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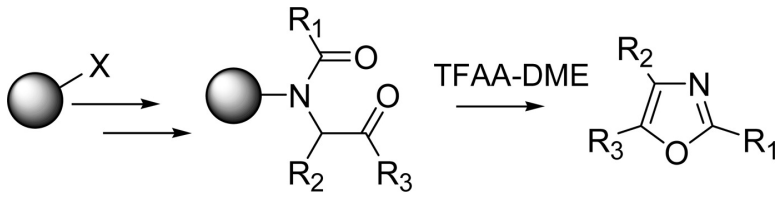

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Trifluoroacetic Anhydride-Mediated Solid-Phase Version of the Robinson−Gabriel Synthesis of Oxazoles

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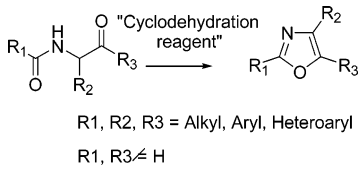
A traceless solid-phase synthesis of oxazoles **4** via Robinson−Gabriel reaction of solid-supported α-acylamino ketones **2** has been achieved. The reaction requires that the cyclization precursor be linked to a benzhydrylic-type linker (compounds **2**) and that trifluoroacetic anhydride be used as the cyclodehydrating agent. The solvent has a dramatic effect on the latter reaction, which goes to completion and follows a cyclative-type mechanism only when an ethereal solvent is used. Different synthetic routes have been investigated toward assembling compounds **2**. The most straightforward one, which we have validated more extensively, comprises the reaction of Merrifield α-methoxyphenyl (MAMP) resin with an α-amino ketone to form compounds **1**, which are, in turn, acylated. Other methodologies and strategies allowing for the synthesis of compounds **1** that have been investigated include direct alkylation of Rink amide resin; reductive amination of the latter with α-keto aldehydes; reaction of MAMP resin with α-amino alcohols, followed by oxidation; and protection of Rink amide resin with either 2,4-dinitrosulfonyl or allyl group, followed by alkylation and removal of protecting group. In addition, we disclose a novel variant of the Ugi four-component reaction that allows for the preparation of compounds **2** in a single synthetic step.

Introduction

It is nowadays generally accepted that the synthesis of large arrays of diverse compounds greatly enhances the capability to discover new chemical entities endowed with certain properties, that is, biological activity. Toward this end, the assembly of non-peptide small organic molecules on polymeric supports (solid-phase organic synthesis) is one of the most powerful tools that in recent years have become available to organic chemists. This warrants the constant search for new and efficient methodologies for solid-phase organic synthesis of small druglike molecules. Efficiency implies that the applied reactions may be brought to completion, which drives to the ground tedious operations such as workup and purification of the targeted molecules. However, only when the whole synthetic process rests on the use of mild and simple reactions does the methodology acquire an added value that becomes sometimes the key to its success. Here, we introduce a conceptually novel technique that exploits trifluoroacetic anhydride (TFAA) as the means to achieve cyclative cleavages, which works efficiently in a solid-phase version of the Robinson−Gabriel synthesis of oxazoles.

Robinson−Gabriel is the name normally given to the cyclocondensation reaction of α-acylamino ketones. It is one of the oldest methods reported for the synthesis of oxazoles[1] (Scheme 1), and for long it has been accomplished only using rather harsh conditions involving cyclodehydrating agents such as sulfuric acid, phosphorus pentachloride, phosphorus oxychloride, polyphosphoric acid, phosgene, or anhydrous hydrogen fluoride.[2] In 1993, Wipf and Miller introduced a new protocol[3] based on the use of triphenylphosphine/iodine in the presence of triethylamine. This protocol has permitted performance of the reaction of cyclocondensation under milder conditions and also has recently found applications in solid-phase organic synthesis.[4]

Scheme 1



Likewise, another mild procedure developed in 1999 by Brain and Paul[5] and based on the use of Burgess reagent has been adapted to solid-phase versions of the Robinson−Gabriel synthesis of oxazoles.[4c,6] Clearly, all of these methods allow for the preparation of compound libraries in which the oxazole ring is borne by the side chain of a given template, which needs to be cleaved off the resin at the end of the synthetic sequence. In contrast to these methods, we were interested in developing a more general strategy to enable the synthesis of functionalized oxazoles carrying no memory of the original anchoring point. This project implied, therefore, preparing an α-acylamino ketone bound to a suitable linker by means of the only viable atom, that is, the nitrogen, and then treating it with an appropriate dehydrating agent that would mediate a cyclative cleavage, releasing the expected product in solution (Scheme 2).

Results and Discussion

To implement our project, we reasoned that we had to build the resin-supported α-acylamino ketone on a linker that

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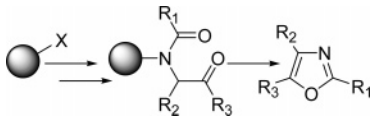
Scheme 2



could assist a mild cyclative cleavage, that is, stabilize the incipient positive charge resulting from the substrate cyclodehydration and product cleavage. Therefore, we first directed our attention to Rink amide linker, which could also provide the nitrogen atom to be decorated with the two diversity portions of the substrate. Treatment of the resin with *p*-methoxyphenacyl bromide followed by capping with benzoyl chloride led us to obtain the supported *N*-[2-(4-methoxyphenyl)-2-ox*o*-ethyl]-benzamide (**2Ab**, Scheme 3). Microcleavage with 20% trifluoroacetic acid (TFA) in dichloromethane (DCM) was used to check the efficiency of this synthetic sequence yielding **3Ab** (over 70% at 220 nm).

Having compounds **2Ab** in hand, we surveyed a series of conditions that could affect cyclocondensation. Only dehydrating agents that could be easily removed from the reaction medium at the end were considered. Trimethyl chlorosilane or phosphoric anhydride, in either DCM or tetrahydrofuran (THF), gave completely negative results, whereas simple heating in toluene at 80 °C yielded the expected oxazole, though contaminated by a number of side products. TFAA alone at either room temperature or 40 °C gave no better results; however, the outcome was different when TFAA was diluted in DCM (1:3). In this case, the desired product was obtained as the main component of the reaction mixture (**4Ab**, 50% at 220 nm, Scheme 3). Moreover, the major side products **3Ab**, **5b**, and **6A**, (18, 20, and 9%, respectively) could all be traced back to the synthetic sequence used to build up the precursor. Higher temperature or prolonged reaction time did not improve the result, addition of an organic base worsened it, and even the use of pentafluoropropionic anhydride at 60 °C gave an analogous outcome: simply compound **5b** was replaced by the corresponding pentafluoropropionic amide.

Table 1. Solid-Phase Cyclization Using Various Solvent Systems

	4Aa, %		**3Aa**, %		ratio **4Aa**/**3Aa**	
solvent system	220 nm	238 nm[a]	220 nm	238 nm[a]	220 nm	238 nm[a]
DCM/TFAA, 3:1	84	46	16	54	5.4	0.9
THF/TFAA, 3:1	100	100				
DIOX/TFAA, 3:1	100	100				
DME/TFAA, 3:1	100	100				
ACN/TFAA, 3:1	80	40	20	60	4.0	0.7
TOL/TFAA, 3:1	86	50	14	50	6.1	1

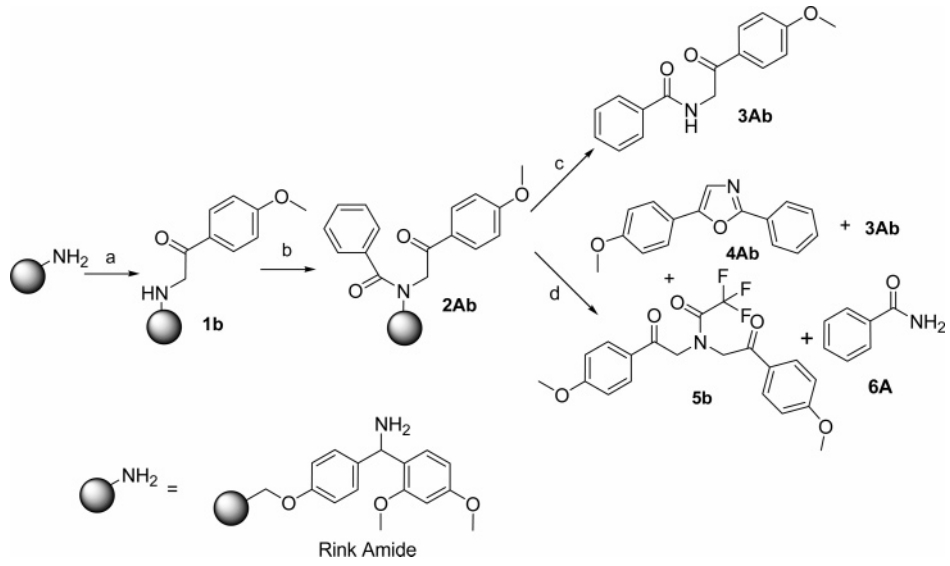
[a] Isosbestic point.

