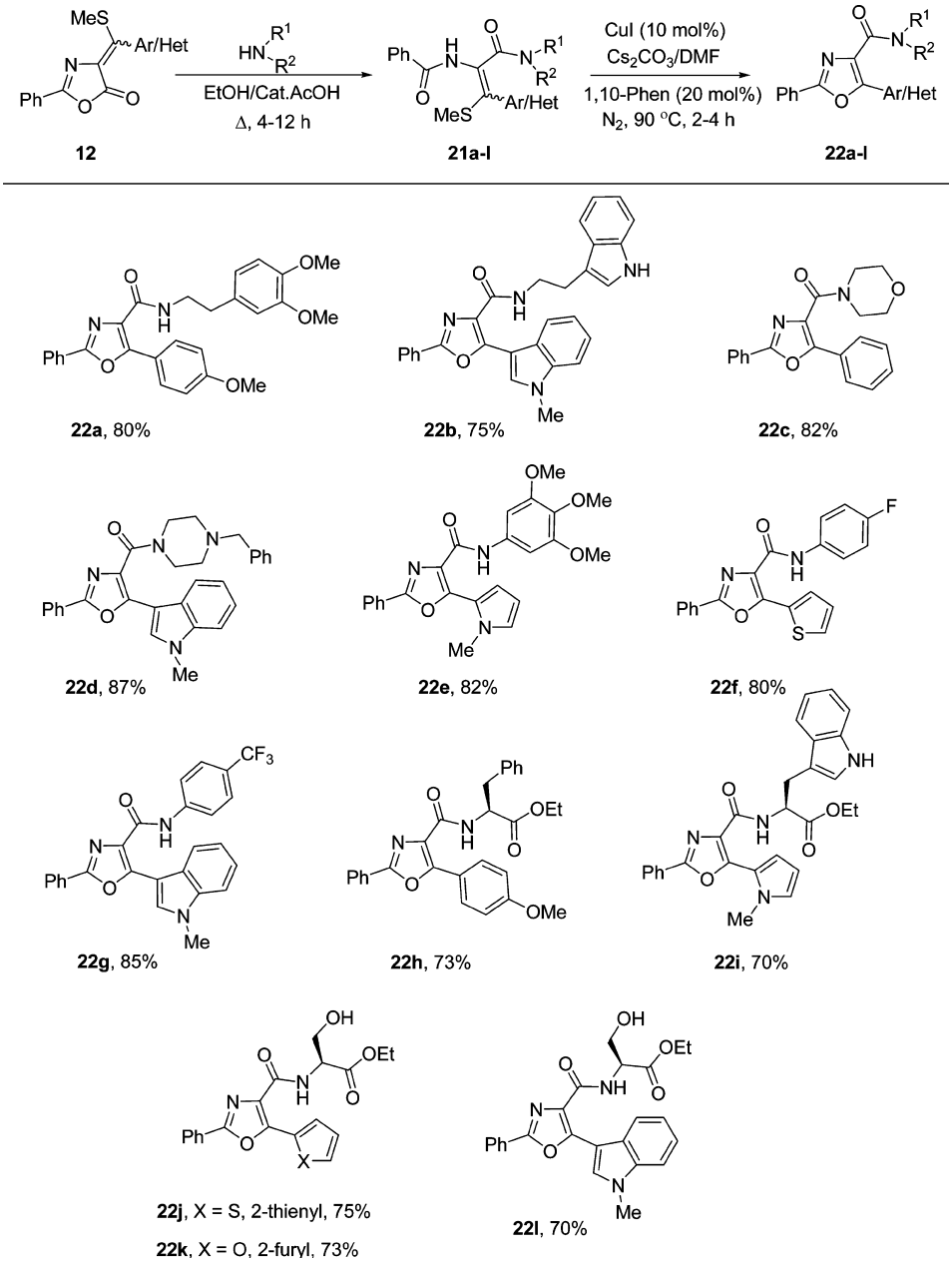
Scheme 6. Synthesis of 2,5-Di(hetero)aryloxazole-4-carboxamides



as base in DMF at 90 °C were used as optimal conditions (Table 1, entry 13) throughout our studies.

With an optimized catalytic system in hand, we next explored the generality of this copper-catalyzed cyclization reaction with various open chain enamide esters **17b−i** (Scheme 4). Thus acyclic ethyl esters bearing substituted aryl (**17b,c**), furyl (**17d**), 3-indolyl (**17e**) and 3-pyridyl (**17f**) moieties readily underwent cyclization under these optimized conditions providing the corresponding ethyl 2-phenyl-5-(hetero)aryloxazole-4-carboxylates **18b−f** in excellent overall yields (Scheme 4). Similarly the *n*-butyl and benzyl 2-phenyl-5-(3-indolyl)-oxozole-4-carboxylates **18g,h** could be obtained in excellent yields from the acyclic precursors **17g,h**. Interestingly, the corresponding *t*-butyl 2,5-diaryloxazole-4-carboxylate **18i** could also be obtained in 80% yield from **17i**, without any side reactions under identical conditions (Scheme 4).

Having established the facile ring closing copper-catalyzed cyclization protocol for a broad range of 2,5-(hetero)-aryloxozole-4-carboxylates **18a−i**, we exploited these newly synthesized oxozole-4-carboxylates as precursors for 2,5-di(hetero)aryloxazole natural products by removal of 4-ester functionality through a two-step hydrolysis and decarboxylation protocol (Scheme 5). Hodgetts and Kershaw[11a] have synthesized balsoxine **7a** following this strategy from ethyl 2-phenyl-5-(3,4-bismethoxyphenyl)oxazole-4-carboxylate **18b**, which was obtained in six steps from ethyl 2-aminooxazole carboxylate in Suzuki−Miyaura approach. Hoarau and co-workers[32] have reported a five-step synthesis of balsoxine **7a** and texaline **7c** (Figure 1) and other 2,5-di(hetero)aryloxazoles by regiocontrolled palladium-catalyzed 2- and 5-(hetero)-arylation of oxazole-4-carboxylates and subsequent hydrolysis−decarboxylation (CuO) of the resulting 2,5-di(hetero)-aryl-4-carboxylates.[32] We undertook the synthesis of two

