Synthesis A. Safrygin et al. Paper

Efficient Conversion of Tertiary Propargylamides into Imidazoles via Hydroamination–Cyclization

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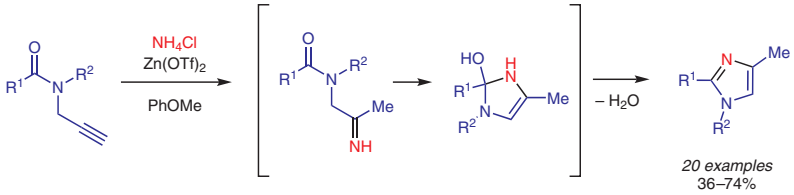

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Abstract A method to convert tertiary *N*-propargylamides into 1,2,4-trisubstituted imidazoles using ammonium chloride and zinc triflate as the catalyst is reported. The method is convenient, practical and employs conventional heating. It is also applicable to *N*-propargyl lactams and tends to populate the so-called 'lead-like' chemistry space.

Keywords *N*-propargylamides, hydroamination, cyclodehydration, Lewis acid catalysis, privileged structures, imidazoles, lead-oriented synthesis

The importance of the imidazole moiety in the design of biologically active compounds—and ultimately, drugs—cannot be overstated. Thus, imidazole should be regarded as a privileged structure.[2] This compact, polar, planar aromatic motif with two nitrogen atoms can act as a partner in various contacts with a protein target by donating or accepting a hydrogen bond as well as participating in π-stacking interactions.[3] This is why imidazole is likely to be explored as a peripheral group in virtually any drug discovery program. As a core scaffold, imidazole is similarly versatile: in addition to forming said non-covalent interactions with the biotarget, it can project, in a spatially defined fashion, up to four peripheral groups, all of which can be independently varied depending on the chemistry employed to assemble the imidazole compound.[4] The diversity of clinical applications of drugs containing an imidazole moiety in their structure is quite striking. Illustrative of this range are therapeutic agents such as the anticancer agents nilotinib (**1**)[5] and tipifarnib (**2**),[6] the antifungals ketoconazole (**3**)[7] and luliconazole (**4**),[8] the classical antibacterial nitroimidazoles metronidazole (**5**) and tinidazole (**6**)[9] and the antihypertensive blockbuster drugs losartan (**7**) and eprosartan (**8**)[10] (Figure 1). Considering the versatility of imidazole in drug design, the invention of novel, flexible synthetic methods to assemble imidazole compounds and control their peripher-

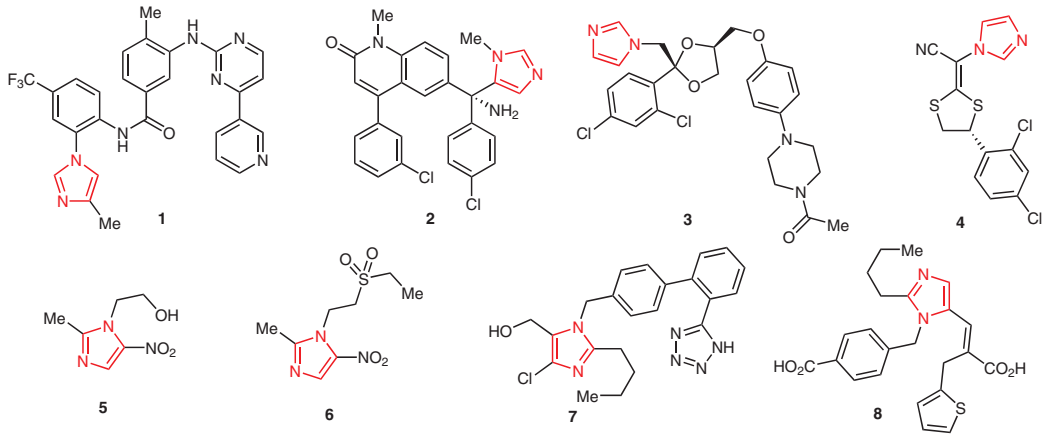
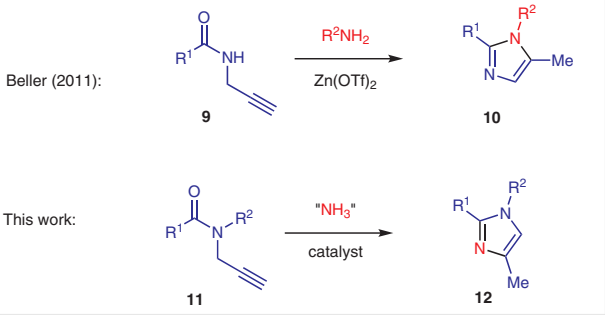


Figure 1 Examples of clinically used imidazole-containing drugs

al substitution patterns remains a worthy goal in synthetic organic chemistry.[11]

In 2011, Beller reported a serendipitous discovery of a powerful method to construct polysubstituted imidazoles.[12] In an attempt to hydroaminate secondary *N*-propargylamides **9** with a primary amine using zinc triflate as the catalyst (initially aiming at the respective imine intermediates[13]), 1,2,5-trisubstituted imidazoles **10** were isolated in good yields, presumably as a result of a hydroamination–cyclization reaction (Scheme 1). The method was expanded to a wide scope of substrates and was recently employed for the preparation of a large library of imidazoles (patented by the Salk Institute for Biological Studies) as PPAR agonists useful for the treatment of muscular, vascular, demyelinating and metabolic diseases.[14]



Scheme 1 The hydroamination–cyclization of *N*-propargylamides reported by Beller[12] and studied in this work

One of the examples reported by Beller included the use of gaseous ammonia (in lieu of a primary amine) in an autoclave, which enabled the preparation of an N-unsubstituted imidazole.[12] Inspired by this example, we became interested in identifying a practical and convenient source of ammonia (such as ammonium salts) and then applying this method to tertiary *N*-propargylamides **11** (including *N*-propargyl lactams, i.e., where R^1 and R^2 form a cycle), which would provide a novel route to 1,2,4-trisubstituted imidazoles **12**, in contrast to the 1,2,5-trisubstituted imidazoles **10** synthesized from secondary *N*-propargylamides and primary amines (Scheme 1). Herein, we report on the successful realization of these goals.

