One-Pot Three-Component Vicinal Diamines Synthesis via *In Situ* Amino Formation and Carboamination**

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Dedication ((optional))

Abstract: A synthesis of vicinal diamines via *in situ* amino formation and carboamination of allyl amines is reported herein. Employing highly electron poor trifluoromethyl aldimines was key to enable both a fast and complete amino formation as well as the palladium-catalyzed carboamination step. The conditions developed allow the introduction of a wide variety of alkynyl, vinyl, aryl and heteroaryl groups with complete regioselectivity and high diastereoselectivity. The reaction exhibits a high functional group tolerance. Importantly, either nitrogen atom of the imidazolidine products can be selectively deprotected, while removal of the amino tether can be achieved in a single step under mild conditions to reveal the free diamine. We expect that this work will promote the further use of mixed amino tethers in organic synthesis.

Vicinal diamines are of utmost importance in natural products, agrochemicals, drugs and as chiral ligands.^[1] Hence, tremendous efforts have been invested to develop new methods to access them efficiently.^[2] Olefins have been widely used as simple and readily available substrates for the preparation of diamines.^[3] The intermolecular diamination of alkenes through the formation of two new C-N bonds for example is one of the most direct synthetic approaches.^[2h,4] However, this strategy is often limited in scope and leads usually to identically substituted nitrogen atoms, thus hampering their differentiation and further elaboration. Tethering both nitrogen atoms to the olefin has been a successful approach to meet this challenge. The diamine motif is then accessed either via intramolecular diamination,^[5] or through formation of one C-N bond when starting from allylamine derivatives and forming a five-membered ring.^[6] The latter might be accompanied by the simultaneous formation of another bond onto the olefin. In particular, ureas and sulfamates have been widely used in both approaches due to their robustness.^[5,6] The use of palladium catalysis is particularly attractive, since it enables both the *mono*- and *di*functionalization of olefins.^[5a,c,6e-k] For example, Wolfe and co-workers described the use of classical sulfamide tethers for carboamination reactions (Scheme 1, **A**).^[6h,j] However, the reaction requires strong *tert*-butoxide bases at elevated temperatures, and final cleavage of the sulfamide tether occurs in presence of HBr at 130 °C for a prolonged period of time. Such harsh conditions are highly detrimental for the tolerance to functional groups and the scope of the reaction.

In this context, we were attracted by the use of aminoals as Csp³ tethers,^[7] which have received much less attention than the classical urea and sulfamide tethers. They offer the precious advantage of being potentially more easily installed and removed, and could still engage efficiently in olefin functionalization

processes. Furthermore, the obtained imidazolidine products provide a direct access to other highly important nitrogen-containing heterocycles such as imidazoles and *N*-heterocyclic carbenes.^[8] Among the scarce reports employing aminoals as tethers, only two groups described the functionalization of non-activated olefins (Scheme 1, **B** and **C**).^[9] The seminal contribution of Hiemstra and coworkers describes the use of amino tethers for Aza-Wacker cyclizations starting from allylic amines. However, tether installation and removal proved to be tedious, requiring five separate steps (Scheme 1, **B**).^[9a] More recently, Beauchemin and coworkers reported a Cope-type hydroamination of simple allyl amines in one step (Scheme 1, **B**).^[9b-f] While elegant, both works remain limited to a single C-N bond formation.

A. Wolfe: Carboamination using sulfamides tethers

B. Hiemstra: Aza-Wacker

C. Beauchemin: Cope hydroamination

D. This work: 3-component amino formation - carboamination

Scheme 1. Synthesis of diamines using a tether approach.

Recently, our group has demonstrated that vicinal amino alcohols could be synthesized from allyl amines using an acetal tether and a palladium catalyst to form simultaneously one new C-O and C-C bond.^[10a] We envisioned that an allylic amine and an imine could *in situ* form an aminoal, which would undergo a Pd-catalyzed carboamination reaction to generate an imidazolidine via formation of both a C-N and a C-C bond (Scheme 1, **D**).^[11] All the reported mixed aminoals employed for olefin functionalization bear electron-withdrawing groups on both nitrogen atoms, which greatly stabilize them. However, the poor nucleophilicity of the amine precursor prevents their fast synthesis.^[7] We thought to use nucleophilic allyl amines to solve this issue. Three challenging conditions must be met to ensure the success of the envisioned transformation:

(i) formation of the aminoal must be complete, fast and selective to avoid side reactions or catalyst deactivation,

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(ii) the mixed aminal formed needs to be both stable *and* suitable for the envisioned Pd-catalyzed carboamination, (iii) the imidazolidine obtained must be stable under the reaction conditions to avoid catalyst poisoning, but still be amenable to a straightforward deprotection to free the diamine.

The efficient implementation of this approach is reported herein, employing electron-rich allyl amines, carbamate-protected trifluoroaldehydes and a bromide, in presence of a commercially available palladium source and phosphine ligands. The developed conditions allowed for a broad scope in both allyl amines and alkynyl, aryl or vinyl bromides, as well as for high stereo-, regio- and diastereoselectivity.

We started our studies with benzylallyl amine (**1**) and silyl acetylene **3** as efficient electrophilic partner in Pd⁰/Pd^{II} catalyzed olefin functionalization (Table 1).^[10,12] We identified aldimine precursor **2a** as efficient tethering reagent in combination with Pd₂dba₃ as palladium source, P(2-furyl)₃ as ligand, and cesium carbonate as base. Under these conditions, imidazolidine **4** was isolated in excellent yield and diastereoselectivity (95%, *dr* > 20:1) (entry 1). Importantly, **2a** is easily available on multigram scale,^[13] bench stable for months, and only a slight excess is required to achieve complete conversion to **4**. As anticipated, the choice of the tether played a crucial role on the reaction outcome. Electron neutral aldimine **2b**

was ineffective (entry 2), while more activated *N*-Boc aryl imines still suffered from poor reactivity (entries 3-4). Various *N*-protected trifluoromethyl aldehydes did provide some improvement, but furnished inferior results than **2a** (entries 5-9). Changing the ligand had also a profound effect. Whereas using simple triphenylphosphine decreased the yield (entry 10), the bulky PhDavePhos afforded **4** in high yield (entry 11). The electron-rich DavePhos was not efficient (entry 12). Regarding bidentate phosphines, BINAP was not competent, DPEPhos yielded 90% of **4**, and the closely related XANTPhos only 58% (entries 13-15). Switching to cesium hydrogen carbonate as base still afforded significant amount of **4**, while potassium carbonate provided 89% of the desired imidazolidine (entries 16-17). The use of such mild bases is very rare for Pd⁰/Pd^{II}-catalyzed carboamination reactions, which often require stronger alkoxides. Deactivating the allylamine with a carbamate protecting group led to very low conversion (entry 18). Finally, without palladium or ligand or base, **4** was not observed (entry 19).

Table 1. Optimization of the tethered aminoalkynylation.^[a]

Entry	Changes from standard conditions	Yield (%) ^[b]
1	none	99 (95) ^[c]
2	2b instead of 2a	<3
3	2c instead of 2a	15
4	2d instead of 2a	36
5	2e instead of 2a	5
6	2f instead of 2a	35
7	2g instead of 2a	45
8	2h instead of 2a	5
9	2i instead of 2a	7
10	PPh ₃ (12 mol%) instead of P(2-furyl) ₃	39
11	PhDavePhos (11 mol%) instead of P(2-furyl) ₃	81
12	DavePhos (11 mol%) instead of P(2-furyl) ₃	11
13	BINAP (6 mol%) instead of P(2-furyl) ₃	3
14	DPEPhos (6 mol%) instead of P(2-furyl) ₃	90
15	XANTPhos (6 mol%) instead of P(2-furyl) ₃	58
16	CsHCO ₃ instead of Cs ₂ CO ₃	44
17	K ₂ CO ₃ instead of Cs ₂ CO ₃	89
18	Benzyl allylcarbamate instead of 1	8
19	without Pd ₂ dba ₃ or P(2-furyl) ₃ or base	<3

^[a]Reactions conditions: 0.10 mmol **1**, 0.11 mmol **2a**, 0.13 mmol **3**, 0.33 M in PhMe, 20 h. ^[b]NMR yield using 3,4,5-trichloropyridine as internal standard.

^[c]Isolated yield on 0.30 mmol scale.

The scope of the reaction was then examined (Scheme 2). We performed an assessment of functional group tolerance and electronic effects by varying the substitution on the nitrogen atoms (Scheme 2, **A**). The use of a methyl carbamate protected tether also provided product **5** in excellent yield. Modifying the benzyl group with electron donating or withdrawing groups had only minor influence (products **5-10**). Both the useful aryl bromide (product **8**) and chloride (product **9**) were preserved under these conditions. When performed on gram-scale, compound **10** was obtained in quantitative yield. A simple allyl group was also tolerated, with no Heck side reaction observed (product **11**). Imidazolidines bearing a furan heterocycle or a ferrocene group were obtained in 92 and 89% yield respectively (products **12** and **13**). The use of primary allyl amines was also possible (product **14**). Finally, replacing an aliphatic amine by an aniline still furnished the desired imidazolidine **15** in high yield.

Geminal substitution of the olefin was possible when using PhDavePhos as ligand (Scheme 2, **B**). α -Tertiary amine **16** and **17** were formed in good to high yields and with high diastereoselectivity (*dr* > 20:1).

Next, we investigated α -substituted allyl amines (Scheme 2, **C**).^[14] This class of substrates required the use of cesium triflate as additive to ensure high conversions.^[15] Substitution by a methyl group furnished the desired imidazolidines **18** in high yield, albeit in low diastereoselectivity. A bis-allylic amine delivered **19** in good yield and diastereoselectivity. Bicyclic and tricyclic imidazolidines **20**, **21** and **22** were formed in high diastereoselectivity. These results highlight the fast access to complex structures with control on up to four stereocenters in a single step.

The scope of organohalides was then examined. Alkynes derived from secondary and tertiary propargylic alcohols underwent the desired transformation in good to excellent yields (Scheme 2, **D**, products **23-26**). Notably, both aliphatic and aromatic substituents were tolerated at the propargylic position. We then turned our attention to aryl bromides (Schemes 2, **E** and **F**). This class of electrophiles could be used as long as they were slightly activated with an electron-withdrawing group. While DPEPhos was a competent ligand in certain cases, the combination of P(2-furyl)₃ with cesium

Scheme 2. Scope of the tandem amination formation carboamination reaction^[a]

^[a] *dr* > 20:1 unless otherwise noted; *dr* in parenthesis represents the diastereoisomeric ratio in the crude reaction mixture if different from the one of the isolated compound. ^[b] P(2-Furyl)₃ (12 mol%) was used as ligand. ^[c] PhDavePhos (15-20 mol%) was used as ligand. ^[d] P(2-Furyl)₃ (24 mol%) was used as ligand and cesium triflate as additive (1.2 equiv). ^[e] DPEPhos (12 mol%) was used as ligand.

triflate as additive was more general and reliable. *Ortho* and *para* substitution were well tolerated (products **27-32**). 1,2-Dibromo aryls underwent the reaction smoothly to afford brominated products **29** and **30**, which open up possibilities for further derivatizations. Substitution at the *meta* positions cleanly delivered the desired products **33** and **34** bearing an α -secondary and an α -tertiary amine respectively. Due to the importance of aromatic heterocycles in the agrochemical and pharmaceutical industries, several heteroaryl bromides were then submitted to the reaction conditions (Scheme 2, **F**). Gratifyingly, both fluoropyridine and chloropyrimidine were introduced in good to excellent yields (products **35** and **36**). Imidazolidines **37** and **38** bearing either a furan or a thiophene ring could be obtained in 81 and 82% yield respectively. Finally, aminoalkenylation was also possible (Scheme 2, **G**). Trifluoromethyl-substituted olefin **39** could be isolated in 87% yield.

To highlight the synthetic potential of the obtained building blocks, we synthesized either of the free amines selectively (Scheme 3). Starting from **10**, oxidative cleavage of the *para*-methoxybenzyl (PMB) protecting group lead to free amine **14** in high yield, while heating under microwave irradiation cleanly removed the boc group to access **40** in nearly quantitative yield. TIPS removal with TBAF yielded terminal alkyne **41** in 98% yield. Finally, cleavage of the amination was performed. Using HCl in methanol delivered diamine salt **42** in 89% yield. Treatment of imidazolidines **20** and **34** with trifluoroacetic acid followed by addition of methanol allowed full removal of the tether in excellent yields, without any further purification. The mild acidic conditions used are routinely applied in peptide chemistry.

Scheme 3. Orthogonal deprotections. Reaction conditions: a) DDQ, MeCN, H₂O, rt; b) microwave irradiation (160 °C), H₂O/Ethanol; c) TBAF, THF, 0 °C to rt; d) HCl, MeOH, -40 °C to rt; e) TFA, CH₂Cl₂ then MeOH, 0 °C to rt.

In conclusion, we have developed the first palladium-catalyzed carboamination of allyl amines employing an *in situ* installed Csp³ amina tether for the synthesis of 1,2-diamines. The use of carbamate-protected trifluoroaldimines allowed excellent regio- and diastereoselectivities under mild reactions conditions, a high functional-group tolerance and a broad scope. The versatility of our method was demonstrated by the introduction of alkynyl, aryl, heteroaryl and vinyl groups onto the allyl amines. Both free amines could be obtained orthogonally, while complete tether cleavage to give diamines was performed under mild conditions. Based on our results, we expect that the use of amina tethers will find much broader application in the future.

Acknowledgements

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Keywords: vicinal diamines, tether, amina, Pd-catalysis, alkenes.

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One-Pot Three-Component Vicinal
Diamines Synthesis via *In Situ* Amination
Formation and Carboamination

A novel synthesis of vicinal diamines via *in situ* amination and Pd-catalyzed carboamination of allylamines is reported herein. A wide variety of alkynyl, vinyl, aryl and heteroaryl groups could be introduced with complete regioselectivity and high diastereoselectivity. Key to the reaction was the use of carbamate-protected trifluoromethyl aldimine in its stable hemiaminal form. Cleavage of the amination tether was achieved in one step under mild conditions.

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1. General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et₂O, CH₃CN, toluene, hexane and CH₂Cl₂ were dried by passage over activated alumina under nitrogen atmosphere (H₂O content < 10 ppm, *Karl-Fischer* titration). In some cases solvents were degassed using freeze-thaw cycle. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Fluorochem, Aplichem or Merck and used without further purification, unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F₂₅₄ TLC aluminium plates and visualized with UV light and potassium permanganate stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ¹H-NMR spectra were recorded on a Bruker DPX-400 400 MHz spectrometer in chloroform-d unless otherwise stated. All signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard unless otherwise stated. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation). ¹³C-NMR spectra were recorded with ¹H-decoupling on a Bruker DPX-400 100 MHz spectrometer in chloroform-d unless otherwise stated. All signals are reported in ppm with the internal chloroform signal at 77.16 ppm as standard unless otherwise stated. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm⁻¹ (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. Cesium carbonate was purchased from Aldrich and used without further purification. The bulk of this material was stored under nitrogen in a Vacuum Atmospheres Glovebox. Small portions (3-5 g) were removed from the glovebox in glass vials and weighed in the air. DPEPhos was purchased from Acros, PhDavePhos from ABCR and tri(2-furyl)phosphine was purchased from Aldrich. N-benzylprop-2-en-1-amine (**1**), N-(4-bromobenzyl)prop-2-en-1-amine, N-(4-methoxybenzyl)prop-2-en-1-amine, N-(2-chlorobenzyl)prop-2-en-1-amine, diallylamine, N-(furan-2-ylmethyl)prop-2-en-1-amine, allylamine (**49**), N-allyl-4-methoxyaniline, N-benzyl-2-methylprop-2-en-1-amine and N,1-diphenylmethanimine (**2b**) are commercially available from Fluorochem, Aldrich and Acros. Aldimine **2c**,¹ **2d**,² **2e**,³ **2g**⁴ were synthesized according to reported procedures. Aryl and vinyl bromides were bought from Aldrich, Acros, ABCR, TCI and Fluorochem, and used as received. Diastereomeric mixtures have been assigned by 1D and 2D NMR experiments including COSY/NOESY/HSQC/HMBC.