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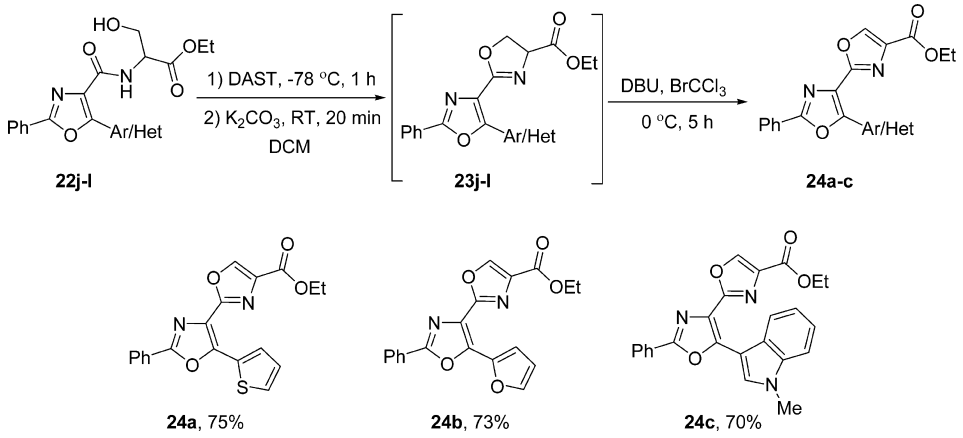
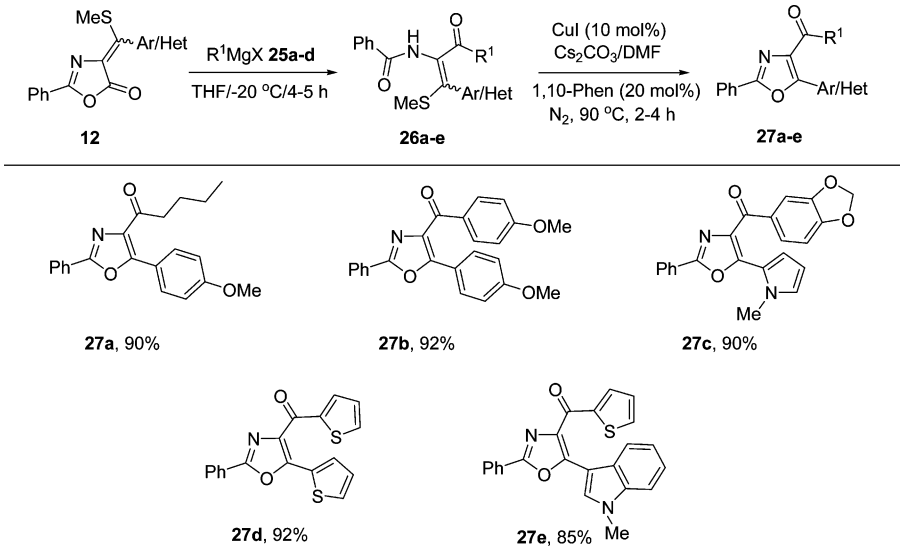
Scheme 7. Synthesis of 2,5-Substituted 4,2′-Bisoxazole-4′-carboxylates



Scheme 8. Synthesis of 2,5-Di(hetero)aryl-4-acyloxazoles



natural products, i.e., texamine **7b** (isolated from *Amyris texana*),[23b,d,33a−d] uguenenazole **8b** (recently isolated form *Vepris uguenensis*),[33b,34] and 2-phenyl-5-(3-indolyl)oxazole **20** from the respective 2,5-di(hetero)aryloxazole-4-carboxylates **18a**, **18c** and **18e** as shown in the Scheme 5. Thus the oxazole esters were subjected to hydrolysis in ethanolic NaOH furnishing the respective carboxylic acids **19** in nearly quantitative yields. Thermal decarboxylation of **19a**, **19c** and **19e** in H_2O/DMF (1:1) afforded uguenenazole **8b**, texamine **7b**, and 2-phenyl-5-(3-indolyl)-oxazole **20**, respectively, in 69−71% overall yields in a four-step sequence (Scheme 5).

Having optimized the reaction conditions for copper-catalyzed 5-*endo* cyclization of enamides bearing a carboxylate functionality, we next evaluated the scope of the reaction for the synthesis of 2,5-di(hetero)aryloxazole-4-carboxamides **22** by ring-opening of **12** with various primary and secondary amines followed by copper-catalyzed 5-*endo* cyclization of the resulting enamides **21** (Scheme 6). We were pleased to find that 4-(hetero)arylideneoxazolones **12a**,**b** and **12h** underwent smooth ring-opening with primary and secondary aliphatic acyclic/cyclic amines to afford the corresponding open-chain adducts **21a−d** in excellent yields.[27] Similarly, aromatic amines with both electron donating and withdrawing groups also reacted smoothly with few selected oxazolones (**12e**,**f**,**h**) yielding acyclic precursors **21e−g** in good yields.[27] The ring-opening of **12** was found to be equally facile with amino acid esters (phenylalanine, tryptophan and serine) leading to novel peptidomimetic motifs **21h−l** in moderate to good yields.[27] Further, to our delight, the optimized copper-catalyzed reaction conditions turned out to be equally successful for intramolecular cyclization of acyclic amide precursors **21a−l** furnishing the novel 2-phenyl-5-(hetero)aryloxazole-4-carboxamides **22a−l** in excellent yields (Scheme 6). Thus, a diverse range of 2,5-disubstituted oxazole-4-carboxamides derived from primary aliphatic/aromatic and cyclic secondary amines and amino acid derivatives **22a−l** could be readily synthesized in two steps from easily accessible precursors. The newly synthesized serine-derived 2,5-disubstitued oxazole-4-(*β*-hydroxy)amides **22j−l** were subjected to one-pot dehydrative cyclization−dehydrohalgenation by sequential treatment with diethylaminosulphur trifluoride (DAST) at −78 °C for 30 min and bromotrichloromethane/DBU to furnish 2,5-substitued 4,2′-bisoxazole-4′-carboxylates **24a−c** in 70−75% yields (Scheme 7).[10a] The 4,2′-bisoxazoles are common motifs in many natural products (diazonamide, hennoxazole A, telomestatin) displaying a broad range of biological activity.[1]

Finally, after successful implementation of this two-step protocol for the introduction of 4-carboxylate and 4-