Initial screening of the reaction conditions suitable for carrying out the hydroamination–cyclization of tertiary *N*-propargylamides was carried out for substrate **11a**, which allowed quantitative determination of the yield of the corresponding imidazole **12a** by gas chromatography (Table 1).

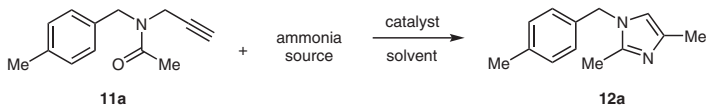
The best result (entry 19) was achieved in methoxybenzene as the solvent with ammonium chloride as the ammonia source. Prolonged conventional heating (150 °C, 40 h) appears to be a prerequisite for a successful reaction: in contrast to the method reported by Beller,[12] conducting the same reaction in a microwave reactor led to incomplete conversion and, consequently, a lower yield. However, similar to the published results,[12] using a greater amount of the catalyst [10% $Zn(OTf)_2$] lowered the reaction yield nearly twofold. Using other ammonium salts led to product formation, albeit in lower (t-$BuCO_2NH_4$) or negligible (NH_4OAc) yields. Interestingly, apart from PhOMe (giving the best result), the reaction appears to be relatively insensitive to the solvent as well as the Lewis acid catalyst [except for $AuNTf_2{\cdot}PPh_3$ (entry 7), which gave no product at all]. Indeed, most of the GC yields listed in Table 1 are in the low to moderate range. Notably, the $Zn(OTf)_2$-catalyzed reaction in toluene (entry 2) gave an extremely low product yield due to the poor solubility of NH_4Cl in this solvent. Contrasting with this result is the high-yielding conversion of **9** into **10** conducted in toluene under microwave irradiation.[12] Notably, however, the reaction appears to be distinctly sensitive to temperature. Indeed, raising (entry 10 vs entry 3) or lowering (entry 9 vs entry 3) the reaction temperature gave significantly worse results. Thus, the conditions (entry 19) which had been established to give the best yield of **12a** were employed for the preparation of other imidazoles **12b–t** (Table 2).

As follows from the results presented in Table 2, the newly developed transformation works well for a variety of tertiary *N*-propargylamides **11a–r**. A notable part of the reaction scope is the ability to transform *N*-propargyl lactams **11s**,**t** into the corresponding bicyclic imidazoles **12s**,**t**. This type of cycloalkane–imidazole fusion is of special importance in the biologically active chemical space and is present, for example, in recently reported cyclin-dependent kinase inhibitors,[15] antiallergy compounds,[16] and the approved drug alcaftadine (a histamine receptor antagonist) marketed under the trade name Lastacaft for the treatment of conjunctivitis.[17] All of the starting *N*-propargylamide substrates were prepared using conventional methods (see the experimental section for details).

From a mechanistic perspective, the observed conversion of *N*-propargylamides **11** into imidazoles **12** is likely to involve hydroamination of the alkyne moiety followed by dehydrative cyclization of the initial imine intermediate **13**, presumably driven by the formation of the aromatic imidazole nucleus (Scheme 2).

Besides having emphasized the scope, we would regard the method described above as a transformation particularly suitable for lead-oriented synthesis,[18] i.e., a method that tends to populate the chemical space corresponding to lower molecular weight (MW <300) and lower lipophilicity characteristics (cLogP <3) compared to Lipinski's rule-of-five criteria of druglikeness (MW <500, cLogP <5).[19] This allows ample room for medicinal chemistry optimization, which normally results in an increase of these crucial molecular parameters. Indeed, all the compounds synthesized in this work have molecular weights lower than 300 and only a few compounds (**12l**, **12n–q**) exceed the lead-likeness threshold of cLogP (Figure 2).

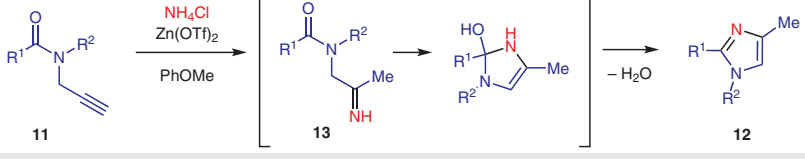
Table 1 Screening of the Hydroamination–Cyclization Reaction Conditions for the Conversion of **11a** into **12a**[a]



11a **12a**

Entry	Ammonia source	Solvent	Catalyst	T (°C)	Time (h)	Yield (%)[b]
1	NH_4OAc	toluene	$Zn(OTf)_2$	150	40	52
2	NH_4Cl	toluene	$Zn(OTf)_2$	150	40	3
3	NH_4Cl	diglyme	$Zn(OTf)_2$	150	40	37
4	NH_4Cl	diglyme	$Sc(OTf)_3$	150	40	21
5	NH_4Cl	diglyme	$Yb(OTf)_3$	150	40	39
6	NH_4Cl	diglyme	$InCl_3$	150	40	33
7	NH_4Cl	diglyme	$AuNTf_2$·PPh_3	100	40	–
8	NH_4Cl	diglyme	$Zn(OTf)_2$	150	60	32
9	NH_4Cl	diglyme	$Zn(OTf)_2$	100	40	–
10	NH_4Cl	diglyme	$Zn(OTf)_2$	180	40	complex mixture
11	NH_4OAc	diglyme	$Zn(OTf)_2$	150	40	4
12	*t*-$BuCO_2NH_4$	diglyme	$Zn(OTf)_2$	150	40	13
13	$Ph_2C{=}NH$	diglyme	$Zn(OTf)_2$	150	40	–
14	*t*-$BuNH_2$	diglyme	$Zn(OTf)_2$	150	40	–
15	NH_4Cl	PhCl	$Zn(OTf)_2$	150	40	48
16	*t*-$BuCO_2NH_4$	PhCl	$Zn(OTf)_2$	150	40	56
17	NH_4Cl	1,2-$C_6H_3Cl_2$	$Zn(OTf)_2$	150	40	38
18	*t*-$BuCO_2NH_4$	1,2-$C_6H_3Cl_2$	$Zn(OTf)_2$	150	40	54
19	NH_4Cl	PhOMe	$Zn(OTf)_2$	150	40	72[c]
20	*t*-$BuCO_2NH_4$	PhOMe	$Zn(OTf)_2$	150	40	52
21	NH_4Cl	$PhCF_3$	$Zn(OTf)_2$	150	40	26
22	*t*-$BuCO_2NH_4$	$PhCF_3$	$Zn(OTf)_2$	150	40	43
23	NH_4Cl	pyridine	$Zn(OTf)_2$	150	40	36
24	*t*-$BuCO_2NH_4$	pyridine	$Zn(OTf)_2$	150	40	19
25	NH_4Cl	DMAA	$Zn(OTf)_2$	150	40	46
26	*t*-$BuCO_2NH_4$	DMAA	$Zn(OTf)_2$	150	40	38
27	NH_4Cl	$(CH_2OH)_2$	$Sc(OTf)_3$	150	40	17
28	*t*-$BuCO_2NH_4$	$(CH_2OH)_2$	$Sc(OTf)_3$	150	40	51

