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Selective Formation of 2-Imidazolines and 2-Substituted Oxazoles by Using a Three-Component Reaction

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Abstract: Selective formation of 2*H*-2-imidazolines and 2-substituted oxazoles by using a multicomponent reaction of amines, either aldehydes or ketones, and α-acidic isocyano amides or esters is described. By selecting the appropriate solvent, Ag^I or Cu^I catalyst, or by employing a weak Brønsted acid, the product formation can be fully controlled and directed quantitatively to the desired heterocyclic scaffold. The described experimental procedures not only significantly increase the scope of compatible inputs for this complexity-generating three-component reaction, but also allow for considerable chemical diversity: At least four diversity points in two distinct scaffolds can be exploited in this way.

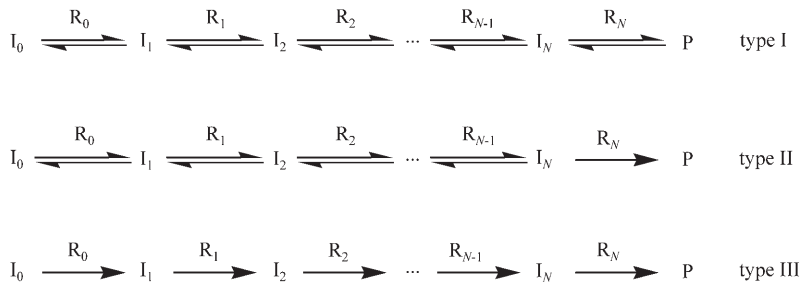
Keywords: heterocycles · imidazolines · multicomponent reactions · oxazoles · selectivity

Introduction

Multicomponent reactions (MCRs) combine at least three different substrates in one reaction flask.[1] As such, MCRs have emerged as useful and atom-efficient strategies for the rapid introduction of molecular complexity and diversity starting from rather simple building blocks.[2] Developments are fast in this area and several classes of interesting heterocycles with potential biological activities are now accessible through using MCRs.[1]

MCRs are a subclass of domino or tandem reactions and hence are one-pot sequences of two or more reactions.[3] Clearly, much of the success of such processes depends on to which extent the reactions leading to intermediate reaction products (I_1, I_2, …, I_N) and the final reaction product (P) are reversible (Scheme 1).

As already suggested by Ugi et al.,[1a] distinction can be made between three categories of MCRs. Type I MCRs are sequences of reversible reactions, whereas type II MCRs are sequences of reversible reactions that are terminated by an irreversible reaction step. Finally, type III MCRs are sequences of irreversible elementary reactions. Type I MCRs are only rarely successful, because the yield of the final product (P) strongly depends on thermodynamics. However, with type II and III MCRs thermodynamics at least favor the final reaction step and efficient product formation is possible. Most of the reported MCRs to date are of type II. It should, however, be realized that an irreversible last reaction step does not exclude the formation of side products, because all preceding reactions are equilibria and more than



Scheme 1. Type I, II, and III multicomponent reactions.[1a]

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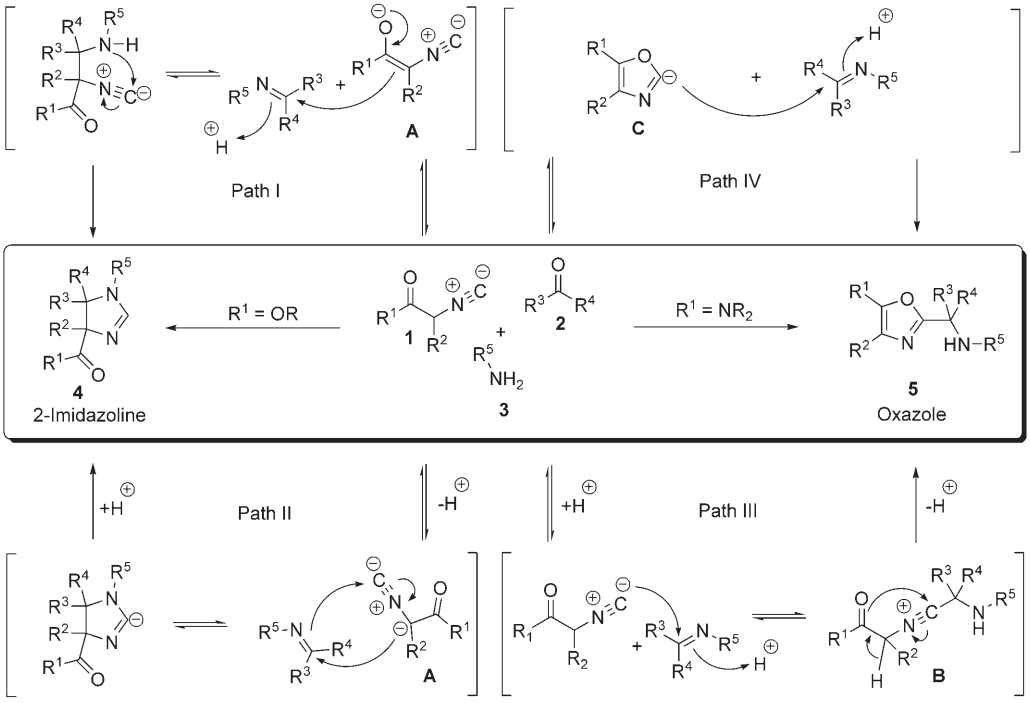
one reactive species may be present at the same time. The reactivity of the starting materials and in situ-generated intermediates may result in competitive reaction paths, and consequently, in (uncontrolled) formation of (side) products.[4] Careful optimization of the reaction conditions of type II MCRs is therefore often crucial for useful synthetic application.

Recently, we reported a flexible and easy to perform type II MCR for the formation of 2*H*-2-imidazolines[5] (**4**) starting from α-acidic isocyanides (**1**), aldehydes or ketones (**2**), and primary amines (**3**) (Scheme 2).[6] A wide variety of aldehydes and amines can be used in this MCR. Careful optimization of the reaction conditions showed that the scope of compatible isocyanides could be expanded considerably by selecting MeOH as the solvent.[5] The reaction mechanism probably involves a Mannich-type addition of deprotonated isocyanide intermediate **A** to a (protonated) imine, followed by ring closure to the heterocyclic product, and a proton shift (Scheme 2, path I). However, a concerted [2+3] cycloaddition of **A** to the imine, followed by protonation of the resulting anion (path II) cannot be excluded. The reaction rates and the scope of compatible isocyanides can be increased even further by employing a catalytic amount of AgOAc.[7] The reactions can be run at high concentration (2.0 M) without special solvent/reagent handling. The reagents can be mixed in equimolar amounts without pre-formation of the imine, which simplifies the experimental and work-up procedure. Consequently, this MCR is easily scaleable but also applicable in a combinatorial setup for the easy generation of libraries of 2*H*-2-imidazolines (**4**).[5]

In addition to the formation of 2-imidazolines (**4**), a second MCR yielding 2-substituted oxazoles[8] (**5**) and involving essentially the same components has been reported.[9] The reaction has been well studied for the use of isocyano amides, in which morpholine is typically chosen as the R^1 substituent, although other dialkylamino substituents can be used as well.[9a,d,f,j] The mechanism of this reaction presumably starts with attack of the terminal isonitrile carbon atom to the (pre-formed) imine leading to intermediate **B** followed by proton abstraction and ring closure (Scheme 2, path III).[9c,d,g,i,k] However, initial (base-promoted) ring closure (reported for the formation of 2*H*-oxazoles[10i]) followed by attack of the oxazolide anion **C** to the (protonated) imine cannot be excluded (path IV). The R^2 substituent of the isocyanide can be varied to a considerable extent (Ph, H, Me, Bn, *i*Pr) and either aldehydes or ketones can be used as the carbonyl input. In addition, the MCR tolerates both primary and secondary amines, although in the case of primary amines the isolated yields are typically somewhat lower. Again, optimization of reaction conditions appeared crucial for optimal performance. Toluene and MeOH were found to be excellent solvents, and the MCR can be accelerated by using weak Brønsted acids like NH_4Cl, pyridine·HCl, or Et_3N·HCl. Also in this reaction the substrates can be mixed in equimolar amounts to simplify the work-up procedure.[9b]

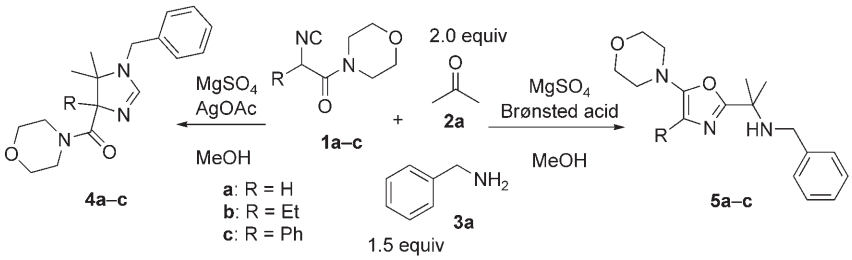
Recently, Zhu and co-workers reported that the MCR towards formation of oxazoles (**5**) can also be performed by using an isocyano ester with a strongly electron-withdrawing group at the α position (Scheme 2; R^1 = OMe, R^2 = *p*-NO_2–



Scheme 2. Possible reaction paths for the MCR between amines, either aldehydes or ketones, and α-acidic isocyanides, which leads to either 2-imidazolines or oxazoles.

Ph).[9k] Although isocyano esters are substrates that typically yield 2-imidazolines (**4**),[5,6] a wide variety of aldehydes and amines were used in this MCR to afford the corresponding 5-methoxyoxazoles in moderate to excellent yields.

The results reported by Zhu, as well as those reported by us, clearly indicate that several reaction pathways are available for the same type of substrates and that the reaction path that is followed cannot be correlated to the class of isocyanide used. This observation led us to believe that it is possible to control and direct the outcome of the MCR between α-acidic isocyanides, (primary) amines, and either aldehydes or ketones. We envisioned that by carefully tuning the reaction conditions, either the 2*H*-2-imidazolines (**4**) or 2-substituted oxazoles (**5**) could be formed selectively and in good yields. Here, we describe in detail our efforts to control and direct the three-component reaction (3-CR). The tuning of conditions is based on the mechanistic considerations as summarized in Scheme 2, which evolves from all the available experimental data for both imidazoline and oxazole formation by means of this 3-CR. In addition, the following considerations and observations are also crucial for understanding the setup of the studies reported in this paper: 1) 2-Imidazoline formation is stimulated by the addition of an Ag^I salt, such as AgOAc, because the MCR is accelerated due to an increased concentration of the (silver-coordinated) isocyanide anion **A** (Scheme 2, paths I and II).[7] Furthermore, when path III is considered, AgOAc may block oxazole formation by coordination of the isocyanide carbon atom to Ag^I, thus reducing its nucleophilicity.[11] 2) Oxazole formation is accelerated by addition of a weak Brønsted acid, which activates the imine.[9b] In addition, the slight decrease in pH of the reaction medium will probably lower the concentration of deprotonated isocyanide anion **A**, which may favor reaction path III (Scheme 2).



Scheme 3. Course of the MCR using AgOAc or a Brønsted acid.

The 3-CR employing isocyano amides: All reactions were performed in MeOH at room temperature with the isocyano amide (**1a–c**; 0.2 M concentration), compounds **2a** and **3a**, and in the presence of $MgSO_4$ (Scheme 3). The first experiment, in which the glycine-derived isocyano amide **1a** (R = H) was employed, already showed formation of a nearly 1:1 mixture of 2-imidazoline **4a** and oxazole **5a** (Table 1, entry 1), which indicated that oxazole and 2-imidazoline formation occur simultaneously. The conversion was increased when the reaction was run at 60 °C (entry 2), without affecting the product ratio. In agreement with our concept, addition of a catalytic amount (2 mol %) of AgOAc resulted in a significantly increased product ratio in favor of 2-imidazoline (97:3, entry 3). By increasing the catalyst loading to 5 mol %, 2-imidazoline **4a** was formed nearly quantitatively after 4 h (entry 4). Formation of oxazole **5a** was not observed at all upon slow addition of isocyanide **1a** over 21 h, thus allowing the isolation of **4a** in 91 % yield (entry 5).

As discussed above, running the 3-CR in the presence of a weak Brønsted acid should favor oxazole formation. Indeed, when the condensation between **1a**, **2a**, and **3a** was performed in the presence of two equivalents of NH_4Cl, quantitative conversion of isocyanide **1a** was observed after 22 h (entry 6) and no traces of 2-imidazoline **4a** were detected in the crude reaction mixture. Although the formation of **4a** was not observed, the ^1H NMR spectrum of the crude mixture did indicate the presence of many (unidentified)

Results and Discussion

To obtain comparable data for our studies to control and direct the 3-CR towards selective formation of either the 2-imidazoline or the 2-substituted oxazole, test systems were selected in which only the type of isocyanide (**1**) was varied. The oxo and amine components (acetone (**2a**) and benzylamine (**3a**), respectively) were kept the same in all reactions.