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carboxamide functionalities in the trisubstituted oxazoles **18** and **22** (Schemes 4, 6), we next focused our studies on the synthesis of 2,5-substituted 4-acyl(aroyl)oxazoles via ring-opening of oxazolones **12** with alkyl/aryl Grignard reagents **25a−d** (Scheme 8). Thus, treatment of **12a** with *n*-butylmagnesium bromide **25a** gave the α-acylenamide **26a** (72%) exclusively with no trace of conjugate addition−elimination product.[27] The enamide **26a** was subjected to copper-catalyzed cyclization under optimized conditions to furnish the 2-phenyl-5-(4-methoxyphenyl)-4-(*n*-pentanoyl)-oxazole **27a** in 90% yield. Similarly, the ring-opening of **12a** and **12f** with aryl Grignard reagents **25b,c** also proceeded smoothly, leading to 4-aroyloxazoles **27b,c** in excellent yields after subsequent cyclization of the resulting enamides **26b,c** under copper catalysis.[27] The versatility of the methodology was further demonstrated by the synthesis of two 2-phenyl-5-(hetero)aryl-4-thienoyloxazoles **27d,e** in high yields under identical sequence by initial treatment of either **12e** or **12h** with 2-thienyl Grignard reagent **25d** (Scheme 8).

CONCLUSION

In summary, we have developed an efficient two step synthesis of highly functionalized 2-phenyl-4,5-substitued oxazoles from readily available novel 4-[(methylthio)(aryl/heteroary)-methylene]-2-phenyl-5-oxazolone precursors **12**. The overall process involves highly regioselective nucleophilic ring-opening of **12** by oxygen, nitrogen and carbon nucleophiles and subsequent copper-catalyzed intramolecular cyclization of the resulting functionalized β-[(methylthio)hetero(aryl)]enamides to 2-phenyl-4,5-substituted oxazoles as the key step. The protocol displays broad substrate scope and wide functional group compatibility with flexible substitution at 4,5-positions of oxazoles. The 4-carboxylate functionality can be easily removed to readily afford the corresponding 2,5-di(hetero)aryloxazoles, and the method is applied for the synthesis of 2,5-di(hetero)-aryloxazole natural products texamine **7b**, uguenenazole **8b** and 2-phenyl-5-(3-indolyl) oxazole **20** in overall high yields (Scheme 5). Additionally, the amino acid derived enamides **21h−l** provide access to a range of chiral potentially biologically relevant oxazoles **22h−l** (Scheme 6). The ease of further elaboration was demonstrated by facile dehydrative cyclization−aromatization of serine-derived oxazoles **22j−l** to 4,2′-bisoxazoles **25a−c** (Scheme 7), which are structural components of several biologically active bisoxazole-containing natural products. The copper-catalyzed cyclization of these highly functionalized β-(methylthio)enamides to oxazoles complements the growing collection of copper-catalyzed heterocyclization reactions and provides practical and economical advantage over previously reported[4] silver carbonate mediated cyclization (requiring 4 equiv of Ag_2CO_3) in terms of inexpensive copper catalyst and better yields. We believe that the present method is attractive for further library construction for diversity oriented synthesis of oxazoles as well as related natural products. The easy availability of starting materials along with the convenience and efficiency of the present method should make it useful complement to the existing methods for the synthesis of multisubstituted oxazoles.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of 4-[(Methylthio)(aryl/heteroaryl)methylene]-2-phenyloxazol-5-ones (12a−i). To a stirred suspension of NaH (0.31 g, 7.8 mmol) and appropriate (hetero)aryl dithioester (3.0 mmol) in DMF (10 mL), a solution of 2-phenyloxazol-5-one **15**[35] (0.5 g, 3.0 mmol) in DMF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 0.5−1 h, cooled to −20 °C, followed by addition of MeI (0.28 mL, 4.5 mmol) and further stirring at room temperature for 30 min. It was then poured into saturated NH_4Cl solution (100 mL), extracted with EtOAc (3 × 50 mL), washed with water (2 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure to give crude products, which were purified by column chromatography over silica gel using EtOAc−hexane as eluent.

All oxazolones **12a−i** were obtained as mixture of *E*/*Z* stereoisomers. The *E*/*Z* stereochemistry of **12a−i** was established on the basis of chemical shift value of methylthio group, which appears at higher δ value in *E* isomer because of the deshielding effect of *cis* carbonyl group of azalactone.

(*E*/*Z*) 4-[(4-Methoxyphenyl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one (12a). Obtained from oxazolone **15** and dithioester **16a**, (*E*:*Z* = 60:40), yellow solid (0.805 g, 80%): mp 134−136 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3076, 2959, 2928, 2834, 1768, 1627, 1502, 1298, 1251, 1173, 1008, 820, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.08 (m, 1.2H), 7.98−7.96 (m, 0.8H), 7.56−7.40 (m, 3.8H), 7.35−7.32 (m, 1.2H), 7.04−6.98 (m, 2H), 3.89 (s, 1.2H), 3.87 (s, 1.8H), 2.27 (s, 1.8H), 2.22 (s, 1.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.6, 161.4, 161.2, 160.1, 159.1, 157.6, 156.9, 132.6, 132.3, 132.2, 131.0, 129.4, 128.9, 128.2, 128.1, 127.9, 127.7, 126.8, 126.3, 126.2, 124.9, 114.4, 114.1, 55.6, 55.5, 17.4, 16.9; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}NO_3S$ $[M + Na]^+$ 348.0670, found 348.0681.

(*E*/*Z*) 4-[(1-Methyl-1*H*-indol-3-yl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one (12h). Obtained from oxazolone **15** and dithioester **16h**, (*E*:*Z* = 64:36), yellow solid (0.84 g, 78%): mp 186−188 °C; R_f 0.5 (1:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3106, 2927, 1767, 1727, 1619, 1522, 1325, 1131, 887, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.09 (m, 1.34H), 7.99−7.97 (m, 0.66H), 7.93 (d, *J* = 8 Hz, 0.33H), 7.73 (s, 0.33H), 7.71 (s, 0.67H), 7.56 (s, 1H), 7.53−7.42 (m, 3H), 7.40−7.37 (m, 1H), 7.33−7.31 (m, 1.34H), 7.27 (d, *J* = 1.2 Hz, 0.33H), 7.25−7.23 (m, 0.67H), 3.92 (s, 0.99H), 3.89 (s, 2.01H), 2.45 (s, 2.01H), 2.44 (s, 0.99H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.1, 158.3, 157.8, 151.8, 151.5, 138.0, 137.8, 135.2, 133.8, 132.1, 131.9, 128.9, 128.8, 127.6, 127.4, 126.7, 126.65, 126.59, 126.3, 123.2, 123.0, 122.0, 121.8, 121.7, 121.2, 111.6, 110.3, 110.2, 108.5, 33.73, 33.65, 18.7, 18.1; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{16}N_2O_2S$ $[M + Na]^+$ 371.0830, found 371.0833.