The next goals consisted of both improving the cyclization method to avoid noncyclized compound **3** and accomplishing a more effective synthesis of the precursor **2**, which would eliminate the side products **5** and **6**.

Efficient preparation of precursors **2** could rapidly be achieved by reversing the approach, that is, reacting the commercially available phenacylamines and MAMP resin, followed by capping with benzoyl chloride (Scheme 4). This could yield an α-acylamino ketone (**2Aa**) supported on a benzhydrylic-type linker in high loading and purity.

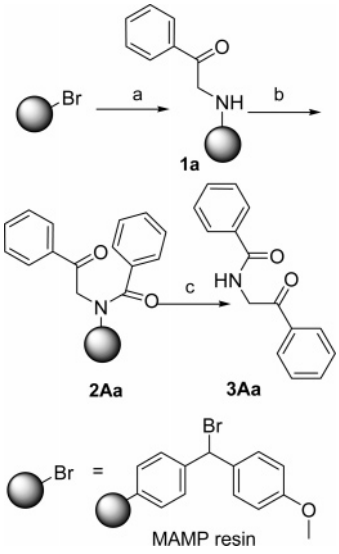
Subsequently, the cyclocondensation reaction was investigated. For this purpose, we screened a number of solvent systems against the supported *N*-(2-oxo-2-phenylethyl)-benzamide (**2Aa**) and took the ratio between the amount of compounds **3Aa** and **4Aa** (after 18 h) as a means to assess cyclization efficiency (Table 1): all ethereal solvents, that is, THF, dimethoxyethane (DME), and 1,4-dioxane, were found to work very efficiently, giving rise to an almost quantitative recovery of the expected oxazole compound **4Aa** alone, as opposed to the result obtained with DCM, toluene, and acetonitrile (ACN), in which compound **3Aa** was always present as a contaminant. During the course of our experiments, we subsequently focused on the use of DME as the solvent of choice, since use of THF resulted sometimes in the formation of jelly material, probably related to solvent

Scheme 3[a]



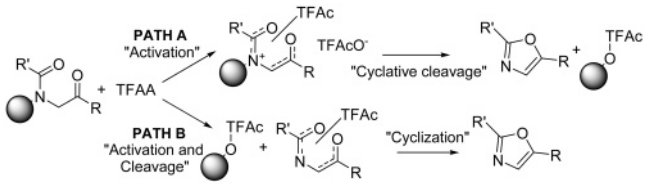
[a] (a) *p*-Methoxyphenacyl bromide, 1.3 equiv; TEA, 2 equiv; DCM; room temp. (b) Benzoyl chloride, 2.5 equiv; TEA, 4 equiv; DCM; room temp. (c) TFA/DCM 20%. (d) TFAA/DCM 1:3, o.n., room temp.

Scheme 4[a]



[a] (a) Phenacylamine, 5 equiv; DIPEA, 8 equiv; DCM. (b) Benzoyl chloride, 2.5 equiv; DIPEA, 4 equiv; DCM, room temp. (c) TFA/DCM 2:8.

Scheme 5



polymerization, and 1,4-dioxane simply has a higher boiling point than DME.

Such a dramatic solvent effect during cyclization reflects a difference in the reaction mechanism according to the very nature of the solvent used. It has been demonstrated that under strong acidic conditions, the Robinson−Gabriel synthesis proceeds with expulsion of the ketone oxygen and incorporation of the amide oxygen in the final oxazole,[7] and a similar mechanism has been suggested by Wipf for the PPh_3-I_2-mediated protocol.[3] On the other hand, Fleury has shown that the TFAA-mediated cyclization of α-acylamino amides to form 5-aminooxazoles occurs involving the attack of the anhydride by either of the amidic oxygen atoms.[8] Whichever is the mechanism in this solid-phase reaction (i.e., activation of the ketone oxygen or activation of the amide oxygen), two possible pathways can be envisaged: ring formation and cleavage from the resin are concerted in a truly cyclative cleavage mechanism (Scheme 5, path A) or the α-acylamino ketone **3** is first released in solution and only subsequently cyclizes to form the oxazole (Scheme 5, path B).

To help clarify the mechanism involved, we have studied the time course of the reaction both in solution and on solid phase using both DME and DCM as the solvents. By plotting the ratio between compounds **4** and **3** found in solution as a function of time (in Figure 1 data for **4Ab** and **3Ab** at 220 nm are shown), it can be concluded that when the solvent is DCM, there is little difference between solution and solid-phase reaction. In the latter case, a few minutes after starting the reaction, compound **3Ab** is the major component of the

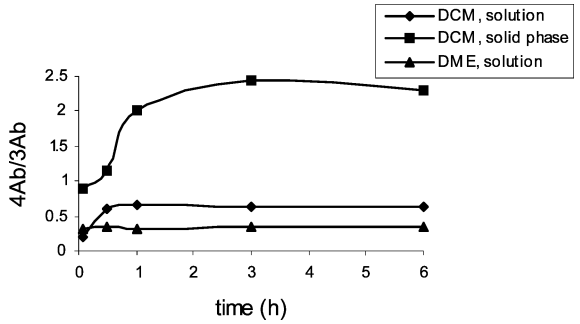


Figure 1. Time-dependent oxazole formation in solution (DCM and DME as solvents) and solid phase (DCM as solvent).

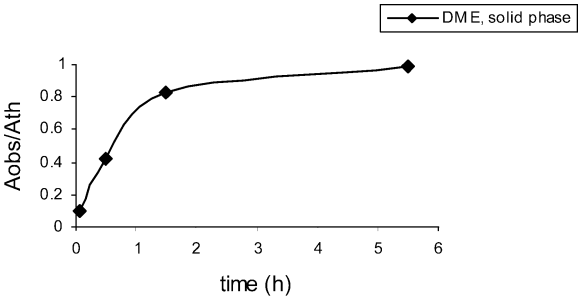


Figure 2. Time-dependent oxazole formation in solid phase (DME as solvent).

solution and slowly cyclizes to yield **4Ab**. However, both reactions never reach completion, and after 5−6 h, the ratio between **4Ab** and **3Ab** remains constant (though the solid-phase reaction seems somewhat more efficient).

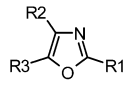
DME appears to be a worse solvent in solution phase (Figure 1): the **4Ab**/**3Ab** ratio increases at the beginning, but soon, the reaction slows down, and even after 24 h, the amount of **3Ab** far exceeds that of **4Ab**. However, the outcome of the reaction is totally different on solid phase (Figure 2). Here, compound **3Ab** is never detected in solution, and calculating the yield of **4Ab** (with respect to the theoretical one) against time, it turns out that full conversion is achieved in 6 h.

This result strongly supports a cyclative cleavage mechanism when DME is used as the solvent and prevalently a cleavage, followed by cyclization, when the reaction is performed in DCM.