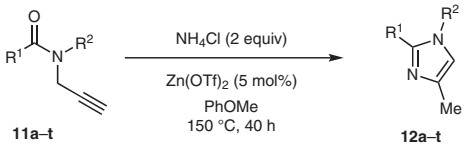
[a] All reactions were carried out with ammonia source (2 equiv), catalyst (5 mol%) and solvent (4 mL).
[b] GC yield.
[c] Yield of isolated product (GC yield: 85%).



11 **13** **12**

Scheme 2 $Zn(OTf)_2$-catalyzed conversion of *N*-propargylamides **11** into imidazoles **12**

Table 2 Imidazoles **12a–t** Prepared in this Work



11a–t **12a–t**

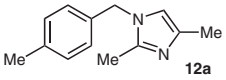
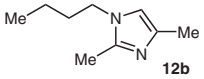
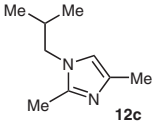
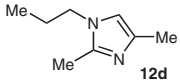
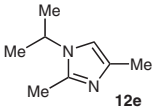
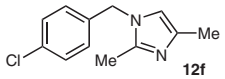
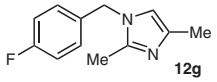
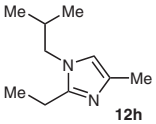
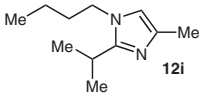
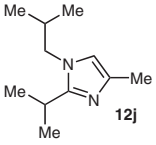
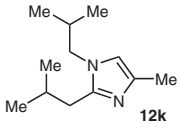
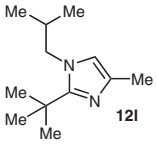
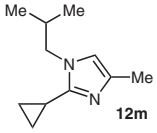
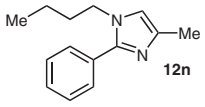
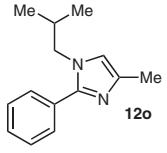
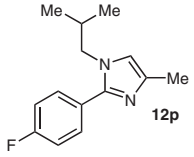
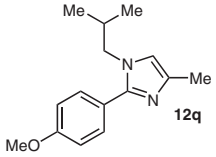
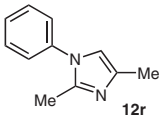
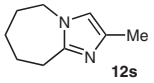
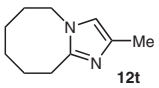
Entry	Substrate	R^1	R^2	Product	Yield (%)[a]
1	**11a**	Me	4-$MeC_6H_4CH_2$	 **12a**	72
2	**11b**	Me	$CH_3CH_2CH_2CH_2$	 **12b**	67
3	**11c**	Me	$(CH_3)_2CHCH_2$	 **12c**	64
4	**11d**	Me	$CH_3CH_2CH_2$	 **12d**	74
5	**11e**	Me	$(CH_3)_2CH$	 **12e**	51
6	**11f**	Me	*p*-Cl-$C_6H_4CH_2$	 **12f**	62
7	**11g**	Me	*p*-F-$C_6H_4CH_2$	 **12g**	60
8	**11h**	Et	$(CH_3)_2CHCH_2$	 **12h**	71
9	**11i**	$(CH_3)_2CH$	$CH_3CH_2CH_2CH_2$	 **12i**	65
10	**11j**	$(CH_3)_2CH$	$(CH_3)_2CHCH_2$	 **12j**	60

Table 2 (continued)

Entry	Substrate	R^1	R^2	Product	Yield (%)[a]
11	**11k**	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	 **12k**	72
12	**11l**	$(CH_3)_3C$	$(CH_3)_2CHCH_2$	 **12l**	45
13	**11m**	c-C_3H_7	$(CH_3)_2CHCH_2$	 **12m**	37
14	**11n**	Ph	$CH_3CH_2CH_2CH_2$	 **12n**	54
15	**11o**	Ph	$(CH_3)_2CHCH_2$	 **12o**	48
16	**11p**	*p*-F-C_6H_4	$(CH_3)_2CHCH_2$	 **12p**	52
17	**11q**	*p*-MeO-C_6H_4	$(CH_3)_2CHCH_2$	 **12q**	46
18	**11r**	Me	Ph	 **12r**	36
19	**11s**	$(CH_2)_5$		 **12s**	65
20	**11t**	$(CH_2)_6$		 **12t**	68

[a] Yield of isolated product.

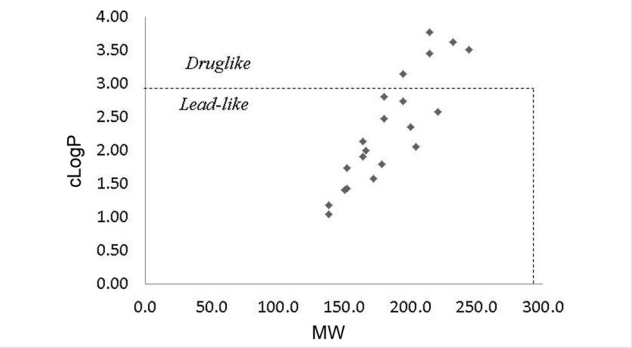


Figure 2 Molecular weights and cLogP parameters of compounds **12a–t**. cLogP values were calculated using publicly available software (www.molinspiration.com)

In conclusion, we have developed an efficient, convenient and practical method to convert tertiary *N*-propargylamides into 1,2,4-trisubstituted imidazoles using ammonium chloride and zinc triflate. The substrate scope of this method includes *N*-propargyl lactams, which allows the preparation of medicinally important cycloalkane-fused imidazoles. The method offers a practical and convenient alternative to the earlier reported protocol involving the use of gaseous ammonia and an autoclave. The imidazoles obtained in this work predominantly conform to the criteria of lead-likeness, which make them suitable starting points for medicinal chemistry optimization.