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2. Optimization.

General method for the optimization:

A sealed oven-dry microwave vial under nitrogen was charged with dry degassed toluene (0.3 mL), the tether, the allylamine (0.100 mmol, 1.0 eq), the base and (bromoethynyl)triisopropylsilane (34 mg, 0.13 mmol, 1.3 eq). The resulting solution was stirred 30-60 min at 50 °C. Then a premixed solution of the palladium source and the ligand in dry degassed toluene (0.20 mL) was added. The resulting mixture was stirred at 60-70 °C for 15-20 h. The reaction mixture was cooled to 23 °C, filtered and concentrated under reduced pressure and analyzed by NMR spectroscopy. The yield was determined using either 3,4,5-trichloropyridine for ¹H NMR (integration of propargylic protons) or benzonitrile for the ¹⁹F NMR as internal standards.

Table 1. Optimization for the mono-substituted allyl amines.

Entry	Changes from standard conditions	Yield (%) ^b
1	none	99 (95) ^c
2	Na ₂ CO ₃ instead of Cs ₂ CO ₃	<5
3	Rb ₂ CO ₃ instead of Cs ₂ CO ₃	80
4	KOt-Bu instead of Cs ₂ CO ₃	78
5	MTBD instead of Cs ₂ CO ₃	38
6	Phosphazene P ₂ Et instead of Cs ₂ CO ₃	55
7	1.8 equiv of 2a instead of 1.1	94
8	2.5 equiv of 2a instead of 1.1	76
9	0.4 M instead of 0.33 M	92
10	0.2 M instead of 0.33 M	80
11	1 mol% of Pd ₂ dba ₃ instead of 2 mol%	81
12	[(cinnamyl)PdCp] instead of Pd ₂ dba ₃	88

^aReaction conditions: 0.10 mmol **1**, 0.11 mmol **2a**, 0.13 mmol **3**, 0.33 M in PhMe, 20 h. ^bNMR yield using 3,4,5-trichloropyridine as internal standard. ^cIsolated yield on 0.30 mmol scale.

Table 2. Optimization for the gem-disubstituted allyl amines.

Entry	Changes from standard conditions	Yield (%) ^b
1	none	93 (85) ^c
2	DPEPhos (9 mol%) instead of PhDavePhos	40
3	XantPhos (9 mol%) instead of PhDavePhos	16
4	(4-CF ₃ -C ₆ H ₄)DavePhos (15 mol%) instead of	13
5	P(2-furyl) ₃ (18 mol%) instead of PhDavePhos	8
6	0.28 M instead of 0.33 M	85

^aReaction conditions: 0.10 mmol **45**, 0.11 mmol **2a**, 0.13 mmol **3**, 0.33 M in PhMe, 20 h. ^bNMR yield using 3,4,5-trichloropyridine as internal standard. ^cIsolated yield on 0.30 mmol scale.

Table 3. Optimization for the α-branched substituted allyl amines.

Entry	Changes from standard conditions	Yield (%) ^b
1	none	80
2	0.05 M instead of 0.33 M	32
3	0.1 M instead of 0.33 M	45
4	0.2 M instead of 0.33 M	75
5	PPh ₃ instead of P(2-furyl) ₃	7
6	P(4-CF ₃ -C ₆ H ₄) ₃ (24 mol%) instead of P(2-furyl) ₃	31
7	P(2-thienyl) ₃ (24 mol%) instead of P(2-furyl) ₃	18
8	CyPPh ₂ (24 mol%) instead of P(2-furyl) ₃	<5
9	dppf (12 mol%) instead of P(2-furyl) ₃	<5
10	DPEPhos (12 mol%) instead of P(2-furyl) ₃	35
11	XantPhos (12 mol%) instead of P(2-furyl) ₃	6
12	At 65 °C instead of 75 °C	62

13	At 85 °C instead of 75 °C	70
14	[(cinnamyl)PdCp] instead of Pd ₂ dba ₃	63
15	Pd(dba) ₂ instead of Pd ₂ dba ₃	64
16	Pd(OAc) ₂ instead of Pd ₂ dba ₃	42
17	PhCF ₃ instead of PhMe	44
18	Dioxane instead of PhMe	53
19	<i>t</i> -amyl alcohol:PhMe 5:1 instead of PhMe	70
20	LiOt-Bu instead of Cs ₂ CO ₃	32
21	NaOt-Bu instead of Cs ₂ CO ₃	38
22	KOt-Bu instead of Cs ₂ CO ₃	63
23	With LiOTf (1.2 equiv) as additive	88
24	With NaOTf (1.2 equiv) as additive	85
25	With KOTf (1.2 equiv) as additive	65
26	With CsOTf (1.2 equiv) as additive	97

^aReaction conditions: 0.10 mmol **46**, 0.11 mmol **2a**, 0.13 mmol **3**, 0.33 M in PhMe, 20 h. ^bNMR yield using trifluorotoluene as internal standard.

Table 4. Optimization for the aryl bromides.

Entry	Changes from standard conditions	Yield (%) ^b
1	none	90 (82) ^c
2	without CsOTf	41
3	DPEPhos (12 mol%) instead of P(2-furyl) ₃	83
4	DPEPhos (12 mol%) instead of P(2-furyl) ₃ without CsOTf	78
5	XANTPhos (12 mol%) instead of P(2-furyl) ₃ without CsOTf	65
6	PhDavePhos (20 mol%) instead of P(2-furyl) ₃ without CsOTf	15
7	At 50 °C instead of 70 °C.	30

^aReaction conditions: 0.10 mmol **1**, 0.11 mmol **2a**, 0.15 mmol **47**, CsOTf (1.2 equiv), 0.30 M in PhMe, 20 h. ^bNMR yield using 3,4,5-trichloropyridine as internal standard.

3. Proposed mechanism.

Based on observations and detailed mechanistic studies of the Wolfe's group,⁵ and observation in our group,⁶ we proposed the following mechanism for the aminoalkynylation reaction (Scheme S1). First oxidative addition of alkynyl bromide **3** onto the Pd⁰ catalyst **I** would form Pd^{II}-alkynyl intermediate **II**. Ligand exchange of the bromine with the in situ generated mixed aminal **V** give complex **VII**. Then, intramolecular aminopalladation of the olefins would likely occur in a *syn* manner to deliver the alkyl-Pd complex **VII**. Finally, reductive elimination would yield the imidazolidine **IX** and regenerate the Pd⁰ catalyst **I**. The diastereoselectivity observed would arise from a highly organized chair-like transition-state in which the Pd-N bond is eclipsed with the olefin. The CF₃ would adopt a pseudo-axial conformation to minimize A^{1,3}-strain with the Boc group, while the R¹ group would adopt a pseudo-equatorial conformation to minimize 1,3-diaxial interaction.

Regarding the formation of the mixed aminal **V**, it would start with the formation of the Boc-protected trifluoromethyl aldimine **III** under basic conditions. Subsequent nucleophilic addition of allylamine **IV** onto **III** would yield **V**. The stability of **V** most likely arises from the trifluoromethyl group that disfavor the formation of highly destabilized iminium **VI**.

⁵ (a) J. E. Ney, J. P. Wolfe, *J. Am. Chem. Soc.*, **2005**, 127, 8644. (b) J. D. Neukom, N. S. Perch, J. P. Wolfe, *J. Am. Chem. Soc.*, **2010**, 132, 6276. (c) J. D. Neukom, N. S. Perch, J. P. Wolfe, *Organometallics*, **2011**, 30, 1269.

⁶ S. Nicolai, R. Sedigh-Zadeh, J. Waser, *J. Org. Chem* **2013**, 78, 3783.

Scheme S1. Proposed mechanism for the aminoalkynylation reaction.

4. Preparation of allylamines.

N-(4-(Trifluoromethyl)benzyl)prop-2-en-1-amine (50)

4-(Trifluoromethyl)benzaldehyde (**48**) (1.37 mL, 10.0 mmol, 1.0 eq) and prop-2-en-1-amine (**49**) (0.571 g, 10.0 mmol, 1.0 eq) were mixed in 1,2-dichloroethane (35 mL) and then treated with sodium triacetoxyborohydride (3.0 g, 14 mmol, 1.4 eq). The mixture was stirred at rt under a N₂ atmosphere for 2.5 h. The reaction mixture was quenched by adding aqueous saturated NaHCO₃ (15 mL), and the product was extracted with EtOAc (3x30 mL). The EtOAc extract was dried (MgSO₄), and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO₂, 10:1:0.1 Pentane:EtOAc:Et₃N) to afford the title compound **50** as a pale yellow oil (1.83 g, 8.50 mmol, 85% yield).

R_f 0.20 (Pentane:EtOAc 4:1).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.45 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.92 (ddt, *J* = 17.2, 10.3, 6.0 Hz, 1H, CHCH₂), 5.21 (m, 1H, CHCH₂), 5.14 (m, 1H, CHCH₂), 3.86 (s, 2H, ArCH₂), 3.28 (m, 2H, NCH₂), 1.65 (bs, 1H, NH).

¹³C NMR (101 MHz, Chloroform-*d*) δ 144.4, 136.5, 129.4 (q, *J* = 32.2 Hz), 128.5, 125.5 (m), 124.5 (q, *J* = 272.2 Hz), 116.5, 52.7, 51.8.

IR ν_{max} 3394 (w), 2831 (w), 2830 (w), 1646 (w), 1620 (w), 1458 (w), 1420 (w), 1329 (s), 1167 (m), 1127 (s), 1069 (w), 1021 (w), 925 (w), 844 (w), 823 (w), 796 (w), 784 (w), 763 (w), 728 (w).

HRMS (ESI) calcd. for C₁₁H₁₃F₃N⁺ [M+H]⁺ 216.0995; found 216.0994.

4-((Allylamino)methyl)benzaldehyde (52)

To a solution of commercially available 4-((allylamino)methyl)benzonitrile (**51**) (0.861 g, 5.00 mmol, 1.0 eq) in anhydrous toluene (12.5 mL) was added DIBAL-H (1 M in hexane, 6.50 mL, 6.50 mmol, 1.3 eq), keeping the internal temperature between -10 and -5 °C. After stirring at 0 °C for 2 h, ice cold HCl (10% aq. sol., 50 mL) was added carefully. The layers were separated and the aqueous phase washed with CH₂Cl₂ (3x15 mL). The resulting aqueous layer was basified (pH 14) with KOH and extracted with CH₂Cl₂ (3x50 mL). The combined organic layers were washed with saturated aqueous NaCl and dried (MgSO₄). The solvent was evaporated to give the crude product that was purified by passing through a short pad of silica, eluting with EtOAc to afford the pure title compound **52** as a pale yellow oil (0.797 g, 4.55 mmol, 91% yield).

N. B.: this compound readily polymerized, preventing us from obtaining a clean ¹³C NMR spectrum.

¹H NMR (400 MHz, Chloroform-*d*) δ 10.00 (s, 1H, CHO), 7.89 – 7.78 (m, 2H, Ar*H*), 7.57 – 7.45 (m, 2H, Ar*H*), 5.93 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H, CHCH₂), 5.25 – 5.17 (m, 1H, CHCH₂), 5.16 – 5.10 (m, 1H, CHCH₂), 3.89 (s, 2H, ArCH₂), 3.29 (m, 2H, NCH₂), 1.52 (bs, 1H, NH).

IR ν_{max} 3664 (w), 3074 (w), 2995 (w), 2916 (w), 2827 (m), 2735 (w), 1698 (s), 1643 (w), 1607 (m), 1578 (w), 1449 (w), 1420 (w), 1389 (w), 1363 (w), 1341 (w), 1304 (w), 1254 (w), 1210 (m), 1166 (m), 1108 (w), 1072 (w), 997 (m), 922 (m), 848 (m), 823 (m), 783 (m).

HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{14}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 176.1070; found 176.1068.

Ferrocenylmethyl allylamine (**54**)

Following a slightly modified procedure,⁷ to a solution of ferrocenecarboxaldehyde (**53**) (700 mg, 3.27 mmol) in MeOH (14 mL) was added allylamine (**49**) (0.270 mL, 3.60 mmol, 1.1 equiv) and the mixture was stirred at room temperature for 30 min. The mixture was cooled to 0 °C and solid NaBH_4 (0.148 g, 3.92 mmol, 1.2 equiv) was added in two portions. Then the solution was allowed to warm to room temperature and was stirred for another 30 min. The solvent was removed, diluted with EtOAc and quenched with saturated aqueous NaHCO_3 . The organic layer was separated, washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. Ferrocenylmethyl allylamine (**54**) was obtained as dark oil (750 mg, 3.22 mmol, 90 %) without further purification.

^1H NMR (400 MHz, Chloroform- d) δ 5.92 (ddt, J = 16.5, 10.3, 6.0 Hz, 1H, CHCH_2), 5.20 (dd, J = 17.2, 1.6 Hz, 1H, CHCH_2), 5.12 (dd, J = 10.3, 1.6 Hz, 1H, CHCH_2), 4.22 – 4.04 (m, 9H, FerroceneH), 3.53 (s, 2H, Ferrocene CH_2), 3.29 (d, J = 6.0 Hz, 2H, NCH_2), 1.67 (s, 1H, NH).

^{13}C NMR (101 MHz, Chloroform- d) δ 137.0, 116.0, 87.0, 68.5, 67.8, 52.1, 48.4.

Spectra data was consistent with the values reported in literature.⁷

N-benzyl-2-((benzyloxy)methyl)prop-2-en-1-amine (**56**)

Multistep procedure:

1) Benzyl alcohol (0.572 mL, 5.50 mmol, 1.1 equiv) was added to a mixture of NaH (120 mg, 5.00 mmol, 1 equiv) in THF (5.0 mL) at rt. The reaction mixture was stirred for 1 h at this temperature and then slowly transferred to a solution of 3-chloro-2-(chloromethyl)prop-1-ene (**55**) (656 mg, 5.25 mmol, 1.05 equiv) in THF (Ratio: 1.000, Volume: 5.0 mL) at 0 °C. The reaction mixture was stirred for 12 h at rt and then quenched with 1N HCl. The crude residue was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 99:1 to 92:8 Pentane:Et₂O) to afford a yellow oil (0.530 g, 2.69 mmol, 54% yield) which was directly used in the next step.

2) (((2-(chloromethyl)allyl)oxy)methyl)benzene (0.415 g, 2.11 mmol) was slowly added to a mixture of K_2CO_3 (0.350 g, 2.53 mmol) and phenylmethanamine (1.20 mL, 11.2 mmol) at 0 °C. The reaction mixture was stirred for 3 h, diluted with DCM (30 mL), filtered and concentrated

⁷ Gobe, V.; Retailleau, P.; Guinchard, X. *Org. Lett.* **2014**, *16*, 5438.

under reduced pressure. The residue was purified by column chromatography (SiO₂, Pentane:EtOAc:Et₃N 100:10:1) to afford the title compound **56** (320 mg, 1.20 mmol, 57%) as a pale yellow oil.