Furthermore, the solid support is not irrelevant to the reaction outcome: if linkers such as the aminoethyl-photolinker or even the Wang linker, which do not provide sufficient carbocation stabilization, are used, the reaction does not occur at all. This highlights the need for an adequate assistance to the formation of a carbocation on the resin in order to trigger the oxazole formation.

To validate this method, we have performed a series of reactions in parallel, as shown in Table 2. Yields are fair to good in most cases, except when a α-substituted- (R2 = methyl) or a strongly deactivated (i.e., *p*-nitro-) phenacylamine is used. This, at least in the former case, reflects a poor efficiency of the standard acylation step, possibly related to steric hindrance, rather than a problem with the cyclization. In fact, a subsequent treatment of the residual resin with 20% TFA in DCM releases only α-trifluoroacetamidopropiophenone.

Table 2. Compounds of General Formula **4**

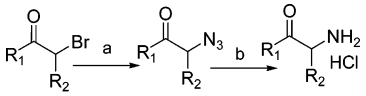
		a			b			c			d			e			f		
		R2 = H															R2 = CH_3		
		R3 = Ph			R3 = 4-CH_3OPh			R3 = 4-BrPh			R3 = 4-ClPh			R3 = 4-NO_2Ph			R3 = Ph		
		UV ([a])	NMR ([b])	Yield	UV ([a])	NMR([b])	Yield	UV ([a])	NMR([b])	Yield	UV ([a])	NMR([b])	Yield	UV ([a])	NMR([b])	Yield	UV ([a])	NMR([b])	Yield
A	R1 = Ph	100	91	94	100	90	89	100	99	78	100	80	40	95	n.a.([c])	55	100	68	12
B	R1 = 4-CH_3Ph	100	84	100	100	93	100	100	97	68	100	97	56	65	30	24	95	50	9
C	R1 = 4-CH_3OPh	100	91	88	100	95	84	-	-	-	100	98	49	95	63	34	90	24	14
D	R1 = 4-$(CH_3)_2$NPh([d])	95	88	61	100	100	62	100	75	45	100	80	41	50	n.d.	25	-	-	-
E	R1 = 4-NO_2Ph	100	87	66	100	100	62	100	95	69	100	95	30	100	n.a.([c])	14	n.a.([c])	n.a.([c])	86
F	R1 = 4-ClPh	100	100	80	100	100	43	100	96	65	100	91	41	80	n.d.	25	100	44	12
G	R1 = 2-Thienyl	100	100	93	100	85	100	100	98	73	95	86	40	90	69	36	-	-	-
H	R1 = 4-Pyridinyl([d])	100	83	36	100	74	13	100	70	24	100	57	21	-	-	-	-	-	-

[a] Integration of peak area between 210 and 400 nm. [b] Quantitation performed using BTMSB as an internal standard.[9] [c] Due to sample precipitation. [d] Obtained as trifluoroacetates.

We have assessed quality of crudes by using both the area from PDA in the HPLC/MS trace between 210 and 400 nm and the ^{1}H NMR spectra obtained in the presence of an internal standard.[9] The former furnishes the relative purity of samples against any other UV detectable species. The latter gives an indication of the effective concentration of product in the sample, which might be affected by the presence of non-UV−visible (and non-NMR detectable) species. Although purity is very satisfactory in almost any instance, NMR data indicate that when preparation of the cyclization precursors **2** is somehow hampered or cyclization is less efficient, then the titer of oxazoles **4** is lower, which only partly reflects the presence of side products. It has to be noted here, however, that simple passage of the crudes through a silica gel plug usually increases the NMR titer.

α-Amino ketones are readily available both commercially and by synthesis. Their preparation exploiting various starting materials and strategies has been reported in dozens of papers. The most viable synthetic routes include elaboration of the carboxylic function of α-amino acids[10] or α-acylation of their Schiff base.[11] Assembling and reduction of α-nitro ketones[12] is also frequently employed; however, most commonly, they are obtained by reaction of α-halo ketones with a suitable nitrogen source followed by functional group manipulation. The latter may include hydrolysis of hexamethylentetrammonium salts,[13] phthalimide,[14] and diformylimide[15] derivatives or reduction of azide, usually accomplished catalytically,[16] or using a phosphorus(III) species (in the presence of a suitable electrophile, Staudinger reaction).[17] For the purpose of this work, we have exploited the azide reduction strategy designing a two-step protocol in which the azide is prepared from the corresponding bromide in acetone and then reduced with tin chloride in ethanol.[18] This is very straightforward, yields the compatible product in high purity and is amenable to parallelization (Scheme 6).

Scheme 6[a]



7 **8**

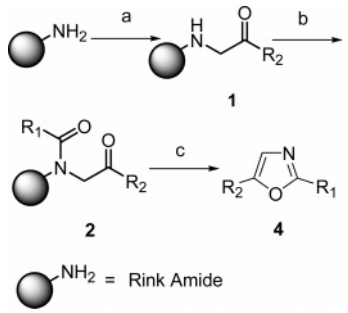
[a] (a) NaN_3, 1.5 equiv; acetone. (b) $SnCl_2$, 1.5 equiv; EtOH.

As an ideal follow-up to this methodology, we next started studying alternative routes to assembling solid-supported α-acylamino ketones.

We have considered both nucleophilic (amine core) and electrophilic (brominated) resins, provided that they have a benzhydrylic-type linker.

As for the former, we first reassessed the use of α-bromo ketones with a set of commercially available resins, including Rink amide, Sieber, Rink amide MBHA, Rink amide AM, DOD resin, and NOVASYN TGR. We applied the protocol described in Scheme 3 and systematically investigated the reagents' ratio, base, solvent, and reaction time of the alkylation step (data not shown); however, despite our efforts, this exercise did not allow us to identify a general protocol.

Scheme 7[a]



[a] (a) $R_2C(O)C(O)H$, 5 equiv; AcOH cat.; Cl_3SiH, 10 equiv; DCM. (b) Acyl chloride, 2.5 equiv; DIPEA, 4 equiv; DCM. (c) TFAA/DME 1:3, o.n., room temp.

Table 3

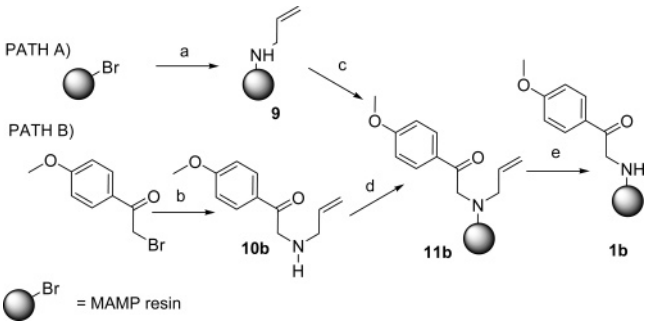
		a				g			
		R2 = Ph				R2= CH_3			
		UV ([a])	NMR ([b])	CNLD	Yield	UV ([c])	NMR ([b])	CNLD	Yield
A	R1 = Ph	95	69	70	71	10	n.d.	n.d.	n.d.
C	R1 = 4-CH_3OPh	-	-	-	-	35	n.d.	n.d.	n.d.
I	R1 = 4-BrPh	95	71	78	72	-	-	-	-

[a] Integration of peak area between 210 and 400 nm. [b] Quantitation performed using BTMSB as an internal standard.[9] [c] Integration of peak at 220 nm.

To duly exploit the reactivity of phenacyl bromides with Rink amide-type resins, we had to devise a strategy involving the protection, alkylation and deprotection of the resin primary amino group. However, alkylation of either the benzamide[19] or the Cbz carbamate[20] failed, while the Fukuyama protocol, based on the use of 2,4-dinitrosulfonyl chloride as a means for selectively protecting the amino group[21] (experimental details are in the Supporting Information section) led to only partial success: oxazole **4Ab** was obtained in 25% purity (at 220 nm). We suggest that acidity of both the reacting α-bromo ketone[22] and resulting α-sulfonylamino ketone[23] are responsible for this result.