(*E*/*Z*) 4-[Methylthio(pyridin-3-yl)methylene]-2-phenyloxazol-5(4*H*)-one (12i). Obtained from oxazolone **15** and dithioester **16i**, (*E*:*Z* = 57:43), yellow solid (0.55 g, 75%): mp 100−102 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 1760, 1619, 1572, 1008, 867, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72−8.71 (m, 1.14H), 8.62 (d, *J* = 1.6 Hz, 0.86H), 8.11−8.09 (m, 1.14H), 7.96−7.94 (m, 0.86H), 7.81 (dt, *J* = 7.6 Hz, 1.8 Hz, 0.43H), 7.71 (dt, *J* = 8 Hz, 1.8 Hz, 0.57H), 7.59−7.47 (m, 2.7H), 7.45−7.41 (m, 1.3H), 2.32 (s, 1.71H), 2.2 (s, 1.29H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.5, 161.5, 160.3, 152.0, 151.7, 151.1, 150.8, 150.6, 149.6, 137.7, 136.9, 133.2, 132.9, 131.1, 130.8, 129.6, 129.5, 129.12, 129.0, 128.2, 128.0, 125.9, 125.8, 123.6, 123.5, 17.1, 16.9; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{12}N_2O_2S$ $[M + H]^+$ 297.0698, found 297.0698.

Nucleophilic Ring-Opening of 2-Phenyl 4-[(methylthio)-(hetero)arylidene]-oxazole-5-ones 12 with Sodium Alkoxides: General Procedure for the Synthesis of α-[(Methylthio)-(hetero)arylidene]-*N*-benzoylglycinates 17a−i. To a stirred suspension of the corresponding sodium alkoxide [freshly prepared from sodium (20 mg, 1.0 mmol) in the respective alkanol (5 mL)], a solution of the appropriate 5-oxazolone **12** (0.325 g, 1.0 mmol) in 10 mL of alkanol was added dropwise, and the reaction mixture was further stirred at room temperature for 2−3 h (monitored by TLC). It was then concentrated under reduced pressure, poured into water (100 mL), extracted with EtOAc (3 × 50 mL), and washed with brine (1 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was triturated with diethyl ether to give open-chain esters **17a−i** as white solids. All the open-chain esters **17a−i** were

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found to be inseparable mixture of *E*/*Z* stereoisomers from their ^{1}H NMR spectra.[27]

(*E*/*Z*) Ethyl 2-benzamido-3-(4-methoxyphenyl)-3-(methylthio)acrylate (17a). Obtained from oxazolone **12a** and sodium ethoxide, (*E*:*Z* = 40:60), white solid (0.326 g, 88%): mp 146−148 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3326, 2983, 2926, 1715, 1658, 1511, 1467, 1288, 1244, 1028, 709; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.9 (s, 0.6H), 9.4 (s, 0.4H), 7.98 (d, J = 7.6 Hz, 1.2H), 7.60−7.57 (m, 1.2H), 7.53−7.48 (m, 1.8H), 7.40−7.36 (m, 0.8H), 7.19 (d, J = 8.8 Hz, 0.8H), 7.15 (d, J = 8.8 Hz, 1.2H), 7.0 (d, J = 8.8 Hz, 1.2H), 6.95 (d, J = 8.8 Hz, 0.8H), 4.15 (q, J = 7.2 Hz, 0.8H), 3.80 (q, J = 7.2 Hz, 1.2H), 3.79 (s, 1.8H), 3.72 (s, 1.2H), 1.9 (s, 1.8H), 1.78 (s, 1.2H), 1.18 (t, J = 7.2 Hz, 1.2H), 0.79 (t, J = 7.2 Hz, 1.8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 165.3, 164.5, 163.7, 159.5, 158.9, 151.1, 144.3, 133.8, 133.2, 131.8, 131.4, 129.9, 129.5, 128.4, 128.2, 127.8, 127.7, 127.5, 127.3, 123.5, 120.7, 113.8, 113.7, 60.2, 59.9, 55.2, 55.1, 16.1, 14.9, 14.1, 13.5. Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.57; H, 5.67; N, 3.71.

(*E*/*Z*) *n*-Butyl 2-benzamido-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)acrylate (17g). Obtained from oxazolone **12h** and sodium *n*-butoxide, (*E*:*Z* = 45:55), white solid (0.290 g, 80%): mp 144−146 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3297, 2956, 2925, 1711, 1660, 1526, 1466, 1300, 1170, 742, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 0.55H), 7.93 (d, J = 7.2 Hz, 1H); 7.80 (d, J = 8 Hz, 0.55H), 7.62 (d, J = 8 Hz, 0.45H), 7.58−7.54 (m, 0.62H), 7.50−7.47 (m, 1.2H), 7.43−7.27 (m, 4.26H), 7.24−7.23 (m, 0.86H), 7.15 (td, J = 8 Hz, 0.8 Hz, 1H), 7.10 (s, 0.51H), 4.34 (t, J = 6.4 Hz, 0.9H), 3.90 (t, J = 6.4 Hz, 1.1H), 3.81 (s, 1.35H), 3.79 (s, 1.65), 2.0 (s, 1.35H), 1.98 (s, 1.65H), 1.74 (quin, J = 7.2 Hz, 0.9H), 1.45 (sex, J = 7.2 Hz, 0.9H), 1.14 (quin, J = 7.2 Hz, 1.1H). 0.94 (t, J = 7.2 Hz, 1.35H), 0.77 (sex, J = 7.2 Hz, 1.1H), 0.59 (t, J = 7.2 Hz, 1.65H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 165.2, 164.8, 137.3, 137.2, 133.7, 133.4, 132.2, 131.8, 130.0, 129.5, 128.8, 128.6, 127.6, 127.4, 127.2, 125.9, 125.6, 124.1, 122.8, 122.6, 121.0, 120.5, 120.3, 120.2, 110.1, 109.7, 109.5, 65.4, 65.2, 33.3, 33.1, 30.7, 30.1, 19.4, 18.7, 17.0, 15.7, 13.9, 13.6. Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63. Found: C, 68.32; H, 6.17; N, 6.57.