Column chromatography was performed on Merck silica gel 60 (230–400 mesh). TLC analysis was performed using Sorbfil UV254 silica gel coated plates. Melting points were measured with a SMP 50 instrument and are uncorrected. NMR spectroscopic data were recorded with a Bruker Avance III 400 MHz (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) spectrometer in $CDCl_3$ or DMSO-d_6 and were referenced to residual solvent signals (δ_H = 7.26 and δ_C = 77.2 for $CDCl_3$; δ_H = 2.51 and δ_C = 40.6 for DMSO-d_6). Coupling constants (J) are reported in Hz. Mass spectra were recorded with a Bruker QTOF maXis II HRMS-ESI-qTOF spectrometer (electrospray ionization mode).

N-Propargyl Amides 11a–q; General Procedure

A mixture of the corresponding aldehyde (or acetone for **11d**) (10 mmol), propargyl amine (10 mmol, 551 mg) and anhydrous $MgSO_4$ (500 mg) in CH_2Cl_2 (5 mL) was stirred at r.t. overnight. The solids were filtered off and washed twice with CH_2Cl_2. After removal of the solvent in vacuo, the residue was dissolved in MeOH (8 mL). $NaBH_4$ (15 mmol, 567 mg) was added in portions and the resulting mixture was stirred at r.t. for 2 h. H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL) and sat. aq $NaHCO_3$ (20 mL), dried over anhydrous $MgSO_4$ and concentrated to a volume of 25 mL. The solution was cooled in an ice bath, Et_3N (20 mmol, 2.024 g) was added followed by slow addition of the corresponding acyl chloride (10 mmol) with stirring. The mixture was stirred for an additional 2 h at r.t., washed with H_2O (20 mL), brine (20 mL) and sat. aq $NaHCO_3$ (2 × 20 mL) and concentrated in vacuo. The residue was purified by column chromatography using *n*-hexane/EtOAc (1:1) as eluent.

N-(4-Methylbenzyl)-*N*-(prop-2-yn-1-yl)acetamide (11a)

Yield: 1.449 g (72%); yellow oil; R_f = 0.3.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 7.16 (s, 4 H), 4.58 (s, 2 H), 4.09 (d, J = 2.4 Hz, 2 H), 2.93 (br s, 1 H), 2.31 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 170.2, 136.9, 134.7, 129.5, 127.8, 80.1, 74.4, 49.6, 36.0, 21.6, 20.9.

HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NNaO$: 224.1046; found: 224.1054.

N-Butyl-*N*-(prop-2-yn-1-yl)acetamide (11b)

Yield: 1.042 g (68%); dark yellow oil; R_f = 0.25.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.12 (d, J = 2.4 Hz, 2 H), 3.37 (t, J = 7.4 Hz, 2 H), 2.94 (br s, 1 H), 2.05 (s, 3 H), 1.57 (quin, J = 7.4 Hz, 2 H), 1.33 (sext, J = 7.3 Hz, 2 H), 0.93 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 169.7, 80.7, 73.8, 47.0, 35.7, 30.3, 21.4, 19.9, 13.8.

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_9H_{16}NO$: 154.1226; found: 154.1225.

N-Isobutyl-*N*-(prop-2-yn-1-yl)acetamide (11c)

Yield: 1.088 g (71%); orange oil; R_f = 0.25.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.12 (d, J = 2.5 Hz, 2 H), 3.21 (d, J = 7.4 Hz, 2 H), 2.95 (br s, 1 H), 2.06 (s, 3 H), 1.99 (nonet, J = 6.8 Hz, 1 H), 0.90 (d, J = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 170.1, 80.6, 73.9, 54.7, 36.6, 27.2, 21.6, 20.2.

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_9H_{16}NO$: 154.1226; found: 154.1230.

N-(Prop-2-yn-1-yl)-*N*-propylacetamide (11d)

Yield: 0.487 g (35%); orange oil; R_f = 0.2.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.12 (d, J = 2.5 Hz, 2 H), 3.34 (t, J = 7.4 Hz, 2 H), 2.94 (br s, 1 H), 2.05 (s, 3 H), 1.60 (sext, J = 7.4 Hz, 2 H), 0.89 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 169.7, 80.7, 73.8, 48.9, 36.0, 21.4, 21.3, 11.3.

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_8H_{14}NO$: 140.1070; found: 140.1073.

N-Isopropyl-*N*-(prop-2-yn-1-yl)acetamide (11e)

Yield: 0.445 g (32%); orange oil; R_f = 0.2.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.38 (br s, 1 H), 4.01 (d, J = 2.4 Hz, 2 H), 2.88 (br s, 1 H), 2.07 (s, 3 H), 1.19 (d, J = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 169.5, 82.4, 72.9, 47.0, 31.2, 22.0, 20.6.

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_8H_{14}NO$: 140.1070; found: 140.1065.

N-(4-Chlorobenzyl)-*N*-(prop-2-yn-1-yl)acetamide (11f)

Yield: 1.840 g (83%); dark yellow oil; R_f = 0.25.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 7.40–7.36 (m, 2 H), 7.32–7.28 (m, 2 H), 4.61 (s, 2 H), 4.13 (d, J = 2.4 Hz, 2 H), 2.98 (br s, 1 H), 2.12 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 170.3, 136.9, 132.5, 129.7, 128.8, 80.0, 74.7, 49.5, 36.8, 21.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}ClNNaO$: 244.0500; found: 244.0509.

***N*-(4-Fluorobenzyl)-*N*-(prop-2-yn-1-yl)acetamide (11g)**

Yield: 1.170 g (57%); dark yellow oil; R_f = 0.25.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 7.35–7.29 (m, 2 H), 7.16–7.09 (m, 2 H), 4.60 (s, 2 H), 4.12 (d, *J* = 2.4 Hz, 2 H), 2.97 (br s, 1 H), 2.12 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 170.3, 162.1 (d, $^1J_{C–F}$ = 243.5 Hz), 134.0, 129.9, 115.5 (d, $^2J_{C–F}$ = 21.2 Hz), 80.0, 74.5, 49.4, 36.6, 21.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}FNNaO$: 228.0795; found: 228.0806.