R_f 0.25 (Pentane:EtOAc 4:1).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.29 (m, 8H, ArH), 7.29 – 7.22 (m, 2H, ArH), 5.20 – 5.17 (m, 1H, C=CH₂), 5.17 – 5.15 (m, 1H, C=CH₂), 4.51 (s, 2H, PhCH₂O), 4.07 (s, 2H, OCH₂CCH₂), 3.78 (s, 2H PhCH₂N), 3.36 – 3.30 (m, 2H, CH₂N), 1.58 – 1.38 (m, 1H, NH).

¹³C NMR (101 MHz, Chloroform-*d*) δ 144.4, 140.5, 138.4, 128.5, 128.5, 128.3, 127.8, 127.7, 127.0, 113.4, 72.3, 72.2, 53.3, 51.7.

IR ν_{max} 3523 (w), 3450 (w), 3347 (w), 3308 (w), 3068 (m), 3029 (m), 2842 (m), 1956 (w), 1877 (w), 1818 (w), 1683 (w), 1658 (w), 1603 (w), 1493 (w), 1451 (m), 1365 (w), 1308 (w), 1080 (s), 1026 (m), 974 (w), 912 (m), 817 (w).

HRMS (ESI) calcd. for C₁₈H₂₂NO⁺ [M+H]⁺ 268.1696; found 268.1691.

N-Benzylbut-3-en-2-amine (46)

Following a reported procedure,⁸

1) MeSO₂Cl (2.86 g, 25.0 mmol, 1.25 eq) was added dropwise at 0 °C to a CH₂Cl₂ (60 mL) solution of but-3-en-2-ol (**57**) (1.44 g, 20.0 mmol, 1.0 eq) and Et₃N (3.04 g, 30.0 mmol, 1.5 eq). The mixture was stirred at the same temperature for 2 h, resulting in a large amount of white precipitate. Saturated Na₂CO₃ (30 mL) was then added to quench the reaction. After the separation of the organic layer, extraction of the aqueous layer with CH₂Cl₂ (20 mL x 2) and washing with brine, the combined organic layer was dried with MgSO₄. The solvent was removed under reduced pressure, and the residue was dried under vacuum to afford but-3-en-2-yl methanesulfonate (3.15 g, 21.0 mmol, <= 100%), which was used directly in next step.

2) But-3-en-2-yl methanesulfonate (2.13 g, 14.0 mmol, 1.0 eq) was added dropwise to a rapidly stirring neat benzyl amine solution (4.50 g, 42.0 mmol, 3.0 eq) at room temperature. After stirring overnight, NaOH (10%, 10 mL) was added. After extraction with CH₂Cl₂ (20 mL), separation of organic layer, drying with Na₂SO₄, and removal of the solvent under reduced pressure, the residue was purified by column chromatography (EtOAc:Hexanes 3:1) to afford the title compound **46** as a colorless oil (2.48 g, 15.4 mmol, 77% yield for 2 steps).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.30-7.22 (m, 5H, ArH), 5.72 (ddd, *J* = 17.6, 10.1, 7.6 Hz 1H, CHCH₂), 5.14 (m, 1H, CHCH₂), 5.09 (m, 1H, CHCH₂), 3.80 (d, *J* = 13.1 Hz 1H, PhCH₂), 3.67 (d, *J* = 13.1 Hz 1H, PhCH₂), 3.20 (m, 1H, NCH), 1.26 (br, NH, 1H, NH) 1.16 (d, *J* = 6.5 Hz, 3H, Me).

¹³C NMR (100 MHz, Chloroform-*d*) δ 142.7, 140.8, 128.5, 128.3, 126.9, 114.8, 56.2, 51.5, 21.9.

¹H NMR data is consistent with the values reported in literature.⁹

⁸ Zhao, S.-B.; Bilodeau, E.; Lemieux, V.; Beauchemin, A. M. *Org. Lett.* **2012**, *14*, 5082.

⁹ Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172.

N-benzylpenta-1,4-dien-3-amine (59)

Multistep procedure:

1) Following a slightly modified procedure,¹⁰ to a solution of acrylaldehyde (**58**) (1.74 mL, 25.8 mmol, 1.25 equiv) and 2-methylpropane-2-sulfinamide (2.50 g, 20.6 mmol) in DCM (15 mL) was added tetraethoxytitanium (12.1 mL, 58.0 mmol, 2.8 equiv). The mixture was stirred at room temperature for 1.5 h, then poured into a mixture of ice/water and stirred for 30 min. The white suspension was filtered through Celite and the cake rinsed with DCM. The organic layer was separated and the aqueous layer extracted with DCM (3x20 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (SiO₂, DCM) afforded the desired imine (2.53 g, 15.9 mmol, 77%) as a light yellow oil.

2) Vinylmagnesium bromide (1.0 M solution in THF, 10.3 mL, 10.3 mmol, 2 equiv) was slowly added to a solution of the imine (820 mg, 5.15 mmol) in DCM (26 mL) at -40 °C. The reaction mixture was slowly warmed up to rt overnight. The reaction was quenched with a 1:1:1 mixture of water, brine and NH₄Cl (30 mL). The layers were separated and the aqueous layer extracted with DCM (3x20 mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography (SiO₂, Pentane:EtOAc 5:1 to 1:1) to afford the desired sulfinamide (460 mg, 2.46 mmol, 48%) which was directly engaged in the next step.

3) A flame-dried flask was charged with the sulfinamide (300 mg, 1.60 mmol) and DMF (5.3 mL). The resulting solution was cooled to -40 °C. LiHMDS (1 M in THF, 1.60 mL, 1.60 mmol, 1.05 equiv) was added dropwise over 5 minutes. The solution was allowed to stir for 1 h at this temperature. Then benzyl bromide (0.38 mL, 3.2 mmol, 2 equiv) was added dropwise over 10 minutes. At this time, the resulting solution was warmed up to room temperature and was stirred for 2 h. The reaction was slowly quenched at 0 °C by the addition of a saturated aqueous solution of ammonium chloride, the layers of the resulting biphasic mixture were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with water (4x) and brine (2x), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO₂, Pentane:EtOAc 20:1 to 4:1) to afford the desired sulfinamide (312 mg, 1.13 mmol, 70%) which was directly engaged in the next step.

4) A solution of the sulfinamide (220 mg, 0.793 mmol) in methanol (1.6 mL) was treated with a 4N solution of HCl in CPME (0.80 mL, 2.0 mmol, 2.0 equiv) at -78 °C. The reaction mixture was then slowly warmed up to rt overnight. Nitrogen was bubbled in the reaction mixture for 10 min and then the solvent was removed under reduced pressure and the crude amine salt was triturated with cold ether to afford the pure title compound **59** (140 mg, 0.668 mmol, 84% yield) as a white solid.

m.p.: 146-147 °C.

¹⁰ Bonazzi, S.; Cheng, B.; Wzorek, J. S.; Evans, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9338.

¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 9.90 (s, 2H, NH), 7.67 – 7.58 (m, 2H, ArH), 7.45 – 7.31 (m, 3H, ArH), 6.14 (ddd, *J* = 17.2, 10.5, 7.7 Hz, 2H, CH=CH₂), 5.45 – 5.43 (m, 2H, CH=CH₂), 5.43 – 5.38 (m, 2H, CH=CH₂), 4.12 (d, *J* = 6.8 Hz, 1H, NCH), 4.02 (d, *J* = 4.7 Hz, 2H, PhCH₂).
¹³C NMR (101 MHz, CD₃CN) δ 132.8, 132.1, 131.5, 130.0, 129.6, 122.67, 63.3, 49.1.
IR ν_{max} 3391 (w), 3077 (w), 2927 (m), 2854 (w), 1638 (w), 1456 (m), 1301 (w), 1268 (w), 1121 (w), 996 (m), 923 (s).
HRMS (ESI) calcd for C₁₂H₁₆N⁺ [M+H]⁺ 174.1277; found 174.1277.

2-vinylpyrrolidine hydrochloride (**61**)

Multistep procedure:

1) DMP (3.56 g, 8.40 mmol, 1.2 equiv) was added portion-wise over 10 min to a stirred solution of commercially available *tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (**60**) (1.41 g, 7.00 mmol) in DCM (25 mL). The reaction mixture was stirred at rt for 12 h, then filtered over Celite and purified by column chromatography (Pentane:EtOAc 9:1) to afford the desired aldehyde (1.21 g, 6.07 mmol, 87%) which was engaged directly in the next step.

2) Following a slightly modified procedure,¹¹ methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol, 2 equiv) was added to a stirred solution of potassium *tert*-butoxide (1.23 g, 11.0 mmol, 2 equiv) in Et₂O (25 mL). The reaction mixture was stirred at reflux for 1 h, then cooled down to -5 °C and a solution of *tert*-butyl 2-formylpyrrolidine-1-carboxylate (1.10 g, 5.50 mmol) in Et₂O (25 mL) was added over 5 min. The reaction mixture was stirred at rt for 3 h. The reaction mixture was quenched with water (20 mL). The layers were separated and the aqueous one extracted with ether (3x10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO₂, Pentane:EtOAc 10:1) to afford the desired olefin (640 mg, 3.24 mmol, 59% yield) as an oil, which was engaged directly in the next step.

3) Following a slightly modified procedure,¹² a 2N HCl solution (4.8 mL, 9.7 mmol, 3 equiv) in ether was added to a stirred solution of *tert*-butyl 2-vinylpyrrolidine-1-carboxylate (640 mg, 3.24 mmol) in ether (3 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h, then the volatiles were removed and the crude was washed with dry ether (3x2 mL) and then dried under high vacuum for 1 h to afford the desired amine salt **61** (280 mg, 2.10 mmol, 65%).

¹H NMR (400 MHz, CDCl₃) δ 10.0 (bs, 1H, NH), 9.48 (bs, 1H, NH), 6.09 (ddd, *J* = 17.0, 10.3, 7.6 Hz, 1H, CHCH₂), 5.50 (d, 1H, *J* = 17.1 Hz, CHCH₂), 5.38 (d, 1H, *J* = 10.3 Hz, CHCH₂), 4.12–3.99 (m, 1H, NCH), 3.48–3.26 (m, 2H, NCH₂), 2.24–1.96 (m, 4H, 2xCH₂).

¹³C NMR (101 MHz, Chloroform-*d*) δ 132.4, 122.0, 62.6, 46.2, 31.2, 24.1.

Spectra data was consistent with the values reported in literature.¹³

¹¹ Morales-Chamorro, M.; Meza-Gonzalez, J.; Cordero-Vargas, A. *Tetrahedron Letters*, **2015**, 56, 4892.

¹² Donets, P. A.; Van der Eycken, E. V. *Synthesis*, **2011**, 2147.

¹³ Jurberg, I. D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, 51, 1950.

2-vinylpiperidine 2,2,2-trifluoroacetate (**63**)

Multistep procedure:

1) DMP (8.14 g, 19.2 mmol, 1.6 equiv) was added portion-wise over 10 min to a stirred solution of commercially available *tert*-butyl 2-(hydroxymethyl)piperidine-1-carboxylate (**62**) (2.58 g, 12.0 mmol) in DCM (60 mL). The reaction mixture was stirred at rt for 12 h, then filtered over Celite and purified by column chromatography (EtOAc in pentane 12-20%) to afford the desired aldehyde (2.15 g, 10.1 mmol, 84%) which was engaged in the next step.

2) Following a slightly modified procedure,¹⁴ methyltriphenylphosphonium bromide (3.95 g, 11.1 mmol, 2 equiv) was added to a stirred solution of potassium *tert*-butoxide (1.24 g, 11.1 mmol, 2 equiv) in Et₂O (40 mL). The reaction mixture was stirred at reflux for 1 h, then cooled down to 0 °C and a solution of the aldehyde (1.18 g, 5.53 mmol) in Et₂O (10 mL) was added over 5 min. The reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with water (20 mL). The layers were separated and the aqueous one extracted with ether (3x10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO₂, Pentane:Et₂O 10:1 to 5:1) to afford the desired olefin (1.03 g, 4.87 mmol, 88%) as an oil, which was engaged directly in the next step.

3) To a solution of the olefin was added TFA (11.3 mL, 146 mmol, 30 equiv) at 0 °C. The reaction mixture was stirred at rt for 3 h and then the volatiles were removed under reduced pressure. The crude residue was taken up in water (40 mL). The aqueous layer was washed with ether (3x20 mL) and then concentrated under reduced pressure. The crude residue was dried by co-evaporation with toluene (3x10 mL) to afford 2-vinylpiperidine 2,2,2-trifluoroacetate (**63**) (1.05 g, 4.66 mmol, 96 %) as an oil as an oil.

¹H NMR (400 MHz, CDCl₃) δ 9.29 (bs, 1H, NH), 8.76 (bs, 1H, NH), 5.84 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H, CHCH₂), 5.39 (dd, *J* = 17.4, 1.0 Hz, 1H, CHCH₂), 5.31 (d, *J* = 10.5 Hz, 1H, CHCH₂), 3.54 (q, *J* = 10.3 Hz, 1H, NCH), 3.37 (d, *J* = 12.6 Hz, 1H, NCH₂), 2.98 – 2.86 (m, 1H, NCH₂), 1.97 – 1.88 (m, 2H, 2xNCH₂CH₂), 1.85 – 1.70 (m, 3H, 2xNCH₂CH₂ and NCH₂CH₂CH₂), 1.58 – 1.46 (m, 1H, NCH₂CH₂CH₂).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (q, *J* = 36.8 Hz), 133.5, 120.7, 116.3 (q, *J* = 289.2 Hz), 58.8, 44.6, 28.7, 22.2, 22.0.

IR ν_{max} 3501 (w), 3015 (w), 2840 (w), 2753 (w), 2533 (w), 2436 (w), 1779 (w), 1670 (s), 1431 (w), 1177 (s), 1135 (s), 992 (w), 944 (w), 838 (w).

HRMS (ESI) calcd for C₇H₁₄N [M⁺] 112.1121; found 112.1116

¹⁴ Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6040.

Cis-1,3-divinylisoindoline (**65**)

Multistep procedure:

1) Following a slightly modified procedure,¹⁵ isoamyl nitrite (3.22 mL, 23.9 mmol, 2 equiv) was slowly added to a stirred solution of 2-aminobenzoic acid (2.050 g, 14.95 mmol, 1.25 equiv) and 2,2,2-trichloroacetic acid (17 mg, 0.11 mmol, 0.9 mol%) in dry THF (35 mL) at 0 °C for 30 min and the mixture was stirred at room temperature for 1.5 h. The dark yellow precipitate of benzenediazonium-2-carboxylate was collected by filtration and washed with cold THF using minimal suction for draining taking care to prevent complete drying. The salt was immediately transferred to a flask. DCE (30 mL) and *tert*-butyl 1H-pyrrole-1-carboxylate (**64**) (2.00 g, 12.0 mmol) were added. The mixture was heated at 60 °C for 45 min and the black mixture was cooled to room temperature. After concentration under reduced pressure, the residue was purified by flash column chromatography (hexane/ethyl acetate = 95/5) and recrystallization with hexane gave *tert*-butyl 1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (1.69 g, 6.95 mmol, 58 % yield), which was directly used in the next step.