Table 1. Optimization of conditions to direct the MCR of either isocyanide **1a** or **1b** with **2a** and **3a**.[a]

Entry	**1**	Promoter	*T* [°C]/Time	Conversion [%]	[**4**/**5**]	Isolated yield [%]
1	**1a**	none	RT/3 d	54	[48:52]	
2	**1a**	none	60/22 h	100	[46:54]	
3	**1a**	AgOAc (2 mol %)	RT/22 h	100	[97:03]	
4	**1a**	AgOAc (5 mol %)	RT/4 h	100	[99:01]	
5[b]	**1a**	AgOAc (2 mol %)	RT/22 h	100	[100:0]	91 (**4a**)
6	**1a**	NH_4Cl (2.0 equiv)	RT/22 h	100[c]	[0:100]	
7	**1a**	NH_4Cl (2.0 equiv)	60/2 h	100[c]	[0:100]	
8[d]	**1a**	NH_4Cl (2.0 equiv)	60/22 h	48	[29:71]	
9	**1a**	Et_3N·HCl (2.0 equiv)	60/5 h	100[c]	[0:100]	
10	**1b**	none	RT/2 d	n.d.[c]	[0:100]	
11	**1b**	AgOAc (2 mol %)	RT/4 d	0		
12	**1b**	AgOAc (2 mol %)	60/24 h	n.d.[c]	[0:100]	
13	**1b**	Et_3N·HCl (1.0 equiv)	60/5 h	100[c]	[0:100]	49 (**5b**)

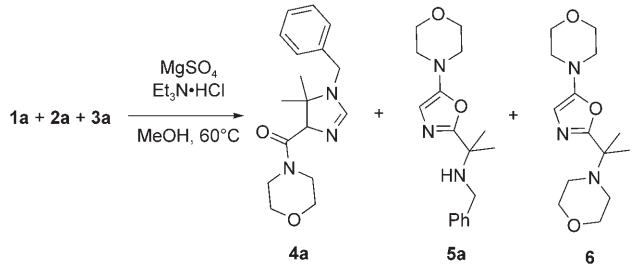
[a] Reactions were performed in MeOH at RT on a 1.0 mmol scale (0.2 M of **1a** or **1b**). Conversions and product ratios were determined by ^1H NMR spectroscopy. [b] The isocyanide was added over 21 h, followed by 1 h additional reaction time. [c] Unidentified side products detected. [d] Reaction performed in toluene.

side products. Performing the same reaction at 60 °C increased the reaction rate (entry 7), but did not result in a cleaner reaction. When toluene was used as the solvent instead of MeOH, the side products were not detected. However, the slow conversion (48 % after 22 h) and, more importantly, the detection of imidazoline **4a**, indicated that we were not tuning the conditions in the desired direction (entry 8). In this reaction NH_3 may react as the amine component instead of **3a** and in this way interfere with the MCR.[12] To exclude this possibility we decided to follow the conditions described earlier by Zhu, by employing $Et_3N{\cdot}HCl$ as the Brønsted acid.[9] In this case, again, the product formation was found to be entirely in favor of the oxazole (entry 9). However, the MCR suffered from another side product, that is, oxazole **6** (11 % isolated yield, Table 2). Apparently, morpholine was partially liberated, most likely through transamidation of the isocyanide,[13] and reacted in the 3-CR instead of benzylamine (**3a**). The overall conversion of **1a** is independent of the amount of Brønsted acid used (Table 2), but the amount of **6** relative to **5a** decreases when less of the Brønsted acid is used. However, by using substoichiometric amounts of $Et_3N{\cdot}HCl$, 2-imidazoline **4a** can be detected in the crude reaction mixture (Table 2, entries 3 and 4). Under optimized conditions, that is, heating the substrates at 60 °C for 5 h in the presence of one equivalent of $Et_3N{\cdot}HCl$, the desired oxazole **5a** could be isolated in a very respectable 73 % yield (Table 2, entry 2). In conclusion, with this set of inputs it is possible to control and direct the 3-CR to an acceptable extent and selectively access either 2-imidazoline **4a** or oxazole **5a**.

Encouraged by these initial results we decided to investigate the influence of electron-donating versus electron-withdrawing α substituents (R) in the isocyanide input on the outcome of the 3-CR. First, the behavior of isocyanide **1b** with an electron-donating group (R = Et) was studied. When **1b** was stirred with **2a** and **3a** in the absence of a promoter (AgOAc or $Et_3N{\cdot}HCl$) only the corresponding oxazole **5b** could be identified while considerable amounts of unidentified (side) products were detected as well (Table 1, entry 10). When the same reaction was performed in the presence of AgOAc (2 mol %), no reaction could be observed at all after stirring for four days (entry 11). Only the corresponding imine and unreacted **1b** were detected, which suggests that indeed reaction path III (Scheme 2) is followed. Heating the reaction mixture at 60 °C immediately resulted in the formation of a black metallic precipitate most likely originating from AgOAc. Consequently, the same results were obtained as those for the reaction run in the absence of promoter (entries 12 and 10, respectively). On the other hand, when the 3-CR between **1b**, **2a**, and **3a** was performed in the presence of one equivalent of $Et_3N{\cdot}HCl$ as reported above, formation of **5b** was relatively clean (entry 13, isolated yield 49 %).

These results suggest that the 3-CR of isocyano amides with an electron-donating group at the α-carbon atom, benzylamine (**3a**), and acetone (**2a**) can be directed towards oxazoles in a straightforward procedure but not to 2-imidazolines. Next, we investigated the use of isocyanide **1c**, which has an electron-withdrawing phenyl group at the α position. Stirring the components (**1c**, **2a**, and **3a**) for two days under the standard conditions resulted in a 10:90 product mixture in favor of oxazole **5c** (Table 3, entry 1). When this reaction was performed under the optimized conditions as described for the 3-CR of **1a**, **2a**, and **3a** (1 equiv $Et_3N{\cdot}HCl$; see above), product formation was complete within 5 h and oxazole **5c** was the sole product observed, which allowed its isolation in 56 % yield (entry 2). On the other hand, when the same reaction was performed in the presence of 2 mol % AgOAc, formation of 2-imidazoline increased to 19 %. However, the major product formed was not **5c** but rather 2*H*-oxazole **7** (entry 3). This product is most likely formed by coordination of **1c** to Ag^I followed by loss of the α proton and intramolecular attack of the carbonyl oxygen to the (silver-coordinated) isocyanide carbon atom (Scheme 4).[7] This reaction path is clearly catalyst controlled, since increasing the amount of AgOAc had a negative effect on the 2-imidazoline formation (**4c**/**7** 8:92,

Table 2. Influence of the amount of $Et_3N{\cdot}HCl$ on the ratio of products formed from the 3-CR between isocyanide **1a** with **2a** and **3a**.[a]



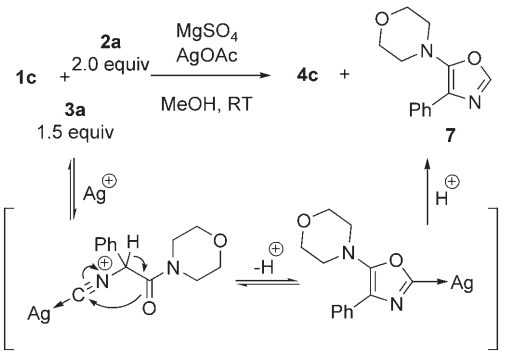
Entry	$Et_3N{\cdot}HCl$ [equiv]	$t = 6.5$ h Conv. [%]	[**4a**/**5a**/**6**]	$t = 20$ h Conv. [%]	[**4a**/**5a**/**6**]	Isolated yield [%]
1	2.0	66	[00:89:11]	100	[00:62:38]	
2	1.0	63	[00:92:08]	100	[00:73:27]	73 (**5a**) 11 (**6**)
3	0.5	63	[07:89:04]	100	[11:73:16]	
4	0.25	60	[15:83:02]	96	[16:73:11]	

[a] Reactions were performed in MeOH at RT in equimolar substrate ratios on a 1.0 mmol scale (0.2 M). Conversions (Conv.) and product ratios were determined by ^1H NMR spectroscopy.

Table 3. Optimization of conditions to direct the MCR using isocyanide **1c** with **2a** and **3a**.[a]

Entry	Promoter	Time	Conv. [%]	[**7**/**4c**/**5c**]	Isolated yield [%]
1	none	2 d	63	[0:10:90]	
2[b]	$Et_3N{\cdot}HCl$ (1 equiv)	5 h	100	[0:0:100]	56 (**5c**)
3	AgOAc (2 mol %)	21 h	100	[81:19:0]	65 (**7**)
4	AgOAc (10 mol %)	21 h	100	[92:08:0]	
5[c]	AgOAc (1 mol %)	6.5 h	100	[64:36:0]	
6[c]	CuI (2 mol %)	4 d	100	[0:72:28]	60 (**4c**)

[a] Reactions were performed in MeOH at RT on a 1.0 mmol scale (0.2 M of **1c**). Conversions and product ratios were determined by ^1H NMR spectroscopy. [b] Reaction performed at 60 °C. [c] Reaction performed at 2.0 M concentration.



Scheme 4. Ag^I-catalyzed formation of 2*H*-oxazole **7** in an MCR between **1c**, **2a**, and **3a**.

entry 4). On the other hand, increasing the overall concentration of the reaction mixture to 2.0 M in combination with decreasing the catalyst loading to 1 mol% facilitated imidazoline formation (entry 5), although oxazole **7** remained the major product.

The use of counterions other than $^-$OAc for the Ag^I catalyst generally had only a minor influence on the product ratio between **4c**, **5c**, and **7** (Figure 1). With PF_6^-, Br^-, Cl^-, BPh_4^-, and I^- as counterions for Ag^I, 2-imidazoline **4c** (gray bars) could be detected in higher relative amounts than that found when using $^-$OAc, although the overall reaction time to reach completion increased in some cases (AgI: 64% conversion after 21 h). The only trend that could be observed is that larger anions like BPh_4^- and I^- tend to give less of the undesired oxazole **7** (black bars). A possible rationalization for this observation is that larger anions increase the steric bulk around the terminal isocyanide carbon atom, thus leading to less facile intramolecular ring closure through attack of the carbonyl oxygen atom. Consequently, oxazole formation is less favored. When other Group 14 metal salts were used in the 3-CR, 2*H*-oxazole **7** was not formed at all. For example, performing the reaction in the presence of 2 mol% AuCl·THT (THT: tetrahydrothiophene) or $AuCl{\cdot}SMe_2$ resulted in the rather slow formation of a 1:1 mixture of **4c** and **5c** (Figure 1, 63 and 74% after 3 d, respectively). When the amount of Au^I catalyst was increased to 10 mol%, quantitative conversion of **1c** was observed in 21 h. However, oxazole **5c** was the major product (**4c**/**5c** 30:70), which indicated that the MCR towards formation of oxazoles might also be facilitated by this Au^I salt.[14a] On the other hand, the relative amount of 2-imidazoline **4c** increased when Cu^I salts were used as the catalyst.[14b] Again, the size of the anion is important for the ratio in which **4c** is formed. On the basis of these conditions we were able to isolate **4c** in 60% yield by increasing the overall reaction concentration to 2.0 M and stirring the reaction mixture for four days in the presence of 2 mol% CuI (Table 3, entry 6).

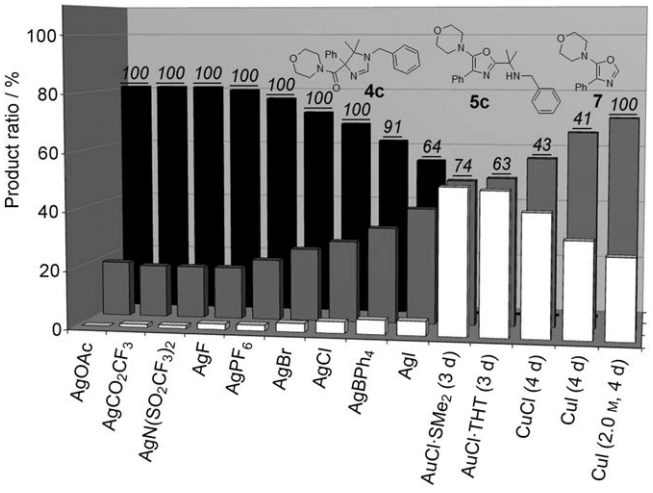
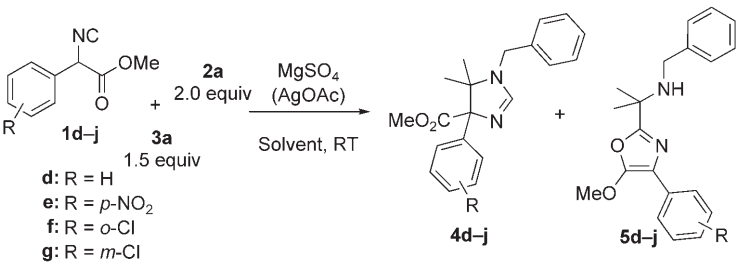


Figure 1. Metal salt versus product ratio and conversion (after 21 h, numbers in italics [%]) for the MCR between acetone (**2a**), benzylamine (**3a**), and isocyanide **1c**. The white bars show data for oxazole **5c**, gray bars show data for imidazole **4c**, and black bars show data for oxazole **7**.