As an alternative strategy, we considered the reductive amination of glyoxals with Rink amide resin, which was successfully achieved (Scheme 7) by implementing a solid-phase version of a known protocol.[24] Accordingly, we employed both phenyl and methyl glyoxals, running four reactions in parallel to validate the method. The characterization of crudes is shown in Table 3, where in addition to yield, UV, and NMR, CLND purities are also reported (which are in good agreement with NMR data). The data tell us that the protocol did not work properly when using methyl glyoxal but gave satisfactory results with phenyl glyoxal, suggesting a higher efficiency of the reaction sequence when using aromatic ketones.

Scheme 8[a]



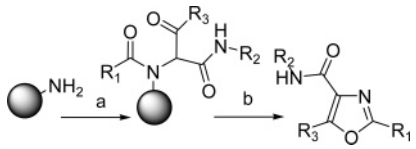
[a] (a) Allylamine, 10 equiv; DCM; 3 h; room temp. (b) Allylamine, 2.5 equiv; DIPEA, 3 equiv; DCM; 1 h, room temp. (c) 4-Methoxyphenacyl bromide, 6 equiv; BEMP, 8 equiv; DMF; o.n.(2 cycles). (d) MAMP resin; DIPEA, 5 equiv; DCM; 2 h; room temp. (e) Dimethylbarbituric acid, 5 equiv; $Pd(PPh_3)_4$ cat.; DCM; o.n.; room temp.

To exploit electrophilic resins, we first considered the conspicuous pool of *β*-amino alcohols as possible precursors of α-amino ketones. After loading 2-amino-1-phenyl ethanol on MAMP resin, we examined several well-known non-acid protocols that have already been performed in solid-phase oxidations. These include sulfur trioxide/pyridine complex,[25] Dess−Martin periodinane,[26] pyridinium chlorochromate,[27] chromium trioxide/pyridine complex,[28] and the Swern method[25] (experimental details in the Supporting Information section), which was the only one to give partial conversion (20% at 220 nm). We speculate that steric hindrance of the MAMP resin may have affected the outcome.

At the end, we devised a novel strategy for the synthesis of resin-bound secondary amines based on the use of allyl as a temporary protecting and activating functionality of primary amino groups. The allyl and related derivatives have been widely exploited as protecting groups in organic synthesis, and a number of different protocols[29−32] are known for their removal. To our purpose, we first quenched MAMP resin with allylamine and then alkylated it with *p*-methoxyphenacyl bromide (Scheme 8, path A). Then we assayed reactions based on palladium catalysis, which promote transfer of the allyl group to a suitable scavenger,[29] as well as reactions based on rhodium[30] or ruthenium,[31] which isomerize it to a hydrolyzable imine. Experiments with metal-free reactions, such as those exploiting the AIBN-mediated radical formation of a thioaminal derivative eventually resulting in the allyl-N bond cleavage,[32] have also been included.

We found out that in this case, two reaction cycles with $Pd(PPh_3)_4$ in DCM worked quite efficiently when using DNMBA[29a] as the allyl scavenger.[33] However, capping with benzoyl chloride after deprotection followed by cleavage revealed that the expected **3Ab** was contaminated by *N*-allyl benzamide, suggesting that the alkylation step needed improvement. Eventually, a more efficient variant of this method was implemented, which consisted of the preformation of the secondary allylamine **10b** in solution followed by its capture by MAMP resin (Scheme 8, path B). Therefore, allylamine and the α-bromo ketone (2.5:1 ratio) were mixed in solution followed by evaporation to dryness to completely

Scheme 9[a]

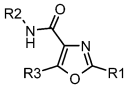


[a] (a) R_1COOH, R_2NC, $R_3C(O)C(O)H$, 5 equiv; DCM/MeOH 2:1, 24 h, room temp. (b) TFAA/DME, 6 h, room temp.

Table 4

R1 = 4-CF_3-Pyridin-3-yl

R3 = CH_3



		Crude				After purification[c]			
		UV (%)	NMR (%)[b]	CLND	Yield	UV (%)	NMR (%)[b]	CNLD	Yield
4Jh	R2 = n-Butyl	100	53	48	39	100	81	-	14
4Ji	R2 = Cyclohexyl	100	45	42	40	100	78	-	15

[a] Integration of peak area between 210 and 400 nm. [b] Quantitation performed using BTMSB as an internal standard.[9] [c] Passage through a silica gel plug (DCM-MeOH 98:2).

eliminate excess reagent. Dissolution in DCM and addition of MAMP resin in the presence of DIEA as a base quantitatively afforded the expected supported tertiary allylamine. To validate the whole protocol, we prepared compounds **4Ba** (25%) and **4Ca** (20%), whose crudes had UV purity (at 220 nm) of 95 and 65%, respectively (70 and 50% NMR strength respectively).

In the search for alternative fashions to assemble the α-acylamino ketone, we turned our attention to multicomponent reactions[34] and realized that we could synthesize precursors **2** exploiting at least a couple of such strategies.

First, we envisaged a Ugi four-component reaction.[35] In fact, by exploiting Rink amide resin as the amino component and a glyoxylic-type carbonylic reactant, this transformation would allow us to assemble in a single step a solid-supported functionalized α-acylamino ketone that, in turn, would yield a 2,4,5-trisubstituted oxazole on cyclization with TFAA (Scheme 9). This strategy is here illustrated with a very efficient synthesis of two 4-trifluoromethyl-3-oxazolylpyridines, which are known as pesticides.[36] Accordingly, treatment of a DCM/MeOH (4:1) solution of 4-(trifuoromethyl)-nicotinic acid, aqueous methyl glyoxal, and either butyl- or cyclohexylisonitrile (5 equiv each) with Rink amide resin for 1 day afforded the expected supported α-acylamino ketone, which was subsequently cyclized with TFAA under standard conditions. Albeit with modest yield (Table 4, 40%), compounds are obtained in a single synthetic step followed by cyclative cleavage, with good purity further improvable by simple passage through a silica gel plug. It is noteworthy that the reaction works even with methyl glyoxal. Giving the large availability of the building blocks involved, this methodology is potentially suitable to the synthesis of large arrays of diverse oxazoles.

In principle, the Petasis protocol[37] could have been used to assemble α-amino ketones on Rink resin. However, despite similar transformations having been reported to work efficiently both in solution[38] and solid-phase[39] reactions, our attempts at performing the two-step sequence Petasis acylation reaction on Rink resin always failed.

In summary, compounds **2** can be assembled following linear procedures as well as one-pot multistep approaches. In the former case, preparation of compounds **1** has to be achieved first. Toward this end, reductive amination of Rink amide resin or removal of the allyl, used as a temporary activating and protecting group of the amine, makes up the most viable alternatives to the direct reaction of α-amino ketones with MAMP resin. Among one-pot syntheses, the Ugi four-component reaction efficiently serves the goal of preparing functionalized compounds **2**.

