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Note

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Synthesis of differentially substituted 2-aminoimidazolidines *via* a microwave-assisted tandem Staudinger/aza-Wittig cyclization

Rakesh Kumar, Denis S. Ermolat'ev,* and Erik V. Van der Eycken*[a]

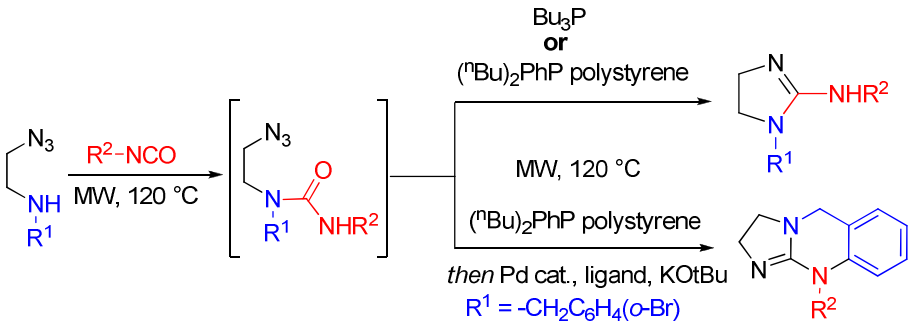
Laboratory for Organic & Microwave-Assisted Chemistry

(LOMAC), Department of Chemistry, University of Leuven

(KU Leuven), Celestijnenlaan 200F, B-3001, Leuven, Belgium.

E-mails: erik.vandereycken@chem.kuleuven.be

denis.ermolatev@chem.kuleuven.be



Abstract: A new route for the construction of 2-aminoimidazolidines including analogues of the α_2 adrenergic agonist drug clonidine is elaborated. The key step is an intramolecular microwave-assisted Staudinger/aza-Wittig cyclization of an *in situ* generated urea intermediate (formed by the reaction of *β*-amino azide and isocyanate) upon treatment with Bu_3P or polymer-supported phosphine reagent, allowing the introduction of various substituents at the N1 and the 2-amino function. Furthermore, a useful one-pot Staudinger/aza-Wittig/Buchwald-Hartwig protocol leading to bicyclic guanidines has been elaborated.

The cyclic guanidine structure (2-aminoimidazolidine) represents an important structural motif prevalent in a myriad of natural products and pharmacologically active molecules.[1-2] In particular, the 2-aminoimidazolidine core is an integral part of many drugs, therapeutic leads (e.g. potent DNA minor groove binder)[2a,b] and bioactive natural products. For instance, the centrally acting α_2-adrenergic agonist drugs clonidine (antihypertensive/anaesthetic) and brimonidine (antiglaucoma) contain the 2-aminoimidazolidine core as the active pharmacophore in their structure (Figure 1). Similarly, natural compounds such as the antibiotics of the Streptothricin family and the antitumour agent NA22598A1 contain the 2-aminoimidazolidine scaffold (Figure 1). Besides this, 2-aminoimidazolidines and their bicyclic analogues have found numerous applications[3-4] as e.g. in catalytic deprotonation processes (due to their superbasic nature), in asymmetric catalysis or as sensors for anion recognition.

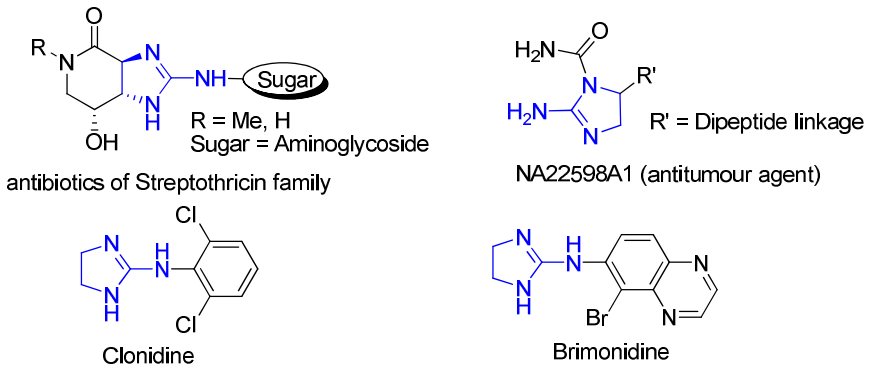
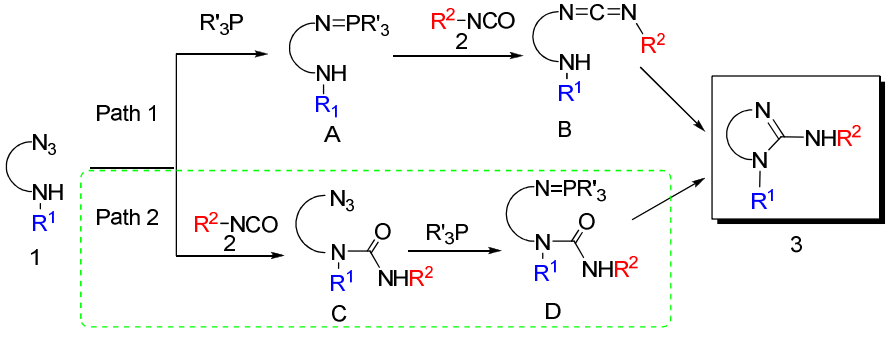


Figure 1. Natural products and drug candidates containing the 2-aminoimidazolidine core.

Owing to the immense potential, the development of novel synthetic methodologies for the construction of 2-aminoimidazolidines is challenging. Moreover these structures show a high basicity.[4] The common approaches[4-7] for their synthesis utilize assembled amine/diamine precursors,[4,5] modification/cyclization of the guanidine core[6] etc.. Other strategies[7] include the reaction of olefins with cyanimides (using NBS),[7a] cycloguanidation of olefins (using metal catalyst),[7b,c] Tiemann rearrangement[7d] etc.. However, a majority of the above protocols are either

limited in terms of diversity regarding the N1 and 2-amino substitution pattern, or utilize multistep protection-deprotection.