The 3-CR employing α-aryl isocyano esters: Although the above results demonstrate that careful tuning of the reaction conditions allows control over the course of the 3-CR when isocyano amides **1a–c** are used, the frequent formation of side products hampers straightforward application towards selective formation of either 2-imidazolines (**4**) or 2-substituted oxazoles (**5**). We turned our attention to the use of α-aryl-substituted isocyano esters **1d–j** in the 3-CR (Scheme 5). As mentioned in the introduction, so far isocyano esters have been reported to selectively produce 2-imidazolines (**4**),[5,6] the only notable exception being α-(*p*-nitrophenyl)-α-isocyanoacetate (**1e**), which was found to undergo the MCR leading to the corresponding 5-methoxyoxazoles.[9k] Stirring isocyanide **1d** (R = H) with acetone (**2a**) and benzylamine (**3a**) in the absence of promoter and under the same general conditions as described for **1a–c** resulted in the formation of a 14:86 mixture of 2-imidazoline **4d** and oxazole **5d**, respectively (Table 4, entry 1). Encouraged by this initial result, which indicates that the scope for the 3-CR towards 5-methoxyoxazole formation can be expanded with respect to the isocyanide and carbonyl inputs,[15] we further optimized the conditions towards selective formation of the oxazoles. However, no major influence on either the product ratio or the reaction rate could be observed in the presence of one equivalent of $Et_3N{\cdot}HCl$ (Table 4, entry 2).



Scheme 5. MCRs using α-phenyl isocyano esters **1d–j**.

Table 4. Screening for optimal solvents for the MCR of isocyanide **1d** (R = H) with **2a** and **3a**.[a]

Entry	Solvent	*t* [h]	Conv. [%]	[**4d**/**5d**]	Isolated yield [%]
1	MeOH	24	100	[14:86]	
2[b]	MeOH	24	100	[11:89]	
3	CH_2Cl_2	20	60	[0:100]	
4	toluene	20	83	[0:100]	
5	MeCN	20	100	[0:100]	
6	DMF	4	100	[0:100]	59 (**5d**)
7[c]	MeOH	22	100	[100:0]	65 (**4d**)

[a] Reactions were performed at RT on 1.0 mmol scale (0.2 M of **1d**). Conversions and product ratios were determined by ^{1}H NMR spectroscopy. [b] 1 equiv Et_3N·HCl added. [c] 2 mol% AgOAc used as catalyst; isocyanide **1d** added as a 1 M solution over 21 h, followed by 1 h additional reaction time.

From our earlier work it became clear that the 2-imidazoline 3-CR is relatively fast in protic polar solvents.[5] Thus, changing the reaction medium from MeOH to any aprotic solvent would retard the 2-imidazoline formation, and may favor formation of 5-methoxyoxazoles. This approach indeed proved successful. When the reaction between **1d**, **2a**, and **3a** was run in either polar (MeCN and DMF) or apolar (CH_2Cl_2 and toluene) aprotic solvents instead of MeOH, the corresponding oxazole **5d** was the sole product detected (Table 4, entries 3–6). The reaction rate was strongly dependent on the solvent used. For example, when CH_2Cl_2 or toluene was used, the isocyanide substrate **1d** could still be detected in the reaction mixture after 20 h (60 and 83% conversion, respectively, entries 3 and 4), whereas in MeCN full conversion was observed (entry 5). DMF proved to be the solvent of choice, and led to the complete conversion of **1d** to oxazole **5d** within four hours (entry 6, 59% isolated yield). As reported by us earlier,[6b] 2-imidazoline **4d** is formed selectively by performing the reaction in the presence of AgOAc (Table 4, entry 7, 65% isolated yield). In conclusion, the course of the 3-CR depends critically on the solvent used. By carefully selecting the right solvent and promoter, complete control towards either 2-imidazoline or 5-methoxyoxazole formation can be achieved.

The pK_a of the α proton in the isocyanide inputs is believed to be of critical importance[6b] and, most likely, governs the reaction path of the 3-CR and, consequently, the ratio in which the products are formed. To investigate the extent to which the electronic properties of the R group in the α-aryl isocyano esters determines the course of the 3-CR, six additional α-aryl isocyano esters (**1e–j**, Scheme 5) were studied. For each isocyanide the 3-CR was performed under three different reaction conditions. First, the standard conditions in the absence of promoter (method A, Figure 2) were employed, which usually give mixtures of the corresponding 2-imidazolines (**4d–j**) and oxazoles (**5d–j**). Then, conditions for each isocyanide were selected that should selectively produce either the 2-imidazoline or the oxazole (methods B and C, respectively, Table 5).

As expected, the ratio in which **4d–j** (Figure 2, black bars) and **5d–j** (Figure 2, white bars) are formed in the absence of promoter (method A) is clearly governed by the

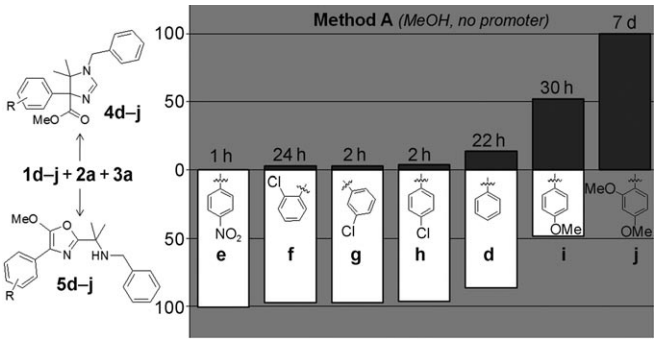


Figure 2. Reaction time and product ratio **4d–j**/**5d–j** (black and white bars, respectively), influenced by the pK_a of the α proton in the α-phenyl isocyano esters (**1d–j**) using reaction method A (MeOH, in the absence of a promoter).

Table 5. Applying optimal conditions for directing the 3-CR to either 2-imidazoline (method B) or oxazole (method C) formation using α-aryl isocyano esters **1e–j**.[a]

Entry	**1**	Method B[b]			Method C[c]	
		[**4**/**5**]	Isolated yield [%]	Time	[**4**/**5**]	Isolated yield [%]
1[d]	**1e**	[81:19]		0.5 h	[0:100]	62 (**5e**)
2[d,e]	**1e**	[100:0]	72 (**4e**)			
3	**1f**	[40:60][f]		11 h	[0:100]	59 (**5f**)
4[e]	**1f**	[45:55][g]	25 (**4f**)			
5	**1g**	[100:0]	n.d.	2 h	[0:100]	48 (**5g**)
6	**1h**	[100:0]	67 (**4h**)	2 h	[0:100]	57 (**5h**)
7	**1i**	[100:0]	75 (**4i**)	8 h	[0:100]	64 (**5i**)
8	**1j**	[100:0][h]	87 (**4j**)	7 d	no reaction observed	

[a] Reactions were performed on a 1.0 mmol scale (0.2 M of **1e–j**). Conversions and product ratios were determined by ^{1}H NMR spectroscopy. [b] MeOH used as solvent; 2 mol% AgOAc added as catalyst; isocyanides were added as a 1 M solution in MeOH over 21 h, followed by 1 h additional reaction time. [c] DMF used as solvent. [d] **1e** was added as a 1 M solution in CH_2Cl_2 due to its poor solubility in MeOH. [e] 5 mol% AgOAc. [f] 55% conversion. [g] 79% conversion. [h] 52% conversion after 22 h; 48 h total reaction time.

electronic nature of the R substituent(s) present on the α-aryl group of **1**. When **1e** (R = *p*-NO_2) was combined with **2a** and **3a** the product ratio was found to be entirely in favor of oxazole **5e** (Figure 2, [0:100]). The same conditions but now using an isocyano ester with a chloro substituent at the *ortho*, *meta*, or *para* position (**1f–h**) still predominantly gave the corresponding oxazoles (**5f–h**), but minor amounts of the 2-imidazolines (**4f–h**) could be detected in the reaction mixture as well (2–3%, black bars). As discussed above, when **1d** (R = H) was employed under identical conditions, the corresponding oxazole was still the major product formed (**4d**/**5d** 14:86). However, when the α-aryl group was equipped with electron-donating R groups (**1i**, **1j**) the 3-CR (in the absence of promoter) favored formation of 2-imidazoline (Figure 2). Thus, one-pot reaction of **1i** (R = *p*-OMe), **2a**, and **3a** in MeOH gave a 52:48 mixture of **4i** and **5i**, respectively. This ratio completely turned in favor of the corresponding 2-imidazoline (**4j**) when **1j** (R = *o*,*p*-$(OMe)_2$) was employed as the isocyanide input. The electronic nature

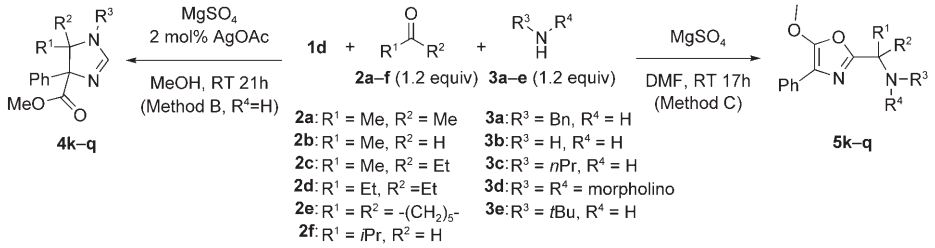
of the R substituent in **1d–j** not only has a profound influence on the observed product ratios, but also has a clear effect on the reaction rates. By using method A, the MCR with **1e** (R = *p*-NO_2) was complete within one hour, whereas with **1j** (R = *o*,*p*-$(OMe)_2$) only 45% conversion was reached after seven days (all other reactions reached completion within the time shown). It should, however, be noted that besides the pK_a of the α proton, the extended reaction times may also be attributed to steric congestion due to *ortho* substitution at the α-phenyl ring of some of the isocyanides used. This is supported by the observation that the 3-CR of **1f**, **2a**, and **3a** proceeds much slower under the standard conditions than the same reaction using **1g** or **1h** (Figure 2).

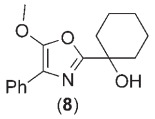
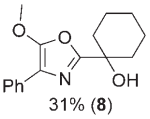
In most cases the course of the 3-CR could be directed completely to 2-imidazoline (**4e–j**) by slow addition of the α-aryl isocyano ester (**1e–j**) to a mixture of **2a** and **3a** in MeOH in the presence of 2 mol% AgOAc (Table 5, method B).[16] In some cases 5 mol% AgOAc was required to selectively produce the 2-imidazoline (entry 2). A notable exception is the selective formation of **4f**, which could not be achieved. It appears that the relatively large *o*-Cl substituent in **1f** makes the nucleophilic attack of the deprotonated α-carbon atom in **1f** more difficult (Scheme 2, paths I and II), which hampers selective formation of **4f**. Even with the use of 5 mol% AgOAc, imidazoline **4f** was only formed as the minor product (entry 4). In most cases, however, the isolated yields are typical for 2-imidazolines (67–87%).[5,6]

When the reactions of **1e–i** with **2a** and **3a** were performed in DMF (Table 5, method C) the corresponding oxazoles **5e–i** were formed quantitatively. Typically, the conversion of the isocyanides proceeds twice as fast in this polar aprotic solvent than the reactions performed in MeOH (method A, Figure 2). The isolated yields reported for **5e–i** (entries 1, 3, 5, 6 and 7) are typical and comparable to yields reported by Zhu et al. for similar reactions employing primary amines (48–62%).[9] It should be noted that reaction of isocyanide **1j** with **2a** and **3a** in DMF did not take place at all. Because formation of intermediate **B** (Scheme 2, path III) through nucleophilic attack of the terminal NC carbon atom on the imine should be easy in the case of isocyanide **1j**, this result might indicate that MeOH and/or Ag^I catalysis is essential for abstraction of the α proton.