***N*-Isobutyl-*N*-(prop-2-yn-1-yl)propionamide (11h)**

Yield: 1.371 g (82%); yellow oil; R_f = 0.4.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.13 (d, *J* = 2.5 Hz, 2 H), 3.22 (d, *J* = 7.4 Hz, 2 H), 2.94 (br s, 1 H), 2.38 (q, *J* = 7.4 Hz, 2 H), 1.99 (nonet, *J* = 6.9 Hz, 1 H), 1.06 (t, *J* = 7.4 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 173.4, 80.7, 73.8, 54.0, 36.4, 27.1, 26.1, 20.2, 9.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{17}NNaO$: 190.1202; found 190.1207.

***N*-Butyl-*N*-(prop-2-yn-1-yl)isobutyramide (11i)**

Yield: 1.106 g (61%); light orange oil; R_f = 0.5.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.14 (br s, 2 H), 3.37 (t, *J* = 7.4 Hz, 2 H), 3.09 (s, 1 H), 2.86 (br s, 1 H), 1.54 (br s, 2 H), 1.30 (sext, *J* = 7.1 Hz, 2 H), 1.04 (d, *J* = 6.7 Hz, 6 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 176.4, 80.9, 73.7, 46.5, 35.9, 30.5, 29.9, 19.9, 13.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{20}NO$: 182.1539; found: 182.1531.

***N*-Isobutyl-*N*-(prop-2-yn-1-yl)isobutyramide (11j)**

Yield: 1.178 g (65%); yellow oil; R_f = 0.5.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.14 (d, *J* = 2.5 Hz, 2 H), 3.23 (d, *J* = 7.4 Hz, 2 H), 2.95 (s, 1 H), 2.91 (sept, *J* = 6.7 Hz, 1 H), 1.99 (nonet, *J* = 6.9 Hz, 1 H), 1.06 (d, *J* = 6.7 Hz, 6 H), 0.89 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 176.8, 80.8, 73.9, 53.9, 36.5, 30.0, 27.2, 20.2, 19.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{20}NO$: 182.1539; found: 182.1536.

***N*-Isobutyl-3-methyl-*N*-(prop-2-yn-1-yl)butanamide (11k)**

Yield: 1.602 g (82%); yellow oil; R_f = 0.5.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.13 (d, *J* = 2.4 Hz, 2 H), 3.22 (d, *J* = 7.4 Hz, 2 H), 2.94 (br s, 1 H), 2.26 (d, *J* = 6.8 Hz, 2 H), 2.10 (nonet, *J* = 6.7 Hz, 1 H), 1.99 (nonet, *J* = 6.9 Hz, 1 H), 0.95 (d, *J* = 6.6 Hz, 6 H), 0.90 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 172.0, 80.7, 73.8, 54.0, 41.9, 36.6, 27.2, 25.6, 22.8, 20.2.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{21}NNaO$: 218.1515; found: 218.1523.

***N*-Isobutyl-*N*-(prop-2-yn-1-yl)pivalamide (11l)**

Yield: 1.191 g (61%); yellow oil; R_f = 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.23 (d, *J* = 2.4 Hz, 2 H), 3.34 (d, *J* = 7.6 Hz, 2 H), 2.23 (t, *J* = 2.4 Hz, 1 H), 2.07 (nonet, *J* = 7.0 Hz, 1 H), 1.33 (s, 9 H), 0.93 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.5, 79.4, 71.8, 54.0, 39.0, 37.4, 28.6, 26.4, 20.0.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{21}NNaO$: 218.1515; found: 218.1522.

***N*-Isobutyl-*N*-(prop-2-yn-1-yl)cyclopropanecarboxamide (11m)**

Yield: 1.524 g (85%); light yellow oil; R_f = 0.25.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 4.22 (br s, 2 H), 3.34 (d, *J* = 7.2 Hz, 2 H), 2.94 (br s, 1 H), 2.04 (nonet, *J* = 6.8 Hz, 1 H), 1.96–1.88 (m, 1 H), 0.92 (d, *J* = 6.7 Hz, 6 H), 0.83–0.72 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 173.0, 80.8, 73.8, 54.3, 36.7, 27.4, 20.2, 11.6, 7.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{18}NO$: 180.1383; found: 180.1389.

***N*-Butyl-*N*-(prop-2-yn-1-yl)benzamide (11n)**

Yield: 1.615 g (75%); yellow viscous oil; R_f = 0.5.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 7.49–7.43 (m, 3 H), 7.42–7.37 (m, 2 H), 4.17 (d, *J* = 1.9 Hz, 2 H), 3.43 (t, *J* = 7.3, 2 H), 3.03 (t, *J* = 2.3 Hz, 1 H), 1.62 (quin, *J* = 7.4 Hz, 2 H), 1.28 (sext, *J* = 7.3 Hz, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 170.8, 137.0, 129.8, 128.8, 126.9, 80.3, 74.5, 47.0, 36.8, 29.9, 19.8, 13.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO$: 216.1383; found: 216.1379.

***N*-Isobutyl-*N*-(prop-2-yn-1-yl)benzamide (11o)**

Yield: 1.744 g (81%); dark yellow viscous oil; R_f = 0.5.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 7.48–7.43 (m, 3 H), 7.43–7.37 (m, 2 H), 4.16 (d, *J* = 2.3 Hz, 2 H), 3.31 (d, *J* = 7.4 Hz, 2 H), 3.03 (t, *J* = 2.4 Hz, 1 H), 2.07 (nonet, *J* = 6.9 Hz, 1 H), 0.88 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 171.2, 137.1, 130.0, 128.8, 127.0, 80.1, 74.6, 54.3, 37.6, 26.8, 20.3.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO$: 216.1383; found: 216.1389.