Conclusions

The use of TFAA is deep-rooted in organic synthesis,[40] where it has been used for a number of applications both as a reagent[41] and a reactant, ranging in this case from protection of functional groups[42] to direct participation in the formation of complex molecules, such as trifluormethyl heterocycles[43] (including a here noteworthy variant of the Dakin−West reaction yielding 5-trifluoromethyloxazoles[44]). A survey of the recent literature reveals that the keywords normally associated with the employment of TFAA are "clean",[45] "mild",[46] and the like, highlighting the benefits of using this compound. However, despite this, we are aware of only a relatively few papers dealing with the use of TFAA in solid-phase organic synthesis. For instance, the generation of trifluoroacetamido groups on resin-supported templates has been reported as a means to create diversity elements.[47] More often, the introduction of such a group has been instrumental to the upcoming step in the synthetic sequence.[48] An example of non-oxidative Pummerer reaction based on the TFAA activation of sulfoxides has been recently reported for the release of 1,2-diols from a novel solid-phase linker,[49] and the TBAN-TFAA methodology has been exploited in the nitration of resin bound adenosine analogues.[50] Activation of carboxylic group by the formation of mixed anhydride by means of TFAA has been described as a method for attaching peptides to insoluble resins,[51] whereas more recently, its use has been reported for the immobilization of various nucleophiles on polystyrene supports, thanks to the formation of linker trifluoroacetates.[52]

Therefore, the use of TFAA as a promoter of oxazole formation by means of cyclative cleavage from benzhydrylic-type resins, as disclosed here, represents a novel solid-phase application of this compound. This methodology is not only amenable to parallelization, but thanks to the availability of several routes to assemble cyclization precursors **2**, it also represents a convenient entry to the high-throughput production of diverse oxazole-containing small organic molecules.

The development of a TFAA-mediated platform for the solid-phase synthesis of other hetrocyclic compounds is currently under evaluation.

Experimental Section

General. All commercially available chemicals were used without further purification. All solvents were used without further drying or purification. TFAA was originally distilled on P_2O_5 but no difference was observed when using commercially available sample without purification. *Caution! Trifluoroacetic anhydride is hygroscopic and hazardous. Caution should be taken when handling this reagent. For the latest hazard information, please refer to the Material Safety Data Sheet.*

Parallel syntheses were performed on a Quest 210 (Argonaut) in 5-mL reaction vessels.

NMR Samples Preparation. The NMR samples were prepared by mixing 200 μL of a 10 mM stock solution with 200 μL of the 5/9 mM 1,4-bis(trimethylsilyl)benzene (BTMSB) solution and 200 μL of DMSO-d_6 directly in the NMR tube (Wilmad 507PP). In the final NMR solutions, the concentration ratio of silane to test molecule (assumed 100% pure) is 1:18, which exactly compensates for the 18 protons of the two trimethylsilyl moieties corresponding to the reference signal.

NMR Acquisition Parameter and Data Processing. All NMR spectra were acquired on a Varian MercuryVx-400 instrument (operating at 400.45 MHz for proton) equipped with a 5-mm double resonance $^1H\{^{15}N-^{31}P\}$ ID-PFG Varian probe with single-axis (*z*) gradient coil. Samples were loaded into the magnet with an automatic sample changer (Zymark-Zymate XP Robot); deuterium gradient shimming and data acquisition were automatically performed by the acquisition software (VNMR, version 6.1B).

HPLC−UV−MS Method. Mass spectra were recorded on a Finnigan MAT LCQ ion trap instrument equipped with an electrospray (ESI) ion source; the mass spectrometer is directly connected to a Spectra System P4000 HPLC pump (Thermo Separation Products) equipped with an AS3000 autosampler and an UV6000LP diode array detector.

Ions were generated under the following conditions: ESI sprayer voltage of 4.0 kV, heated capillary temperature of 255 °C, and sheat gas nitrogen with a pressure of 5.5 bar. Full-scan spectra in the mass range 100−1000 amu. Positive and negative ions spectra were acquired in separate chromatographic runs.

HPLC chromatography was carried out using a Waters XTerra RP 18 column (3.5-μm particles, 4.6 mm − 50 mm) at room temperature and 1.0 mL/min flow rate. Mobile phase A consisted of 5 mM ammonium acetate−acetic acid buffer (pH 5)/acetonitrile 9:1 (v/v). Mobile phase B consisted of 5 mM ammonium acetate−acetic acid buffer (pH 5)/acetonitrile 1:9 (v/v). Chromatographic separation was achieved using a gradient from 0 to 100% of B in 7 min and isocratic at 100% of B in another 2 min. This was followed by a gradient from 100 to 0% of B in 0.1 min and was isocratic at 100% of A for 0.9 min (total acquisition time was 10 min). The UV detection range was 210−400 nm.

HRMS Determination. Exact mass was determined as reported by Colombo et al.[53]

CLND Method. Purity of the products was determined using HPLC system connected to a chemiluminescent nitrogen detector (Antek 8060). HPLC chromatography was carried out using a Zorbax SB C8 column (60 × 4.6 mm, 5 μm) with 1.0 mL/min flow rate. Mobile phase A consisted of 0.01% formic acid solution, and mobile phase B consisted of 0.01% of formic acid in MeOH. Chromatographic separation was achieved using a gradient from 5 to 95% of B in 10 min and isocratic at 95% of B in another 2 min. The nitrogen detection was determined with argon flow of 60 mL/min, oxigen flow of 240 mL/min, and ozone flow of 25 mL/min. The furnace temperature was 1050 °C.

MAMP Resin. MAMP resin was purchased from Novabiochem (capacity = 2.2 mmol/g, bead size = 200−400 mesh), and the experimental loading was determined according to the following procedure: to a suspension of 200 mg (theoretical loading = 2.2 mmol/g, 0.442 mmol) of resin in 3 mL of DCM, DIEA (8 equiv, 640 μL) and phenacylamine hydrochloride (5 equiv, 380 mg) were added. After stirring at room temperature overnight, the resin was filtered and washed with MeOH and DCM. Acylation was performed in 3 mL of DCM with DIEA (7.5 equiv, 560 μL) and benzoyl chloride (5 equiv, 250 μL). Treatment with TFA/DCM 5% afforded 61.3 mg (0.256 mmol) of *N*-(2-oxo-2-phenylethyl)-benzamide with UV purity 100% and NMR 88%. Calculated loading was (0.256 mmol/0.200 g) = 1.28 mmol/g.

***N*-(2-Oxo-2-phenylethyl)-benzamide (3Aa).** ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.80 (d, J = 5.73 Hz, 2H), 7.48−7.54 (m, 2H), 7.55−7.62 (m, 3H), 7.67−7.73 (m, 1H), 7.89−7.93 (m, 2H), 8.03−8.09 (m, 2H), 8.86 (t, J = 5.61 Hz, 1H); *m/z* (ES^+) 240 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{14}NO_2$ ($[M + H]^+$) 240.1019, found 240.1019.

Via Phenacylamines. General Procedure. Phenacylamine Loading. To a suspension of 212 mg (calculated loading = 1.28 mmol/g, 0.27 mmol) of MAMP resin in 3 mL of DCM, DIEA (8 equiv, 640 μL) and the suitable phenacylamine (5 equiv) were added. After stirring overnight at room temperature, the solution was discharged, and the resin was washed with MeOH and DCM and dried under vacuum.

Acylation. To the suspension of the dry resin in 2.5 mL of DCM, DIEA (600 μL, 7.5 equiv) and the acyl chloride (5 equiv) were added dropwise. After 5 h at room temperature, the resin was filtered and washed with MeOH and DCM (three cycles).

Cyclization. Treatment with 1.5 mL of DME and 0.5 mL of TFAA afforded the expected oxazoles as a unique product after 6 h at room temperature.

Via Allylamine. General Procedure. Synthesis of N-Substituted Allylamine and Loading. To a solution of α-bromo ketone (0.5 mmol) in 3 mL of DCM, DIEA (3 equiv, 256 μL) and allylamine (2.5 equiv, 94 μL) were added in a round-bottom flask. The reaction was monitored by TLC (DCM) until consumption of the alkylating agent. After 2 h at room temperature, the solvent, allylamine in excess, and DIEA were removed under vacuum, and the residue was redissolved in DCM, and additional DIEA (300 μL) and

MAMP resin (120 mg, calculated loading = 1.569 mmol/g, 0.188 mmol) were added. The suspension was gently stirred for ~1 h at room temperature, and the resin turned from brown to yellow. After filtration and washing with DCM and MeOH, the resin was dried.