(*E*/*Z*) *t*-Butyl 2-benzamido-3-(4-methoxyphenyl)-3-(methylthio)acrylate (17i). Obtained from oxazolone **12a** and sodium *t*-butoxide, (*E*:*Z* = 50:50), white solid (0.330 g, 90%): mp 165−167 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3212, 2977, 2925, 1689, 1646, 1506, 1256, 1160, 1021, 706; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 0.5H), 9.24 (s, 0.5H), 7.97 (d, J = 7.2 Hz, 1H); 7.59−7.56 (m, 1.5H), 7.52−7.45 (m, 1.5H), 7.38 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 3.79 (s, 1.5H), 3.73 (s, 1.5H), 1.87 (s, 1.5H), 1.77 (s, 1.5H), 1.43 (s, 4.5H), 1.09 (s, 4.5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 165.2, 163.6, 162.6, 159.4, 158.9, 149.3, 142.6, 134.1, 133.4, 131.8, 131.3, 130.1, 129.5, 128.4, 128.2, 128.1, 127.7, 127.67, 127.3, 124.9, 122.2, 113.8, 113.6, 80.4, 79.8, 55.3, 55.1, 27.8, 27.2, 16.1, 14.9. Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.15; H, 6.11; N, 3.71.

Nucleophilic Ring-Opening of 2-Phenyl 4-[(methylthio)-(hetero)arylidene]-oxazole-5-ones 12 with Amines and Amino Acid Esters: General Procedure for the Synthesis of α-[(Methylthio)(hetero)arylidene]-(*N*-benzoyl)-*N*-glycinamides 21a−l. *Procedure A.* A solution of appropriate oxazolone **12** (0.9 mmol) and respective amine/amino acid ester (0.9 mmol) in EtOH (15 mL) was stirred at room temperature for 35−40 h (monitored by TLC). The ethanol was evaporated under reduced pressure, and the residue was triturated with diethyl ether to give **21** as white solids, which were filtered and crystallized (EtOAc) for characterization. The products **21a−d** and **21h** were obtained following this procedure either as pure stereoisomers or as *E*/*Z* mixtures.[27] The product **21h** from oxazolone **12a** and phenylalanine ester was purified by column chromatography on silica gel to give single stereoisomer.

Procedure B. A solution of appropriate oxazolone **12** (0.9 mmol) and the corresponding amine/amino acid ester (0.9 mmol) in EtOH (15 mL) and trace of acetic acid (0.1 mL) was refluxed for 10−16 h (monitored by TLC) and worked up as in the procedure A. The product **21e** was separated as pure solid on trituration with diethyl ether, whereas products **21f,g**, **21i−k** were purified by column chromatography over silica gel using EtOAc:hexane as eluent.[27] The open-chain precursor **21l** from oxazolone **12h** and serine ethyl ester could not be purified by column chromatography and was used as such for Cu-catalyzed cyclization without purification.

***N*-[1-(3,4-Dimethoxyphenethylamino)-3-(4-methoxyphenyl)-3-(methylthio)-1-oxoprop-2-en-2-yl]benzamide (21a).** Obtained from the oxazolone **12a** and 3,4-dimethoxyphenylethylamine, (Procedure A) as single stereoisomer, white solid (0.373 g, 80%): mp 132−134 °C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3264, 2920, 1633, 1517, 1261, 1028, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.41 (m, 3H), 7.32−7.29 (m, 3H), 7.22 (d, J = 8.8 Hz, 2H); 6.87 (d, J = 8.8 Hz, 2H), 6.82−6.80 (br m, 1H), 6.79 (d, J = 1.6 Hz, 1H), 6.76 (dd, J = 8.4 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.77 (s. 3H), 3.63 (q, J = 6.8 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 165.4, 159.8, 149.1, 147.7, 141.5, 133.4, 132.0, 131.8, 129.9, 128.7, 127.6, 127.3, 125.4, 120.9, 114.5, 112.3, 111.5, 55.9, 55.4, 41.2, 35.2, 16.4; HRMS (ESI) m/z calcd for $C_{28}H_{30}N_2O_5S$ $[M + H]^+$ 507.1954, found 507.1934.

***N*-(1-(4-Benzylpiperazin-1-yl)-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)-1-oxoprop-2-en-2-yl)benzamide (21d).** Obtained from oxazolone **12h** and N-benzylpiperazine (Procedure A) as single stereoisomer, white solid (0.384 g, 85%): mp 158−160 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3370, 2921, 2810, 1632, 1531, 1467, 1301, 741, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.94−7.92 (m, 3H), 7.56−7.46 (m, 3H), 7.36−7.28 (m, 2H), 7.18−7.14 (m, 5H); 7.11−7.09 (m, 2H), 3.78 (s, 3H), 3.54 (br s, 1H), 3.40 (br s. 2H), 3.19 (d, J = 12.4 Hz, 1H), 3.10 (d, J = 12.4 Hz, 1H), 3.01 (br s, 1H), 2.42 (br s, 1H), 2.13 (br s, 1H), 1.99 (s, 3H), 1.78 (br s, 1H), 1.09 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.3, 137.8, 137.2, 133.5, 132.1, 130.3, 129.2, 128.8, 128.3, 127.6, 127.2, 127.1, 122.6, 120.6, 120.2, 119.1, 109.7, 108.4, 62.9, 52.2, 51.8, 46.6, 41.4, 33.1, 15.6. Anal. Calcd for $C_{31}H_{32}N_4O_2S$: C, 70.96; H, 6.15; N, 10.68. Found: C, 71.04; H, 6.11; N, 10.63.

Ethyl 2-(2-benzamido-3-(methylthio)-3-(thiophen-2-yl)-acrylamido)-3-hydroxypropanoate (21j). Obtained from oxazolone **12e** and serine ethyl ester (Procedure B) as single stereoisomer, off-white solid (0.303 g, 70%): mp 100−102 °C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3403, 2977, 2918, 1735, 1640, 1518, 1467, 1283, 1193, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.52−7.51 (m, 1H), 7.46 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.39−7.36 (m, 2H), 7.28 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.11 (dd, J = 5.2 Hz, 3.6 Hz, 1H); 7.07 (br d, J = 6.8 Hz, 1H), 4.69 (ddd, J = 8 Hz, 3.2 Hz, 2,8 Hz, 1H), 4.42 (dd, J = 11.6 Hz, 2.8 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.95 (br d, J = 11.6 Hz, 1H), 3.75 (br s, 1H), 2.17 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 165.1, 164.3, 138.3, 132.6, 132.4, 131.1, 129.3, 128.9, 128.7, 128.0, 127.6, 122.3, 62.2, 61.7, 56.0, 17.6, 14.3; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_5S_2$ $[M + H]^+$ 435.1048, found 435.1024.