4-Fluoro-*N*-isobutyl-*N*-(prop-2-yn-1-yl)benzamide (11p)

Yield: 1.143 g (49%); yellow viscous oil; R_f = 0.6.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 7.50–7.43 (m, 2 H), 7.28–7.21 (m, 2 H), 4.15 (d, *J* = 2.1 Hz, 2 H), 3.30 (d, *J* = 7.4 Hz, 2 H), 3.04 (t, *J* = 2.4 Hz, 1 H), 2.06 (nonet, *J* = 6.8 Hz, 1 H), 0.88 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 170.3, 163.1 (d, $^1J_{C–F}$ = 247.1 Hz), 133.4 (d, $^4J_{C–F}$ = 3.1 Hz), 129.6 (d, $^3J_{C–F}$ = 8.5 Hz), 115.7 (d, $^2J_{C–F}$ = 21.8 Hz), 80.0, 74.7, 54.5, 37.8, 26.8, 20.3.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}FNO$: 234.1289; found: 234.1300.

***N*-Isobutyl-4-methoxy-*N*-(prop-2-yn-1-yl)benzamide (11q)**

Yield: 0.957 g (39%); light yellow viscous oil; R_f = 0.4.

^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ = 7.40–7.35 (m, 2 H), 7.02–6.97 (m, 2 H), 4.16 (d, *J* = 2.4 Hz, 2 H), 3.83 (s, 3 H), 3.32 (d, *J* = 7.4 Hz, 2 H), 3.03 (t, *J* = 2.4 Hz, 1 H), 2.07 (nonet, *J* = 6.8 Hz, 1 H), 0.88 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6, 110 °C): δ = 171.1, 160.9, 129.2, 129.0, 114.4, 80.3, 74.6, 55.9, 54.5, 37.8, 26.8, 20.3.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}NO_2$: 246.1489; found: 246.1492.

N-Phenyl-*N*-(prop-2-yn-1-yl)acetamide (11r)

To a mixture of *N*-phenylacetamide (10 mmol, 1.35 g) and anhydrous DMF (15 mL) was slowly added NaH (60% suspension in mineral oil, 10 mmol, 0.40 g) while stirring. Stirring was continued at r.t. for 2 h. Propargyl bromide (14 mmol, 1.67 g) was then added dropwise. The resulting mixture was stirred at r.t. for 3 h. The solvent was evaporated, H_2O (50 mL) and Et_2O (50 mL) were added, and the mixture was shaken thoroughly. The organic layer was separated, the solvent removed, and the residue purified by column chromatography with *n*-hexane/EtOAc (1:1) as eluent.

Yield: 1.213 g (70%); light yellow crystals; mp 74–75 °C; R_f = 0.35.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.38 (m, 3 H), 7.33–7.28 (m, 2 H), 4.50 (d, *J* = 2.2 Hz, 2 H), 2.22 (t, *J* = 2.2 Hz, 1 H), 1.89 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 142.3, 129.7, 128.4, 128.1, 79.2, 72.0, 38.2, 22.4.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{11}NNaO$: 196.0733; found: 196.0742.

N-Propargyl Lactams 11s,t; General Procedure

To a stirred solution of the corresponding lactam (10 mmol) in anhydrous THF (50 mL) was added NaH (60% suspension in mineral oil, 12 mmol, 0.48 g) in portions. The stirring was continued at r.t. for 45 min and then propargyl bromide (20 mmol, 2.379 g) was added dropwise. The resulting mixture was heated at reflux for 4 h, cooled to r.t. and stirred overnight. The solvent was evaporated and the residue was treated with Et_2O (50 mL), filtered through a small bed of Celite (which was then washed twice with Et_2O). The filtrate and washings were combined, the solvent removed under reduced pressure and the residue purified by column chromatography on silica gel using *n*-hexane/EtOAc (1:1) as eluent.

1-(Prop-2-yn-1-yl)azepan-2-one (11s)

Yield: 1.285 g (85%); yellow viscous oil; R_f = 0.25.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 (d, *J* = 2.5 Hz, 2 H), 3.50–3.44 (m, 2 H), 2.57–2.51 (m, 2 H), 2.19 (t, *J* = 2.5 Hz, 1 H), 1.78–1.65 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.4, 79.3, 71.3, 48.7, 36.9, 36.3, 29.9, 28.2, 23.2.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{13}NNaO$: 174.0889; found: 174.0897.

1-(Prop-2-yn-1-yl)azocan-2-one (11t)

Yield: 0.744 g (45%); light yellow crystals; mp 75–76 °C; R_f = 0.25.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (d, *J* = 2.4 Hz, 2 H), 3.67–3.60 (m, 2 H), 2.56–2.48 (m, 2 H), 2.21 (t, *J* = 2.5 Hz, 1 H), 1.85–1.69 (m, 4 H), 1.60–1.45 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.6, 79.3, 71.6, 46.4, 34.1, 33.8, 28.9, 28.8, 26.2, 24.3.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{15}NNaO$: 188.1046; found: 188.1054.

Imidazoles 12a–t; General Procedure

A mixture of the corresponding *N*-propargyl amide **11** (1 mmol), NH_4Cl (2 mmol, 107 mg) and $Zn(OTf)_2$ triflate (0.05 mmol, 18 mg) in anhydrous anisole (4 mL) was heated in an oil bath at 150 °C with stirring for 40 h. The solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc (15 mL) and sat. aq $NaHCO_3$ (15 mL) and the aq phase was additionally extracted with EtOAc (2 × 10 mL). The combined organic phases were concentrated in vacuo and the residue was purified by column chromatography on silica gel using the indicated eluent.

2,4-Dimethyl-1-(4-methylbenzyl)-1*H*-imidazole (12a)

Eluted with EtOAc/EtOH (10:1).

Yield: 144 mg (72%); brown viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (br d, *J* = 7.9 Hz, 2 H), 6.98 (br d, *J* = 7.9 Hz, 2 H), 6.54 (br s, 1 H), 4.95 (s, 2 H), 2.35 (s, 3 H), 2.34 (s, 3 H), 2.20 (br s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.0, 137.8, 135.5, 133.3, 129.6, 126.8, 116.2, 49.4, 21.1, 13.1, 12.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2$: 201.1386; found: 201.1385.

1-Butyl-2,4-dimethyl-1*H*-imidazole (12b)

Eluted with EtOAc/EtOH (10:1).