Recently, the Staudinger/aza-Wittig reaction has received much attention for the synthesis of substituted *N*-containing heterocycles.[8] In this context, the reaction of *β*-amino azides **1** with isocyanates **2** seems an attractive proposition to access differentially substituted 2-aminoimidazolidines (possible reaction pathways are depicted in Scheme 1). Path 1 would proceed through the formation of the iminophosphorane **A**, followed by the carbodiimide intermediate **B** and finally intramolecular cyclization to the desired compound **3**. However, isocyanate can lead to a side reaction with the NH-group of **A**, besides formation of the desired carbodiimide **B**. To avoid this problem, the protection of the NH-group would be indispensable. Shipman *et al*.[9] explored a similar strategy using protected *β*-amino azide (R^1 = Boc, Cbz, etc.) with isocyanates. We envisioned that, reaction of **1** with **2** would generate intermediate **C** (Path 2). Staudinger reaction of **C** with a suitable phosphine reagent would lead to intermediate **D** which on heating is expected to undergo cyclization to afford the desired guanidine **3.** To the best of our knowledge, such a tandem route involving a Staudinger/aza-Wittig cyclization of an *in situ* formed urea intermediate **C** has so far not been reported. This approach should also avoid the necessity to protect the secondary amine **1** (Path 1).



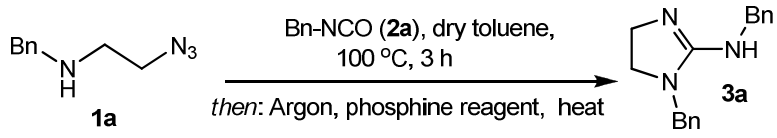
Scheme 1. Possible reaction pathways for 2-aminoimidazolidines from *β*-amino azide and isocyanates; Path 1) carbodiimide route, Path 2) urea route.

Our ongoing interest in the synthesis of 2-aminoimidazole derivatives as novel antibiofilm compounds[10] encouraged us to explore this new approach towards the related 2-aminoimidazolidines. We herein disclose our results starting from *β*-amino azides and isocyanates employing a tandem Staudinger/aza-Wittig cyclization without any protection-deprotection manipulations. The protocol allows a facile access to a various substitution pattern on N1 as well as on the 2-amino function. Initially, the Staudinger/aza-Wittig cyclization was performed using 2-azido-*N*-benzylethanamine (**1a**) and benzyl isocyanate (**2a**) as substrates (Table 1). A mixture of **1a** (0.71 mmol), **2a** (0.71 mmol) in dry toluene (1 mL) was heated at 100 ^{o}C to form the urea intermediate. Thereafter, Bu_3P (1 equiv.) was added, and the resulting mixture was further heated at 100 ^{o}C for 20h (Table 1, entry 1). This condition afforded the desired product **3a** without any side product.[11] However, **3a** could not be isolated efficiently through column chromatography over silica gel due to the superbasic nature of this compound which was also amalgamated with Bu_3P=O. Attempt to purify the highly polar **3a** by reversed phase preparative HPLC (ACN/H_2O with 0.1% HCOOH) resulted in the corresponding formate salt **3a'**.[12]

Finally, we were able to purify **3a** (93%, Table 1, entry 1) using neutral alumina as stationary phase. Subsequently, a detailed optimization study was conducted to evaluate the effect of temperature, time and phosphine reagent (Table 1). The reaction resulted in a comparable yield when performed at 120 ^{o}C (Table 1, entries 1 and 2). However at higher temperature (140 ^{o}C) some decomposition of the product was observed (Table 1, entry 3). Interestingly, cyclization could not be completed at lower temperature as below 100 ^{o}C some open chain intermediates were detected by NMR (Table 1, entries 4, 5 and 6). Replacement of benzyl isocyanate by the corresponding isothiocyanate also provided **3a** in a comparative yield

of 82% (Table 1, entry 7). Screening of other phosphine reagents such as PPh_3, $(o\text{-tol})_3P$, 1,4-bis(diphenylphosphino)butane (DPPB) or stericaly hindered $(t\text{-Bu}_3)P$, provided **3a** in significantly lower yields than $n\text{-Bu}_3P$ (Table 1, entries 8-11). Furthermore, shortening the reaction time (using $n\text{-Bu}_3P$) from 20h to 5h or 10h decreased the yield of **3a** (Table 1, entry 12). To our satisfaction the application of microwave irradiation (120 °C) dramatically enhanced the reaction rate as **3a** could be accessed within 25 min (5 min for the first step and 20 min for the cyclization step) in 95% yield (Table 1, entry 15).

Table 1. Optimization of the one-pot synthesis of 2-aminoimidazolidines.[a]