Influence of the imine on the course of the 3-CR: From the experimental data presented in the previous sections, it is clear that judicious selection of the reaction conditions offers full control over the course of the 3-CR towards either 2-imidazoline or oxazole products from the same starting materials. For full control, the steric and electronic properties of the isocyanide used are of major importance. However a clear influence of the in situ-generated imine is observed as well. For a number of different imines (generated from **2a–f** and **3a–e**, Table 6) in combination with isocyano ester **1d** we studied the outcome of the 3-CR under optimal conditions as described above for 2-imidazoline formation (method B) and for 5-methoxyoxazole formation (method C). When **1d**, benzylamine, and a series of carbonyl components with increasingly sterically demanding substituents R^1 and R^2 were allowed to react under the conditions of method B (AgOAc, MeOH), formation of the corresponding 2-imidazolines (**4d**,**k**,**l**,**m**) decreased gradually (Table 6, entries 1–4). However, when the same reactions were performed in DMF (method C), 5-methoxyoxazole (**5d**,**k**,**l**,**m**) formation increased with larger R^1 and R^2 substituents in the oxo component (Table 6, entries 1–4). The same trend was observed when the steric constraints of the amine component **3** were increased (entries 5–8). The reaction of **1d**, cyclohexanone (**2e**), and the smallest possible amine, ammonia (**3b**), could be fully directed to either the formation of 2-imidazoline **4n** or oxazole **5n** (using method B and C, respectively; entry 5). However, under the condi-

Table 6. Influence of the carbonyl and amine components on the 3-CR with isocyano ester **1d**.[a]



Entry	R^1	R^2	R^3	R^4	Method B[b] [**4**/**5**]	Method B[b] Isolated yield [%]	Method C[c] [**4**/**5**]	Method C[c] Isolated yield [%]
1[d]	Me	H	Bn	H	[100:0]	89 (**4k**)	[100:0]	0 (**5k**)
2	Me	Me	Bn	H	[100:0]	65 (**4d**)	[0:100]	59 (**5d**)
3	Me	Et	Bn	H	[31:69]	16 (**4l**)	[0:100]	53 (**5l**)
4	Et	Et	Bn	H	[0:100]	0 (**4m**)	[0:100]	49 (**5m**)
5[e]	$-(CH_2)_5-$		H	H	[100:0]	63 (**4n**)	[0:100]	69 (**5n**)
6	$-(CH_2)_5-$		*n*Pr	H	[0:100]	0 (**4o**)	[0:100]	63 (**5o**)
7	$-(CH_2)_5-$		morpholino		[0:100]	0 (**4p**)	[0:100]	61 (**5p**)
8	$-(CH_2)_5-$		*t*Bu	H	[00:00][f]	 (**8**)	[00:00]	 31% (**8**)
9	*i*Pr	H	*t*Bu	H	[46:54]	26 (**4q**)	[0:100]	59 (**5q**)

[a] Reactions were performed on a 1.0 mmol scale (0.5 M of **1d**). Product ratios were determined by ^{1}H NMR spectroscopy. [b] MeOH used as solvent, 2 mol% AgOAc added as catalyst, and isocyanide added as a 1 M solution in MeOH over 21 h (0.33 M), followed by 1 h additional reaction time. [c] DMF used as solvent. [d] 2.0 equiv acetaldehyde used. [e] NH_4Cl (2 mmol) used as amine component in combination with Et_3N (2.0 mmol). [f] 50% conversion.

tions optimized for initial attack of the α-carbon atom of the isocyanide to the imine (Scheme 2, paths I and II), only oxazole formation was observed by using amine inputs that were more sterically demanding. Thus, combination of **1d**, cyclohexanone (**2e**), and either *n*-propylamine (**3c**) or benzylamine (**3a**) led to the sole formation of **5o** and **5p** (entries 6 and 7, respectively). When the steric constraints were further increased (*t*-butylamine, entry 8) even the corresponding 5-methoxyoxazole product was not formed. Instead, as reported by Zhu et al.,[9k,17] 2-(hydroxyalkyl)-5-methoxyoxazole (**8**) was obtained as the major product. Even prolonged stirring of cyclohexanone and *t*-butylamine in the presence of 3 Å molecular sieves before addition of the isocyanide only resulted in the formation of **8** as judged by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. However, application of *t*-butylamine as a bulky amine input is tolerated in the 3-CR for both 2-imidazoline and oxazole formation when a less sterically demanding carbonyl component is used (entry 9).[6b]

Clearly, imines with relatively small substituents give the corresponding 2-imidazolines under the conditions of method B, whereas imines that are more sterically demanding tend to give the corresponding oxazoles under the conditions of method C. This is in agreement with the reaction pathways shown in Scheme 2. For 2-imidazoline formation, the α-carbon atom of the isocyanide is most likely involved in the initial reaction step (paths I and II), whereas for oxazole formation the terminal isocyanide carbon atom is believed to react first (path III). With imines that are more sterically demanding the α-carbon atom of the isocyanide, which is sterically less accessible, cannot effectively approach the imine sp^2-carbon atom, which results in decreased formation of the imidazoline and favors oxazole formation by means of direct attack of the terminal isocyanide carbon atom.

Conclusion

Judicious selection of the reaction conditions for the 3-CR between amines, either α-isocyano esters or amides, and either aldehydes or ketones results in selective formation of either 2-imidazolines or oxazoles. The range of compatible isocyanides for the MCR that leads to imidazolines has been expanded to include the use of isocyano amides, whereas the range of compatible isocyanides for 5-methoxyoxazole formation has been expanded to include a wider range of α-aryl isocyano esters. Under standard reaction conditions using MeOH (method A), competitive formation of 2-imidazolines and oxazoles is often observed. The reaction path followed seems to be mainly governed by two factors: 1) the relative ease of α-proton abstraction in the isocyanide input and 2) the steric constraints of both the isocyanide and the in situ-generated imine. α-Aryl isocyano esters bearing electron-withdrawing substituents favor oxazole formation due to stabilization of the α-anionic species (**A**). On the other hand, electron-donating substituents favor imidazoline formation because of the higher nucleophilicity of the α anion in the deprotonated isocyanide. Obviously, the C–C bond formation between two quaternary carbon atoms is strongly influenced by steric bulk around the isocyanide and imine. Consequently, preference for oxazole formation increases with the application of inputs that are more sterically demanding. However, for a synthetically useful range of reactant combinations, the 3-CR can be completely directed towards either imidazoline or oxazole formation by selecting the appropriate conditions. Thus, Ag^I (or Cu^I) catalysis produces 2-imidazolines, and application of a Brønsted acid and/or use of an aprotic solvent selectively provides the corresponding oxazoles. The described experimental procedures not only significantly increase the scope of compatible inputs for this complexity-generating 3-CR, but also allows considerable chemical diversity to be addressed: At least four diversity points in two distinct scaffolds can be exploited.

Experimental Section

General: Unless stated otherwise, all solvents and commercially available reagents were used as purchased (without any further purification). Slow additions were performed by using a New Era NE-1800 multisyringe pump. Melting points were measured by using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with neat samples on KBr tablets by using a Matteson Instrument 6030 Galaxy Series FTIR spectrophotometer. ^{1}H and ^{13}C (attached proton test) NMR spectra were recorded on a Bruker Avance 400 (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) or a Bruker Avance 250 (250.13 MHz for ^{1}H and 62.90 MHz for ^{13}C) spectrometer using $CHCl_3$ as the internal standard (^{1}H: $\delta = 7.26$ ppm; ^{13}C{^{1}H}: $\delta = 77.0$ ppm). Fast atom bombardment (FAB) mass spectrometry was carried out using a JEOL JMS SX/SX 102A four-sector mass spectrometer, coupled to a JEOL MS-MP9021D/UPD system program (samples were loaded in a matrix solution (3-nitrobenzyl alcohol) onto a stainless-steel probe and bombarded with xenon atoms (3 KeV)). Electron impact (EI) mass spectrometry was carried out using a Finnigan MAT900 spectrometer (electron ionization voltage 70 eV). Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and Merck 90 standardized Al_2O_3 (activity II–III, particle size 0.063–0.200 mm, 70–230 mesh ASTM) or Silicycle Silia-P flash silica gel (particle size 40–63 μm, pore diameter 60 Å). Thin-layer chromatography was performed using TLC plates from Merck (Al_2O_3, 60 F254 on aluminum with fluorescence indicator or silica gel, Kieselgel 60 F254 neutral, on aluminum with fluorescence indicator). Compounds on TLC were visualized by using UV light. Isocyanides **1a**,[18] **1b**,[18b] **1c**,[19] **1d**,[6a] and **1e**[9k] were synthesized according to literature procedures.

General procedure 1—Screening of reaction conditions: Unless stated otherwise, a 10 mL reaction vial was charged with isocyanide **1a–d** (1.0 mmol), the appropriate solvent (5.0 mL), $MgSO_4$ (100 mg), benzylamine (**3a**; 162 μL, 160 mg, 1.5 mmol), acetone (**2a**; 150 μL, 118 mg, 2.0 mmol), and reported promoter. Reactions were performed at RT and aliquots (100 μL) were taken, until the given time or full conversion of the isocyanide. Samples were analyzed by using ^{1}H NMR ($CDCl_3$) spectroscopy after filtration and evaporation of the sample to dryness.

General procedure 2—Synthesis of the α-phenyl isocyano esters: Isocyano esters **1f–j** were synthesized from their corresponding amino acids in three steps following our previously reported procedure.[5]

*Methyl 2-(o-chlorophenyl)-2-isocyanoacetate (**1f**)*: General procedure 2 was followed using (±)-2-chlorophenylglycine (10.0 g, 53.8 mmol) to give **1f** as a clear red oil (6.99 g, 33.4 mmol, 62%). Purification was performed by means of column chromatography (silica gel, EtOAc/cyclohex-

ane 1:2, $R_f = 0.59$). ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.59$–7.57 (m, 1H), 7.46–7.44 (m, 1H), 7.39–7.36 (m, 2H), 5.85 (s, 1H), 3.82 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): $\delta = 165.4$ (C), 161.6 (C), 133.1 (C), 130.9 (CH), 130.3 (C), 130.1 (CH), 128.6 (CH), 127.8 (CH), 57.1 (CH), 53.9 ppm (CH_3); IR (KBr): $\tilde{\nu} = 2146$ (s), 1759 (s), 1477 (m), 1437 (m), 1433 (m), 1223 (s), 1033 cm^{-1} (m); MS (FAB, 3 KeV): *m/z* (%): 210 (18) $[M+H]^+$, 183 (100) $[M-NC]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{10}H_9ClNO_2$ $[M+H]^+$: 210.0322; found: 210.0318.

*Methyl 2-(*m*-chlorophenyl)-2-isocyanoacetate (**1g**)*: General procedure 2 was followed using (±)-3-chlorophenylglycine[20] (4.85 g, 21.2 mmol) to give **1g**, after 1 h of stirring at 0 °C, as a dark red oil (0.76 g, 3.6 mmol, 17%). Purification was performed by means of two column chromatography steps (silica gel, EtOAc/cyclohexane 1:1, $R_f = 0.80$; silica gel, EtOAc/cyclohexane 1:2, $R_f = 0.59$). The isolated product was sufficiently pure for follow-up reactions. ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.49$–7.31 (m, 4H), 5.34 (s, 1H), 3.81 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$):[21] $\delta = 165.5$ (C), 135.2 (C), 133.4 (C), 130.5 (CH), 129.9 (CH), 126.9 (CH), 124.9 (CH), 59.6 (CH), 54.0 ppm (CH_3); IR (KBr): $\tilde{\nu} = 2149$ (s), 1859 (w), 1758 (s), 1637 (m), 1597 (m), 1433 (m), 1251 (s), 1031 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 209 (88) $[M]^+$, 150 (100) $[M-C_2H_3O_2]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{10}H_8ClNO_2$ $[M]^+$: 209.02436; found: 209.02520.

*Methyl 2-(*p*-chlorophenyl)-2-isocyanoacetate (**1h**)*: General procedure 2 was followed using (±)-4-chlorophenylglycine (15.4 g, 67.4 mmol) to give **1h**, after 1 h of stirring at 0 °C, as a dark red oil (5.65 g, 26.8 mmol, 40%). Purification was performed by means of column chromatography (silica gel, EtOAc/cyclohexane 1:4, $R_f = 0.25$). ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.42$ (s, 4H), 5.35 (s, 1H), 3.80 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): $\delta = 165.6$ (C), 162.2 (C), 135.8 (C), 130.2 (C), 129.4 (2CH), 128.0 (2CH), 59.6 (CH), 53.9 ppm (CH_3); IR (KBr): $\tilde{\nu} = 2149$ (s), 1758 (s), 1637 (m), 1495 (m), 1436 (w), 1252 (s), 1093 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 209 (54) $[M]^+$, 177 (54) $[M-CH_4O]^+$, 150 (100) $[M-C_2H_3O_2]^+$, 124 (37) $[C_7H_5Cl]^+$, 111 (10) $[C_6H_4Cl]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{10}H_8ClNO_2$ $[M]^+$: 209.02436; found: 209.02431.