Yield: 102 mg (67%); brown viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (br s, 1 H), 3.75 (t, *J* = 7.2 Hz, 2 H), 2.34 (s, 3 H), 2.17 (br s, 3 H), 1.68 (quin, *J* = 7.4 Hz, 2 H), 1.34 (sext, *J* = 7.4 Hz, 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.4, 135.5, 115.3, 45.6, 32.8, 19.8, 13.6, 13.3, 12.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{17}N_2$: 153.1386; found: 153.1379.

1-Isobutyl-2,4-dimethyl-1*H*-imidazole (12c)

Eluted with EtOAc/EtOH (10:1).

Yield: 97 mg (64%); brown viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (br s, 1 H), 3.55 (d, *J* = 7.4 Hz, 2 H), 2.33 (s, 3 H), 2.18 (br s, 3 H), 1.98 (nonet, *J* = 6.8 Hz, 1 H), 0.92 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.7, 135.5, 115.8, 53.3, 29.9, 19.9, 13.4, 13.0.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{17}N_2$: 153.1386; found: 153.1389.

1-Propyl-2,4-dimethyl-1*H*-imidazole (12d)

Eluted with EtOAc/EtOH (10:1).

Yield: 102 mg (74%); brown viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (br s, 1 H), 3.72 (t, *J* = 7.2 Hz, 2 H), 2.33 (s, 3 H), 2.17 (br s, 3 H), 1.73 (sext, *J* = 7.3 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5, 135.6, 115.3, 47.4, 24.0, 13.3, 12.8, 11.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_8H_{15}N_2$: 139.1230; found: 139.1234.

1-Isopropyl-2,4-dimethyl-1*H*-imidazole (12e)

Eluted with EtOAc/EtOH (10:1).

Yield: 70 mg (51%), brown viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (br s, 1 H), 4.23 (sept, *J* = 6.8 Hz, 1 H), 2.35 (s, 3 H), 2.18 (br s, 3 H), 1.38 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.7, 135.8, 110.9, 47.1, 23.3, 13.4, 12.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_8H_{15}N_2$: 139.1230; found: 139.1232.

1-(4-Chlorobenzyl)-2,4-dimethyl-1*H*-imidazole (12f)

Eluted with EtOAc/EtOH (10:1).

Yield: 137 mg (62%); light brown crystals; mp 93–94 °C; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 2 H), 7.03–6.98 (m, 2 H), 6.53 (br s, 1 H), 4.96 (s, 2 H), 2.31 (s, 3 H), 2.20 (br s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.0, 136.4, 135.1, 133.8, 129.1, 128.0, 116.0, 48.9, 13.5, 13.0.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}ClN_2$: 221.0840; found: 221.0835.

1-(4-Fluorobenzyl)-2,4-dimethyl-1*H*-imidazole (12g)

Eluted with EtOAc/EtOH (10:1).

Yield: 123 mg (60%); dark brown viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.01 (m, 4 H), 6.53 (br s, 1 H), 4.95 (s, 2 H), 2.31 (s, 3 H), 2.19 (br s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3 (d, $^1J_{C-F}$ = 246.6 Hz), 144.0, 136.2, 132.3 (d, $^4J_{C-F}$ = 3.2 Hz), 128.4 (d, $^3J_{C-F}$ = 8.2 Hz), 116.0, 115.9 (d, $^2J_{C-F}$ = 21.7 Hz), 48.9, 13.3, 12.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}FN_2$: 205.1136; found: 205.1140.

2-Ethyl-1-isobutyl-4-methyl-1*H*-imidazole (12h)

Eluted with EtOAc.

Yield: 118 mg (71%); orange viscous oil; R_f = 0.15.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (br s, 1 H), 3.56 (d, *J* = 7.5 Hz, 2 H), 2.64 (q, *J* = 7.6 Hz, 2 H), 2.20 (br s, 3 H), 1.99 (nonet, *J* = 6.9 Hz, 1 H), 1.32 (t, *J* = 7.6 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.6, 135.6, 115.7, 53.0, 30.0, 20.1, 20.0, 13.5, 12.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{19}N_2$: 167.1543; found: 167.1546.

1-Butyl-2-isopropyl-4-methyl-1*H*-imidazole (12i)

Eluted with EtOAc.

Yield: 117 mg (65%); dark brown viscous oil; R_f = 0.25.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (br s, 1 H), 3.78 (t, *J* = 7.4 Hz, 2 H), 2.96 (sept, *J* = 6.9 Hz, 1 H), 2.21 (br s, 3 H), 1.70 (quin, *J* = 7.5 Hz, 2 H), 1.36 (sext, *J* = 7.7 Hz, 2 H), 1.33 (d, *J* = 6.9 Hz, 6 H), 0.96 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.0, 135.6, 114.8, 45.0, 33.3, 25.7, 21.9, 19.9, 13.7, 13.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{21}N_2$: 181.1699; found: 181.1695.

1-Isobutyl-2-isopropyl-4-methyl-1*H*-imidazole (12j)

Eluted with EtOAc.

Yield: 108 mg (60%); dark brown viscous oil; R_f = 0.25.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (br s, 1 H), 3.57 (d, *J* = 7.5 Hz, 2 H), 2.93 (sept, *J* = 6.9 Hz, 1 H), 2.19 (br s, 3 H), 1.97 (nonet, *J* = 6.9 Hz, 1 H), 1.30 (d, *J* = 6.9 Hz, 6 H), 0.91 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.4, 135.6, 115.3, 52.7, 30.1, 25.7, 22.0, 20.0, 13.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{21}N_2$: 181.1699; found: 181.1705.

1,2-Diisobutyl-4-methyl-1*H*-imidazole (12k)

Eluted with EtOAc.

Yield: 140 mg (72%); dark brown viscous oil; R_f = 0.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (br s, 1 H), 3.55 (d, *J* = 7.5 Hz, 2 H), 2.47 (d, *J* = 7.3 Hz, 2 H), 2.20 (br s, 3 H), 2.14 (nonet, *J* = 6.8 Hz, 1 H), 1.98 (nonet, *J* = 6.9 Hz, 1 H), 0.96 (d, *J* = 6.6 Hz, 6 H), 0.91 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.0, 135.8, 115.3, 53.1, 35.8, 30.0, 28.4, 22.6, 20.0, 13.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{23}N_2$: 195.1856; found: 195.1855.

2-(*tert*-Butyl)-1-isobutyl-4-methyl-1*H*-imidazole (12l)

Eluted with EtOAc.