Nucleophilic Ring-Opening of 2-Phenyl 4-[(methylthio)-(hetero)arylidene]-oxazole-5-ones 12 with Grignard Reagents: General Procedure for the Synthesis of Alkyl/(hetero)aryl-α-(*N*-benzoyl)-β-[(methylthio)(hetero)arylidene]ketones 26a−e. To a stirred, cooled (−20 °C) solution of the corresponding 5-oxazolone **12** (2.0 mmol) in dry THF (10 mL), appropriate Grignard reagent (2.3 mmol) [freshly prepared from the corresponding alkyl/(hetero)aryl bromides (2.3 mmol) and magnesium metal (3.45 mmol) in 10 mL of THF] was added slowly with the help of syringe. The reaction mixture was further stirred for 2−3 h at −20 °C (monitored by TLC), brought to room temperature and poured into saturated NH_4Cl solution (100 mL). It was then extracted with EtOAc (3 × 50 mL), washed with H_2O, brine (1 × 50 mL), and the organic layer was dried (Na_2SO_4) and evaporated under reduced pressure, and the residue was triturated with diethyl ether to give open-chain ketones **26a−e** as white solids.[27]

***N*-(1-(4-Methoxyphenyl)-1-(methylthio)-3-oxohept-1-en-2-yl)benzamide (26a).** Obtained from oxazolone **12a** and *n*-butylmagnesium bromide as single stereoisomer, white solid (0.265

g, 75%): mp 150−152 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3307, 2956, 1651, 1466, 1250, 1034, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.57−7.54 (m, 1H), 7.51−7.46 (m, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.24 (t, J = 7.6 Hz, 2H), 1.95 (s, 3H), 1.43 (quin, J = 7.2 Hz, 2H), 1.08 (sex, J = 7.2 Hz, 2H), 0.719 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 160.5, 134.9, 133.2, 132.3, 131.4, 130.1, 128.9, 127.6, 127.3, 114.8, 114.5, 55.5, 42.1, 26.1, 22.2, 15.7, 13.9; HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_3S$ $[M + Na]^+$ 406.1453, found 406.1452.

***N*-[3-(1-Methyl-1*H*-indol-3-yl)-3-(methylthio)-1-oxo-1-(thiophen-2-yl)prop-2-en-2-yl]benzamide (26e).** Obtained from oxazolone **12h** and 2-thienylmagnesium bromide (*E*:*Z* = 17:83), pale yellow solid (0.604 g, 70%): mp 160−163 °C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3364, 2918, 1660, 1632, 1530, 1464, 1303, 1263, 742, 708 ; ^1H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 0.83H), 9.76 (s, 0.17H), 8.0 (d, J = 7.2 Hz, 1.66H), 7.85 (dd, J = 6.6 Hz, 4.8 Hz, 0.37H), 7.74 (d, J = 7.2 Hz, 1.06H), 7.60−7.57 (m, 1.3H), 7.53−7.42 (m, 4H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 (s, 0.83H), 7.19−7.15 (m, 1H), 7.08 (t, J = 7.2 Hz, 0.83H), 6.99 (t, J = 7.2 Hz, 0.17H), 6.68 (dd, J = 4.8 Hz, 4.0 Hz, 0.83H), 3.87 (s, 0.51H), 3.64 (s, 2.49H), 2.05 (s, 2.49H), 1.85 (s, 0.51H); ^{13}CNMR (100 MHz, DMSO-d_6) δ 184.6, 184.2, 165.3, 164.8, 145.5, 144.0, 137.3, 136.9, 135.2, 133.1, 133.0, 132.6, 132.4, 132.2, 131.9, 131.8, 131.5, 131.4, 131.3, 129.5, 129.1, 128.4, 128.1, 128.0, 127.69, 127.65, 127.6, 126.9, 126.3, 125.6, 122.0, 121.7, 120.1, 120.0, 119.9, 119.5, 110.4, 110.1, 109.6, 109.2, 32.8, 32.4, 16.2, 15.4; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2O_2S_2$ $[M + Na]^+$ 455.0864, found 455.0862.

General Procedure for Copper-Catalyzed Intramolecular Cyclization of Open-Chain Precursors 17a−i, 21a−l and 26a−e: Synthesis of 2-Phenyl-5-(hetero)aryl-4-Substituted Oxazoles 18a−i, 22a−l and 27a−e. To a stirred solution of the corresponding open-chain precursors **17**, **21** or **26** (1.0 mmol) in DMF (3 mL) were added CuI (19 mg, 0.1 mmol), 1,10-phenanthroline (36 mg, 0.2 mmol) and Cs_2CO_3 (32 mg, 1.0 mmol), and the reaction mixture was heated at 90 °C with stirring for 2−3 h (monitored by TLC). It was then poured into ice-cold water (20 mL), extracted with EtOAc (3 × 10 mL), washed with brine (1 × 10 mL), dried over Na_2SO_4 followed by removal of the solvent to give crude oxazoles, which were purified by column chromatography over silica gel using EtOAc−hexane as eluent.

Ethyl 5-(4-methoxyphenyl)-2-phenyloxazole-4-carboxylate (18a). Obtained from enamide **17a**, white solid (160 mg, 92%): mp 148−149 °C; R_f 0.5 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1715, 1505, 1212, 1091, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16−8.15 (m, 2H), 8.11 (d, J = 8.8 Hz, 2H), 7.49−7.48 (m, 3H), 7.02 (d, J = 8.8 Hz, 2H), 4.46 (q, J = 7.21 Hz, 2H), 3.87 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 161.3, 159.4, 155.6, 131.0,130.4, 128.9, 127.3, 126.9, 126.7, 119.9, 114.0, 61.5, 55.6, 14.5; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_4$ $[M + Na]^+$ 346.1055, found 346.1051.