*Methyl 2-(*p*-methoxyphenyl)-2-isocyanoacetate (**1i**)*: General procedure 2 was followed using (±)-4-methoxyphenylglycine[20] (3.86 g, 17.3 mmol) to give **1i** as a dark red oil (1.76 g, 8.58 mmol, 50%). Purification was performed by means of column chromatography (silica gel, EtOAc/cyclohexane 1:1, $R_f = 0.66$). ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.38$ (m, 2H), 6.93 (m, 2H), 5.31 (s, 1H), 3.82 (s, 3H), 3.78 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): $\delta = 166.3$ (C), 161.0 (C), 160.5 (C), 128.0 (2CH), 123.9 (C), 114.5 (2CH), 59.7 (CH), 55.4 (CH_3), 53.6 ppm (CH_3); IR (KBr): $\tilde{\nu} = 2957$ (w), 2149 (s), 1757 (s), 1611 (m), 1512 (s), 1438 (m), 1254 (s), 1178 (m), 1031 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 205 (23) $[M]^+$, 173 (3) $[M-CH_4O]^+$, 146 (100) $[M-C_2H_3O_2]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{11}H_{11}NO_3$ $[M]^+$: 205.07389; found: 205.07333.

*Methyl 2-(*o,p*-dimethoxyphenyl)-2-isocyanoacetate (**1j**)*: General procedure 2 was followed using (±)-2,4-dimethoxyphenylglycine[20] (2.87 g, 11.3 mmol) to give **1j** as an orange oil (1.34 g, 5.70 mmol, 50%). Purification was performed by means of column chromatography (silica gel, EtOAc/cyclohexane 1:1, $R_f = 0.66$). ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.31$ (d, $^3J = 8.4$ Hz, 1H), 6.53 (dd, $^3J = 8.4$ Hz, $^4J = 2.4$ Hz, 1H), 6.48 (d, $^4J = 2.4$ Hz, 1H), 5.65 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): $\delta = 166.6$ (C), 162.0 (C), 159.3 (C), 157.3 (C), 129.0 (CH), 113.7 (C), 105.0 (CH), 98.8 (CH), 55.8 (CH_3), 55.4 (CH_3), 54.3 (CH), 53.4 ppm (CH_3); IR (KBr): $\tilde{\nu} = 2961$ (w), 2840 (w), 2148 (s), 1757 (s), 1614 (s), 1590 (m), 1509 (m), 1212 (s), 1031 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 235 (19) $[M]^+$, 176 (100) $[M-C_2H_3O_2]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{12}H_{13}NO_4$ $[M]^+$: 235.08446; found: 235.08525.

General procedure 3—Synthesis of 2-imidazolines 4a,c–j: Isocyanide (**4a,c–j**; 1 mL of a 1 M solution, 1.0 mmol) in MeOH was added over 21 h to a stirred solution of **3a** (162 μL, 160 mg, 1.5 mmol), **2a** (150 μL, 118 mg, 2.0 mmol), $MgSO_4$ (100 mg), and 2.0 mol% AgOAc (3.3 mg, 0.020 mmol) in MeOH (4 mL). After 1 h of additional stirring, water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting 2-imidazoline was purified by means of column chromatography.

*(1-Benzyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazol-4-yl)(morpholino)methanone (**4a**)*: General procedure 3 was followed using **1a** (154 mg, 1.0 mmol) to give **4a** as a pale brown oil (274 mg, 0.91 mmol, 91%). $R_f = 0.33$ (Al_2O_3, EtOAc/MeOH (10%)); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.38$–7.27 (m, 5H), 6.90 (d, $^4J = 1.4$ Hz, 1H), 4.70 (d, $^4J = 1.4$ Hz, 1H), 4.24 (d, $^2J = 15.2$ Hz, 1H), 4.21 (d, $^2J = 15.2$ Hz, 1H), 3.72–3.69 (m, 8H), 1.33 (s, 3H), 1.18 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): $\delta = 168.8$ (C), 156.2 (CH), 138.0 (C), 128.7 (2CH), 127.7 (2CH), 127.7 (CH), 76.3 (CH), 67.1 (CH_2), 66.8 (CH_2), 64.5 (C), 46.4 (CH_2), 45.9 (CH_2), 42.5 (CH_2), 27.4 (CH_3), 20.9 ppm (CH_3); IR (KBr): $\tilde{\nu} = 2860$ (w), 1648 (s), 1602 (s), 1454 (m), 1229 (m), 1003 cm^{-1} (w); MS (EI, 70 eV): *m/z* (%): 301 (8) $[M]^+$, 286 (6) $[M-CH_3]^+$, 187 (100) $[M-C_5H_8NO_2]^+$, 91 (91) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{23}N_3O_2$ $[M]^+$: 301.17903; found: 301.17772.

*(1-Benzyl-5,5-dimethyl-4-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)(morpholino)methanone (**4c**)*: General procedure 3 was followed using **1c** (230 mg, 1.0 mmol) to give **4c** as a yellow oil (266 mg, 0.60 mmol, 60%). $R_f = 0.50$ (silica gel, EtOAc); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.35$–7.15 (m, 10H), 7.11 (s, 1H), 4.19 (d, $^2J = 15.0$ Hz, 1H), 4.03 (d, $^2J = 15.0$ Hz, 1H), 3.85–3.65 (m, 5H), 3.58–3.50 (m, 2H), 2.81–2.75 (m, 1H), 1.52 (s, 3H), 0.89 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): $\delta = 170.2$ (C), 156.4 (CH), 138.0 (C), 136.9 (C), 128.6 (2CH), 128.1 (2CH), 127.6 (2CH), 127.6 (CH), 127.5 (CH), 126.9 (2CH), 83.9 (C), 71.4, 66.6 and 66.2 (2CH_2 and C), 47.8 (CH_2), 45.5 (CH_2), 43.2 (CH_2), 22.5 (CH_3), 21.2 ppm (CH_3); IR (KBr): $\tilde{\nu} = 3026$ (w), 2963 (w), 2854 (w), 1951 (w), 1634 (s), 1598 (s), 1456 (m), 1251 (s), 1113 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 377 (10) $[M]^+$, 376 (20) $[M-H]^+$, 362 (100) $[M-CH_3]^+$, 286 (25) $[M-C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{23}H_{27}N_3O_2$ $[M]^+$: 377.21033; found: 377.20942.

*Methyl 1-benzyl-5,5-dimethyl-4-(4-nitrophenyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4e**)*: General procedure 3 was followed using **1e** (220 mg, 1.0 mmol) to give **4e** as a red oil (264 mg, 0.72 mmol, 72%). Due to poor solubility of the isocyanide in MeOH, **1e** was added as a 1 M solution in CH_2Cl_2, with 5 mol% AgOAc used as catalyst. $R_f = 0.40$ (silica gel, EtOAc); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 8.19$ (d, $^3J = 9.3$ Hz, 2H), 7.88 (d, $^3J = 9.3$ Hz, 2H), 7.39–7.24 (m, 5H), 7.15 (s, 1H), 4.22 (s, 2H), 3.77 (s, 3H), 1.41 (s, 3H), 0.80 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): $\delta = 171.3$ (C), 156.8 (CH), 147.4 (C), 145.0 (C), 137.5 (C), 129.1 (2CH), 128.8 (2CH), 127.8 (CH), 127.5 (2CH), 122.7 (2CH), 84.4 (C), 69.2 (C), 52.6 (CH_3), 46.1 (CH_2), 23.0 (CH_3), 22.5 ppm (CH_3); IR (KBr): $\tilde{\nu} = 2989$ (w), 2947 (w), 1728 (s), 1607 (m), 1592 (s), 1517 (s), 1348 (s), 1227 (m), 1042 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 308 (51) $[M-C_2H_3O_2]^+$, 91 (100) $[C_7H_7]^+$; MS (FAB, 3 KeV): *m/z* (%): 368 (100) $[M+H]^+$, 308 (20) $[M-C_2H_3O_2]^+$, 91 (100) $[C_7H_7]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{20}H_{22}N_3O_4$ $[M+H]^+$: 368.1610; found: 368.1614.

*Methyl 1-benzyl-4-(2-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4f**)*: General procedure 3 was followed using **1f** (210 mg, 1.0 mmol) to give **4f** as an orange oil (89 mg, 0.25 mmol, 25%). AgOAc (5 mol%) was used as catalyst. $R_f = 0.32$ (silica gel, EtOAc/cyclohexane 1:1); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.90$ (dd, $^3J = 7.5$ Hz, $^4J = 2.0$ Hz, 1H), 7.42–7.19 (m, 8H), 6.99 (s, 1H), 4.29 (s, 2H), 3.65 (s, 3H), 1.94 (s, 3H), 0.66 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): $\delta = 170.4$ (C), 156.3 (CH), 138.1 (C), 137.9 (C), 132.9 (C), 131.1 (CH), 129.6 (CH), 128.8 (2CH), 128.6 (CH), 127.6 (CH), 127.5 (2CH), 126.4 (CH), 84.2 (C), 68.4 (C), 52.2 (CH_3), 45.9 (CH_2), 25.6 (CH_3), 21.6 ppm (CH_3); IR (KBr): $\tilde{\nu} = 3031$ (w), 2943 (w), 1733 (s), 1597 (s), 1467 (m), 1225 (s), 1167 (m), 1051 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 356 (6) $[M]^+$, 297 (100) $[M-C_2H_3O_2]^+$, 265 (10) $[M-C_7H_7]^+$, 91 (64) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{21}ClN_2O_2$ $[M^+]$: 356.12916; found: 356.12879.

*Methyl 1-benzyl-4-(3-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4g**)*: General procedure 3 was followed using **1g** (210 mg, 1.0 mmol) to give **4g** as a yellow oil (46 mg, 0.13 mmol, 13%). $R_f = 0.13$ (silica gel, EtOAc); ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.66$ (m, 1H), 7.54–7.51 (m, 1H), 7.36–7.23 (m, 7H), 7.12 (s, 1H), 4.20 (d, $^2J = 16.0$ Hz, 1H), 4.18 (d, $^2J = 16.0$ Hz, 1H), 3.76 (s, 3H), 1.37 (s, 3H),

0.82 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ = 171.6 (C), 156.5 (CH), 139.3 (C), 137.8 (C), 134.0 (C), 128.9 (CH), 128.8 (2CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.5 (2CH), 126.0 (CH), 84.2 (C), 69.1 (C), 52.4 (CH_3), 46.0 (CH_2), 22.9 (CH_3), 22.3 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 2971 (w), 1727 (s), 1602 (s), 1458 (w), 1397 (w), 1230 (s), 1164 (m), 1037 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 356 (1) $[M]^+$, 297 (100) $[M-C_2H_3O_2]^+$, 91 (100) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{21}ClN_2O_2$ $[M^+]$: 356.12916; found: 356.12875.

*Methyl 1-benzyl-4-(4-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4h**)*: General procedure 3 was followed using **1h** (210 mg, 1.0 mmol) to give **4h** as an orange oil (239 mg, 0.67 mmol, 67%). R_f = 0.43 (Al_2O_3, EtOAc/cyclohexane 1:2); ^1H NMR (250.13 MHz, $CDCl_3$): δ = 7.62–7.56 (m, 2H), 7.38–7.23 (m, 7H), 7.11 (s, 1H), 4.18 (s, 2H), 3.75 (s, 3H), 1.36 (s, 3H), 0.82 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): δ = 171.9 (C), 156.4 (CH), 137.9 (C), 135.8 (C), 133.6 (C), 129.3 (2CH), 128.8 (2CH), 127.9 (2CH), 127.7 (CH), 127.5 (2CH), 84.1 (C), 69.0 (C), 52.4 (CH_3), 46.0 (CH_2), 22.9 (CH_3), 22.3 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 2972 (w), 1901 (w), 1727 (s), 1603 (s), 1490 (m), 1230 (s), 1165 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 356 (1) $[M]^+$, 297 (86) $[M-C_2H_3O_2]^+$, 265 (6) $[M-C_7H_7]^+$, 168 (7) $[M-C_{12}H_9Cl]^+$, 91 (100) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{21}ClN_2O_2$ $[M^+]$: 356.12916; found: 356.13038.

*Methyl 1-benzyl-4-(4-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4i**)*: General procedure 3 was followed using **1i** (205 mg, 1.0 mmol) to give **4i** as a yellow oil (264 mg, 0.75 mmol, 75%). R_f = 0.29 (silica gel, EtOAc/MeOH (5%)); ^1H NMR (250.13 MHz, $CDCl_3$): δ = 7.54 (d, ^3J = 8.8 Hz, 2H), 7.36–7.23 (m, 5H), 7.11 (s, 1H), 6.86 (d, ^3J = 8.8 Hz, 2H), 4.19 (d, ^2J = 15.8 Hz, 1H), 4.16 (d, ^2J = 15.8 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 1.36 (s, 3H), 0.84 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): δ = 172.2 (C), 159.0 (C), 156.1 (CH), 138.1 (C), 129.1 (C), 128.8 (2CH), 128.7 (2CH), 127.6 (2CH), 127.5 (2CH), 113.1 (2CH), 84.0 (C), 69.0 (C), 55.2 (CH_3), 52.3 (CH_3), 46.0 (CH_2), 22.8 (CH_3), 22.2 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 2945 (m), 2835 (w), 1725 (s), 1605 (s), 1510 (m), 1454 (m), 1248 (s), 1175 (m), 1038 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 352 (6) $[M]^+$, 293 (100) $[M-C_2H_3O_2]^+$, 261 (6) $[M-C_7H_7]^+$, 91 (80) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{21}H_{24}N_2O_3$ $[M^+]$: 352.17869; found: 352.17799.