Yield: 87 mg (45%); dark brown viscous oil; R_f = 0.3.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (br s, 1 H), 3.76 (d, *J* = 7.6 Hz, 2 H), 2.19 (br s, 3 H), 2.10 (nonet, *J* = 6.8 Hz, 1 H), 1.43 (s, 9 H), 0.97 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.5, 134.6, 116.9, 54.3, 33.3, 30.3, 29.9, 20.2, 13.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{23}N_2$: 195.1856; found: 195.1860.

2-Cyclopropyl-1-isobutyl-4-methyl-1*H*-imidazole (12m)

Eluted with EtOAc/*n*-hexane (1:1).

Yield: 66 mg (37%); orange viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (br s, 1H), 3.70 (d, *J* = 7.4 Hz, 2 H), 2.16 (br s, 3 H), 2.07 (nonet, *J* = 6.6 Hz, 1 H), 1.73 (tt, *J* = 8.3, 5.0 Hz, 1 H), 1.03–0.98 (m, 2 H), 0.95 (d, *J* = 6.7 Hz, 6 H), 0.94–0.88 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.5, 135.3, 116.0, 52.9, 30.0, 20.1, 13.6, 7.2, 6.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{19}N_2$: 179.1543; found: 179.1549.

1-Butyl-4-methyl-2-phenyl-1*H*-imidazole (12n)

Eluted with EtOAc/*n*-hexane (1:1).

Yield: 116 mg (54%); light brown viscous oil; R_f = 0.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.54 (m, 2 H), 7.47–7.36 (m, 3 H), 6.74 (br s, 1 H), 3.93 (t, *J* = 7.5 Hz, 2 H), 2.30 (br s, 3 H), 1.72 (quin, *J* = 7.5 Hz, 2 H), 1.29 (sext, *J* = 7.4 Hz, 2 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.0, 137.4, 131.2, 128.8, 128.4, 116.8, 46.3, 33.2, 19.8, 13.7, 13.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}N_2$: 215.1543; found: 215.1553.

1-Isobutyl-4-methyl-2-phenyl-1*H*-imidazole (12o)

Eluted with EtOAc/*n*-hexane (1:1).

Yield: 103 mg (48%); dark brown viscous oil; R_f = 0.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.54 (m, 2 H), 7.47–7.37 (m, 3 H), 6.72 (br s, 1 H), 3.75 (d, *J* = 7.5 Hz, 2 H), 2.29 (br s, 3 H), 1.98 (nonet, *J* = 6.9 Hz, 1 H), 0.83 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.3, 137.2, 131.4, 129.0, 128.4, 117.2, 54.0, 30.1, 19.9, 13.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}N_2$: 215.1543; found: 215.1546.

2-(4-Fluorophenyl)-1-isobutyl-4-methyl-1*H*-imidazole (12p)

Eluted with EtOAc/*n*-hexane (1:1).

Yield: 121 mg (52%); light brown crystals; mp 52–53 °C; R_f = 0.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.49 (m, 2 H), 7.16–7.09 (m, 2 H), 6.70 (br s, 1 H), 3.71 (d, *J* = 7.5 Hz, 2 H), 2.28 (br s, 3 H), 1.95 (nonet, *J* = 6.9 Hz, 1 H), 0.82 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.8 (d, $^1J_{C-F}$ = 248.3 Hz), 146.4, 137.3, 130.9 (d, $^3J_{C-F}$ = 8.1 Hz), 127.6 (d, $^4J_{C-F}$ = 3.2 Hz), 117.3, 115.5 (d, $^2J_{C-F}$ = 21.7 Hz), 54.0, 30.1, 19.9, 13.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}FN_2$: 233.1449; found: 233.1457.

1-Isobutyl-2-(4-methoxyphenyl)-4-methyl-1*H*-imidazole (12q)

Eluted with EtOAc/*n*-hexane (1:1).

Yield: 112 mg (46%); light brown viscous oil; R_f = 0.3.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.45 (m, 2 H), 6.98–6.93 (m, 2 H), 6.68 (br s, 1 H), 3.85 (s, 3 H), 3.71 (d, *J* = 7.5 Hz, 2 H), 2.27 (br s, 3 H), 1.96 (nonet, *J* = 6.9 Hz, 1 H), 0.82 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 147.2, 136.9, 130.4, 123.8, 116.9, 113.8, 55.3, 54.0, 30.0, 19.9, 13.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}N_2O$: 245.1648; found: 245.1657.

2,4-Dimethyl-1-phenyl-1*H*-imidazole (12r)

Eluted with EtOAc.

Yield: 62 mg (36%); light yellow viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.44 (m, 2 H), 7.43–7.37 (m, 1 H), 7.29–7.25 (m, 2 H), 6.73 (br s, 1 H), 2.34 (s, 3 H, Me), 2.25 (br s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.8, 138.0, 136.2, 129.4, 128.0, 125.4, 117.0, 13.6, 13.2.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}N_2$: 173.1073; found: 173.1069.

2-Methyl-6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*]azepine (12s)

Eluted with EtOAc/EtOH (10:1).

Yield: 98 mg (65%); light yellow viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.46 (br s, 1 H), 3.88–3.82 (m, 2 H), 2.88–2.83 (m, 2 H), 2.16 (br s, 3 H), 1.88–1.80 (m, 2 H), 1.80–1.72 (m, 2 H), 1.72–1.64 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.7, 134.4, 117.2, 48.1, 30.8, 29.2, 29.0, 25.8, 13.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{15}N_2$: 151.1230; found: 151.1230.

2-Methyl-5,6,7,8,9,10-hexahydroimidazo[1,2-*a*]azocine (12t)

Eluted with EtOAc/EtOH (10:1).

Yield: 112 mg (68%); light yellow viscous oil; R_f = 0.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.46 (br s, 1 H), 3.94–3.90 (m, 2 H), 2.80–2.75 (m, 2 H), 2.19 (br s, 3 H), 1.81–1.70 (m, 4 H), 1.49–1.41 (m, 2 H), 1.32–1.24 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.8, 136.2, 115.0, 43.9, 31.7, 31.3, 26.2, 25.6, 23.8, 13.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{17}N_2$: 165.1386; found: 165.1381.

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