Allyl Removal. The resin was transferred into a two-neck round-bottom flask under inert atmosphere and swollen in 3 mL of DCM. Dimethylbarbituric acid (5 equiv, 123 mg) and $Pd(PPh_3)_4$ (5 mg) were added, and the suspension was stirred overnight at room temperature. After filtration, the resin was washed with MeOH and DCM, and the reaction was repeated another time under the same conditions.

Acylation and Cyclization. As described above.

Rink Amide Resin. Rink amide resin was purchased from Novabiochem (capacity = 0.61 mmol/g, bead size = 100−200 mesh), and the experimental loading was determined according to the following procedure. A 200-mg portion of Fmoc protected Rink amide resin (theoretical loading = 0.61 mmol/g) was treated with piperidine/DMF 20% (two cycles of 20 min each), then washed with DCM and swollen in 3 mL of DIEA (11 equiv, 240 μL), 2-bromoacetophenone (8 equiv, 200 mg) was added, and the suspension was gently stirred overnight. After washing with MeOH and DCM, the resin was treated with TFA/DCM 5% for 2 h and afforded 41.4 mg (0.113 mmol) of 2-(2-oxo-2-phenylethylamino)-1-phenylethanone trifluoroacetate with UV purity of 100% and NMR 95%. Calculated loading is (0.113 mmol/0.200 g) = 0.565 mmol/g.

2-(2-Oxo-2-phenylethylamino)-1-phenylethanone Trifluoroacetate (5a). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 4H), 7.60−7.68 (m, 4H), 7.74−7.82 (m, 2H), 7.98−8.07 (m, 4H), 9.55 (br. s, 1H); *m*/*z* (ES^+) 254 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{16}NO_2$ ($[M + H]^+$) 254.1175, found 254.1174.

Via Glyoxals. General Procedure. Fmoc Deprotection and Reductive Amination. A 230-mg portion of Rink amide resin (calculated loading = 0.565 mmol/g, 0.130 mmol) was treated with a 20% piperidine solution in DMF (2 cycles of 20 min each) to remove protection. After washing with DMF and DCM, the resin was swollen in 3 mL of THF, and glyoxal (5 equiv) was added; trichlorosilane (10 equiv, 150μL) was added after 7 h of stirring and allowed to react overnight at room temperature. The resin was washed with DMF, MeOH, and DCM.

Acylation and Cyclization. As described above.

2,5-Diphenyl-1,3-oxazole (4Aa). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.38−7.45 (m, 1H), 7.48−7.63 (m, 5H), 7.85 (s, 1H), 7.86−7.90 (m, 2H), 8.08−8.14 (m, 2H); *m*/*z* (ES^+) 222 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{12}NO$ ($[M + H^+$) 222.0913, found 222.0909.

5-(4-Methoxyphenyl)-2-phenyl-1,3-oxazole (4Ab). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.84 (s, 3H), 7.10 (d, 2H), 7.52−7.61 (m, 3H), 7.70 (s, 1H), 7.78 (d, 2H), 8.05−8.12 (m, 2H); *m*/*z* (ES^+) 252 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{14}NO_2$ ($[M + H]^+$) 252.1019, found 252.1018.

5-(4-Bromophenyl)-2-phenyl-1,3-oxazole (4Ac). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.54−7.62 (m, 3H), 7.70−7.76 (m, 2H), 7.80−7.87 (m, 2H), 7.92 (s, 1H), 8.08−8.16 (m, 2H); *m*/*z* (ES^+) 300 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{11}BrNO$ ($[M + H]^+$) 300.0018, found 300.0026.

5-(4-Chlorophenyl)-2-phenyl-1,3-oxazole (4Ad). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.54−7.63 (m, 5H), 7.85−7.93 (m, 3H), 8.07−8.16 (m, 2H); *m*/*z* (ES^+) 256 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{11}ClNO$ ($[M + H]^+$) 256.0524, found 256.0519.

5-(4-Nitrophenyl)-2-phenyl-1,3-oxazole (4Ae). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.58−7.64 (m, 3H), 8.12−8.14 (m, 1H), 8.14−8.21 (m, 4H), 8.32−8.42 (m, 2H); *m*/*z* (ES^+) 267 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{11}N_2O_3$ ($[M + H]^+$) 267.0764, found 267.0775.

4-Methyl-2,5-diphenyl-1,3-oxazole (4Af). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.47 (s, 3H), 7.38−7.45 (m, 1H), 7.51−7.62 (m, 5H), 7.74−7.80 (m, 2H), 8.04−8.12 (m, 2H); *m*/*z* (ES^+) 236 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{14}NO$ ($[M + H]^+$) 236.1070, found 236.1067.

2-(4-Methylphenyl)-5-phenyl-1,3-oxazole (4Ba). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3H), 7.36−7.43 (m, 3H), 7.48−7.55 (m, 2H), 7.82 (s, 1H), 7.83−7.88 (m, 2H), 7.97−8.03 (m, 2H); *m*/*z* (ES^+) 236 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{14}NO$ ($[M + H]^+$) 236.1070, found 236.1073.

5-(4-Methoxyphenyl)-2-(4-methylphenyl)-1,3-oxazole (4Bb). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3H), 3.83 (s, 3H), 7.05−7.11 (m, 2H), 7.34−7.40 (m, 2H), 7.66 (s, 1H), 7.74−7.82 (m, 2H), 7.94−8.00 (m, 1H); *m*/*z* (ES^+) 266 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{16}NO_2$ ($[M + H]^+$) 266.1175, found 266.1186.

5-(4-Bromophenyl)-2-(4-methylphenyl)-1,3-oxazole (4Bc). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3H), 7.36−7.42 (m, 2H), 7.68−7.75 (m, 2H), 7.78−7.85 (m, 2H), 7.88 (s, 1H), 7.97−8.04 (m, 2H); *m*/*z* (ES^+) 314 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}BrNO$ ($[M + H]^+$) 314.0175, found 314.0190.

5-(4-Chlorophenyl)-2-(4-methylphenyl)-1,3-oxazole (4Bd). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36−2.44 (m, 3H), 7.36−7.42 (m, 2H), 7.55−7.61 (m, 2H), 7.84−7.91 (m, 3H), 7.97−8.03 (m, 2H); *m*/*z* (ES^+) 270 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}ClNO$ ($[M + H]^+$) 270.0680, found 270.0672.

2-(4-Methylphenyl)-5-(4-nitrophenyl)-1,3-oxazole (4Be). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.35−2.47 (s, 3H), 7.38−7.45 (m, 2H), 8.02−8.07 (m, 2H), 8.09−8.14 (m, 2H), 8.14−8.16 (m, 1H), 8.32−8.36 (m, 2H).

4-Methyl-2-(4-methylphenyl)-5-phenyl-1,3-oxazole (4Bf). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3H), 2.45 (s, 3H), 7.34−7.43 (m, 3H), 7.51−7.57 (m, 2H), 7.72−7.78 (m, 2H), 7.94−7.99 (m, 2H); *m*/*z* (ES^+) 250 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{16}NO$ ($[M + H]^+$) 250.1226, found 250.1230.

2-(4-Methoxyphenyl)-5-phenyl-1,3-oxazole (4Ca). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.86 (s, 3H), 7.10−7.16 (m, 2H), 7.36−7.42 (m, 1H), 7.47−7.55 (m, 2H), 7.78 (s, 1H), 7.81−7.86 (m, 2H), 8.00−8.08 (m, 2H); *m*/*z* (ES^+) 252 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{14}NO_2$ ($[M + H]^+$) 252.1019, found 252.1013.

2,5-bis(4-Methoxyphenyl)-1,3-oxazole (4Cb). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.83 (s, 3H), 3.85−3.87 (m,

3H), 7.03−7.16 (m, 4H), 7.62 (s, 1H), 7.73−7.80 (m, 2H), 7.97−8.05 (m, 2H); *m/z* (ES^+) 282 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{16}NO_3$ ($[M + H]^+$) 282.1125, found 282.1137.