2) Following a slightly modified procedure,¹⁶ a 250 mL round-bottom flask equipped with a stirring bar and charged with *tert*-butyl 1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (0.260 g, 1.07 mmol) and dry DCM (105 mL). The flask was put under house vacuum and backfilled with nitrogen (3x), then put under vacuum and backfilled with ethylene gas. The solution was stirred with an ethylene atmosphere for 30 min and then Grubbs II catalyst (27 mg, 0.032 mmol, 3 mol%) was added. The reaction was stirred at rt under ethylene atmosphere for 15 h. Then 2 drops of water were added and solvent was then removed and the product purified by column chromatography (Pentane:EtOAc 97:3 to 92:8) affording *tert*-butyl *cis*-1,3-divinylisoindoline-2-carboxylate (238 mg, 0.877 mmol, 82 % yield) as a pale yellow oil, which was directly used in the next step.

3) To a solution of *tert*-butyl *cis*-1,3-divinylisoindoline-2-carboxylate (0.238 g, 0.978 mmol) in dry DCM (3 mL) at 0 °C was slowly added TFA (1.51 mL, 19.6 mmol, 20 equiv). The reaction mixture was stirred at rt for 1.5 h and then the volatiles were removed. The crude residue was taken up in 1 N NaOH and extracted with DCM (3x10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The compound was passed through a short plug of silica, eluting with pure ether to afford the title compound *cis*-1,3-divinylisoindoline **65** (143 mg, 0.835 mmol, 85 % yield) as an oil.

R_f 0.20 (Pentane:EtOAc 4:1).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 2H, ArH), 7.21 – 7.15 (m, 2H, ArH), 5.92 (ddd, *J* = 16.9, 9.9, 7.9 Hz, 2H, CHCH₂), 5.38 (dt, *J* = 17.1, 1.1 Hz, 2H, CHCH₂), 5.22 (dd, *J* = 10.0, 1.6 Hz, 2H, CHCH₂), 4.88 (d, *J* = 7.8 Hz, 2H, NCH), 2.32 (s, 1H, NH).

¹³C NMR (101 MHz, Chloroform-*d*) δ 142.9, 140.6, 127.4, 123.0, 116.3, 66.2.

¹⁵ Cho, Y.-h.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837.

¹⁶ Bulchert, M.; Meinke, S.; Prenzel, A. H. G. P.; Deppermann, N.; Maison, W. *Org. Lett.* **2006**, *8*, 5553.

IR ν_{max} 3356 (w), 3075 (w), 2975 (w), 2804 (w), 1638 (w), 1611 (w), 1468 (w), 1420 (w), 1294 (w), 1060 (w), 994 (m), 925 (s).

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{14}\text{N}^+$ $[\text{M}+\text{H}]^+$ 172.1121; found 172.1119.

5. Preparation of aldimines.

1-((*Tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**)

Following a slightly modified procedure,¹⁷ a 100 mL pressure tube was charged with *tert*-butyl carbamate (7.03 g, 60.0 mmol), 2,2,2-trifluoro-1-methoxyethanol (**66**) (7.69 mL, 66.0 mmol, 1.1 equiv), 4Å MS (10 g) and dioxane (80 mL). The tube was sealed under nitrogen atmosphere. The resulting mixture was heated at 100 °C for 5 d and then cooled down to rt. The mixture was filtered over Celite and the cake was washed with ether (3x20 mL). The volatiles were removed under reduced pressure and the resulting solid was recrystallized in chloroform to afford white crystals (8.20 g, 38.1 mmol, 64% for 2 crops).

To a solution of pyridine (1.84 mL, 22.8 mmol, 1.4 equiv) and DMAP (50 mg, 0.41 mmol, 2.5 mol%) in dichloromethane (80 mL) at 0 °C was slowly added acetyl chloride (1.39 mL, 19.5 mmol, 1.2 equiv). To the resulting mixture was added *tert*-butyl (2,2,2-trifluoro-1-hydroxyethyl)carbamate (3.50 g, 16.3 mmol) portion-wise. Then the mixture was stirred at 0 °C for 20 min and quenched with water (10 mL). The pH was adjusted to 2 by addition of 0.1 N HCl and the layers were separated. The organic layer was washed with 0.1 N HCl (3x20 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (Pentane:EtOAc 10:1) affording the title compound **2a** (4.05 g, 15.8 mmol, 97 % yield) as a white solid.

m.p.: 60-61 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 6.87 – 6.57 (m, 1H, *CHCF*₃), 5.48 – 5.16 (m, 1H, *NH*), 2.14 (s, 3H, Me), 1.47 (s, 9H, *t*-Bu).

¹³C NMR (101 MHz, CDCl₃) δ 168.2, 153.1, 121.8 (q, *J* = 281.2 Hz), 82.3, 72.1 (q, *J* = 39.3 Hz), 28.2, 20.7.

IR ν_{max} 2984 (w), 1770 (m), 1731 (m), 1522 (w), 1373 (m), 1252 (w), 1199 (s), 1162 (s), 1023 (m), 837 (w).

HRMS (ESI) calcd for C₉H₁₄F₃NNaO₄⁺ [*M*+Na]⁺ 280.0767; found 280.0770.

2,2,2-Trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**)

Following a slightly modified procedure,¹⁷ a 20 mL microwave vial was charged with methyl carbamate (2.25 g, 30.0 mmol), 2,2,2-trifluoro-1-methoxyethanol (**66**) (3.84 mL, 33.0 mmol, 1.1 equiv), 4Å MS (4 g) and was filled with dioxane (*ca* 16 mL). The tube was sealed under nitrogen atmosphere. The resulting mixture was heated at 100 °C for 5 d and then cooled down to rt. The mixture was filtered over Celite and the cake was washed with ethyl acetate (3x20 mL). The volatiles were removed under reduced pressure and the residue was purified by column

¹⁷ Ingrassia, L.; Mulliez, M. *Synthesis*, **1999**, 10, 1731.

chromatography (SiO₂, Pentane:EtOAc 4:1) to afford the title compound (3.93 g, 22.7 mmol, 75 % yield) as a white solid.

To a solution of pyridine (1.96 mL, 24.3 mmol, 1.4 equiv) and DMAP (53 mg, 0.43 mmol, 2.5 mol%) in dichloromethane (87 mL) at 0 °C was slowly added acetyl chloride (1.48 mL, 20.8 mmol, 1.2 equiv). To the resulting mixture was added methyl (2,2,2-trifluoro-1-hydroxyethyl)carbamate (3.00 g, 17.3 mmol) portionwise. Then the mixture was stirred at 0 °C for 20 min and quenched with water (10 mL). The pH was adjusted to 2 by addition of 0.1 N HCl and the layers were separated. The organic layer was washed with 0.1 N HCl (3x20 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (Pentane:EtOAc 5:1) affording the title compound **2aa** (3.55 g, 16.5 mmol, 95 % yield) as a white solid.

R_f 0.50 (Pentane:EtOAc 3:1).

m.p.: 84–86 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 6.90 – 6.66 (m, 1H, *CHCF*₃), 5.77 – 5.40 (m, 1H, *NH*), 3.76 (s, 3H, OMe), 2.14 (s, 2H, Ac).

¹³C NMR (101 MHz, CDCl₃) δ 168.1, 154.9, 121.7 (q, *J* = 281.0 Hz), 72.3 (q, *J* = 36.9 Hz), 53.4, 20.6.

IR ν_{max} 3316 (w), 2996 (w), 2961 (w), 2225 (w), 1767 (s), 1732 (m), 1538 (m), 1381 (m), 1254 (s), 1208 (s), 1162 (s), 1029 (s), 966 (m).

HRMS (ESI) calcd for C₆H₈F₃NNaO₄⁺ [*M*+Na]⁺ 238.0298; found 238.0299.

4-((1-Ethoxy-2,2,2-trifluoroethyl)amino)benzonitrile (**2f**)

A round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with 1-ethoxy-2,2,2-trifluoroethanol (**67**) (2.20 mL, 16.1 mmol, 3.35 equiv) and ethanol (10 mL). Then 4-aminobenzonitrile (**68**) (0.567 g, 4.80 mmol) and PTSA (0.052 g, 0.30 mmol, 6.3 mol%) were added to the reaction flask, and the mixture was stirred at reflux. After the reaction was complete (monitoring by TLC, Pentane:EtOAc 4:1), and cooled to room temperature, 10% aqueous NaHCO₃ (30 mL) was added. The mixture was extracted with ethyl acetate (2x30 mL), dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 Pentane:EtOAc to 60:40 Pentane:EtOAc) to afford the title compound **2f** (1.05 g, 4.30 mmol, 90 % yield) as a white solid.

R_f 0.60 (Pentane:EtOAc 4:1).

m.p.: 94–96 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.43 (m, 2H, *ArH*), 6.84 – 6.73 (m, 2H, *ArH*), 5.10 (dq, *J* = 9.5, 4.6 Hz, 1H, CF₃CH), 4.87 (d, *J* = 9.5 Hz, 1H, *NH*), 3.75 (dq, *J* = 9.3, 7.1 Hz, 1H, OCH₂), 3.66 (dq, *J* = 9.2, 7.0 Hz, 1H, OCH₂), 1.22 (t, *J* = 7.0 Hz, 3H, Me).

¹³C NMR (101 MHz, CDCl₃) δ 148.4, 134.0, 122.7 (q, *J* = 283.7 Hz), 119.6, 114.1, 102.4, 81.2 (q, *J* = 34.1 Hz), 65.0, 15.0.

IR $\nu_{\max}$ 3342 (w), 2985 (w), 2220 (m), 1609 (s), 1525 (m), 1328 (w), 1259 (m), 1176 (s), 1140 (s), 1092 (s), 913 (w), 829 (m).

HRMS (ESI) calcd for $C_{11}H_{12}F_3N_2O^+$ $[M+H]^+$ 245.0896; found 245.0893.

N-(1-Ethoxy-2,2,2-trifluoroethyl)-4-nitrobenzenesulfonamide (2h)¹⁸

Following a slightly modified procedure,¹⁹ a round-bottomed flask equipped with a magnetic stirring bar under nitrogen atmosphere was charged with 4-nitrobenzenesulfonamide (**69**) (2.02 g, 10.0 mmol) and DCM (20 mL). Then 1-ethoxy-2,2,2-trifluoroethanol (**67**) (1.53 mL, 11.0 mmol, 1.1 equiv) and $TiCl_4$ (2.21 mL, 20.0 mmol, 2 equiv) were added dropwise. The resulting mixture was stirred at 80 °C for 15 h and then treated with ethanol (3.50 mL, 60.0 mmol, 6 equiv). The crude residue was purified by column chromatography (SiO_2 , Pentane:EtOAc 3:1) to afford the title compound **2h** (1.45 g, 4.42 mmol, 44%) as a white solid.

R_f 0.20 (Pentane:EtOAc 3:1).

m.p.: 92–93 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 – 8.28 (m, 2H, ArH), 8.20 – 7.91 (m, 2H, ArH), 5.42 (d, J = 9.9 Hz, 1H, NH), 5.03 (dq, J = 9.9, 4.5 Hz, 1H, CF_3CH), 3.88 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2), 3.70 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2), 1.23 (t, J = 7.0 Hz, 3H, Me).

¹³C NMR (101 MHz, $CDCl_3$) δ 150.4, 146.3, 128.3, 124.6, 121.7 (d, J = 282.6 Hz), 81.6 (q, J = 35.6 Hz), 66.0, 14.7.

IR $\nu_{\max}$ 3282 (w), 2987 (w), 2895 (w), 1610 (w), 1534 (s), 1454 (w), 1351 (s), 1313 (m), 1276 (m), 1169 (s), 1109 (s), 1065 (s), 936 (m), 856 (m).

2,2,2-Trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (2i)

Following a slightly modified procedure,²⁰ a 25 mL round-bottom flask was charged with acetamide (1.18 g, 20.0 mmol), 2,2,2-trifluoro-1-methoxyethanol (**66**) (2.56 mL, 22.0 mmol, 1.1 equiv), 4Å MS (3 g) and dioxane (10 mL) and then sealed under nitrogen atmosphere. The resulting mixture was heated at 100 °C for 5 d. The mixture was filtered over Celite and the cake was washed with ethylacetate. The volatiles were removed under reduced pressure. The residue was dried under a nitrogen flow overnight. DCM (40 mL) was added and heated to reflux. The

¹⁸ The molecule ion could not be observed by high resolution mass spectrometry.

¹⁹ Kumadaki, I.; Jonoshita, S.; Harada, A.; Omote, M.; Ando, A. *J. Fluorine Chem.* **1999**, 97, 61

²⁰ Tanaka, K.; Ishiguro, Y.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1993**, 66, 661.

mixture was filtered. The mother liquor was concentrated to half its volume and filtered again. The solids were combined affording *N*-(2,2,2-trifluoro-1-hydroxyethyl)acetamide (1.51 g, 9.61 mmol, 48%) as a white solid.

Acetyl chloride (1.8 mL, 26 mmol, 4 equiv) was slowly added to a solution of pyridine (2.3 mL, 29 mmol, 4.5 equiv) and DMAP (39 mg, 0.32 mmol, 5 mol%) in dichloromethane (50 mL) at 0 °C. To the resulting mixture was added *N*-(2,2,2-trifluoro-1-hydroxyethyl)acetamide (1.00 g, 6.37 mmol) portionwise. Then the mixture was stirred at 0 °C for 20 min and quenched with water (10 mL). The pH was adjusted to 2 by addition of 0.1 N HCl and the layers were separated. The organic layer was washed with 0.1 N HCl (3x20 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was recrystallized in DCM to afford the title compound **2i** (860 mg, 4.32 mmol, 68%) as a white solid.

m.p.: 123-126 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.00 (dq, *J* = 10.4, 5.3 Hz, 1H, CF₃CH), 6.44 – 6.33 (m, 1H, *NH*), 2.14 (s, 3H, OAc), 2.09 (s, 3H, NAc).

¹³C NMR (101 MHz, CDCl₃) δ 169.5, 167.9, 121.9 (q, *J* = 280.9 Hz), 69.8 (q, *J* = 36.8 Hz), 23.2, 20.5.

IR ν_{max} 3280 (m), 3058 (w), 1759 (s), 1680 (s), 1545 (m), 1433 (w), 1382 (m), 1259 (s), 1219 (s), 1164 (s), 1050 (m), 978 (m), 914 (w).

HRMS (ESI) calcd for C₆H₈F₃NNaO₃ [M+Na] 222.0354; found 222.0359.

6. Preparation of bromoalkynes.

General procedure for the bromination of terminal alkynes:²¹

The terminal alkyne (1.0 equiv) is dissolved in acetone (ca. 6.8 mL per mmol of alkyne). N-bromosuccinimide (1.2 equiv) and AgNO₃ (0.1 equiv) are added to the resulting solution in this order and the mixture is stirred at rt for 3-6 hours, until complete consumption of the starting material according to TLC. It was then poured onto iced water. The aqueous layer was extracted with pentane (3 times) and the combined organic extracts were dried over MgSO₄, filtered and the solvent removed by evaporation under reduced pressure. The bromo alkyne was isolated by column chromatography in 95-99% purity as judged by ¹H NMR.

2-Bromo-1-triisopropylsilyl acetylene (**3**)

Triisopropylsilylacetylene (**70**) (813 mg, 4.45 mmol, 1.00 equiv) was brominated according to the general procedure. Bromoalkyne **3** was obtained as a colorless oil (1.16 g, 4.43 mmol, 99%) without further purification.

¹H NMR (400 MHz, CDCl₃) δ 1.20-0.97 (m, 21 H, TIPS).

¹³C NMR (100 MHz, CDCl₃) δ 83.5, 61.7, 18.5, 11.3.