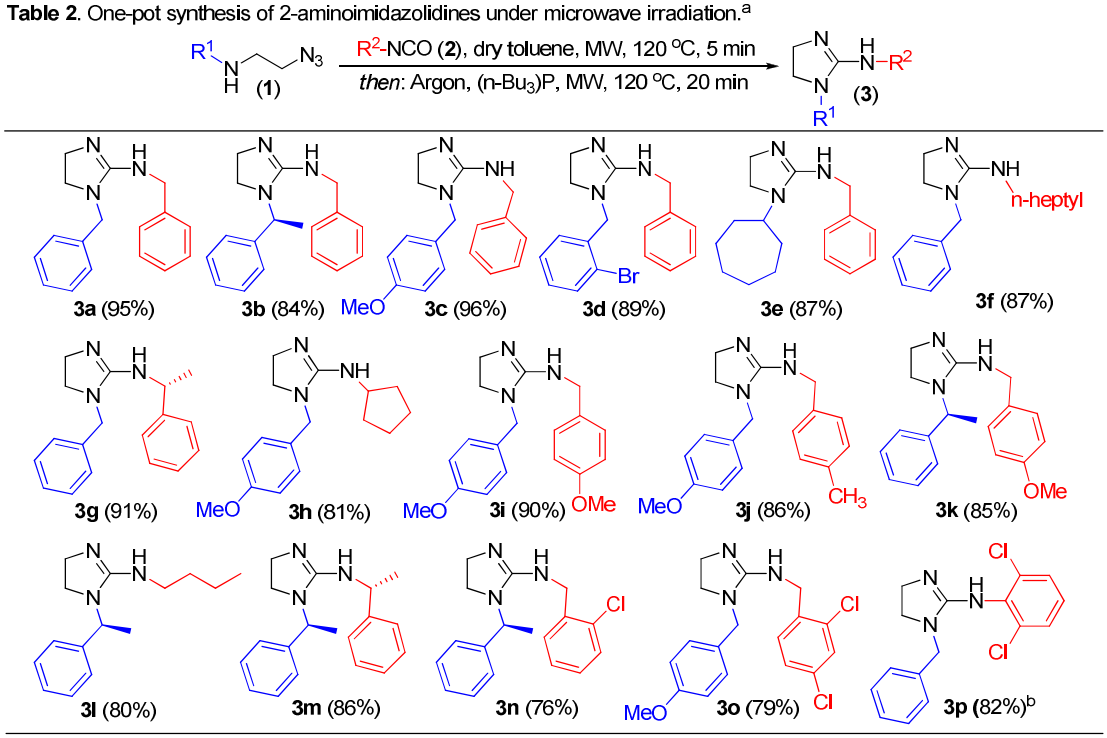


Entry	Temperature (°C)	Phosphine reagent	Yield (%)[b] of **3a**
1	100	$(n\text{-Bu})_3P$	93
2	120	$(n\text{-Bu})_3P$	91
3	140	$(n\text{-Bu})_3P$	86
4	80	$(n\text{-Bu})_3P$	69
5	50	$(n\text{-Bu})_3P$	38
6[c]	r.t.	$(n\text{-Bu})_3P$	< 5
7[d]	100	$(n\text{-Bu})_3P$	82
8	100	PPh_3	49
9	100	$(t\text{-Bu})_3P$	51
10	100	$(o\text{-tol})_3P$	36
11[e]	100	DPPB	74
12	100	$(n\text{-Bu})_3P$	58, 88[f]
13[g]	100	$(n\text{-Bu})_3P$	75
14[h]	120	$(n\text{-Bu})_3P$	90
15[h,i]	120	$(n\text{-Bu})_3P$	95

[a]General conditions: **1a** (0.71 mmol), Bn-NCO (0.71 mmol), dry toluene (1 mL), 100 °C, 3 h; then phosphine reagent (0.71 mmol) under Ar atmosphere, stirring for 20 min and finally heating for 20 h. [b]Yield of isolated product after column chromatography using neutral alumina. [c]Stirring at r.t. for 72 h. [d]Bn-NCS was used instead of Bn-NCO. [e]0.36 mmol of DPPB was used. [f]Yield after 5 h and 10 h respectively. [g]MW, 100 °C; 1st step for 5 min then 2nd step for 1 h. [h]MW, 120 °C; 1st step for 5 min then 2nd step for 20 min. [i]Use of 0.78 mmol of $(n\text{-Bu})_3P$.

The utility of our optimized microwave conditions (Table 1, entry 15) was further ascertained through the tandem synthesis of other 2-aminoimidazolidines bearing electron- donating as well as electron withdrawing substituents either on the parts derived from the *β*-amino azide or the isocyanate (Table 2).

Table 2. One-pot synthesis of 2-aminoimidazolidines under microwave irradiation.[a]



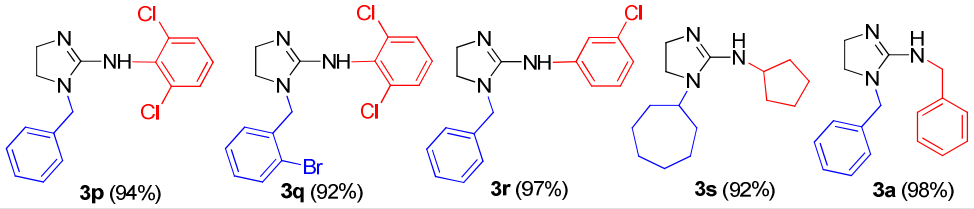
[a]See Experimental Section; Yields in parentheses are of pure isolated product after column chromatography using neutral alumina. [b]Yield on the basis of NMR using 1,3,5-trimethoxybenzene as internal standard.

In particular, aliphatic as well as cyclic coupling partners could be successfully employed (Table 2, **3e**, **3f**, **3h** and **3l**). Importantly, chiral imidazolidine derivatives, finding huge potential in asymmetric catalysis,[3c-e,5d] could be easily accessed by incorporating the chirality of the parent isocyanate or *β*–amino azide (Table 2, see products; **3b**, **3g** and **3k-3n**).

Then, we turned our attention to the synthesis of biologically important clonidine derivatives. Employing the optimized conditions, the reaction of **1a** with 2,6-dichlorophenyl isocyanate (**2j**) provided the product **3p** in 82% yield (NMR basis) (Table 2). However,

particularly in this example, the complete removal of $Bu_3P=O$ proved to be difficult, although the corresponding benzyl analogs **3n** and **3o** (using 2-chlorobenzyl isocycanate and 2,4-dichlorobenzyl isocycanate) could be isolated in good yields (Table 2). To solve the purification problem we investigated the possibility to use polymer-supported phosphine reagent. Satisfactorily the reaction between **1a** and **2j**, when performed with $(^nBu)_2PhP$ cross-linked polystyrene, finally provided **3p** in an excellent yield of 94% (Table 3) without the need of column purification. The generality of this protocol was extended with the synthesis of various clonidine analogues (Table 3, **3q**-**3r**) and other 2-aminoimidazolidines (Table 3, **3s**, **3a**).