Ethyl 5-(3,4-dimethoxyphenyl)-2-phenyloxazole-4-carboxylate (18b).[32] Obtained from enamide **17b**, white solid (154 mg, 88%): mp 165−166 °C (lit. 165−166 °C);[32] R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3030, 2836, 1711, 1513, 1259, 708; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17−8.14 (m, 2H), 7.88 (d, J = 2 Hz, 1H), 7.76 (dd, J = 8.6 Hz, 2 Hz, 1H), 7.49 (m, 3H), 6.98 (d, J = 8.6 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 159.1, 155.2, 150.8, 148.7, 130.9, 128.8, 127.3, 126.8, 126.5, 121.9, 119.9, 111.8, 110.8, 61.39, 56.12, 55.99, 14.39; HRMS (ESI) m/z calcd for $C_{20}H_{19}NO_5$ $[M + Na]^+$ 376.1161, found 376.1161.

***n*-Butyl 5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazole-4-carboxylate (18g).** Obtained from enamide **17g**, white solid (160 mg, 90%): mp 144−145 °C; R_f 0.7 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2996, 2867, 1693, 1567, 1220, 731; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.33−8.31 (m, 1H), 8.22 (d, J = 6.8 Hz, 2H), 7.55−7.49 (m, 3H), 7.42−7.35 (m, 3H), 4.44 (t, J = 7.2 Hz, 2H), 3.90 (s, 3H), 1.87 (quint, J = 7.2 Hz, 2H), 1.50 (quint, J = 7.2 Hz, 2H), 1.0 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 157.9, 154.8, 137.0, 134.1, 130.6, 128.9, 127.1, 126.7, 126.1, 124.5, 123.1, 121.7, 121.5, 110.1, 103.0, 65.1, 33.6, 31.1, 19.4, 13.9; HRMS (ESI) m/z calcd for $C_{23}H_{22}N_2O_3$ $[M + Na]^+$ 397.1528, found 397.1529.

***N*-(3,4-Dimethoxyphenethyl)-5-(4-methoxyphenyl)-2-phenyloxazole-4-carboxamide (22a).** Obtained from enamide **21a**, white solid (140 mg, 80%): mp 138−140 °C; R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3336, 2913, 2838, 1643, 1529, 1255, 836, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 2H), 8.06−8.04 (m, 2H), 7.53−7.48 (m, 4H), 7.01 (d, J = 10 Hz, 2H), 6.84−6.81 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.69 (q, J = 6.8, 2 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 161.0, 157.9, 152,6, 149.2, 147.8, 131.8, 130.9, 130.1, 129.3, 129.0, 126.8, 126.6, 120.9, 120.1, 113.9, 112.2, 111.6, 56.1, 55.9, 55.5, 40.9, 35.8; HRMS (ESI) m/z calcd for $C_{27}H_{26}N_2O_5$ $[M + Na]^+$ 481.1739, found 481.1738.

(4-Benzylpiperazin-1-yl)[5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazol-4-yl]methanone (22d). Obtained from enamide **21d**, off-white solid (158 mg, 87%): mp 160−162 °C; R_f 0.45 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 2909, 2802, 1624, 1442, 1228, 737; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.21 (d, J = 6.8 Hz, 1H), 8.14 (d, J = 6.8, Hz, 2H), 7.54−7.47 (m, 3H), 7.40−7.29 (m, 8H), 3.94 (br s, 2H), 3.87 (s, 3H), 3.85 (br s, 2H), 3.55 (s, 2H), 2.58 (br s, 2H), 2.52 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 157.3, 151.4, 137.9, 137.1, 132.1, 131.1, 130.4, 129.3, 129.0, 128.5, 127.6, 127.5, 127.4, 126.3, 126.0, 122.8, 121.2, 121.1, 109.9, 103.2, 63.1, 53.7, 53.1, 47.5, 42.7, 33.4; HRMS (ESI) m/z calcd for $C_{30}H_{28}N_4O_2$ $[M + Na]^+$ 499.2110, found 499.2113.

5-(1-Methyl-1*H*-indol-3-yl)-2-phenyl-*N*-[4-(trifluoromethyl)-phenyl]oxazole-4-carboxamide (22g). Obtained from enamide **21g**, white solid (153 mg, 85%): mp 258−260 °C; R_f 0.8 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3351, 2942, 1673, 1581, 1326, 1114, 736; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 9.02 (s, 1H), 8.36−8.33 (m, 1H), 8.21 (m, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.59−7.54 (m, 3H), 7.45−7.36 (m, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.7, 156.9, 153.1, 141.4, 137.2, 134.7, 130.8, 129.2, 126.9, 126.5, 126.46, 126.43, 126.39, 126.1, 125.9, 123.1, 121.7, 121.5, 119.5, 110.2, 102.9, 33.6; HRMS (ESI) m/z calcd for $C_{26}H_{18}F_3N_3O_2$ $[M + Na]^+$ 484.1249, found 484.1249.

(2*S*)-Ethyl 3-(1*H*-indol-3-yl)-2-(5-(1-methyl-1*H*-pyrrol-2-yl)-2-phenyloxazole-4-carboxamido)propanoate (22i). Obtained from enamide **21i**, white solid (125 mg, 70%): mp 94−96 °C; R_f 0.5 (1:2 EtOAc:hexane); $[\alpha]_D^{25}$ = +31.4 (*c*, 0.58, $CHCl_3$); IR (KBr, cm^{-1}) 3385, 3268, 3056, 2926, 1736, 1661, 1529, 1235, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.96 (m, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.48−7.45 (m, 3H), 7.35 (d, J = 8.4 Hz, 1H), 7.22 (dd, J = 4 Hz, 1.6 Hz, 1H), 7.20 (t, 7.2 Hz, 1H), 7.12−7,10 (m, 2H), 6.79 (dd, J = 2.8 Hz, 1.6 Hz, 1H), 6.24 (dd, J = 4 Hz, 2.8 Hz, 1H), 5.08 (dt, J = 8 Hz, 2.8 Hz, 1H), 4.18−4.10 (m, 2H), 3.82 (s, 3H), 3.43 (dd, J = 5.6 Hz, 2.0 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.1, 160.9, 158.2, 146.5, 136.3, 130.9, 129.4, 128.9, 127.9, 126.9, 126.8, 126.6, 122.9, 122.3, 120.0, 119.8, 119.1, 116.4, 111.3, 110.6, 108.9, 61.6, 52.9, 36.5, 28.1, 14.2; HRMS (ESI) m/z calcd for $C_{28}H_{26}N_4O_4$ $[M + H]^+$ 483.2032, found 483.2033.