Spectra data was consistent with the values reported in literature.²¹

((4-Bromo-2-methylbut-3-yn-2-yl)oxy)triisopropylsilane (**73**)

Following a reported procedure,²² 2-methylbut-3-yn-2-ol (**71**) (0.34 mL, 3.5 mmol, 1.0 equiv.) and 2,6-lutidine (freshly distilled on CaH₂, 0.41 mL, 3.5 mmol, 1.0 equiv.) were dissolved in CH₂Cl₂ (12 mL). TIPSOTf (0.94 mL, 3.5 mmol, 1.0 equiv.) was added dropwise to the solution at 0 °C. The solution was allowed to warm to rt overnight and then quenched with a saturated aqueous NaHCO₃ solution and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, pentane) afforded TIPS-protected propargyl alcohol **72** as a colorless oil (622 mg, 2.59 mmol, 74% yield), which was used directly for the next step.

Following a reported procedure,⁶ propargyl alcohol **72** (603 mg, 2.51 mmol, 1.0 equiv) was dissolved in acetone (17 mL). N-bromosuccinimide (535 mg, 3.01 mmol, 1.2 equiv) and

²¹ Jiang, M. X.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.*, **2004**, 126, 5970.

²² Nishimura, T.; Nagaosa, M.; Hayashi, T. *Tetrahedron Lett.* **2011**, 52, 2185.

AgNO₃ (42 mg, 0.25 mmol, 0.1 equiv) are added to the resulting solution in this order and the mixture is stirred at rt for 6 hours, until complete consumption of the starting material according to TLC. It was then poured onto iced water. The aqueous layer was extracted with pentane (3 times) and the combined organic extracts were dried over MgSO₄, filtered and the solvent removed by evaporation under reduced pressure. After purification by column chromatography (SiO₂, pentane), bromoalkyne **73** was obtained as a colorless oil (733 mg, 2.30 mmol, 91% yield).in 95% purity as judged by ¹H NMR.

¹H NMR (400 MHz, CDCl₃) δ 1.51 (s, 6 H), 1.18-1.03 (m, 21 H).

¹³C NMR (100 MHz, CDCl₃) δ 85.4, 67.2, 42.7, 32.9, 18.3, 13.0.

Spectra data was consistent with the values reported in literature.^{Error! Bookmark not defined.}

(((4-Bromo-2-methylbut-3-yn-2-yl)oxy)methyl)benzene (**75**)

Following a reported procedure,²³ NaH (60% suspension in mineral oil, 240 mg, 6.00 mmol, 1.2 equiv) was added portionwise to a solution of 2-methyl-3-butyn-2-ol (**71**) (0.49 mL, 5.0 mmol, 1.0 equiv) in THF (24 mL). The mixture was stirred at rt for 1 hour and then TBAI (92.0 mg, 0.250 mmol, 0.050 equiv) and benzyl bromide (0.72 mL, 6.0 mmol, 1.2 equiv) were added in this order. The reaction mixture was stirred at rt overnight and then diluted with Et₂O (18 mL). The organic solution was washed with water (3 x 15 mL), brine and dried over MgSO₄. Upon filtration, it was concentrated by evaporation under reduced pressure and the resulting crude oil was purified by column chromatography (SiO₂, Pentane/Et₂O 95/5) to afford the pure O-benzylated alcohol **74** as a colorless oil (715 mg, 4.10 mmol, 82% yield) which was directly used in the next step.

O-Benzylated alcohol **74** (523 mg, 3.00 mmol) was brominated according to the general procedure. After purification by column chromatography (SiO₂, Pentane/EtOAc 98/2), bromoalkyne **75** was obtained as a pale yellow oil (631 mg, 2.49 mmol, 83% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.41-7.31 (m, 4 H), 7.27 (m, 1 H), 4.62 (s, 2 H), 1.55 (s, 6 H).

¹³C NMR (101 MHz, CDCl₃) δ 138.7, 128.3, 127.7, 127.4, 82.4, 71.7, 66.7, 44.1, 28.7.

Spectra data was consistent with the values reported in literature.^{Error! Bookmark not defined.}

(((1-Bromonon-1-yn-3-yl)oxy)triisopropylsilane (**78**))

Following a slightly modified reported procedure,²⁴ heptaldehyde (**76**) (1.22 mL, 8.76 mmol, 1.0 equiv.) was added dropwise to a solution of ethynyl magnesium bromide (0.5 M in THF, 22.8

²³ Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186.

²⁴ Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614.

mL, 11.4 mmol, 1.3 equiv.) at 0 °C. After 30 min, the cooling bath was removed to reach rt and the solution was stirred for further 2 h. The reaction was then quenched by addition of aqueous HCl (1.0 M, 15 mL) and the mixture was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (SiO₂, pentane/EtOAc 20/1) afforded the corresponding propargyl alcohol as a yellow oil (943 mg, 6.73 mmol, 77% yield).

TIPSCl (1.36 mL, 6.36 mmol, 1.1 equiv.) and DMAP (777 mg, 6.36 mmol, 1.1 equiv.) were dissolved in CH₂Cl₂ (10 mL) at rt and a solution of propargyl alcohol (810 mg, 5.78 mmol, 1.0 equiv.) in CH₂Cl₂ (30 mL) was slowly added to the reaction mixture. The reaction was stirred overnight and then quenched by sequential addition of H₂O (36 mL) and aqueous HCl (2.0 M, 36 mL). The mixture was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane) afforded the *O*-silylated propargyl alcohol **77** as a colorless oil (1.04 g, 3.51 mmol, 61% yield).

O-Silylated propargyl alcohol **77** (890 mg, 3.00 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by column chromatography (SiO₂, pentane), bromo alkyne **78** was obtained as a colorless oil (1.04 g, 2.77 mmol, 92% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.48 (t, 1 H, *J* = 6.3 Hz), 1.69 (m, 2 H), 1.44 (m, 2 H), 1.36-1.26 (m, 6 H), 1.17-1.04 (m, 21 H), 0.89 (t, *J* = 6.7 Hz).

¹³C NMR (101 MHz, CDCl₃) δ 82.1, 64.0, 43.6, 38.7, 31.8, 29.0, 24.9, 22.6, 18.0, 18.0, 14.1, 12.3.

Spectra data was consistent with the values reported in literature.**Error! Bookmark not defined.**

((4-Bromo-1,1,1-trifluoro-2-phenylbut-3-yn-2-yl)oxy)(tert-butyl)dimethylsilane (**81**)¹⁸

To a 0.5 M solution of ethynylmagnesium bromide (7.0 mL, 3.5 mmol) in THF was slowly added 2,2,2-trifluoro-1-phenylethanone (**79**) (300 mg, 1.72 mmol) in THF (1 mL). After 3 h at rt the reaction mixture was quenched with water (1 mL) and then NH₄Cl sat solution was added (5 mL) and the mixture was diluted with DCM (10 mL). The layers were separated and the aqueous layer was extracted once with DCM (10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to afford a yellow oil that was engaged in the next step without further purification.

TBS-Cl (0.422 g, 2.80 mmol, 1.4 equiv) was slowly added to a solution of the alcohol (0.400 g, 2.00 mmol), DBU (0.452 mL, 3.00 mmol, 1.5 equiv), DMAP (12 mg, 0.10 mmol, 0.05 equiv) in acetonitrile (6 mL) at 0 °C. The reaction mixture was stirred for 12 h at rt. The reaction mixture was quenched with water (5 mL) and extracted with DCM (3x5 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO₂, Pentane) to afford compound **80** (0.460 g, 1.46 mmol, 73 % yield) as a clear oil that was directly engaged in the next step.

O-Silylated propargyl alcohol **80** (450 mg, 1.43 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by column chromatography (SiO₂, pentane), bromo alkyne **81** was obtained as a colorless oil (531 mg, 1.35 mmol, 94% yield).

R_f 0.6 (pentane).

¹H NMR (400 MHz, CDCl₃) δ 7.76 – 7.64 (m, 2H, *ArH*), 7.46 – 7.34 (m, 3H, *ArH*), 0.98 (s, 9H, *t*-Bu), 0.25 (s, 3H, Me), 0.03 (s, 3H, Me).

¹³C NMR (101 MHz, CDCl₃) δ 136.9, 129.5, 128.1, 127.5, 123.1 (q, *J* = 286.3 Hz), 76.7, 75.4 (q, *J* = 32.5 Hz), 51.2, 25.9, 18.5, -3.4, -3.4.

IR ν_{max} 2955 (w), 2860 (w), 2207 (w), 1473 (w), 1264 (m), 1179 (s), 1146 (m), 1081 (s), 942 (m), 863 (s), 841 (s).

7. Pd-catalyzed tandem aminal formation carbo-amination of allylamines.

General procedure A

To an oven-dried 5 mL microwave tube under nitrogen atmosphere was added the aldimine (0.330 mmol, 1.1 equiv) and cesium carbonate (225 mg, 0.690 mmol, 2.3 equiv). The tube was sealed evacuated and backfilled with nitrogen (this was repeated for a total of 3 times). Then dry degassed toluene was added (0.45 mL) followed by allylamine (0.300 mmol, 1.00 equiv). The resulting mixture was stirred for 30 min at 70 °C. Then (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol) was added and a premixed solution of Pd_2dba_3 (5.5 mg, 6.0 μ mol) and Tri(2-furyl)phosphine (8.4 mg, 0.036 mmol) in toluene (0.45 mL). The resulting mixture was stirred for 20 h at 60-70 °C in an oil bath, then cooled down, filtered over Celite eluting with Et₂O and concentrated under reduced pressure to half its volume and directly purified by column chromatography using the indicated solvents.

General procedure B for α -branched allylamines

To an oven-dried 5 mL microwave tube under nitrogen atmosphere was added the aldimine (0.330 mmol, 1.1 equiv), CsOTf (102 mg, 0.360 mmol, 1.2 equiv) and cesium carbonate (225 mg, 0.690 mmol, 2.3 equiv). The tube was sealed, evacuated and backfilled with nitrogen (this was repeated for a total of 3 times). Then dry degassed toluene was added (0.45 mL) followed by allylamine (0.300 mmol, 1.00 equiv). The resulting mixture was stirred for 1 to 4 h at 70 °C. Then (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol) was added and a premixed solution of Pd_2dba_3 (11 mg, 12 μ mol) and Tri(2-furyl)phosphine (17 mg, 0.072 mmol) in toluene (0.45 mL). The resulting mixture was stirred for 20 h at 70 °C in an oil bath, then cooled down, filtered over Celite eluting with Et₂O and concentrated under reduced pressure to half its volume and directly purified by column chromatography using the indicated solvents.

General procedure C for 1,1-disubstituted olefins

To an oven-dried 5 mL microwave tube under nitrogen atmosphere was added the aldimine and cesium carbonate (225 mg, 0.690 mmol, 2.3 equiv). The tube was sealed, evacuated and backfilled with nitrogen (this was repeated for a total of 3 times). Then dry degassed toluene was added (0.45 mL) followed by allylamine (0.300 mmol, 1.00 equiv). The resulting mixture was stirred for 1 to 4 h at 70 °C. Then the bromo derivative was added and a premixed solution of Pd_2dba_3 (11 mg, 12 μ mol) and PhDavePhos (23 mg, 0.060 mmol) in toluene (0.45 mL). The resulting mixture was stirred for 20 h at 70 °C in an oil bath, then cooled down, filtered over Celite eluting with Et₂O and concentrated under reduced pressure to half its volume and directly purified by column chromatography using the indicated solvents.

General procedure D for aryl and vinyl bromides

To an oven-dried 5 mL microwave tube under nitrogen atmosphere was added the aldimine (0.330 mmol, 1.1 equiv), CsOTf (102 mg, 0.360 mmol, 1.2 equiv) and cesium carbonate (239 mg, 0.735 mmol, 2.45 equiv). The tube was sealed, evacuated and backfilled with nitrogen (this was repeated for a total of 3 times). Then dry degassed toluene was added (0.50 mL) followed by allylamine (0.300 mmol, 1.00 equiv). The resulting mixture was stirred for 30 min at 70 °C. Then the aryl or vinyl bromide (0.450 mmol, 1.5 equiv) was added and a premixed solution of Pd₂dba₃ (11 mg, 12 μmol) and Tri(2-furyl)phosphine (17 mg, 0.072 mmol) in toluene (0.50 mL). The resulting mixture was stirred for 20 h at 70 °C in an oil bath, then cooled down, filtered over Celite eluting with Et₂O and concentrated under reduced pressure to half its volume and directly purified by column chromatography using the indicated solvents.

NB: when a solid aryl bromide was used, it was added in solution in toluene.

The stereochemistry of the imidazolidines was assigned by analogy with compounds **16**, **19** and **22** for which 2D ROESY and 1D NOESY experiments were performed.

Tert-butyl 3-benzyl-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**4**)

pale yellow oil.

Following General Procedure A, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 92:8 to 40:60 Pentane:CH₂Cl₂) affording the title compound **4** (150 mg, 0.286 mmol, 95 % yield, *dr* > 20:1 in the crude ¹⁹F NMR) as a

R_f 0.40 (Pentane/CH₂Cl₂ 2/1).

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.28 (m, 5H, ArH), 5.11 – 4.74 (m, 1H, CHCF₃), 4.16–3.90 (m, 1H, CHN), 3.90 – 3.77 (m, 2H, PhCH₂), 3.27 (app d, *J* = 7.5, 2H, CH₂N), 3.00 (bs, 1H, CH₂CC), 2.30 (dd, *J* = 16.4, 10.5 Hz, 1H, CH₂CC), 1.49 (s, 9H, Boc), 1.07 – 0.99 (m, 21H, TIPS).

¹³C NMR (101 MHz, CDCl₃) δ 154.2, 137.2, 128.9, 128.7, 128.0, 124.3 (q, *J* = 284.4 Hz), 104.4, 82.6, 81.6, 77.4 (q, *J* = 33.5 Hz), 60.0, 57.1, 56.1, 28.3, 25.1, 18.7, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -76.7.

IR *v*_{max} 2942 (m), 2867 (m), 2175 (w), 1707 (s), 1464 (w), 1375 (s), 1155 (s), 913 (m).

HRMS calcd for C₂₈H₄₄F₃N₂O₂Si⁺ [*M*+H]⁺ 525.3119; found 525.3119.

Methyl 3-benzyl-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**5**)

Following General Procedure A, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg,

S25

0.390 mmol, 1.3 equiv). The crude oil was purified by column chromatography (SiO₂ 2:1 Pentane: CH₂Cl₂) affording the title compound **5** (136 mg, 0.282 mmol, 94% yield, *dr* > 20:1 in the crude ¹⁹F NMR) as a clear oil.

R_f 0.20 (Pentane/CH₂Cl₂ 2/1).

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.27 (m, 5H, ArH), 5.15 – 4.77 (m, 1H, CHCF₃), 4.06–3.93 (m, 1H, CHN), 3.87 (d, *J* = 13.2 Hz, 1H, PhCH₂), 3.79 (d, *J* = 13.2 Hz, 1H, CH₂Ph), 3.75 (s, 3H, CH₃O), 3.26 (app. dd, *J* = 7.7, 1.6 Hz, 2H, CH₂N), 2.97 (m, 1H, CH₂CC), 2.31 (dd, *J* = 16.4, 10.5 Hz, 1H, CH₂CC), 1.31 – 0.80 (m, 21H, TIPS).

¹³C NMR (101 MHz, CDCl₃) 155.6, 137.1, 128.9, 128.7, 128.0, 124.1 (q, *J* = 284.3 Hz), 104.1, 82.9, 77.5 (m), 59.9, 57.2, 56.2, 53.3, 25.0, 18.7, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -76.7.

IR *v*_{max} 2949 (m), 2866 (m), 2175 (w), 1723 (s), 1450 (m), 1360 (s), 1140 (s), 989 (m), 882 (w).