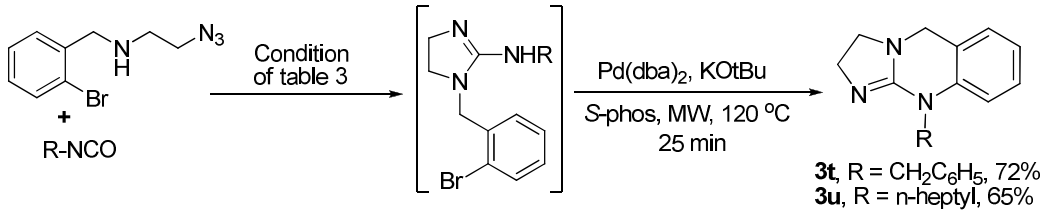
Table 3. Application of polymer-supported phosphine reagent in the synthesis of clonidine analogues and other 2-aminoimidazolidines.[a]



3p (94%) **3q** (92%) **3r** (97%) **3s** (92%) **3a** (98%)

[a]See Experimental Section; Yields in parentheses are of pure isolated product after passing through a small bed of neutral alumina.

Interestingly, the above approach was also found to be applicable for the first concise synthesis of non-symmetrical {6,5}-bicyclic guanidines[13] *via* a hitherto unknown tandem Staudinger/aza-Wittig/Buchwald-Hartwig coupling strategy (Scheme 2). Notably, the Buchwald-Hartwig step using CuI could not provide complete conversion, even after a long reaction time, whereas reaction with a Pd catalyst was found quite effective. The resulting guanidine framework has important applications[3,13] in organocatalysis, anion recognition and supramolecular chemistry. Moreover, the known synthetic methodologies for such a scaffold predominantly rely on the use of multistep procedures using harsh reaction conditions and expensive starting materials.[13]



Scheme 2. One-pot Staudinger/aza-Wittig/Buchwald-Hartwig coupling approach for the synthesis of bicyclic guanidines.

CONCLUSIONS

In conclusion, a new route to 2-aminoimidazolidines *via* a tandem Staudinger/aza-Wittig reaction has been elaborated. A various substitution pattern at the N1 as well as the amino function could be introduced. Interestingly, the application of a polymer-supported phosphine reagent allowed the easy access to clonidine analogues without the need of purification. Furthermore, a novel Staudinger/aza-Wittig/Buchwald-Hartwig tandem protocol was elaborated for the synthesis of bicyclic guanidines.

EXPERIMENTAL SECTION

General experimental methods. All the reagents (isocyanates and phosphine reagents) and solvents used for isolation/purification of final compounds were purchased from commercial sources and used as such. Anhydrous toluene (stored over molecular sieves) was used. For thin-layer chromatography, pre-coated TLC plates (0.2 mm, Aluminium oxide N/UV_{254}) were used. Column chromatography was performed using neutral alumina (Brockmann 1, 50-200 µm). All microwave irradiation experiments were carried out in a CEM Discover© monomode microwave operating at a frequency of 2.45 GHz. The reactions were carried out in 10-mL glass tubes, sealed with Teflon septum. The temperature of reactions in microwave experiments was measured by an inbuilt infrared temperature probe. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a 300 MHz spectrometer using tetramethylsilane as internal reference. In addition, the ^{1}H NMR spectra of compound **3c** at different temperature was recorded on a 400

MHz spectrometer (see, supporting information). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet, q = quartet. The ^{13}C NMR spectra are proton decoupled. Mass spectra were recorded at ion source temperature of 150-250°C, as required. High resolution EI-mass spectra (using double focusing magnetic sector as mass analyzer) were performed with a resolution of 10,000.

Synthesis of starting *β*-amino azides (1a-1e): *β*-Amino azides were synthesized from bromo ethanol (8.55 mmol) using an earlier reported procedures.[14] The NMR spectral data are given below:

2-Azido-*N*-benzylethanamine[14] (1a): Colorless oil (1.09 g, yield 73%), ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.33-7.23 (m, 5H), 3.81(s, 2H), 3.43 (t, *J* = 5.4 Hz, 2H), 2.83 (t, *J* = 5.8 Hz, 2H), 1.53 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 139.9, 128.4, 128.0, 127.0, 53.5, 51.4, 47.9. HRMS-EI: m/z $[M]^+$ for $C_8H_{10}N$, calculated 120.0813; observed 120.0809.

(*R*)-2-Azido-*N*-(1-phenylethyl)ethanamine (1b): Colorless oil (1.08 g, yield 67%), ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.35-7.21 (m, 5H), 3.80 (q, *J* = 6.6 Hz, 1H), 3.42-3.28 (m, 2H), 2.72-2.56 (m, 2H), 1.68 (bs, 1H), 1.37 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 145.2, 128.5, 127.0, 126.5, 58.0, 51.6, 46.4, 24.4. HRMS-EI: m/z $[M]^+$ for $C_9H_{12}N$, calculated 134.0970; observed 134.0972.

2-Azido-*N*-(4-methoxybenzyl)ethanamine (1c): Light yellow oil (1.27 g, yield 72%), ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 2H), 3.43 (t, *J* = 5.6 Hz, 2H), 2.82 (t, *J* = 5.8 Hz, 2H), 1.60 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 158.7, 132.0, 129.2, 113.8, 55.2, 52.9, 51.4, 47.8. HRMS-EI: m/z $[M]^+$ for $C_9H_{12}NO$, calculated 150.0919; observed 150.0924.