(2*S*)-Ethyl 3-hydroxy-2-[2-phenyl-5-(thiophen-2-yl)oxazole-4-carboxamido]propanoate (22j). Obtained from enamide **21j**, off-white solid (133 mg, 75%): mp 194−196 °C; R_f 0.55 (1:1 EtOAc:hexane); $[\alpha]_D^{25}$ = +20.0 (*c*, 0.55, $CHCl_3$); IR (KBr, cm^{-1}) 3384, 3332, 2956, 1740, 1640, 1531, 1269, 1058, 703; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 4 Hz, 1.2 Hz, 1H), 8.13−8.06 (m, 2H), 8.07 (br d, J = 7.2 Hz, 1H), 7.52−7.50 (m, 4H), 7.16 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 4.88 (dt, 7.2 Hz, 4.0 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 4.11 (dd, J = 4.4 Hz, 4.0 Hz, 2H), 2.61 (br s, 1H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 161.9, 158.3, 149.0, 131.3, 130.1, 129.4, 129.1, 128.8, 127.9, 127.8, 126.8, 126.3, 63.9, 62.2, 55.0, 14.3; HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_5S$ $[M + Na]^+$ 409.0834, found 409.0833.

1-[5-(4-Methoxyphenyl)-2-phenyloxazol-4-yl]pentan-1-one (27a). Obtained from enamide **26a**, white solid (157 mg, 90%): mp 78−80 °C; R_f 0.7 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2925, 1679, 1496, 1255, 830, 706; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 9.2

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Hz, 2H), 8.14−8.11 (m, 2H), 7.51−7.49 (m, 3H), 7.01 (d, J = 9.2 Hz, 2H), 3.89 (s, 3H), 3.15 (t, J = 7.6 Hz, 2H), 1.78−1.70 (m, 2H), 1.49−1.40 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 161.5, 158.1, 153.5, 134.4, 130.9, 130.1, 129.0, 127.0, 126.7, 120.2, 114.0, 55.5, 40.7, 26.4, 22.6, 14.2; HRMS (ESI) m/z calcd for $C_{21}H_{21}NO_3$ $[M + Na]^+$ 358.1419, found 358.1418.

[5-(*N*-Methyl-1*H*-indol-3-yl)-2-phenyloxazol-4-yl](thiophen-2-yl)methanone (27e). Obtained from enamide **26e**, yellow solid (150 mg, 85%): mp 214−218 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1631, 1539, 1388, 1231, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.86 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 8.40−8.36 (m, 1H), 8.25 (m, 2H), 7.72 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.59−7.50 (m, 3H), 7.43−7.36 (m, 3H), 7.24 (dd, J = 4.8 Hz, 4.0 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 156.9, 155.6, 144.2, 137.4, 135.4, 135.2, 134.2, 131.7, 130.6, 129.1, 128.0, 127.3, 126.6, 126.2, 123.2, 121.9, 121.8, 110.2, 103.8, 33.7; HRMS (ESI) m/z calcd for $C_{23}H_{16}N_2O_2S$ $[M + Na]^+$ 407.0830, found 407.0831.

5-(4-Methoxyphenyl)-2-phenyloxazole-4-carboxylic acid (19a).[9e] Obtained from ester **18a**, white solid (85 mg, 95%): mp 193−194 °C (lit. 192−194 °C);[9e] R_f 0.3 (EtOAc); IR (KBr, cm^{-1}) 2933, 1690, 1513, 1256, 1183, 830, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 2H), 8.13−8.10 (m, 2H), 7.53 (m, 3H), 7.03 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ163.5, 161.7, 158.6, 155.8, 131.4, 130.3, 129.1, 126.9, 126.1, 125.8, 119.1, 114.3, 55.6; HRMS (ESI) m/z calcd for $C_{17}H_{13}NO_4$ $[M + Na]^+$ 318.0742, found 318.0742.

5-(Benzo[d][1,3]dioxol-5-yl)-2-phenyloxazole (7b) (Texamine).[23d] Obtained from carboxylic acid **19c**, white solid (29 mg, 70%): mp 135−137 °C (lit. 134−136.5 °C);[23d] R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2906, 1479, 1231, 1036, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (m, 2H), 7.50−7.45 (m, 3H), 7.31 (s, 1H), 7.24 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.18 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 151.2, 148.2, 147.9, 130.2, 128.8, 127.5, 126.2, 122.4, 122.3, 118.4, 108.9, 104.9, 101.4; HRMS (ESI) m/z calcd for $C_{16}H_{11}NO_3$ $[M + H]^+$ 266.0817, found 266.0819.

5-(4-Methoxyphenyl)-2-phenyloxazole (8b) (Uguenenazole).[34a,b] Obtained from carboxylic acid **19a**, white solid (30 mg, 70%): mp 134−135 °C (lit. 133−135 °C);[34] R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2957, 2831, 1507, 1255, 1022, 827, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 6.2 Hz, 1.2 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.51−7.45 (m, 3H), 7.33 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 160.0, 151.5, 130.3, 128.9, 127.7, 126.3, 125.9, 121.9, 121.0, 114.6, 55.5; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ $[M + H]^+$ 252.1025, found 252.1024.

Ethyl 2-phenyl-5-(1-methyl-1*H*-indol-3-yl)-[4,2′]bisoxazole-4′-carboxylate (24c). Obtained from **22l**, brown solid (33 mg, 70%): mp 214−216 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1717, 1577, 1307, 1113, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.36−8.35 (m, 1H), 8.34 (s, 1H), 8.25 (br d, J = 6.8 Hz, 2H), 7.57−7.51 (m, 3H), 7.45−7.36 (m, 3H), 4.45 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.8, 157.7, 150.4, 143.1, 137.2, 134.4, 133.8, 130.7, 129.1, 127.0, 126.6, 125.9, 123.1, 121.6, 121.5, 121.1, 110.1, 103.1, 61.3, 33.8, 14.5; HRMS (ESI) m/z calcd for $C_{24}H_{19}N_3O_4$ $[M + Na]^+$ 436.1273, found 436.1272.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data, copies of ^{1}H NMR, ^{13}C NMR and NOESY NMR spectra for all new compounds, stereochemical assignment of enamide precursors **17a−i**, **21a−l** and **26a−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Lutz F. Tietze on his 70th birthday.

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