HRMS calcd for C₂₅H₃₈F₃N₂O₂Si⁺ [M+H]⁺ 483.2649; found 483.2641.

Methyl 2-(trifluoromethyl)-3-(4-(trifluoromethyl)benzyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (6**)**

Following General Procedure A, the title compound was prepared from N-(4-(trifluoromethyl)benzyl)prop-2-en-1-amine (**50**) (64.6 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil was purified by column chromatography (SiO₂ 2:1 Pentane:CH₂Cl₂) affording the title compound **6** (156 mg, 0.283 mmol, 94% yield, *dr* > 20:1 in the crude ¹⁹F NMR) as a pale yellow oil.

R_f 0.50 (Pentane/CH₂Cl₂ 1/1).

¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, *J* = 8.1 Hz, 2H, ArH), 7.46 (d, *J* = 8.0 Hz, 2H, ArH), 5.02 – 4.81 (m, 1H, CHCF₃), 4.23 – 4.04 (m, 1H, CHN), 3.97 (d, *J* = 13.3 Hz, 1H, ArCH₂), 3.82 (d, *J* = 13.5 Hz, 1H, ArCH₂), 3.77 (s, 3H, CH₃O), 3.26 (dd, *J* = 11.6, 7.0 Hz, 1H, CH₂N), 3.15 (dd, *J* = 11.6, 7.7 Hz, 1H, CH₂N), 3.06 – 2.87 (m, 1H, CH₂CC), 2.35 (dd, *J* = 16.4, 10.5 Hz, 1H, CH₂CC), 1.09 – 0.95 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 155.7, 141.4, 130.3 (q, *J* = 32.4 Hz), 129.0, 125.7 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 272.2 Hz), 124.2 (q, *J* = 284.2 Hz), 104.0, 83.2, 77.5 (m, overlapping with chloroform signals), 59.2, 57.2, 56.2, 53.5, 25.0, 18.7, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -62.6, -76.5.

IR *v*_{max} 2960 (m), 2871 (m), 2175 (w), 1724 (s), 1453 (m), 1368 (m), 1323 (s), 1170 (s), 1137 (s), 1074 (m).

HRMS calcd. for C₂₆H₃₇F₆N₂O₂Si⁺ [M+H]⁺ 551.2523; found 551.2528.

Methyl 3-(4-formylbenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (7)

Following General Procedure A, the title compound was prepared from freshly purified 4-((allylamino)methyl)benzaldehyde (**52**) (52.6 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 60:40 to 0:100 Pentane:CH₂Cl₂) affording the title compound **7** (142 mg, 0.278 mmol, 93% yield, *dr* > 20:1 in the crude ¹⁹F NMR) as a yellow oil.

R_f 0.25 (Pentane/CH₂Cl₂ 1/2).

¹H NMR (400 MHz, CDCl₃) δ 10.0 (s, 1H, CHO), 7.90 – 7.82 (m, 2H, ArH), 7.56 – 7.47 (m, 2H, ArH), 5.07 – 4.78 (m, 1H, CHCF₃), 4.25 – 4.04 (m, 1H, CHN), 3.98 (d, *J* = 13.8 Hz, 1H, ArCH₂), 3.86 (d, *J* = 13.8 Hz, 1H, ArCH₂), 3.77 (s, 3H, CH₃O), 3.28 (dd, *J* = 11.9, 7.2 Hz, 1H, CH₂N), 3.17 (dd, *J* = 11.9, 7.3 Hz, 1H, CH₂N), 3.10 – 2.85 (m, 1H, CH₂CC), 2.35 (dd, *J* = 16.4, 10.5 Hz, 1H, CH₂CC), 0.99 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 191.9, 155.7, 144.3, 136.2, 130.2, 129.2, 124.0 (q, *J* = 284.2 Hz), 103.9, 83.2, 77.6 (m overlapping with chloroform signals), 59.5, 57.4, 56.2, 53.5, 25.0, 18.7, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -76.5.

IR *v*_{max} 2948 (w), 2865 (w), 2176 (w), 1714 (s), 1453 (m), 1365 (m), 1289 (m), 1176 (s), 1143 (s), 915 (w).

HRMS calcd. for C₂₆H₃₇F₃N₂NaO₃Si⁺ [M+Na]⁺ 533.2418; found 533.2425.

Methyl 3-(4-bromobenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (8)

Following General Procedure A, the title compound was prepared from N-(4-bromobenzyl)prop-2-en-1-amine (67.8 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil was purified by column chromatography (SiO₂ 5:2 to 2:1 Pentane:CH₂Cl₂) affording the title compound **8** (148 mg, 0.264 mmol, 88% yield, *dr* > 20:1 in the crude ¹⁹F NMR) as a pale yellow oil.

R_f 0.48 (Pentane/CH₂Cl₂ 1/1).

¹H NMR (400 MHz, CDCl₃) δ 7.49 – 7.42 (m, 2H, ArH), 7.23 – 7.16 (m, 2H, ArH), 5.04 – 4.77 (m, 1H, CHCF₃), 4.22 – 3.97 (m, 1H, CHN), 3.83 (d, *J* = 13.6 Hz, 1H, ArCH₂), 3.75 (s, 3H, CH₃O), 3.72 (d, *J* = 13.6 Hz, 1H, ArCH₂), 3.25 (dd, *J* = 12.1, 7.3 Hz, 1H, CH₂N), 3.17 (dd, *J* = 12.1, 7.3 Hz, 1H, CH₂N), 3.03 – 2.87 (m, 1H, CH₂CC), 2.32 (dd, *J* = 16.4, 10.4 Hz, 1H, CH₂CC), 1.10 – 0.93 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 155.7, 136.2, 131.8, 130.4, 124.2 (q, *J* = 283.9 Hz), 121.9, 104.0, 83.1, 77.5 (m overlapping with chloroform signals), 59.1, 57.1, 56.1, 53.4, 25.0, 18.6, 11.3.

^{19}F NMR (376 MHz, CDCl_3) δ -76.6.

IR ν_{max} 2951 (m), 2866 (m), 2175 (w), 1719 (s), 1448 (s), 1364 (s), 1175 (s), 1143 (s).

HRMS calcd. for $\text{C}_{25}\text{H}_{37}^{79}\text{BrF}_3\text{N}_2\text{O}_2\text{Si}^+ [\text{M}+\text{H}]^+$ 561.1754; found 561.1751.

Methyl 3-(2-chlorobenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (9)

Following General Procedure A, the title compound was prepared from N-(2-chlorobenzyl)prop-2-en-1-amine (54.5 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol 1.3 equiv). The crude oil (*dr* 16.5:1 in the crude ^{19}F NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 92:8 to 40:60 Pentane: CH_2Cl_2) affording the title compound **9** (142 mg, 0.275 mmol, 92% yield, *dr* > 20:1 in the ^{19}F NMR) as a pale yellow oil.

R_f 0.40 (Pentane/ CH_2Cl_2 2/1).

^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.47 (m, 1H, ArH), 7.41 – 7.34 (m, 1H, ArH), 7.31 – 7.21 (m, 2H, ArH), 5.13 – 4.84 (m, 1H, CHCF_3), 4.30 – 4.09 (m, 1H, CHN), 4.01 (d, J = 13.9 Hz, 1H, ArCH₂), 3.95 (d, J = 13.9 Hz, 1H, ArCH₂), 3.79 (s, 3H, CH_3O), 3.35 – 3.21 (m, 2H, CH_2N), 3.12 – 2.92 (m, 1H, CH_2CC), 2.35 (dd, J = 16.4, 10.5 Hz, 1H, CH_2CC), 1.07 – 0.97 (m, 21H, TIPS).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.7, 134.9, 134.1, 130.7, 129.7, 129.1, 127.1, 124.0 (q, J = 284.4 Hz), 104.0, 83.0, 78.0 (q, J = 34.0 Hz), 57.2, 56.4, 56.1, 53.4, 24.9, 18.6, 11.3.

^{19}F NMR (376 MHz, CDCl_3) δ -76.6.

IR ν_{max} 2944 (w), 2864 (w), 2175 (w), 1717 (s), 1450 (m), 1362 (s), 1143 (s), 911 (s).

HRMS calcd for $\text{C}_{25}\text{H}_{37}\text{ClF}_3\text{N}_2\text{O}_2\text{Si}^+ [\text{M}+\text{H}]^+$ 517.2259; found 517.2259.

***Tert*-butyl 3-(4-methoxybenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (10)**

To an oven-dried 50 mL schlenk tube under nitrogen atmosphere was added degassed Toluene (4.50 mL), N-(4-methoxybenzyl)prop-2-en-1-amine (0.532 g, 3.00 mmol) and 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (0.849 g, 3.30 mmol, 1.1 equiv) and cesium carbonate (2.15 g, 6.60 mmol, 2.2 equiv). The resulting mixture was stirred for 30 min at 70 °C. Then (bromoethynyl)triisopropylsilane (**3**) (1.019 g, 3.90 mmol, 1.3 equiv) was added followed by a premixed solution of $\text{Pd}_2(\text{dba})_3$ (55.0 mg, 0.0600 mmol, 2 mol%) and tri(2-furyl)phosphine (0.0836 g, 0.360 mmol, 12 mol%) in toluene (4.50 mL). The resulting mixture was stirred for 20 h at 60 °C in an oil bath, then cooled down, filtered over Celite eluting with Et_2O and concentrated under reduced pressure. The crude residue (> 20:1 *dr* by integration of the propargylic peaks in the crude ^1H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 88:12 Pentane: CH_2Cl_2 to 35:65 Pentane: CH_2Cl_2) to afford the title compound **10** (1.65 g, 2.98 mmol, 99 % yield, *dr* > 20:1 in the ^1H NMR) as a yellow oil.

R_f 0.20 (Pentane/ CH_2Cl_2 1/1).

^1H NMR (400 MHz, CDCl_3) δ 7.25 – 7.17 (m, 2H, ArH), 6.90 – 6.82 (m, 2H, ArH), 5.09 – 4.66 (m, 1H, CHCF_3), 4.10 – 3.85 (m, 1H, CHN), 3.80 (s, 3H, OMe), 3.74 (s, 2H, ArCH₂), 3.30 – 3.18

(m, 2H, CH₂N), 2.98 (m, 1H, CH₂CC), 2.26 (dd, *J* = 16.3, 10.5 Hz, 1H, CH₂CC), 1.47 (s, 9H, Boc), 1.06 – 0.98 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 159.4, 154.3, 130.2, 129.3, 124.3 (q, *J* = 284.2 Hz), 114.1, 104.5, 82.6, 81.6, 77.2 (q, *J* = 33.3 Hz, overlapping with chloroform signal), 59.4, 57.12, 56.0, 55.4, 28.3, 25.1, 18.5, 11.3.

IR *v*_{max} 2943 (s), 2870 (m), 2175 (w), 1711 (s), 1374 (s), 1251 (s), 1173 (s), 1036 (m), 881 (w).

HRMS calcd for C₂₉H₄₅F₃N₂NaO₃Si⁺ [M+Na]⁺ 577.3044; found 577.3044.

Methyl 3-allyl-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**11**)

Following General Procedure A, the title compound was prepared from diallylamine (37.3 μl, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (86.0 mg, 0.330 mmol, 1.1 equiv) at 60 °C. The crude oil was purified by column chromatography (SiO₂ 5:2 to 2:1 Pentane:CH₂Cl₂) affording the title compound **11** (124 mg, 0.287 mmol, 96 % yield, *dr* > 20:1 in the crude ¹⁹F NMR) as a pale yellow oil.

R_f 0.33 (Pentane/ CH₂Cl₂ 5/2).

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1H, CHCH₂), 5.24 – 5.20 (m, 1H, CHCH₂), 5.20 – 5.17 (m, 1H, CHCH₂), 5.02 – 4.78 (m, 1H, CHCF₃), 4.20 – 4.01 (m, 1H, CH₂N), 3.75 (s, 3H, CH₃O), 3.27 (app t, *J* = 7.5 Hz, 4H, CH₂N and CH₂CHCH₂), 3.08 – 2.91 (m, 1H, CH₂CC), 2.28 (dd, *J* = 16.4, 10.5 Hz, 1H, CH₂CC), 1.09 – 0.95 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 155.8, 134.0, 124.1 (q, *J* = 284.2 Hz), 119.5, 104.1, 83.0, 77.5 (m overlapping with chloroform signals), 59.1, 57.5, 56.3, 53.4, 25.1, 18.5, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -77.0.

IR *v*_{max} 2953 (m), 2864 (w), 2174 (w), 1715 (m), 1448 (m), 1371 (m), 1177 (m), 1140 (m), 907 (s).

HRMS calcd. for C₂₁H₃₆F₃N₂O₂Si⁺ [M+H]⁺ 433.2493; found 433.2499.

Methyl 3-(furan-2-ylmethyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**12**)

Following General Procedure A, the title compound was prepared from N-(furan-2-ylmethyl)prop-2-en-1-amine (41 mg, 0.30 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 92:8 to 40:60 Pentane:CH₂Cl₂) affording the title compound **12** (134 mg, 0.284 mmol, 92% yield, *dr* > 20:1 in the crude ¹⁹F NMR) as a yellow oil.

R_f 0.30 (Pentane/ CH₂Cl₂ 2/1).

¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.31 (m, 1H, HetArH), 6.36 – 6.28 (m, 1H, HetArH), 6.26 – 6.20 (m, 1H, HetArH), 5.19 – 4.97 (m, 1H, CHCF₃), 3.93 – 3.79 (m, 2H, HetArCH₂), 3.71 (s, 3H, CH₃O), 3.73 – 3.60 (m, 1H, CHN), 3.40 (dd, *J* = 12.5, 7.4 Hz, 1H, CH₂N), 3.31 (dd, *J* = 12.5, 8.7 Hz, 1H, CH₂N), 3.00 – 2.74 (m, 1H, CH₂CC), 2.21 (dd, *J* = 16.4, 10.5 Hz, 1H, CH₂CC), 1.15 – 0.96 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 155.6, 150.7, 143.1, 124.1 (q, *J* = 283.6 Hz), 110.6, 109.4, 104.2, 82.9, 77.7 (q, *J* = 34.2 Hz, overlapping with chloroform signal), 57.7, 56.6, 53.2, 52.3, 25.2, 18.8, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -77.5.

IR *v*_{max} 2955 (s), 2869 (m), 2176 (w), 1722 (s), 1452 (m), 1367 (m), 1287 (w), 1180 (m), 1146 (m), 1022 (w), 883 (w).

HRMS calcd for C₂₃H₃₆F₃N₂O₃Si⁺ [M+H]⁺ 473.2442; found 473.2447.

***Tert*-butyl 3-ferrocenylmethyl-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (13)**

Following General Procedure A, the title compound was prepared from ferrocenylmethyl allylamine (**54**) (76.5 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.3 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil (*dr* > 20:1 by integration of the propargylic peaks in the crude ¹H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 92:8 to 40:60 Pentane:CH₂Cl₂) affording the title compound **13** (168 mg, 0.266 mmol, 89% yield, *dr* > 20:1) as a

dark oil.

R_f 0.20 (Pentane/CH₂Cl₂ 1/1).