2-Azido-*N*-(2-bromobenzyl)ethanamine (1d): Light yellow oil (1.16 g, yield 53%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.55 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 6.6 Hz, 1H), 7.31-7.26 (m, 1H), 7.15-7.10 (m, 1H), 3.89 (s, 2H), 3.45 (t, *J* = 5.4 Hz, 2H), 2.83 (t, *J* = 5.8 Hz, 2H), 1.80 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 138.8, 132.8, 130.1, 128.7, 127.5, 123.9, 53.3, 51.4, 47.7. HRMS-EI: m/z $[M]^+$ for C_7H_8N, calculated 106.0657; observed 106.0645.

***N*-(2-Azidoethyl)cycloheptanamine (1e):** Light yellow oil (0.79 g, yield 51%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.43 (t, *J* = 5.4 Hz, 2H), 2.80 (t, *J* = 5.8 Hz, 2H), 2.67-260 (m, 1H), 1.86-1.78 (m, 2H), 1.69-1.35 (m, 11H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 58.7, 51.8, 46.1, 34.9, 28.2, 24.3. HRMS-EI: m/z $[M]^+$ for $C_8H_{16}N$, calculated 126.1283; observed 126.1273. **CAUTION:** Although the organic azides have not shown any explosive hazard under the developed experimental conditions, appropriate safety measures (e.g. face shield and leather gloves) must always be taken at all times.

Representative procedure for the preparation of *N*,1-Dibenzyl-4,5-dihydro-1*H*-imidazol-2-amine (Table 2, 3a). To a solution of 2-azido-*N*-benzylethanamine (**1a**, 0.71 mmol) in dry toluene (1 mL) benzyl isocyanate (**2a**, 0.71 mmol) was added and the resulting reaction mixture was irradiated at a ceiling temperature of 120 °C (maximum power 250 W) for 5 min. After cooling of the reaction mixture to ambient temperature, n-Bu_3P (0.78 mmol) was added dropwise under argon atmosphere and the reaction mixture was allowed to stir for 20 min. Thereafter the reaction vial was filled with argon, sealed and irradiated at a ceiling temperature of 120 °C (maximum power 250 W) for 20 min. The solvent was evaporated under reduced pressure and the obtained residue was subjected to column chromatography over neutral alumina using 1-5% MeOH in DCM as eluent to afford **3a** as a white sticky solid in 95% yield (179 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.85 & 8.87 (bs, 1H), 7.60-7.57 (m, 2H), 7.24-7.15 (m, 8H), 4.67 (s,

4H), 3.40-3.34 (m, 2H), 3.24-3.18 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 157.6, 136.9, 134.1, 128.8, 128.4 (3), 128.2, 127.6, 49.3, 46.9, 46.0, 40.8. HRMS-EI: m/z $[M]^+$ for $C_{17}H_{19}N_3$, calculated 265.1579; observed 265.1579.

The above procedure was also followed for synthesis of various other 2-aminoimidazolidines[15] (Table 2, **3b-3p**).

(*S*)-*N*-Benzyl-1-(1-phenylethyl)-4,5-dihydro-1*H*-imidazol-2-amine (3b): Viscous liquid (166 mg, yield 84%), ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 9.41 & 8.80 (bs, 1H), 7.41-7.29 (m, 10H), 5.49-5.47 (m, 1H), 4.51 (2H, s), 3.75-3.66 (m, 1H), 3.60-3.50 (m, 2H), 3.29-3.20 (1H, m), 1.56 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ (ppm) 156.9, 138.7, 137.1, 128.6, 128.3, 127.9, 127.4, 127.2, 126.8, 51.2, 45.3, 42.6, 16.6. HRMS-EI: m/z $[M]^+$ for $C_{18}H_{21}N_3$, calculated 279.1735; observed 279.1720.

***N*-Benzyl-1-(4-methoxybenzyl)-4,5-dihydro-1*H*-imidazol-2-amine (3c):** White solid (201 mg, yield 96%), m.p. 145-149°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.83 & 8.84 (bs, 1H), 7.61 (d, J = 6.2 Hz, 2H), 7.26-7.20 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 4.73 (s, 2H), 4.64 (s, 2H), 3.74 (s, 3H), 3.47-3.42 (m, 2H), 3.28-3.23 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 159.5, 157.5, 137.0, 129.9, 128.4 (2), 127.6, 126.1, 114.2, 55.3, 48.7, 46.8, 46.0, 40.8. HRMS-EI: m/z $[M]^+$ for $C_{18}H_{21}N_3O$, calculated 295.1685; observed 295.1684.

***N*-Benzyl-1-(2-bromobenzyl)-4,5-dihydro-1*H*-imidazol-2-amine (3d):** Viscous colourless liquid (217 mg, yield 89%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.75 & 9.07 (bs, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.7 Hz, 1H), 7.28-7.11 (m, 6H), 4.88 (s, 2H), 4.74 (s, 2H), 3.55-3.46 (m, 2H), 3.32-3.26 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 157.6, 136.9, 133.5, 133.1, 130.7, 130.0, 128.5, 128.4, 128.1, 127.6, 124.2, 49.1, 46.9, 46.2, 41.0. HRMS-EI: m/z $[M]^+$ for $C_{17}H_{18}BrN_3$, calculated 343.0684; observed 343.0647.