5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1,3-oxazole (4Cd). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.85 (s, 3H), 7.08−7.15 (m, 2H), 7.54−7.59 (m, 2H), 7.82 (s, 1H), 7.83−7.87 (m, 2H), 8.00−8.06 (m, 2H); *m/z* (ES^+) 286 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}ClNO_2$ ($[M + H]^+$) 286.0629, found 286.0627.

2-(4-Methoxyphenyl)-5-(4-nitrophenyl)-1,3-oxazole (4Ce). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.85 (s, 3H), 7.09−7.16 (m, J = 9.02 Hz, 2H), 8.04−8.13 (m, 5H), 8.29−8.37 (m, J = 8.90 Hz, 2H); *m/z* (ES^+) 297 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}N_2O_4$ ($[M + H]^+$) 297.0870, found 297.0881.

2-(4-Methoxyphenyl)-4-methyl-5-phenyl-1,3-oxazole (4Cf). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.44 (s, 3H), 3.86 (s, 3H), 7.09−7.15 (m, 1H), 7.39 (s, 1H), 7.50−7.57 (m, 2H), 7.71−7.76 (m, 2H), 7.98−8.04 (m, 2H); *m/z* (ES^+) 266 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{16}NO_2$ ($[M + H]^+$) 266.1175, found 266.1186.

2-(4-Dimethylaminophenyl)-5-phenyl-1,3-oxazole Trifluoroacetate (4Da). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.00 (s, 6H), 6.78−6.86 (m, J = 9.15 Hz, 2H), 7.30−7.37 (m, 1H), 7.43−7.50 (m, J = 7.68, 7.68 Hz, 2H), 7.68 (s, 1H), 7.75−7.80 (m, J = 9.51 Hz, 2H), 7.84−7.91 (m, J = 9.02 Hz, 2H); *m/z* (ES^+) 265 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{17}N_2O$ ($[M + H]^+$) 265.1335, found 265.1336.

2-(4-Dimethylaminophenyl)-5-(4-methoxyphenyl)-1,3-oxazole Trifluoroacetate (4Db). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.99 (s, 6H), 3.80 (s, 3H), 6.78−6.84 (m, 2H), 7.00−7.06 (m, J = 8.90 Hz, 2H), 7.52 (s, 1H), 7.67−7.73 (m, J = 8.90 Hz, 2H), 7.82−7.88 (m, J = 9.02 Hz, 2H); *m/z* (ES^+) 295 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{18}H_{19}N_2O_2$ ($[M + H]^+$) 295.1441, found 295.1444.

5-(4-Bromophenyl)-2-(4-dimethylaminophenyl)-1,3-oxazole Trifluoroacetate (4Dc). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.02 (s, 6H), 6.79−6.87 (m, 2H), 7.66−7.72 (m, 2H), 7.73−7.78 (m, 3H), 7.87−7.92 (m, 2H); *m/z* (ES^+) 343 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{16}BrN_2O$ ($[M + H]^+$) 343.0440, found 343.0457.

5-(4-Chlorophenyl)-2-(4-dimethylaminophenyl)-1,3-oxazole Trifluoroacetate (4Dd). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.01 (s, 6H), 6.79−6.86 (m, 2H), 7.51−7.57 (m, 2H), 7.75 (s, 1H), 7.78−7.84 (m, 2H), 7.85−7.93 (m, 2H); *m/z* (ES^+) 299 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{16}ClN_2O$ ($[M + H]^+$) 299.0946, found 299.0943.

2-(4-Dimethylaminophenyl)-5-(4-nitrophenyl)-1,3-oxazole Trifluoroacetate (4De). *m/z* (ES^+) 310 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{16}N_3O_3$ ($[M + H]^+$) 310.1186, found 310.1200.

2-(4-Nitrophenyl)-5-phenyl-1,3-oxazole (4Ea). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.42−7.49 (m, 1H), 7.52−7.59 (m, 2H), 7.88−7.96 (m, 2H), 8.00 (s, 1H), 8.33−8.39 (m, 2H), 8.39−8.45 (m, 2H).

5-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1,3-oxazole (4Eb). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.85 (s, 3H), 7.08−7.15 (m, 2H), 7.82−7.88 (m, 3H), 8.28−8.36 (m, 2H), 8.38−8.44 (m, 2H); *m/z* (ES^+) 297 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}N_2O_4$ ($[M + H]^+$) 297.0870, found 297.0860.

5-(4-Bromophenyl)-2-(4-nitrophenyl)-1,3-oxazole (4Ec). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.73−7.79 (m, 2H), 7.85−7.91 (m, 2H), 8.06 (s, 1H), 8.34−8.39 (m, 2H), 8.39−8.45 (m, 2H).

5-(4-Chlorophenyl)-2-(4-nitrophenyl)-1,3-oxazole (4Ed). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.57−7.65 (m, 2H), 7.89−7.99 (m, 2H), 8.03 (s, 1H), 8.33−8.38 (m, 2H), 8.38−8.43 (m, 2H).

4-Methyl-2-(4-nitrophenyl)-5-phenyl-1,3-oxazole (4Ef). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3H), 7.42−7.49 (m, 1H), 7.54−7.61 (m, 2H), 7.78−7.85 (m, 2H), 8.28−8.35 (m, 2H), 8.37−8.43 (m, 2H); *m/z* (ES^+) 281 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}N_2O_3$ ($[M + H]^+$) 281.0921, found 281.0925.

2-(4-Chlorophenyl)-5-phenyl-1,3-oxazole (4Fa). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.36−7.43 (m, J = 7.99, 7.99 Hz, 1H), 7.46−7.54 (m, 2H), 7.60−7.66 (m, J = 8.78 Hz, 2H), 7.82−7.87 (m, 3H), 8.06−8.13 (m, J = 8.90 Hz, 2H); *m/z* (ES^+) 256 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{11}ClNO$ ($[M + H]^+$) 256.0524, found 256.0522.

2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3-oxazole (4Fb). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.81 (s, 3H), 7.02−7.10 (m, J = 8.90 Hz, 2H), 7.58−7.65 (m, J = 8.78 Hz, 2H), 7.69 (s, 1H), 7.75−7.81 (m, J = 8.90 Hz, 2H), 8.03−8.11 (m, 2H); *m/z* (ES^+) 286 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}ClNO_2$ ($[M + H]^+$) 286.0629, found 286.0617.

5-(4-Bromophenyl)-2-(4-chlorophenyl)-1,3-oxazole (4Fc). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.63−7.69 (m, 2H), 7.70−7.76 (m, 2H), 7.80−7.87 (m, 2H), 7.94 (s, 1H), 8.09−8.15 (m, 2H); *m/z* (ES^+) 333 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{10}BrClNO$ ($[M + H]^+$) 333.9629, found 333.9643.

2,5-bis(4-Chlorophenyl)-1,3-oxazole (4Fd). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.55−7.61 (m, 2H), 7.61−7.66 (m, 2H), 7.86−7.91 (m, 2H), 7.91 (s, 1H), 8.08−8.14 (m, 2H); *m/z* (ES^+) 290 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{10}Cl_2NO$ ($[M + H]^+$) 290.0134, found 290.0130.

2-(4-Chlorophenyl)-4-methyl-5-phenyl-1,3-oxazole (4Ff). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.47 (s, 3H), 7.38−7.45 (m, 1H), 7.52−7.58 (m, 2H), 7.60−7.67 (m, 2H), 7.74−7.80 (m, 2H), 8.05−8.11 (m, 2H); *m/z* (ES^+) 270 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{16}H_{13}ClNO$ ($[M + H]^+$) 270.0680, found 270.0687.

5-Phenyl-2-thien-2-yl-1,3-oxazole (4Ga). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.28 (dd, 1H), 7.37−7.44 (m, 1H), 7.48−7.55 (m, 2H), 7.80 (s, 1H), 7.81−7.85 (m, 4H); *m/z* (ES^+) 228 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{13}H_{10}NOS$ ($[M + H]^+$) 228.0478, found 228.0484.