¹H NMR (400 MHz, CDCl₃) δ 4.98 – 4.73 (m, 1H, CHCF₃), 4.19 – 3.99 (m, 10H, ArH and CHN), 3.68 (d, *J* = 13.9 Hz, 1H, ArCH₂), 3.60 (d, *J* = 13.9 Hz, 1H, ArCH₂), 3.31 – 3.11 (m, 2H, CH₂N), 2.95 – 2.75 (m, 1H, CH₂CC), 2.12 (dd, *J* = 16.3, 10.4 Hz, 1H, CH₂CC), 1.41 (s, 9H, Boc), 1.14 – 0.82 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 153.9, 124.3f (q, *J* = 284.6 Hz), 104.6, 82.4, 82.0, 81.3, 77.5 (m overlapping with chloroform signal), 69.8, 69.3, 69.0, 68.8 (6C), 57.6-56.2 (3C), 28.3, 25.1, 18.7, 11.3.

IR *v*_{max} 2955 (m), 2869 (m), 2176 (w), 1710 (s), 1469 (w), 1373 (s), 1175 (s), 880 (w).

HRMS calcd for C₃₂H₄₇F₃FeN₂NaO₂Si⁺ [M+Na]⁺ 655.2600; found 655.2609.

***Tert*-butyl 2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**14**)**

Following General Procedure **A** with a premixing time of 3 h at 35 °C, the title compound was prepared from allylamine (**49**) (22.5 μ l, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (86.0 mg, 0.330 mmol, 1.1 equiv) at 70 °C. The crude oil was purified by column chromatography (SiO₂ 5:1 to 3:1 Pentane:Et₂O) affording the title compound **14** (89.1 mg, 0.205 mmol, 68 % yield, *dr* > 20:1 in the crude ¹H NMR by integration of the propargylic signals) as a pale yellow oil.

R_f 0.5 (Pentane:Et₂O 2:1).

¹H NMR (400 MHz, CDCl₃) δ 5.25 – 4.99 (m, 1H, *CHCF*₃), 4.06 – 3.84 (m, 1H, *NCH*), 3.61 (dd, *J* = 12.3, 7.5 Hz, 1H, *CH*₂*N*), 3.23 – 3.12 (m, 1H, *CH*₂*N*), 3.13 – 2.97 (m, 1H, *CH*₂*CC*), 2.49 – 2.34 (m, 1H, *NH*), 2.25 (dd, *J* = 16.4, 10.5 Hz, 1H, *CH*₂*CC*), 1.47 (s, 9H, Boc), 1.16 – 0.90 (m, 21H, TIPS).

¹³C NMR (101 MHz, CDCl₃) δ 154.1, 124.4 (q, *J* = 283.8 Hz), 104.3, 82.7, 81.7, 73.3 (q, *J* = 33.7 Hz), 58.0, 52.3, 28.3, 25.4, 18.7, 11.3.

IR ν_{max} 3347 (w), 2944 (m), 2866 (w), 2175 (w), 1702 (s), 1464 (w), 1365 (s), 1282 (w), 1173 (s), 1136 (s), 956 (w), 912 (m), 878 (m).

HRMS (ESI) calcd for C₂₁H₃₇F₃N₂NaO₂Si⁺ [*M*+Na]⁺ 457.2469; found 457.2458.

Methyl 3-(4-methoxyphenyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (15**)**

Following General Procedure **A** with a premixing time of 1 h, the title compound was prepared from *N*-allyl-4-methoxyaniline (49.0 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil (*dr* > 20:1 in the crude ¹⁹F NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 88:12 to 5:95 Pentane:CH₂Cl₂)

affording the title compound **15** (121 mg, 0.243 mmol, 81 % yield, *dr* > 20:1 in the ¹⁹F NMR) as a deep yellow oil.

R_f 0.40 (Pentane/CH₂Cl₂ 1/1).

¹H NMR (400 MHz, CDCl₃) δ 6.90 – 6.81 (m, 2H, *ArH*), 6.81 – 6.71 (m, 2H, *ArH*), 5.83 – 5.62 (m, 1H, *CHCF*₃), 4.38 – 4.20 (m, 1H, *CHN*), 3.94 (app t, *J* = 9.4 Hz, 1H, *CH*₂*N*), 3.80 (s, 3H, *CH*₃*O*), 3.77 (s, 3H, *CH*₃*O*), 3.71 – 3.61 (m, 1H, *CH*₂*N*), 3.13 – 2.99 (m, 1H, *CH*₂*CC*), 2.47 (dd, *J* = 16.6, 10.4 Hz, 1H, *CH*₂*CC*), 1.15 – 0.98 (m, 21H, TIPS).

¹³C NMR (101 MHz, CDCl₃) δ 155.4, 154.1, 139.5, 124.5 (q, *J* = 288.7 Hz), 116.5, 114.9, 103.9, 83.3, 74.0 (q, *J* = 33.9 Hz), 56.4, 55.7, 54.5, 53.6, 25.4, 18.7, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -75.8.

IR ν_{max} 2953 (s), 2869 (m), 2175 (w), 1722 (s), 1517 (s), 1451 (m), 1374 (m), 1253 (s), 1178 (s), 1143 (s), 1038 (m), 911 (s).

HRMS calcd for C₂₅H₃₈F₃N₂O₃Si⁺ [*M*+H]⁺ 499.2598; found 499.2599.

***Tert*-butyl 3-benzyl-5-methyl-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (16)**

Following General Procedure C with a premixing time of 1 h and Pd₂dba₃ (8.2 mg, 9.0 μmol, 3 mol%) and PhDavePhos (17.1 mg, 0.0450 mmol, 15 mol%), the title compound was prepared from N-benzyl-2-methylprop-2-en-1-amine (**45**) (48.4 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil (>20:1 dr determined by integration in the crude ¹H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g,

92:8 Pentane:CH₂Cl₂ to 40:60 Pentane: CH₂Cl₂) to afford the title compound **16** (137 mg, 0.254 mmol, 85 % yield) as a yellow oil.

R_f 0.30 (Pentane/CH₂Cl₂ 2/1).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.21 (m, 5H, ArH), 5.14 – 4.98 (m, 1H, CHCF₃), 4.06 (d, *J* = 12.9 Hz, 1H, CH₂Ph), 3.99 (d, *J* = 13.6 Hz, 1H, CH₂Ph), 3.48 (d, *J* = 11.2 Hz, 1H, NCH₂), 3.26 – 3.02 (m, 1H, CCCH₂), 2.96 (d, *J* = 11.3 Hz, 1H, NCH₂), 2.56 (d, *J* = 16.5 Hz, 1H, CCCH₂), 1.68 (s, 3H, Me), 1.51 (s, 9H, Boc), 1.13 – 0.92 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 152.8, 138.1, 128.7, 128.6, 127.7, 124.9 (d, *J* = 289.8 Hz), 105.3, 82.7, 81.4, 77.5 (q, *J* = 31.9 Hz), 63.6, 63.0, 58.4, 31.2, 28.4, 23.7, 18.8, 11.6.

IR ν_{max} 3064 (w), 2939 (w), 2862 (w), 2174 (w), 1709 (s), 1464 (w), 1363 (s), 1275 (w), 1165 (s), 1065 (m), 1029 (m), 883 (m).

HRMS (ESI) calcd for C₂₉H₄₅F₃N₂NaO₂Si⁺ [M+Na]⁺ 561.3095; found 561.3099.

Stereochemistry assigned by ROESY.

***Tert*-butyl 3-benzyl-5-((benzyloxy)methyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (17)**

Following General Procedure C with a premixing time of 3 h, the title compound was prepared from N-benzyl-2-((benzyloxy)methyl)prop-2-en-1-amine (80.1 mg, 0.300 mmol) (**56**) (125 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 eq). The crude oil (>20:1 dr determined by integration in the crude ¹H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 97:3 Pentane:CH₂Cl₂ to 85:15 Pentane: Et₂O)

to afford the title compound **17** (135 mg, 0.209 mmol, 70 % yield) as a yellow oil.

R_f 0.50 (Pentane/Et₂O 7/1).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.31 (m, 4H, ArH), 7.31 – 7.19 (m, 6H, ArH), 5.06 – 4.90 (m, 1H, CHCF₃), 4.62 (d, *J* = 11.8 Hz, 1H, OCH₂Ph), 4.51 (d, *J* = 11.8 Hz, 1H, OCH₂Ph), 4.29 – 4.07 (m, 1H, OCH₂), 4.06 – 3.94 (m, 2H, NCH₂Ph), 3.79 (d, *J* = 9.4 Hz, 1H, OCH₂), 3.58 (d, *J* = 12.0 Hz, 1H, NCH₂), 3.20 (d, *J* = 12.0 Hz, 1H, NCH₂), 3.07 (d, *J* = 16.9 Hz, 1H, CH₂CC), 2.60 (d, *J* = 16.9 Hz, 1H, CH₂CC), 1.46 (s, 9H, Boc), 1.05 – 0.92 (m, 21H, TIPS).

¹³C NMR (101 MHz, Chloroform-*d*) δ 152.7, 139.1, 138.3, 128.8, 128.6, 128.4, 128.1, 127.9, 127.3, 124.9 (d, *J* = 286.9 Hz), 104.1, 83.4, 81.3, 79.2 (q, *J* = 32.6 Hz), 73.9, 71.2, 65.9, 61.7, 59.9, 28.4, 28.3, 18.7, 11.5.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -76.8.

IR ν_{max} 2945 (m), 2866 (m), 2173 (w), 1710 (m), 1462 (w), 1364 (s), 1276 (w), 1166 (s), 1132 (s), 911 (m).

HRMS (ESI) calcd or C₃₆H₅₂F₃N₂O₃Si⁺ [M+H]⁺ 645.3694; found 645.3691.

***Tert*-butyl 3-benzyl-4-methyl-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (18)**

Following General Procedure **B** with a premixing time of 1 h, the title compound was prepared from N-benzylbut-3-en-2-amine (**46**) (48.4 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil (2.2:1 *dr* determined by integration in the crude ¹⁹F NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 95:5 to 60:40 Pentane:CH₂Cl₂) to afford the title compound **18** (132 mg, 0.245 mmol, 82 % yield, 2:1 *dr*²⁵ determined by integration in the ¹⁹F NMR) as a yellow oil.

R_f 0.50 (Pentane/CH₂Cl₂ 3/2).

¹H NMR (400 MHz, CDCl₃) major diastereoisomer δ 7.39 – 7.26 (m, 5H, ArH), 4.93 – 4.80 (m, 1H, CHCF₃), 3.99 – 3.86 (m, 2H, PhCH₂), 3.82 – 3.69 (m, 1H, CHNBoc), 3.56 – 3.46 (m, 1H, CHNBn), 3.00 – 2.87 (m, 1H, CH₂CC), 2.57 (dd, *J* = 16.6, 10.1 Hz, 1H, CH₂CC), 1.50 (s, 9H, Boc), 1.30 (d, *J* = 6.4 Hz, 3H, Me), 1.14 – 0.89 (m, 21H, TIPS); minor diastereoisomer δ 7.39 – 7.26 (m, 5H, ArH), 4.93 – 4.80 (m, 1H, CHCF₃), 4.29 – 4.20 (m, 1H, CHNBoc), 4.14 (d, *J* = 14.9 Hz, 1H, PhCH₂), 3.93 – 3.87 (m, 1H, PhCH₂), 3.31 – 3.22 (m, 1H, CHNBn), 2.74 – 2.66 (m, 1H, CH₂CC), 2.64 – 2.56 (m, 1H, CH₂CC), 1.48 (s, 9H, Boc), 1.17 (d, *J* = 6.6 Hz, 3H, Me), 1.14 – 0.89 (m, 21H, TIPS).

¹³C NMR (101 MHz, CDCl₃) major diastereoisomer δ 154.2, 138.2, 128.6, 128.4, 127.5, 124.9 (q, *J* = 289.0 Hz), 104.9, 83.1, 81.5, 74.2 (q, *J* = 32.6 Hz), 63.4, 60.5, 50.8, 28.4, 24.6, 18.7, 16.5, 11.5; minor diastereoisomer δ 153.4, 137.4, 128.8, 128.6, 127.6, 124.5 (q, *J* = 284.0 Hz), 106.0, 82.5, 81.5, 75.7 (q, *J* = 33.2 Hz), 61.1, 60.5, 56.7, 28.3, 21.7, 18.7, 15.1, 11.6.

¹⁹F NMR (376 MHz, CDCl₃) δ -73.7, -76.7.

IR ν_{max} 2981 (s), 2904 (s), 2175 (w), 1711 (s), 1460 (m), 1376 (s), 1255 (m), 1160 (s), 1065 (s), 915 (w).

HRMS calcd for C₂₉H₄₆F₃N₂O₂Si⁺ [M+H]⁺ 539.3275; found 539.3281.

²⁵ We assume that the two diastereoisomers arise from different configuration at the center bound to the methyl group.

Tert-butyl 3-benzyl-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)-4-vinylimidazolidine-1-carboxylate (19)

Following General Procedure **B** with a premixing time of 1 h, the title compound was prepared from N-benzylpenta-1,4-dien-3-amine (**59**) (52.0 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (86 mg, 0.39 mmol, 1.1 equiv). The crude oil (87:13 *dr* determined by integration in the crude ^{19}F NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 90:10 to 65:35 Pentane: CH_2Cl_2) to afford the title compound **19** (123 mg, 0.223 mmol, 74 % yield, 93:7 *dr* determined by integration in the ^{19}F NMR) as a yellow oil.

R_f 0.5 (Pentane/ Et_2O 20/1).

^1H NMR (400 MHz, Acetonitrile- d_3) δ 7.37 – 7.23 (m, 5H, ArH), 5.73 (ddd, J = 17.0, 10.2, 9.0 Hz, 1H, $\text{CH}=\text{C}$), 5.31 (dd, J = 10.2, 1.5 Hz, 1H, $\text{CH}_2=\text{C}$), 5.14 (dd, J = 17.0, 1.5 Hz, 1H, $\text{CH}_2=\text{C}$), 4.98 (q, J = 5.3 Hz, 1H, CHCF_3), 4.00 (d, J = 14.3 Hz, 1H, PhCH_2), 3.94 – 3.84 (m, 1H, CHNBoc), 3.88 (d, J = 14.3 Hz, 1H, PhCH_2), 3.74 (dd, J = 9.2, 3.4 Hz, 1H, CHN), 2.72 (dd, J = 16.9, 9.0 Hz, 1H, CH_2CC), 2.63 (dd, J = 17.0, 4.7 Hz, 1H, CH_2CC), 1.46 (s, 9H, Boc), 1.08 – 0.92 (m, 21H, TIPS).

^{13}C NMR (101 MHz, CD_3CN) δ 155.0, 139.1, 135.6, 129.4, 129.18, 128.2, 125.7 (q, J = 287.1 Hz), 121.3, 105.7, 83.6, 82.4, 74.7, 67.7, 63.0, 51.6, 28.3, 24.5, 19.0, 12.0.

^{19}F NMR (376 MHz, CDCl_3) δ -73.8.

IR ν_{max} 2942 (m), 2865 (m), 2176 (w), 1716 (s), 1463 (w), 1370 (s), 1258 (w), 1161 (s), 1065 (w), 1018 (w), 931 (w), 880 (w), 847 (w).

HRMS calcd for $\text{C}_{30}\text{H}_{46}\text{F}_3\text{N}_2\text{O}_2\text{Si}^+ [\text{M}+\text{H}]^+$ 551.3275; found 551.3256.

Stereochemistry assigned by 1D NOESY.