***N*-Benzyl-1-cycloheptyl-4,5-dihydro-1*H*-imidazol-2-amine (3e):** White sticky solid (167 mg, yield 87%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.58 & 8.32 (bs, 1H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.31-7.22 (m, 3H), 4.70 (s, 2H), 4.44-4.40 (m, 1H), 3.56-3.54 (m, 2H), 3.49-3.47 (m, 2H), 1.79-1.47 (m, 12H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 157.1, 137.1, 128.5, 128.2, 127.6, 54.9, 45.9, 42.8, 41.0, 32.2, 27.5, 24.2. HRMS-EI: m/z $[M]^+$ for $C_{17}H_{25}N_3$, calculated 271.2048; observed 271.2036.

1-Benzyl-*N*-heptyl-4,5-dihydro-1*H*-imidazol-2-amine (3f): Viscous colourless liquid (169 mg, yield 87%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.06 & 8.87 (bs, 1H), 7.32-7.25 (m, 5H), 4.76 (s, 2H), 3.57-3.47 (m, 4H), 3.39-3.33 (m, 2H), 1.70-1.65 (m, 2H), 1.27-1.23 (m, 8H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 157.7, 134.5, 128.8, 128.4, 128.2, 49.4, 47.0, 43.9, 40.9, 31.7, 29.2, 29.0, 26.6, 22.6, 14.1. HRMS-EI: m/z $[M]^+$ for $C_{17}H_{27}N_3$, calculated 273.2205; observed 273.2208.

(*R*)-1-Benzyl-N-(1-phenylethyl)-4,5-dihydro-1*H*-imidazol-2-amine (3g): White solid (180 mg, yield 91%), m.p. 85-88°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.39 & 8.75 (bs, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.23-7.17 (m, 8H), 5.29-5.24 (m, 1H), 4.91-4.79 (m, 2H), 3.51-3.42 (m, 1H), 3.35-3.13 (m, 3H), 1.71 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 157.1, 142.7, 134.4, 128.8, 128.5, 128.3, 128.1, 127.5, 126.8, 54.4, 49.6, 47.0, 40.9, 23.1. HRMS-EI: m/z $[M]^+$ for $C_{18}H_{21}N_3$, calculated 279.1735; observed 279.1737.

***N*-Cyclopentyl-1-(4-methoxybenzyl)-4,5-dihydro-1*H*-imidazol-2-amine (3h):** White solid (157 mg, yield 81%), m.p. 214-218°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.88 & 8.42 (bs, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.72 (s, 2H), 4.24-4.20 (m, 1H), 3.79 (s, 3H), 3.60-3.55 (m, 2H), 3.41-3.35 (m, 2H), 1.85-1.55 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 159.5, 157.3, 129.8, 126.6, 114.1, 56.1, 55.3, 49.0, 47.0, 40.9, 32.5, 23.9. HRMS-EI: m/z

$[M]^+$ for $C_{16}H_{23}N_3O$, calculated 273.1841; observed 273.1849.

***N*,1-Bis(4-methoxybenzyl)-4,5-dihydro-1*H*-imidazol-2-amine (3i):** Off white sticky solid (208 mg, yield 90%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.76 & 8.74 (bs, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.79-6.75 (m, 4H), 4.69 (s, 2H), 4.63 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 3.52-3.47 (m, 2H), 3.31-3.25 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 159.5, 159.0, 157.4, 129.9, 129.8, 129.1, 126.1, 114.2, 113.8, 55.2(2), 48.7, 46.8, 45.5, 40.9. HRMS-EI: m/z $[M]^+$ for $C_{19}H_{23}N_3O_2$, calculated 325.1790; observed 325.1798.

1-(4-Methoxybenzyl)-*N*-(4-methylbenzyl)-4,5-dihydro-1*H*-imidazol-2-amine (3j): Viscous liquid (189 mg, yield 86%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.77 & 8.78 (bs, 1H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.03-7.01 (m, 2H), 6.77 (d, *J* = 8.1 Hz, 2H), 4.66 (s, 2H), 4.61 (s, 2H), 3.74 (s, 3H), 3.46-3.40 (m, 2H), 3.26-3.21 (m, 2H), 2.26 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 159.4, 157.6, 137.2, 133.9, 129.9, 129.1, 128.4, 126.1, 114.1, 55.2, 48.8, 46.8, 45.8, 40.9, 21.1. HRMS-EI: m/z $[M]^+$ for $C_{19}H_{23}N_3O$, calculated 309.1841; observed 309.1845.

(*S*)-*N*-(4-Methoxybenzyl)-1-(1-phenylethyl)-4,5-dihydro-1*H*-imidazol-2-amine (3k): Pale yellow solid (187 mg, yield 85%), m.p. 89-93°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.67 & 8.71 (bs, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.26-7.28 (m, 5H), 6.77 (d, *J* = 8.2 Hz, 2H), 5.83 (q, *J* = 6.4 Hz, 1H), 4.69 (s, 2H), 3.72 (s, 3H), 3.55-3.41 (m, 3H), 3.17-3.11 (m, 1H), 1.52 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 159.0, 157.2, 138.1, 129.7, 129.1, 128.7, 128.1, 127.1, 113.8, 55.2, 52.2, 45.4, 42.6, 40.8, 16.2. HRMS-EI: m/z $[M]^+$ for $C_{19}H_{23}N_3O$, calculated 309.1841; observed 309.1849.

(*S*)-*N*-Butyl-1-(1-phenylethyl)-4,5-dihydro-1*H*-imidazol-2-amine (3l): Light yellow oil (139 mg, yield 80%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.93 & 8.83 (bs, 1H), 7.33-7.27 (m, 5H),

5.88 (q, *J* = 6.5 Hz, 1H), 3.60-3.47 (m, 5H), 3.22-3.15 (m, 1H), 1.70-1.61 (m, 2H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.42-1.20 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 157.2, 138.4, 128.7, 128.1, 127.1, 52.0, 43.6, 42.7, 40.7, 31.2, 19.8, 16.2, 13.8. HRMS-EI: m/z $[M]^+$ for $C_{15}H_{23}N_3$, calculated 245.1892; observed 245.1892.