*Methyl 1-benzyl-4-(2,4-dimethoxyphenyl)-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4j**)*: General procedure 3 was followed using **1j** (235 mg, 1.0 mmol) to give **4j** as a pale orange oil (333 mg, 0.87 mmol, 87%). The total reaction time was 48 h. R_f = 0.40 (silica gel, EtOAc); ^1H NMR (250.13 MHz, $CDCl_3$): δ = 7.65 (d, ^3J = 8.5 Hz, 1H), 7.44–7.28 (m, 5H), 6.50 (dd, ^3J = 8.5 Hz, ^4J = 2.3 Hz, 1H), 6.43 (d, ^4J = 2.3 Hz, 1H), 4.31 (d, ^2J = 15.8 Hz, 1H), 4.26 (d, ^2J = 15.8 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.60 (s, 3H), 1.74 (s, 3H), 0.62 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ = 171.4 (C), 159.9 (C), 157.6 (C), 156.1 (CH), 138.2 (C), 129.8 (CH), 128.5 (2CH), 127.3 (2CH), 127.2 (CH), 121.4 (C), 103.5 (CH), 98.7 (CH), 82.7 (C), 68.1 (C), 55.0 (CH_3), 54.7 (CH_3), 51.6 (CH_3), 45.8 (CH_2), 24.7 (CH_3), 20.7 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 2940 (m), 2837 (w), 1731 (s), 1614 (s), 1579 (s), 1505 (m), 1456 (m), 1244 (w), 1207 (s), 1048 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 382 (2) $[M]^+$, 323 (42) $[M-C_2H_3O_2]^+$, 106 (34) $[C_7H_6O]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{22}H_{26}N_2O_4$ $[M^+]$: 382.18926; found: 382.18875.

General procedure 6—Synthesis of 2-imidazolines 4k,l,n: Unless stated otherwise: A 1 M solution of isocyanide **1d** (1 mL, 175 mg, 1.0 mmol) in MeOH was added over 21 h to a stirred solution of either aldehyde or ketone (1.2 mmol), amine (1.2 mmol), $MgSO_4$ (100 mg), and AgOAc (3.3 mg, 0.020 mmol, 2.0 mol%) in MeOH (2 mL). After 1 h of additional stirring, water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting 2-imidazoline was purified by means of column chromatography.

*Methyl 1-benzyl-5-methyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4k**)*: General procedure 6 was followed using **1d** (175 mg, 1.0 mmol), acetaldehyde (**2b**; 112 μL, 88 mg, 2.0 mmol), and benzylamine (**3a**; 131 μL, 128 mg, 1.2 mmol) to give **4k** as an orange oil (274 mg, 0.89 mmol, 89%). R_f = 0.27 (silica gel, EtOAc); isolated as a 38:62 mixture of diastereomers; ^1H NMR (250.13 MHz, $CDCl_3$): major isomer: δ = 7.40–7.11 (m, 10H), 7.17 (s, 1H), 4.45 (d, ^2J = 15.4 Hz, 1H), 4.36 (q, ^3J = 6.5 Hz, 1H), 4.19 (d, ^2J = 15.4 Hz, 1H), 3.74 (s, 3H), 0.66 ppm (d, ^3J = 6.5 Hz, 3H); minor isomer: δ = 7.56–7.52 (m, 2H), 7.40–7.11 (m, 8H), 7.14 (s, 1H), 4.42 (d, ^2J = 15.4 Hz, 1H), 4.21 (d, ^2J = 15.4 Hz, 1H), 3.85 (q, ^3J = 6.6 Hz, 1H), 3.71 (s, 3H), 1.34 ppm (d, ^3J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): major isomer: δ = 174.0 (C), 156.3 (CH), 137.3 (C), 136.2 (C), 128.8 (2CH), 128.1 (2CH), 127.8 (CH), 127.6 (2CH), 127.4 (CH), 126.7 (2CH), 83.0 (C), 59.7 (CH), 52.7 (CH_3), 48.7 (CH_2), 14.5 ppm (CH_3); minor isomer: δ = 171.9 (C), 156.2 (CH), 143.0 (C), 136.2 (C), 128.7 (2CH), 128.1 (2CH), 127.7 (CH), 127.5 (2CH), 127.4 (CH), 126.2 (2CH), 82.5 (C), 63.9 (CH), 52.2 (CH_3), 48.6 (CH_2), 14.7 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 3027 (w), 2948 (w), 1726 (s), 1595 (s), 1493 (w), 1454 (m), 1240 (s), 1178 (m), 731 (m), 700 cm^{-1} (m); MS (FAB, 3 KeV): *m/z* (%): 309 (100) $[M+H]^+$, 249 (33) $[M-C_2H_3O_2]^+$, 91 (60) $[C_7H_7]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$: 309.1603; found: 309.1606.

*Methyl 1-benzyl-5-ethyl-5-methyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (**4l**)*: General procedure 6 was followed using **1d** (175 mg, 1.0 mmol), 2-butanone (**2c**; 107 μL, 87 mg, 1.2 mmol), and **3a** (131 μL, 128 mg, 1.2 mmol) to give **4l** as a colorless oil (54 mg, 0.16 mmol, 16%). R_f = 0.20 (silica gel, EtOAc/cyclohexane 1:3); isolated as a 53:47 mixture of diastereomers; ^1H NMR (250.13 MHz, $CDCl_3$): δ = 7.69 (dd, ^3J = 7.7 Hz, ^4J = 2.0 Hz, 2H), 7.49 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 2H), 7.39–7.19 (m, 16H), 7.17 (s, 1H), 7.16 (s, 1H), 4.29 (d, ^2J = 15.5 Hz, 1H), 4.22 (d, ^2J = 15.3 Hz, 1H), 4.17 (d, ^2J = 15.5, 1H), 4.05 (d, ^2J = 15.3 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.30–2.15 (m, 1H), 1.74–1.59 (m, 1H), 1.54–1.26 (m, 2H), 1.37 (s, 3H), 0.86 (t, ^3J = 7.5 Hz, 3H), 0.83 (s, 3H), 0.50 ppm (t, ^3J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): δ = 172.0 (C), 171.9 (C), 156.5 (CH), 155.9 (CH), 138.1 (C), 137.8 (C), 137.1 (C), 136.9 (C), 128.6 (4CH), 128.1 (2CH), 127.8 (2CH), 127.50 (4CH), 127.47 (2CH), 127.31 (2CH), 127.28 (2CH), 127.2 (2CH), 84.8 (C), 83.2 (C), 71.7 (C), 71.6 (C), 52.2 ($2CH_3$), 46.3 (CH_2), 45.9 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 23.4 (CH_3), 22.0 (CH_3), 9.4 (CH_3), 8.5 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 2947 (m), 2837 (w), 1725 (s), 1606 (s), 1455 (m), 1261 (s), 1052 cm^{-1} (m); MS (FAB, 3 KeV): *m/z* (%): 337 (100) $[M+H]^+$, 277 (27) $[M-C_2H_3O_2]^+$, 91 (66) $[C_7H_7]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{21}H_{25}N_2O_2$ $[M+H]^+$: 337.1916; found: 337.1920.

*Methyl 4-phenyl-1,3-diazaspiro[4.5]dec-2-ene-4-carboxylate (**4n**)*: General procedure 6 was followed using **1d** (175 mg, 1.0 mmol), cyclohexanone (**2e**; 124 μL, 118 mg, 1.2 mmol), NH_4Cl (107 mg, 2.0 mmol), and Et_3N (278 μL, 202 mg, 2.0 mmol) to give **4n** (171 mg, 0.63 mmol, 63%) as a sticky brown solid. (Chromatography: silica gel, EtOAc/methanol gradient.) ^1H NMR (250.13 MHz, $CDCl_3$): δ = 7.67 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 2H), 7.36–7.27 (m, 4H), 4.65 (brs, 1H), 3.71 (s, 3H), 1.90–0.91 ppm (m, 10H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): δ = 172.2 (C), 152.4 (CH), 136.6 (C), 127.5 (2CH), 127.44 (2CH), 127.36 (CH), 80.3 (C), 72.9 (C), 52.1 (CH_3), 34.5 (CH_2), 34.3 (CH_2), 25.2 (CH_2), 23.3 (CH_2), 22.7 ppm (CH_2); IR (KBr): $\tilde{\nu}$ = 3432 (brs), 2929 (m), 2848 (w), 1731 (s), 1615 (s), 1445 (s), 1208 (s), 1016 cm^{-1} (w); MS (FAB, 3 KeV): *m/z* (%): 273 (100) $[M+H]^+$, 213 (33) $[M-C_2H_3O_2]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{16}H_{21}N_2O_2$ $[M+H]^+$: 273.1603; found: 273.1602.

General procedure 4—Synthesis of oxazoles 5a–c: An isocyanide (**1a–c**; 1.0 mmol), **3a** (162 μL, 160 mg, 1.5 mmol), **2a** (150 μL, 118 mg, 2.0 mmol), Et_3N·HCl (138 mg, 1.0 mmol), and $MgSO_4$ (100 mg) were stirred in MeOH (5 mL) for 5 h at 60 °C. Water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting 2-imidazoline was purified by means of column chromatography (Al_2O_3, EtOAc/cyclohexane 1:4).

*N-Benzyl-2-(5-morpholinooxazol-2-yl)propan-2-amine (**5a**)*: General procedure 4 was followed using **1a** (154 mg, 1.0 mmol) to give **5a** as a yellow oil (220 mg, 0.73 mmol, 73%). R_f = 0.43; ^1H NMR (250.13 MHz, $CDCl_3$): δ = 7.30–7.20 (m, 5H), 6.00 (s, 1H), 3.85–3.81 (m, 4H), 3.57 (s, 2H), 3.10–3.07 (m, 4H), 1.66 (brs, 1H), 1.53 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ = 161.5 (C), 157.0 (C), 140.6 (C), 128.4 (2CH), 128.2 (2CH), 126.9 (CH), 102.7 (CH), 66.0 ($2CH_2$), 54.5 (C), 48.5 ($2CH_2$), 48.4 (CH_2), 26.6 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$ = 2976 (m), 2857 (m), 1611 (s), 1567 (w), 1453 (m), 1378 (m), 1243 (m), 1119 (s), 898 cm^{-1} (s);

MS (EI, 70 eV): *m/z* (%): 301 (10) $[M]^+$, 286 (507) $[M-CH_3]^+$, 196 (60) $[M-C_7H_7N]^+$, 195 (26) $[M-C_7H_8N]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (75) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{23}N_3O_2$ $[M]^+$: 301.17903; found: 301.17807.

N-*Benzyl-2-(4-ethyl-5-morpholinooxazol-2-yl)propan-2-amine* (***5b***): General procedure 4 was followed using **1b** (182 mg, 1.0 mmol) to give **5b** as a colorless oil (161 mg, 0.49 mmol, 49%). R_f=0.55; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=7.35–7.18 (m, 5H), 3.81–3.78 (m, 4H), 3.54 (s, 2H), 3.04–3.00 (m, 4H), 2.48 (q, ^3J=7.5 Hz, 2H), 1.80 (brs, 1H), 1.53 (s, 6H), 1.20 ppm (t, ^3J=7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=163.2 (C), 150.4 (C), 140.6 (C), 128.4 (2CH), 128.3 (2CH), 127.3 (C), 126.9 (CH), 67.0 ($2CH_2$), 54.8 (C), 51.4 ($2CH_2$), 48.6 (CH_2), 26.5 ($2CH_3$), 19.1 (CH_2), 13.9 ppm (CH_3); IR (KBr): $\tilde{\nu}$=3393 (s), 2967 (s), 2856 (m), 1679 (s), 1496 (m), 1453 (s), 1378 (m), 1260 (s), 1201 (s), 1116 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 329 (12) $[M]^+$, 314 (27) $[M-CH_3]^+$, 224 (32) $[M-C_7H_7N]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (100) $[C_7H_7]^+$ 70 (60) $[C_4H_8N]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{19}H_{27}N_3O_2$ $[M]^+$: 329.21033; found: 329.21115.