5-(4-Methoxyphenyl)-2-thien-2-yl-1,3-oxazole (4Gb). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.83 (s, 3H), 7.05−7.11 (m, 2H), 7.25 (dd, 2H), 7.64 (s, 1H), 7.72−7.77 (m, 2H), 7.78−7.82 (m, 2H); *m/z* (ES^+) 258 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{14}H_{12}NO_2S$ ($[M + H]^+$) 258.0583, found 258.0595.

5-(4-Bromophenyl)-2-thien-2-yl-1,3-oxazole (4Gc). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.28 (dd, 1H), 7.69−

7.74 (m, 2H), 7.75−7.80 (m, 2H), 7.82−7.86 (m, 2H), 7.87 (s, 1H); *m/z* (ES^+) 305 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{13}H_9BrNOS$ ($[M + H]^+$) 305.9583, found 305.9598.

5-(4-Chlorophenyl)-2-thien-2-yl-1,3-oxazole (4Gd). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.27 (dd, 1H), 7.54−7.60 (m, 2H), 7.81−7.83 (m, 4H), 7.84 (s, 1H); *m/z* (ES^+) 262 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{13}H_9ClNOS$ ($[M + H]^+$) 262.0088, found 262.0087.

5-(4-Nitrophenyl)-2-thien-2-yl-1,3-oxazole (4Ge). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.28 (dd, $J = 4.94$, 3.72 Hz, 1H), 7.87 (dd, $J = 5.00$, 1.22 Hz, 1H), 7.90 (dd, $J = 3.72$, 1.16 Hz, 1H), 8.03−8.09 (m, $J = 9.02$ Hz, 2H), 8.10 (s, 1H), 8.32−8.37 (m, $J = 9.02$ Hz, 2H).

4-[5-Phenyl)-1,3-oxazol-2-yl]pyridine Trifluoroacetate (4Ha). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.39−7.47 (m, 1H), 7.50−7.57 (m, $J = 7.56$, 7.56 Hz, 2H), 7.87−7.93 (m, $J = 9.63$ Hz, 2H), 7.98 (s, 1H), 8.03−8.08 (m, 2H), 8.76−8.82 (m, 2H); *m/z* (ES^+) 223 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{14}H_{11}N_2O$ ($[M + H]^+$) 223.0866, found 223.0877.

4-[5-(4-Methoxyphenyl)-1,3-oxazol-2-yl]pyridine Trifluoroacetate (4Hb). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.85 (s, 3H), 7.08−7.15 (m, 2H), 7.80−7.90 (m, 3H), 8.03−8.09 (m, 1H), 8.76−8.85 (m, 1H); *m/z* (ES^+) 253 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{13}N_2O_2$ ($[M + H]^+$) 253.0971, found 253.0983.

4-[5-(4-Bromophenyl)-1,3-oxazol-2-yl]pyridine Trifluoroacetate (4Hc). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.72−7.80 (m, 2H), 7.86−7.92 (m, 2H), 8.05−8.10 (m, 3H), 8.77−8.85 (m, 2H); *m/z* (ES^+) 300 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{14}H_{10}BrN_2O$ ($[M + H]^+$) 300.9971, found 300.9980.

4-[5-(4-Chlorophenyl)-1,3-oxazol-2-yl]pyridine Trifluoroacetate (4Hd). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.58−7.64 (m, 2H), 7.91−7.98 (m, 2H), 8.03 (s, 1H), 8.04−8.07 (m, 2H), 8.76−8.82 (m, 2H); *m/z* (ES^+) 257 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{14}H_{10}ClN_2O$ ($[M + H]^+$) 257.0476, found 257.0465.

2-(4-Bromophenyl)-5-phenyl-1,3-oxazole (4Ia). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.39−7.46 (m, 1H), 7.49−7.56 (m, 2H), 7.77−7.83 (m, 2H), 7.85−7.90 (m, 2H), 8.02−8.08 (m, 2H); *m/z* (ES^+) 300 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{10}BrNO$ ($[M + H]^+$) 300.0018, found 300.0029.

Via UGI 4 Component Reaction. General Procedure. UGI 4-CR. After treatment of 200 mg (calculated loading = 0.565 mmol/g, 0.113 mmol) of Rink amide resin with a solution of piperidine/DMF 20% (two cycles of 20 min each), the resin was washed and swollen in a mixture of 2 mL of DCM and 1 mL of MeOH. Then the glyoxal derivative (5 equiv), the acid (5 equiv), and the isocyanide (5 equiv) were added. The reaction was stirred at room temperature for 24 h, then the resin was filtered and washed with MeOH and DCM to afford highly functionalized intermediates.

Cyclization. As described above.

***N*-Cyclohexyl-5-methyl-2-[4-(trifluoromethyl)pyridin-3-yl]-1,3-oxazole-4-carboxamide (4Ji).** ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.99−1.94 (m, 10 H), 2.67 (s, 3H), 3.66−3.89 (m, 1H), 7.88 (d, $J = 8.41$ Hz, 1H), 8.00 (d, $J = 5.12$ Hz, 1H), 9.04 (d, $J = 5.12$ Hz, 1H), 9.33 (s, 1H); *m/z* (ES^+) 354 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{17}H_{19}F_3N_3O_2$ ($[M + H]^+$) 354.1424, found 354.1430.

***N*-Butyl-5-methyl-2-[4-(trifluoromethyl)pyridin-3-yl]-1,3-oxazole-4-carboxamide (4Jh).** ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.91 (t, 3H), 1.27−1.40 (m, 2H), 1.46−1.57 (m, 2H), 2.67 (s, 3H), 3.20−3.31 (m, 2H), 8.01 (d, 1H), 8.20 (t, 1H), 9.04 (dd, 1H), 9.31 (d, 1H); *m/z* (ES^+) 328 ($[M + H]^+$); HRMS (ES^+) calcd for $C_{15}H_{17}F_3N_3O_2$ ($[M + H]^+$) 328.1267, found 328.1264.

Synthesis of α-Amino Ketones. 2-Azido-1-phenylpropan-1-one (7f). To a solution of 2-bromo-1-phenylpropan-1-one (1 g, 4.7 mmol) in 8 mL of acetone, sodiumazide (1.5 equiv, 457 mg) was added. The mixture was stirred at room temperature for 6 h, then the solvent was removed under vacuum, and the residue was dissolved in diethyl ether and washed with water. The organic layer was dried on Na_2SO_4 and evaporated, yielding 819 mg of the title compound (99%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (d, 3H), 5.22 (q, 1H), 7.54−7.65 (m, 2H), 7.67−7.75 (m, 1H), 7.97−8.05 (m, 2H).

2-Amino-1-phenylpropan-1-one Hydrochloride (8f). To a solution of 2-azido-1-phenylpropan-1-one (799 mg, 4.56 mmol) in 5 mL of ethanol, tin(II) chloride dihydrate (2 equiv, 2.052 g) was added in one portion (*Caution: exothermic reaction; cool with water bath*). After stirring overnight at room temperature, the solvent was evaporated, and the crude product was diluted with a saturated solution of $NaHCO_3$ and filtered on Celite. The product was extracted with ethyl acetate and treated with concentrated HCl (1 mL). Evaporation under vacuum yielded 506 mg of the product (58% over two steps). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (d, 3H), 5.14 (q, 1H), 7.57−7.70 (m, 2H), 7.71−7.85 (m, 1 H), 8.02−8.14 (m, 2H), 8.32 (s, 2H).

Supporting Information Available. ^1H NMR spectra of all oxazoles **4** (crudes), and representatives of intermediates (**3Aa**, **5a**, **7f**, **8f**). Experimental details on the solid-phase Fukuyama and secondary alcohol oxidation protocols. List of CA numbers. This material is available free of charge via the Internet at http://pubs.acs.org.

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