***N*-((*R*)-1-Phenylethyl)-1-((*S*)-1-phenylethyl)-4,5-dihydro-1*H*-imidazol-2-amine (3m):** White solid (179 mg, yield 86%), m.p. 248-251°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.23 & 8.69 (bs, 1H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.30-7.15 (m, 8H), 6.21 (q, *J* = 6.6 Hz, 1H), 5.29-5.23 (m, 1H), 3.51-3.28 (m, 3H), 3.15-3.06 (m, 1H), 1.68 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 156.6, 142.9, 138.4, 128.7, 128.5, 128.0, 127.3, 127.2, 126.8, 54.4, 52.1, 42.6, 40.8, 23.2, 16.0. HRMS-EI: m/z $[M]^+$ for $C_{19}H_{23}N_3$, calculated 293.1892; observed 293.1901.

(*S*)-*N*-(2-Chlorobenzyl)-1-(1-phenylethyl)-4,5-dihydro-1*H*-imidazol-2-amine (3n): Light yellow solid (169 mg, yield 76%), m.p. 86-90°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.30 & 8.83 (bs, 1H), 7.50-7.47 (m, 1H), 7.32-7.25 (m, 6H), 7.19-7.14 (m, 2H), 5.81 (q, *J* = 6.5 Hz, 1H), 4.83-4.69 (m, 2H), 3.55-3.44 (m, 3H), 3.30-3.21 (m, 1H), 1.56 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 157.6, 138.2, 133.9, 133.2, 129.9, 129.4, 129.1, 128.8, 128.2, 127.1, 127.0, 52.7, 44.6, 43.3, 40.9, 16.8. HRMS-EI: m/z $[M]^+$ for $C_{18}H_{20}ClN_3$, calculated 313.1346; observed 313.1349.

***N*-(2,5-Dichlorobenzyl)-1-(4-methoxybenzyl)-4,5-dihydro-1*H*-imidazol-2-amine (3o):** Off white solid (204 mg, yield 79%), m.p. 150-153°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.49 & 8.88 (bs, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.28 (s, 1H), 7.19-7.12 (m, 3H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.74 (s, 2H), 4.66 (s, 2H), 3.77 (s, 3H), 3.53-3.48 (m, 2H), 3.42-3.37 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 159.6, 157.8, 134.1 (2), 132.7, 130.9, 129.9, 129.2, 127.2, 125.9, 114.2,

55.3, 48.9, 47.2, 44.2, 41.0. HRMS-EI: m/z $[M]^+$ for $C_{18}H_{19}Cl_2N_3O$, calculated 363.0905; observed 363.0902.

Representative procedure for the preparation of 1-Benzyl-*N*-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine (Table 3, 3p) using polymer-supported phosphine reagent [(^{n}Bu)$_2$PhP Polystyrene]. To a solution of 2-azido-*N*-benzylethanamine (**1a**, 0.14 mmol) in dry toluene (1 mL), 2,6-dichlorophenyl isocyanate (**2j**, 0.14 mmol) was added and the resulting reaction mixture was irradiated at a ceiling temperature of 120 °C (maximum power 250 W) for 5 min. After cooling of the reaction mixture to ambient temperature, dry toluene (1.5 mL) followed by (^{n}Bu)$_2$PhP polystyrene (0.25 g, 0.66 mmol/g) were added under argon atmosphere. Thereafter the reaction vial was filled with argon, sealed and irradiated under microwave at a ceiling temperature of 120 °C (maximum power 250 W) for 20 min. The resin was filtered off and washed with DCM. The obtained filtrate was passed through a small bed of neutral alumina to give **3p** as a viscous liquid in 94% yield (42 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.49 (d, *J* = 7.1 Hz, 2H), 7.38-7.27 (m, 5H), 6.85 (t, *J* = 7.7 Hz, 1H), 4.64 (s, 2H), 3.82 (bs, 1H), 3.36-3.38 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 155.0, 145.5, 137.3, 129.4, 128.4, 128.2, 127.3, 122.5, 48.5, 45.7, 40.2. HRMS-EI: m/z $[M]^+$ for $C_{16}H_{15}Cl_2N_3$, calculated 319.0643; observed 319.0615.

The above procedure was also followed for synthesis of various other 2-aminoimidazolidines (Table 3, **3a, 3q-3s**).

1-(2-Bromobenzyl)-*N*-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine (3q): Viscous liquid (51 mg, yield 92%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.71 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.33-7.14 (m, 4H), 6.85 (t, *J* = 7.7 Hz, 1H), 4.78 (s, 2H), 3.84 (bs, 1H), 3.44-3.46 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 154.9, 145.3, 136.4, 132.6, 130.1, 129.4,

128.8, 128.2, 127.7, 123.7, 122.6, 48.1, 46.3, 40.3. HRMS-EI: m/z $[M]^+$ for $C_{16}H_{14}BrCl_2N_3$, calculated 396.9748; observed 396.9723.

1-Benzyl-*N*-(3-chlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine (3r): Viscous liquid (39 mg, yield 97%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.36-7.25 (m, 5H), 7.19-7.14 (m, 1H), 7.00 (s, 1H), 6.93-6.85 (m, 2H), 4.53 (s, 2H), 4.22 (bs, 1H), 3.36-3.34 (m, 2H), 3.30-3.32 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 155.8, 152.6, 137.3, 134.3, 130.0, 128.5, 128.2, 127.3, 123.1, 121.5 (2), 48.6, 45.8, 40.3. HRMS-EI: m/z $[M]^+$ for $C_{16}H_{16}ClN_3$, calculated 285.1033; observed 285.1010.