N-*Benzyl-2-(5-morpholino-4-phenyloxazol-2-yl)propan-2-amine* (***5c***): General procedure 4 was followed using **1c** (230 mg, 1.0 mmol) to give **5c** as a colorless solid (211 mg, 0.56 mmol, 56%). R_f=0.73; m.p. 93–96 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.00 (d, ^3J=8.0 Hz, 2H), 7.42 (t, ^3J=8.0 Hz, 2H), 7.33–7.23 (m, 6H), 3.89–3.86 (m, 4H), 3.65 (s, 2H), 3.14–3.12 (m, 4H), 1.88 (brs, 1H), 1.60 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=163.2 (C), 150.5 (C), 140.5 (C), 132.1 (C), 128.44 (2CH), 128.39 (2CH), 128.3 (2CH), 126.9 (CH), 126.8 (CH), 126.0 (2CH), 123.6 (C), 66.9 ($2CH_2$), 54.9 (C), 50.4 ($2CH_2$), 48.6 (CH_2), 26.5 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=3317 (s), 2977 (s), 2846 (s), 2830 (m), 1649 (s), 1494 (m), 1446 (m), 1376 (s), 1193 (s), 1112 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 377 (1) $[M]^+$, 195 (43) $[M-C_{13}H_{12}N]^+$, 194 (30) $[M-C_{13}H_{13}N]^+$, 148 (52) $[C_{13}H_{13}N_2O_2]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{23}H_{27}N_3O_2$ $[M]^+$: 377.21033; found: 377.20861.

General procedure 5—Synthesis of oxazoles 5d–i: An isocyanide (**1d–i**; 1.0 mmol), **3a** (162 μL, 160 mg, 1.5 mmol), **2a** (150 μL, 118 mg, 2.0 mmol), and $MgSO_4$ (100 mg) were stirred in DMF (5 mL) until complete consumption of the isocyanide (monitored by ^{1}H NMR). Water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting oxazoles were purified by means of column chromatography (silica gel, EtOAc/cyclohexane 1:4, unless stated otherwise).

N-*Benzyl-2-(5-methoxy-4-phenyloxazol-2-yl)propan-2-amine* (***5d***): General procedure 5 was followed using **1d** (175 mg, 1.0 mmol). A 4 h reaction time followed by column chromatography (Al_2O_3, EtOAc/pentane 2:1, R_f=0.85) furnished **5d** as an orange oil (190 mg, 0.59 mmol, 59%). ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=7.85–7.81 (m, 2H), 7.39–7.22 (m, 8H), 4.04 (s, 3H), 3.65 (s, 2H), 1.83 (brs, 1H), 1.59 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): δ=158.9 (C), 154.2 (C), 140.5 (C), 131.5 (C), 128.5 (2CH), 128.4 (2CH), 128.3 (2CH), 126.8 (CH), 126.2 (CH), 124.9 (2CH), 114.3 (C), 60.0 (CH_3), 54.8 (C), 48.6 (CH_2), 26.5 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=3426 (brs), 2985 (w), 2940 (w), 1958 (w), 1644 (m), 1369 (m), 1110 (m), 696 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 322 (1) $[M]^+$, 307 (1) $[M-CH_3]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (44) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{22}O_2N_2$ $[M]^+$: 322.16813; found: 322.16848.

N-*Benzyl-2-[5-methoxy-4-(4-nitrophenyl)oxazol-2-yl]propan-2-amine* (***5e***): General procedure 5 was followed using **1e** (220 mg, 1.0 mmol). A 30 min reaction time followed by column chromatography (silica gel, EtOAc/cyclohexane 1:2, R_f=0.26) furnished **5e** as a red oil (228 mg, 0.62 mmol, 62%). ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=8.23 (d, ^3J=9.0 Hz, 2H), 7.94 (d, ^3J=9.0 Hz, 2H), 7.35–7.23 (m, 5H), 4.13 (s, 3H), 3.67 (s, 2H), 1.90 (brs, 1H), 1.60 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=159.0 (C), 155.9 (C), 145.4 (C), 140.3 (C), 138.4 (C), 128.4 (2CH), 128.2 (2CH), 127.0 (CH), 124.9 (2CH), 124.0 (2CH), 111.7 (C), 59.5 (CH_3), 54.8 (C), 48.5 (CH_2), 26.5 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=3401 (w), 2985 (w), 2940 (w), 1635 (s), 1600 (m), 1508 (s), 1337 (s), 1108 (m), 1024 cm^{-1} (m); MS (FAB, 3 KeV): *m/z* (%): 368 (5) $[M+H]^+$, 352 (11) $[M-CH_3]^+$, 261 (93) $[M-C_7H_8N]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (82) $[C_7H_7]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{20}H_{22}N_3O_4$ $[M+H]^+$: 368.1610; found: 368.1614.

N-*Benzyl-2-[4-(2-chlorophenyl)-5-methoxyoxazol-2-yl]propan-2-amine* (***5f***): General procedure 5 was followed using **1f** (210 mg, 1.0 mmol) to give **5f**, after 11 h reaction time, as a yellow oil (210 mg, 0.59 mmol, 59%). R_f=0.23; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.53 (dd, ^3J=7.2 Hz, ^4J=1.6 Hz, 1H), 7.44 (dd, ^3J=7.6 Hz, ^4J=1.2 Hz, 1H), 7.34–7.22 (m, 7H), 3.94 (s, 3H), 3.68 (s, 2H), 1.81 (brs, 1H), 1.59 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=159.0 (C), 154.6 (C), 140.5 (C), 133.4 (C), 131.5 (CH), 130.4 (C), 129.9 (CH), 128.9 (CH), 128.4 (2CH), 128.3 (2CH), 126.9 (CH), 126.6 (CH), 112.0 (C), 59.9 (CH_3), 54.7 (C), 48.5 (CH_2), 26.5 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=3405 (w), 2984 (m), 2136 (w), 1650 (s), 1463 (m), 1444 (m), 1362 (s), 1199 (m), 1112 (m), 1014 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 356 (1) $[M]^+$, 341 (1) $[M-CH_3]^+$, 297 (1) $[M-C_6H_5]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (48) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{21}ClN_2O_2$ $[M]^+$: 356.12916; found: 356.12804.

N-*Benzyl-2-[4-(3-chlorophenyl)-5-methoxyoxazol-2-yl]propan-2-amine* (***5g***): General procedure 5 was followed using **1g** (210 mg, 1.0 mmol) to give **5g**, after 2 h reaction time, as an orange oil (171 mg, 0.48 mmol, 48%). R_f=0.15; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.83–7.82 (m, 1H), 7.71–7.69 (m, 1H), 7.32–7.17 (m, 7H), 4.06 (s, 3H), 3.65 (s, 2H), 1.83 (brs, 1H), 1.58 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): δ=158.9 (C), 154.5 (C), 140.4 (C), 134.5 (C), 133.5 (C), 129.7 (CH), 128.4 (2CH), 128.3 (2CH), 127.0 (CH), 126.1 (CH), 124.9 (CH), 123.0 (CH), 112.8 (C), 59.8 (CH_3), 54.8 (C), 48.8 (CH_2), 26.5 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=3411 (w), 2984 (m), 1724 (w), 1642 (s), 1599 (m), 1368 (m), 1113 (m), 1033 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 356 (1) $[M]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (56) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{21}ClN_2O_2$ $[M]^+$: 356.12916; found: 356.12864.

N-*Benzyl-2-[4-(3-chlorophenyl)-5-methoxyoxazol-2-yl]propan-2-amine* (***5h***): General procedure 5 was followed using **1h** (210 mg, 1.0 mmol) to give **5h**, after 2 h reaction time, as a red oil (203 mg, 0.57 mmol, 57%). R_f=0.15; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=7.79–7.76 (m, 2H), 7.38–7.27 (m, 7H), 4.05 (s, 3H), 3.67 (s, 2H), 1.90 (brs, 1H), 1.60 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=158.8 (C), 154.2 (C), 140.4 (C), 131.6 (C), 130.2 (C), 128.5 (2CH), 128.4 (2CH), 128.2 (2CH), 126.9 (CH), 126.2 (2CH), 113.1 (C), 59.8 (CH_3), 54.8 (C), 48.5 (CH_2), 26.5 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=2967 (w), 2857 (w), 1901 (w), 1719 (s), 1644 (s), 1495 (m), 1371 (s), 1211 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 356 (1) $[M]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (74) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{21}ClN_2O_2$ $[M]^+$: 356.12916; found: 356.13017.

N-*Benzyl-2-[4-(3-chlorophenyl)-5-methoxyoxazol-2-yl]propan-2-amine* (***5i***): General procedure 5 was followed using **1i** (205 mg, 1.0 mmol) to give **5i**, after 8 h reaction time, as a yellow oil (226 mg, 0.64 mmol, 64%). R_f=0.18; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.75 (d, ^3J=9.2 Hz, 2H), 7.34–7.21 (m, 5H), 6.94 (d, ^3J=9.2 Hz, 2H), 4.02 (s, 3H), 3.84 (s, 3H), 3.65 (s, 2H), 1.84 (brs, 1H), 1.58 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$): δ=158.9 (C), 158.2 (C), 153.4 (C), 140.5 (C), 128.4 (2CH), 128.3 (2CH), 126.9 (CH), 126.4 (2CH), 124.3 (C), 114.4 (C), 114.0 (2CH), 60.2 (CH_3), 55.3 (CH_3), 54.9 (C), 48.6 (CH_2), 26.5 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=3465 (w), 2987 (m), 2834 (m), 1649 (s), 1610 (m), 1515 (s), 1368 (m), 1247 (s), 1112 (m), 1019 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 352 (1) $[M]^+$, 148 (100) $[C_{10}H_{14}N]^+$, 91 (49) $[C_7H_7]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{21}H_{24}N_2O_3$ $[M]^+$: 352.17869; found: 352.17832.

General procedure 7—Synthesis of oxazoles 5l–q: Unless stated otherwise: Isocyanide **1d** (175 mg, 1.0 mmol), either aldehyde or ketone (1.2 mmol), an amine (1.2 mmol), and $MgSO_4$ (100 mg) were stirred in DMF (2 mL) for 17 h. Water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting oxazoles were purified by means of column chromatography (silica gel).

N-*Benzyl-2-(5-methoxy-4-phenyloxazol-2-yl)butan-2-amine* (***5l***): General procedure 7 was followed using **1d** (175 mg, 1.0 mmol), 2-butanone (**2c**; 107 μL, 87 mg, 1.2 mmol), and **3a** (131 μL, 128 mg, 1.2 mmol) to give **5l** as a pale orange oil (179 mg, 0.53 mmol, 53%). R_f=0.44 (EtOAc/cyclohexane 1:3); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=7.87 (dd, ^3J=8.5 Hz, ^4J=1.5 Hz, 2H), 7.45–7.21 (m, 8H), 4.05 (s, 3H), 3.71 (d, ^2J=12.0 Hz, 1H), 3.62 (d, ^2J=12.0 Hz, 1H), 1.94 (q, ^3J=7.5 Hz, 2H), 1.82 (brs, 1H),

1.58 (s, 3H), 0.95 ppm (t, ^3J=7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=158.4 (C), 154.2 (C), 140.6 (C), 131.6 (C), 128.34 (2CH), 128.28 (2CH), 128.2 (2CH), 126.8 (CH), 126.1 (CH), 124.9 (2CH), 114.1 (C), 59.8 (CH_3), 58.1 (C), 48.1 (CH_2), 32.7 (CH_2), 22.0 (CH_3), 8.1 ppm (CH_3); IR (KBr): $\tilde{\nu}$=2974 (s), 2878 (w), 1644 (s), 1602 (w), 1498 (m), 1450 (s), 1372 (s), 1168 (m), 1017 cm^{-1} (s); MS (FAB, 3 KeV): *m/z* (%): 337 (6) $[M+H]^+$, 321 (5) $[M-CH_3]^+$, 307 (9) $[M-C_2H_5]^+$, 230 (100) $[M-C_8H_{10}]^+$, 162 (100) $[C_{11}H_{16}N]^+$, 91 (82) $[C_7H_7]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{21}H_{25}N_2O_2$ $[M+H]^+$: 337.1916; found: 337.1918.

N-*Benzyl-3-(5-methoxy-4-phenyloxazol-2-yl)pentan-3-amine* (***5m***): General procedure 7 was followed using **1d** (175 mg, 1.0 mmol), 3-pentanone (**2d**; 127 μL, 104 mg, 1.2 mmol), and **3a** (131 μL, 128 mg, 1.2 mmol) to give **5m** as a yellow oil (170 mg, 0.49 mmol, 49%). R_f=0.50 (EtOAc/cyclohexane 1:3); ^1H NMR (250.13 MHz, $CDCl_3$): δ=7.90–7.86 (m, 2H), 7.45–7.21 (m, 8H), 4.06 (s, 3H), 3.61 (s, 2H), 2.03–1.90 (m, 4H), 1.73 (brs, 1H), 0.93 ppm (t, ^3J=7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=158.1 (C), 154.2 (C), 140.6 (C), 131.6 (C), 128.3 (2CH), 128.24 (2CH), 128.22 (2CH), 126.8 (CH), 126.1 (CH), 124.9 (2CH), 114.0 (C), 60.9 (C), 59.8 (CH_3), 47.4 (CH_2), 26.9 ($2CH_2$), 7.4 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=2966 (m), 2579 (m), 2496 (m), 1644 (s), 1602 (w), 1454 (s), 1368 (s), 1017 (s), 697 cm^{-1} (s); MS (FAB, 3 KeV): *m/z* (%): 351 (8) $[M+H]^+$, 321 (42) $[M-C_2H_5]^+$, 244 (98) $[M-C_8H_{10}]^+$, 176 (100) $[C_{12}H_{18}N]^+$, 91 (80) $[C_7H_7]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$: 351.2073; found: 351.2072.