1-Cycloheptyl-*N*-cyclopentyl-4,5-dihydro-1*H*-imidazol-2-amine (3s): Brown sticky solid (32 mg, yield 92%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.75 & 8.25 (bs, 1H), 4.66-4.59 (m, 1H), 4.22-4.13 (m, 1H), 3.64-3.52 (m, 4H), 2.09-2.04 (m, 2H), 1.90-1.46 (m, 18H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 156.6, 56.1, 54.4, 42.8, 41.0, 32.4, 32.0, 27.8, 23.9 (2). HRMS-EI: m/z $[M]^+$ for $C_{15}H_{27}N_3$, calculated 249.2205; observed 249.2197.

General Microwave-assisted tandem protocol for the preparation of bicyclic guanidines (3t and 3u, Scheme 2): To a solution of 2-azido-*N*-(2-bromobenzyl)ethanamine (0.14 mmol) in dry toluene (1 mL), isocyanate (0.14 mmol) was added and the resulting reaction mixture was irradiated at a ceiling temperature of 120 °C (maximum power 250 W) for 5 min. After cooling of the reaction mixture to ambient temperature, dry toluene (1.5 mL) followed by $(^nBu)_2PhP$ polystyrene (0.25 g, 0.66 mmol/g) were added under argon atmosphere. Thereafter the reaction vial was filled with argon, sealed and irradiated under microwave at a ceiling temperature of 120 °C (maximum power 250 W) for 20 min to obtain the corresponding 2-aminoimidazolidine. After cooling, $Pd(dba)_2$ (10 mol%), *S*-phos (20 mol%) and KOtBu (2.0 equiv.) were added to the reaction mixture. Thereafter the reaction vial was filled with argon, sealed and irradiated at a

ceiling temperature of 120 °C (maximum power 250 W) for 25 min. After completion of the reaction, the resin was filtered off and washed with DCM. The obtained filtrate was evaporated under reduced pressure. The obtained residue was subjected to column chromatography over neutral alumina using 0.5-2% MeOH in DCM as eluent to afford bicyclic guanidines **3t** and **3u**.

10-benzyl-2,3,5,10-tetrahydroimidazo[2,1-b]quinazoline (3t): White solid (27 mg, yield 72%), m.p. 95-99°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.32-7.19 (m, 5H), 7.16-7.08 (m, 2H), 6.99-6.94 (m, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.34 (s, 2H), 4.29 (s, 2H), 3.86 (t, *J* = 8.4 Hz, 2H), 3.60 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 158.2, 137.0, 136.0, 128.7, 128.6, 127.2, 126.5, 126.3, 122.2, 119.3, 113.8, 52.8, 48.6, 48.5, 47.9. HRMS-EI: m/z $[M]^+$ for $C_{17}H_{17}N_3$, calculated 263.1422; observed 263.1398.

10-heptyl-2,3,5,10-tetrahydroimidazo[2,1-b]quinazoline (3u, Scheme 2): Off white sticky solid (25 mg, yield 65%), ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.33-7.27 (m, 1H), 7.11-7.03 (m, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 4.30 (s, 2H), 4.11 (t, *J* = 7.7 Hz, 2H), 3.91 (t, *J* = 8.6 Hz, 2H), 3.63 (t, *J* = 8.6 Hz, 2H), 1.78-1.68 (m, 2H), 1.48-1.40 (m, 2H), 1.31-1.28 (m, 6H), 0.89 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 156.5, 135.4, 129.0, 126.9, 123.4, 118.8, 113.6, 51.2, 47.5, 45.8, 31.7, 29.1, 26.9, 26.4, 22.6, 14.0. HRMS-EI: m/z $[M]^+$ for $C_{17}H_{25}N_3$, calculated 271.2048; observed 271.2050.

Reversed Phase Preparative HPLC leading to *N*,1-dibenzylimidazolidin-2-amine, formate salt (3a'): To a solution of 2-azido-*N*-benzylethanamine (**1a**, 0.71 mmol) in dry toluene (1 mL) benzyl isocyanate (**2a**, 0.71 mmol) was added and the resulting reaction mixture was heated at 100 °C (oil bath) for 3 h. After cooling of the reaction mixture to ambient temperature, n-Bu_3P (0.71 mmol) was added dropwise under argon atmosphere and the reaction mixture was allowed to stir for 20 min. Thereafter the reaction vial was filled with argon, sealed and heated at 100 °C

for 20 h. The solvent was evaporated under reduced pressure and the obtained residue was subjected to reversed phase preparative HPLC (ACN/H_2O with 0.1% HCOOH). Evaporation of solvent finally led to the formation of corresponding formate salt **3a'** as a colourless oil (197 mg, yield 89%); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.43-9.58 (bs, 1H), 8.44 (s, 1H), 7.33-7.12 (m, 10H), 4.52 (4H, s), 3.45-3.40 (m, 2H), 3.30-3.24 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 167.7, 158.2, 136.9, 134.3, 128.9, 128.5, 128.2, 128.0, 127.7, 127.6, 48.8, 47.2, 46.1, 41.0. HRMS-EI: m/z $[M]^+$ for $C_{17}H_{19}N_3$, calculated 265.1579; observed 265.1558.

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SUPPORTING INFORMATION

Copies of ^{1}H and ^{13}C NMR spectra of all the synthesized compounds. This material is available free of charge via the internet at http://pubs.acs.org/.

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(12) After reversed phase preparative HPLC we obtained an oily compound with EI-MS peak at 265 (same as that of the expected **3a**). The peaks at δ 8.44 ppm (^{1}H NMR) and δ 167.7 ppm (^{13}C & DEPT-135) indicated a HCOO functionality and the compound was confirmed to be the corresponding formate salt **3a'** (for NMR spectra see, supporting information). On the other hand, without using HCOOH in the eluent, no sharp peak shape of product **3a** could be obtained in the HPLC chromatogram.

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