1-(5-Methoxy-4-phenyloxazol-2-yl)cyclohexanamine (***5n***): General procedure 7 was followed using **1d** (175 mg, 1.0 mmol), cyclohexanone (**2e**; 124 μL, 118 mg, 1.2 mmol), NH_3·HCl (107 mg, 2.0 mmol), and Et_3N (278 μL, 202 mg, 2.0 mmol) to give **5n** as a red-brown oil (189 mg, 0.69 mmol, 69%). R_f=0.14 (EtOAc/cyclohexane 1:1); ^1H NMR (250.13 MHz, $CDCl_3$): δ=7.80 (dd, ^3J=8.3 Hz, ^4J=1.3 Hz, 2H), 7.40–7.34 (m, 2H), 7.23–7.16 (m, 1H), 4.04 (s, 3H), 2.20–2.12 (m, 2H), 1.80 (brs, 2H), 1.77–1.46 ppm (m, 8H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=159.9 (C), 153.9 (C), 131.5 (C), 128.4 (2CH), 126.2 (CH), 124.9 (2CH), 114.2 (C), 59.9 (CH_3), 53.0 (C), 36.8 ($2CH_2$), 25.4 (CH_2), 22.1 ppm ($2CH_2$); IR (KBr): $\tilde{\nu}$=3359 (m), 2932 (s), 2855 (s), 1644 (s), 1603 (w), 1448 (m), 1369 (m), 1209 (m), 1017 cm^{-1} (s); MS (FAB, 3 KeV): *m/z* (%): 273 (66) $[M+H]^+$, 256 (100) $[M-NH_2]^+$, 98 (87) $[C_6H_{12}N]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{16}H_{21}N_2O_2$ $[M+H]^+$: 273.1603; found: 273.1603.

1-(5-Methoxy-4-phenyloxazol-2-yl)-N-*propylcyclohexanamine* (***5o***): General procedure 7 was followed using **1d** (175 mg, 1.0 mmol), cyclohexanone (**2e**; 124 μL, 118 mg, 1.2 mmol), and *n*-propylamine (**3c**; 99 μL, 71 mg, 1.2 mmol) to give **5o** as a yellow oil (199 mg, 0.63 mmol, 63%). R_f=0.20 (EtOAc/cyclohexane 1:3); ^1H NMR (250.13 MHz, $CDCl_3$): δ=7.82 (d, ^3J=7.3 Hz, 2H), 7.38 (t, ^3J=7.3 Hz, 2H), 7.20 (t, ^3J=7.3 Hz, 1H), 4.04 (s, 3H), 2.37 (t, ^3J=7.3 Hz, 2H), 2.23–2.15 (m, 2H), 1.73–1.34 (m, 11H), 0.87 ppm (t, ^3J=7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=158.3 (C), 154.0 (C), 131.7 (C), 128.3 (2CH), 126.1 (CH), 124.9 (2CH), 114.0 (C), 59.9 (CH_3), 57.1 (C), 44.6 (CH_2), 34.6 ($2CH_2$), 25.7 (CH_2), 23.7 (CH_2), 22.1 ($2CH_2$), 11.8 ppm (CH_3); IR (KBr): $\tilde{\nu}$=2939 (s), 2858 (m), 2563 (m), 1644 (s), 1498 (w), 1448 (s), 1369 (s), 1018 (s), 696 cm^{-1} (s); MS (FAB, 3 KeV): *m/z* (%): 315 (16) $[M+H]^+$, 256 (100) $[M-C_3H_8N]^+$, 140 (98) $[C_9H_{18}N]^+$, 125 (45) $[C_8H_{15}N]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{19}H_{27}N_2O_2$ $[M+H]^+$: 315.2073; found: 315.2068.

4-[1-(5-Methoxy-4-phenyloxazol-2-yl)cyclohexyl]morpholine (***5p***): General procedure 7 was followed using **1d** (175 mg, 1.0 mmol), cyclohexanone (**2e**; 124 μL, 118 mg, 1.2 mmol), and morpholine (**3d**; 105 μL, 105 mg, 1.2 mmol) to give **5p** as an orange oil (210 mg, 0.61 mmol, 61%). R_f=0.13 (EtOAc/cyclohexane 1:5); ^1H NMR (250.13 MHz, $CDCl_3$): δ=7.82 (dd, ^3J=7.5 Hz, ^4J=1.3 Hz, 2H), 7.38 (t, ^3J=7.5 Hz, 2H), 7.21 (tt, ^3J=7.5 Hz, ^4J=1.3 Hz, 1H), 4.05 (s, 3H), 3.71–3.67 (m, 4H), 2.60–2.57 (m, 4H), 2.30–2.21 (m, 2H), 1.89–1.36 ppm (m, 8H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=155.1 (C), 154.0 (C), 131.6 (C), 128.3 (2CH), 126.1 (CH), 125.0 (2CH), 113.9 (C), 67.7 ($2CH_2$), 60.0 (C), 59.9 (CH_3), 46.6 ($2CH_2$), 32.2 ($2CH_2$), 25.6 (CH_2), 22.0 ppm ($2CH_2$); IR (KBr): $\tilde{\nu}$=2636 (s), 2815 (s), 1643 (s), 1448 (m), 1364 (m), 1116 (s), 1008 (m), 702 cm^{-1} (m); MS (FAB, 3 KeV): *m/z* (%): 343 (2) $[M+H]^+$, 256 (55) $[M-C_4H_8NO]^+$, 168 (100) $[C_{10}H_{18}NO]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{20}H_{27}N_2O_3$ $[M+H]^+$: 343.2022; found: 343.2017.

N-tert-*Butyl-1-(5-methoxy-4-phenyloxazol-2-yl)-2-methylpropan-1-amine* (***5q***): General procedure 7 was followed using **1d** (175 mg, 1.0 mmol), isobutyraldehyde (**2f**; 110 μL, 87 mg, 1.2 mmol), and *t*-butylamine (**3e**; 126 μL, 88 mg, 1.2 mmol) to give **5q** as a yellow oil (177 mg, 0.59 mmol, 59%). R_f=0.32 (EtOAc/cyclohexane 1:5); ^1H NMR (250.13 MHz, $CDCl_3$): δ=7.81 (dd, ^3J=7.5 Hz, ^4J=1.3 Hz, 2H), 7.38 (t, ^3J=7.5 Hz, 2H), 7.21 (tt, ^3J=7.5 Hz, ^4J=1.3 Hz, 1H), 4.03 (s, 3H), 3.56 (d, ^3J=6.8 Hz, 1H), 1.98–1.84 (m, 1H), 1.48 (brs, 1H), 1.04 (s, 9H), 1.00 (d, ^3J=6.8 Hz, 3H), 0.89 ppm (d, ^3J=6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=158.0 (C), 153.9 (C), 131.5 (C), 128.3 (2CH), 126.1 (CH), 125.0 (2CH), 114.3 (C), 60.1 (CH), 56.9 (CH_3), 50.6 (C), 34.0 (CH), 29.5 ($3CH_3$), 19.1 (CH_3), 19.0 ppm (CH_3); IR (KBr): $\tilde{\nu}$=2960 (s), 1644 (s), 1448 (m), 1365 (s), 1229 (s), 1016 cm^{-1} (s); MS (FAB, 3 KeV): *m/z* (%): 303 (37) $[M+H]^+$, 259 (19) $[M-C_3H_7]^+$, 230 (100) $[M-C_4H_{10}N]^+$, 128 (99) $[C_8H_{18}N]^+$, 72 (77) $[C_4H_{10}N]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{18}H_{27}N_2O_2$ $[M+H]^+$: 303.2073; found: 303.2074.

4-(2-(5-Morpholinooxazol-2-yl)propan-2-yl)morpholine (6): General procedure 4 was followed using **1a** (154 mg, 1.0 mmol) to give **6** (31 mg, 0.11 mmol, 11%) as a pale yellow solid. Product eluted from column by flushing with EtOAc (silica gel, EtOAc, R_f=0.16). M.p. 74–78°C; ^1H NMR (250.13 MHz, $CDCl_3$): δ=5.98 (s, 1H), 3.82 (m, 4H), 3.69 (m, 4H), 3.08 (m, 4H), 2.51 (m, 4H), 1.49 ppm (s, 6H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=159.4 (C), 157.1 (C), 102.4 (CH), 67.6 ($2CH_2$), 66.0 ($2CH_2$), 57.8 (C), 48.5 ($2CH_2$), 47.3 ($2CH_2$), 23.6 ppm ($2CH_3$); IR (KBr): $\tilde{\nu}$=2968 (s), 2856 (s), 1655 (m), 1610 (s), 1452 (m), 1243 (m), 1117 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 281 (4) $[M]^+$, 266 (7) $[M-CH_3]^+$, 195 (100) $[C_4H_8NO]^+$, 128 (54) $[C_7H_{14}NO]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{23}N_3O_3$ $[M]^+$ 281.17394; found: 281.17272.

4-(4-Phenyloxazol-5-yl)morpholine (7): Isocyanide **4c** (1.0 mmol), **3a** (162 μL, 160 mg, 1.5 mmol), **2a** (150 μL, 118 mg, 2.0 mmol), $MgSO_4$ (100 mg), and AgOAc (3.3 mg, 0.020 mmol, 2.0 mol%) were stirred in MeOH (5 mL) for 21 h. Water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting mixture was purified by means of column chromatography (silica gel, EtOAc/cyclohexane 1:3, R_f=0.31) to furnish **7** as a pale yellow solid (150 mg, 0.65 mmol, 65%). M.p. 67–70°C; ^1H NMR (250.13 MHz, $CDCl_3$): δ=7.97–7.94 (m, 2H), 7.66 (s, 1H), 7.44–7.24 (m, 3H), 3.88–3.85 (m, 4H), 3.15–3.11 ppm (m, 4H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=151.2 (CH), 146.0 (C), 131.6 (C), 128.5 (2CH), 127.1 (CH), 125.9 (2CH), 123.3 (C), 66.9 ($2CH_2$), 50.3 ppm ($2CH_2$); IR (KBr): $\tilde{\nu}$=3116 (w), 2852 (s), 1645 (s), 1515 (s), 1110 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%): 230 (100) $[M]^+$, 144 (3) $[M-C_4H_8NO]^+$, 77 (10) $[C_6H_5]^+$; HRMS (EI, 70 eV): *m/z* calcd for $C_{13}H_{14}N_2O_2$ $[M]^+$: 230.10608; found: 230.10564.

1-(5-Methoxy-4-phenyloxazol-2-yl)cyclohexanol (8): General procedure 7 was followed using **1d** (175 mg, 1.0 mmol), cyclohexanone (**2e**; 124 μL, 118 mg, 1.2 mmol), and *t*-butylamine (**3e**; 126 μL, 88 mg, 1.2 mmol) to give **8** as a yellow oil (85 mg, 0.31 mmol, 31%). R_f=0.33 (EtOAc/cyclohexane 1:3); ^1H NMR (250.13 MHz, $CDCl_3$): δ=7.80 (d, ^3J=7.8 Hz, 2H), 7.37 (t, ^3J=7.8 Hz, 2H), 7.21 (t, ^3J=7.8 Hz, 1H), 4.05 (s, 3H), 2.57 (s, 1H), 2.13–1.39 ppm (m, 10H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$): δ=158.1 (C), 154.2 (C), 131.2 (C), 128.4 (2CH), 126.3 (CH), 125.0 (2CH), 114.3 (C), 70.7 (C), 59.9 (CH_3), 36.2 ($2CH_2$), 25.1 (CH_2), 21.8 ppm ($2CH_2$); IR (KBr): $\tilde{\nu}$=3406 (s), 2938 (s), 2859 (m), 1643 (s), 1448 (m), 1370 (m), 1213 (m), 1017 (m), 696 cm^{-1} (m); MS (FAB, 3 KeV): *m/z* (%): 274 (79) $[M+H]^+$, 256 (75) $[M-HO]^+$, 175 (100) $[M-C_6H_{10}O]^+$, 77 (75) $[C_6H_5]^+$; HRMS (FAB, 3 KeV): *m/z* calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1443; found: 274.1454.

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