Tert-butyl 3-(trifluoromethyl)-1-(3-(triisopropylsilyl)prop-2-yn-1-yl)tetrahydro-1H-pyrrolo[1,2-c]imidazole-2(3H)-carboxylate (20)

To an oven-dried 5 mL microwave tube under nitrogen atmosphere was added 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv), cesium carbonate (225 mg, 0.690 mmol) and 2-vinylpyrrolidine hydrochloride (**61**) (40.1 mg, 0.300 mmol). The tube was sealed, evacuated and backfilled with nitrogen (this was repeated for a total of 3 times). Then dry toluene was added (0.45 mL) and the resulting mixture was stirred for 4 h at 50 °C. Then the mixture was filtered to an oven-dried 5 mL microwave tube. The volatiles were removed under reduced pressure and cesium carbonate (127 mg, 0.390 mmol) was added. The tube was sealed evacuated and backfilled with nitrogen (this was repeated for a total of 3 times), then a premixed solution of Pd_2dba_3 (11 mg, 12 μmol) and $\text{Tri}(2\text{-furyl})\text{phosphine}$ (17 mg, 0.072 mmol) in toluene (0.90 mL) was added followed by (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol). The resulting mixture was stirred for 20 h at 75 °C in an oil bath, then cooled

down, filtered over Celite eluting with Et₂O and concentrated under reduced pressure. The crude oil (92.5:7.5 *dr* determined by integration in the crude ¹⁹F NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 98:2 to 80:20 Pentane:Et₂O) to afford the title compound **20** (112 mg, 0.236 mmol, 79 % yield, *dr* > 98:2 determined by integration in the ¹⁹F NMR) as a pale yellow oil.

R_f 0.70 (Pentane/Et₂O 6/1).

¹H NMR (400 MHz, CDCl₃) δ 5.10 – 4.77 (m, 1H, CHCF₃), 3.81 – 3.68 (m, 1H, CHN), 3.68 – 3.44 (m, 1H, CHNBoc), 3.32 – 3.21 (m, 1H, CH₂N), 3.17 – 2.92 (m, 1H, CH₂CC), 2.63 (app q, *J* = 8.2 Hz, 1H, CH₂N), 2.29 (dd, *J* = 13.6, 7.8 Hz, 1H, CH₂CC), 2.25 – 2.17 (m, 1H, NCHCH₂), 1.99 – 1.91 (m, 1H, NCHCH₂), 1.91 – 1.81 (m, 2H, NCH₂CH₂), 1.47 (s, 9H, Boc), 1.11 – 0.95 (m, 21H, TIPS).

¹³C NMR (101 MHz, CDCl₃) δ 153.9, 124.0 (q, *J* = 283.1 Hz), 104.0, 82.9, 81.6, 78.7 (q, *J* = 33.8 Hz), 69.5, 63.0, 55.3, 31.9, 28.3, 25.2, 25.0, 18.7, 11.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -78.4.

IR *v*_{max} 2943 (w), 2867 (w), 2174 (w), 1710 (m), 1464 (w), 1369 (s), 1288 (m), 1161 (s), 879 (w).

HRMS calcd for. C₂₄H₄₂F₃N₂O₂Si⁺ [M+H]⁺ 475.2962; found 475.2962.

***Tert*-butyl 3-(trifluoromethyl)-1-(3-(triisopropylsilyl)prop-2-yn-1-yl)hexahydroimidazo[1,5-*a*]pyridine-2(3H)-carboxylate (**21**)**

To an oven-dried 5 mL microwave tube under nitrogen atmosphere was added 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv), cesium carbonate (225 mg, 0.690 mmol) and 2-vinylpiperidine 2,2,2-trifluoroacetate (**63**) (67.6 mg, 0.300 mmol). The tube was sealed, evacuated and backfilled with nitrogen (this was repeated for a total of 3 times). Then dry toluene was added (0.45 mL) and the resulting mixture was stirred for 4 h at 50 °C. Then the mixture was filtered to an oven-dried 5 mL microwave tube. The volatiles were removed under reduced pressure and cesium carbonate (127 mg, 0.390 mmol) was added. The tube was sealed, evacuated and backfilled with nitrogen (this was repeated for a total of 3 times), then a premixed solution of Pd₂dba₃ (11 mg, 12 μmol) and Tri(2-furyl)phosphine (17 mg, 0.072 mmol) in toluene (0.90 mL) was added followed by (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol). The resulting mixture was stirred for 20 h at 75 °C in an oil bath, then cooled down, filtered over Celite eluting with Et₂O and concentrated under reduced pressure. The crude oil (90:10 *dr* determined by integration in the crude ¹H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 95:5 to 80:20 Pentane:Et₂O) to afford the title compound **21** (113 mg, 0.231 mmol, 77 % yield, *dr* > 98:2 determined by integration in the ¹H NMR) as a yellow oil.

R_f 0.75 (Pentane/Et₂O 6/1).

¹H NMR (400 MHz, CDCl₃) δ 4.46 – 4.26 (m, 1H, CHCF₃), 4.26 – 4.04 (m, 1H, CHNBoc), 3.34 – 3.20 (m, 1H, NCH₂), 2.64 (dd, *J* = 17.0, 10.1 Hz, 1H, CH₂CC), 2.56 – 2.43 (overlapping m, 2H, CH₂CC and CHN), 2.32 (td, *J* = 11.0, 3.5 Hz, 1H, NCH₂), 1.85 (app t, *J* = 16.3 Hz, 2H), 1.66 – 1.45 (m, 3H), 1.47 (s, 9H, Boc), 1.34 – 1.14 (m, 1H), 1.11 – 0.96 (m, 21H, TIPS).

¹³C NMR (101 MHz, CDCl₃) δ 153.6, 124.3 (q, *J* = 283.9 Hz), 105.6, 82.0, 81.5, 76.5 – 74.8 (m), 65.2, 61.1 – 58.8 (m), 51.8, 28.3, 26.8, 25.3, 23.8, 21.7, 18.7, 11.4.

IR *v*_{max} 2953 (s), 2865 (s), 2177 (w), 1716 (s), 1464 (w), 1371 (s), 1277 (w), 1166 (s), 1041 (w), 1003 (w), 932 (w), 881 (m), 861 (m).

HRMS calcd for $C_{25}H_{44}F_3N_2O_2Si^+$ $[M+H]^+$ 489.3119; found 489.3125.

***Tert*-butyl 3-(trifluoromethyl)-1-(3-(triisopropylsilyl)prop-2-yn-1-yl)tetrahydro-1H-pyrrolo[1,2-*c*]imidazole-2(3H)-carboxylate (22)**

Following General Procedure **B** with a premixing time of 4 h at 70 °C, the title compound was prepared from *cis*-1,3-divinylisoindoline (**65**) (51.4 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and (bromoethynyl)triisopropylsilane (**3**) (102 mg, 0.390 mmol, 1.3 equiv). The crude oil (*dr* > 98:2 determined by integration in the crude ^{19}F NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 90:10 to 40:60 Pentane:CH₂Cl₂) to afford the title compound **22** (92 mg, 0.168 mmol, 56 % yield, *dr* > 98:2 determined by integration in the ^{19}F NMR) as a yellow oil.

R_f 0.40 (Pentane/CH₂Cl₂ 3/2).

1H NMR (400 MHz, Benzene-*d*₆) δ 7.88 (app d, *J* = 7.5 Hz, 1H, Ar*H*), 7.23 – 7.13 (m overlapping with benzene-*d*₆ signal, 1H, Ar*H*), 7.08 (app t, *J* = 7.6 Hz, 1H, Ar*H*), 6.87 (d, *J* = 7.6 Hz, 1H, Ar*H*), 5.65 – 5.32 (m, 1H, CHCF₃), 5.31 – 5.14 (m, 1H, CHCH₂), 5.10 (d, *J* = 7.2 Hz, 1H, CHN), 4.98 (app d, *J* = 16.9 Hz, 1H, CHCH₂), 4.91 (app d, *J* = 9.8 Hz, 1H, CHCH₂), 4.79 (d, *J* = 9.8 Hz, 1H, CHAr), 3.88 – 3.75 (m, 1H, CHNBoc), 3.27 (app d, *J* = 16.8 Hz, 1H, CCCH₂), 2.69 (dd, *J* = 16.8, 9.9 Hz, 1H, CCCH₂), 1.30 (s, 9H, Boc), 1.24 – 1.09 (m, 21H, TIPS).

^{13}C NMR (101 MHz, C₆D₆) δ 153.2, 141.2, 139.9, 137.7, 128.5, 127.9, 125.4 (q, *J* = 282.9 Hz), 124.8, 123.9, 119.9, 105.9, 84.1, 81.1, 75.7, 74.4 (q, *J* = 34.6 Hz), 72.5, 64.0, 28.2, 25.9, 19.0, 11.9.

^{19}F NMR (376 MHz, CDCl₃) δ -77.7.

IR ν_{max} 2944 (m), 2868 (w), 2172 (w), 1711 (m), 1468 (w), 1363 (s), 1286 (m), 1153 (s), 1004 (w), 932 (w), 877 (w).

HRMS calcd for $C_{30}H_{44}F_3N_2O_2Si^+$ $[M+H]^+$ 549.3119; found 549.3130.

Stereochemistry assigned by 1D NOESY.

***Tert*-butyl 3-benzyl-2-(trifluoromethyl)-5-(4-((triisopropylsilyl)oxy)dec-2-yn-1-yl)imidazolidine-1-carboxylate (**23**)**

Pentane:CH₂Cl₂) to afford the title compound **23** (0.170 g, 0.266 mmol, 89 % yield) as a yellow oil.

R_f 0.28 (Pentane:CH₂Cl₂ 2:1).

¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H, ArH), 5.00 – 4.73 (m, 1H, CHCF₃), 4.37 (td, *J* = 6.4, 1.7 Hz, 1H, CHOTIPS), 4.09 – 3.88 (m, 1H, CHN), 3.88 – 3.76 (m, 2H, CH₂Ph), 3.26 – 3.13 (m, 2H, CH₂N), 3.04 – 2.78 (m, 1H, CH₂CC), 2.25 (app ddt, *J* = 16.3, 10.6, 1.7 Hz, 1H, CH₂CC), 1.64 – 1.57 (m, 2H), 1.52 – 1.44 (m, 10H, Boc and CH₂), 1.44 – 1.33 (m, 1H, CH₂), 1.32 – 1.22 (m, 6H, CH₂CH₂CH₂), 1.12 – 0.97 (m, 21H, TIPS), 0.88 (t, *J* = 6.8 Hz, 3H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ 154.2, 137.4, 128.8, 128.7, 128.0, 124.3 (q, *J* = 284.7 Hz), 84.1, 81.6, 80.0, 77.3 (m overlapping with chloroform signal), 63.3, 60.0, 57.1, 55.9, 39.2, 31.9, 29.2, 28.3, 25.1, 24.0, 22.7, 18.2, 18.1 (diastereoisomer), 14.2, 12.4.

IR ν_{max} 2938 (w), 2853 (w), 1714 (s), 1465 (w), 1364 (s), 1287 (w), 1172 (s), 882 (w).

HRMS (ESI) calcd for C₃₅H₅₇F₃N₂NaO₃Si⁺ [M+Na]⁺ 661.3983; found 661.3980.

***Tert*-butyl 3-benzyl-5-(4-methyl-4-((triisopropylsilyl)oxy)pent-2-yn-1-yl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (**24**)**

title compound **24** (133 mg, 0.228 mmol, 76 % yield) as a yellow oil.

R_f 0.50 (Pentane/CH₂Cl₂ 1/1).

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H, ArH), 5.05 – 4.71 (m, 1H, CHCF₃), 3.98 (s, 1H, CHN), 3.87 – 3.76 (m, 2H, CH₂Ph), 3.23 – 3.12 (m, 2H, CH₂N), 2.97 – 2.77 (m, 1H, CH₂CC), 2.24 (dd, *J* = 16.2, 10.3 Hz, 1H, CH₂CC), 1.47 (s, 9H, Boc), 1.43 (s, 3H, Me), 1.43 (s, 3H, Me), 1.13 – 0.98 (m, 21H, TIPS).

^{13}C NMR (101 MHz, CDCl_3) δ 154.2, 137.4, 128.9, 128.8, 128.0, 124.28 (q, $J = 283.9$ Hz), 87.7, 81.6, 78.1, 77.2 (m overlapping with chloroform signal), 66.3, 60.0, 57.1, 55.7, 33.5, 28.4, 24.0, 18.4, 13.1.

IR ν_{max} 2940 (m), 2866 (w), 2239 (w), 1715 (s), 1464 (w), 1366 (s), 1246 (m), 1165 (s), 1062 (w), 881 (w).

HRMS calcd for $\text{C}_{35}\text{H}_{57}\text{F}_3\text{N}_2\text{NaO}_3\text{Si}^+ [\text{M}+\text{Na}]^+$ 661.3983; found 661.3980.

***Tert*-butyl 3-benzyl-5-(4-(benzyloxy)-4-methylpent-2-yn-1-yl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (25)**

Following General Procedure A, using Pd_2dba_3 (11.0 mg, 12.0 μmol) and DPEPhos (19.4 mg, 0.036 mmol), the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and ((1-bromonon-1-yn-3-yl)oxy)triisopropylsilane (**75**) (0.146 g, 0.390 mmol, 1.3 equiv). The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 80:20 to 0:10 Pentane: CH_2Cl_2) to afford the title compound (95.4 mg, 0.184 mmol, 62 % yield) as a yellow oil.

R_f 0.30 (Pentane: Et_2O 4:1).

^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.28 (m, 9H, ArH), 7.28 – 7.24 (m, 1H, ArH), 4.96 – 4.70 (m, 1H, CHCF_3), 4.54 (s, 2H, CH_2O), 4.13 – 3.88 (m, 1H, CHN), 3.84 – 3.74 (m, 2H, NCH_2Ph), 3.27 – 3.11 (m, 2H, CH_2N), 2.98 – 2.81 (m, 1H, CH_2CC), 2.34 (dd, $J = 16.3, 10.0$ Hz, 1H, CH_2CC), 1.47 (app s, 15H, CH_3 and Boc).

^{13}C NMR (101 MHz, CDCl_3) δ 154.2, 139.3, 137.3, 128.8, 128.7, 128.4, 128.0, 127.7, 127.4, 124.2 (q, $J = 284.5$ Hz), 84.4, 81.7, 80.4, 77.2 (m overlapping with chloroform signal), 70.8, 66.5, 59.9, 56.9, 55.8, 29.2, 28.3, 23.7.

IR ν_{max} 2986 (s), 2906 (m), 2177 (w), 1706 (w), 1385 (m), 1246 (w), 1061 (s), 906 (w).

HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{36}\text{F}_3\text{N}_2\text{O}_3^+ [\text{M}+\text{H}]^+$ 517.2673; found 517.2675.

Methyl 3-benzyl-5-(4-((*tert*-butyldimethylsilyl)oxy)-5,5,5-trifluoro-4-phenylpent-2-yn-1-yl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (26)

Following General Procedure A, using Pd_2dba_3 (11.0 mg, 12.0 μmol) and DPEPhos (19.4 mg, 0.036 mmol), the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2a**) (71 mg, 0.33 mmol, 1.1 equiv) and ((4-bromo-1,1,1-trifluoro-2-phenylbut-3-yn-2-yl)oxy)(*tert*-butyl)dimethylsilane (**81**) (153 mg, 0.390 mmol, 1.3 equiv). The crude oil (1:1 dr at the propargylic center, determined by integration in the crude ^1H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 97:3 to 85:15 Pentane: Et_2O) to afford the title compound **26** (0.177 g, 0.288 mmol, 96 % yield) as a yellow oil.

R_f 0.25 (Pentane: Et_2O 8:1).

¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.62 (m, 2H, ArH), 7.41 – 7.27 (m, 8H, ArH), 5.10 – 4.86 (m, 1H, CHCF₃), 4.24 – 4.04 (m, 1H, CHN), 3.98 – 3.86 (m, 1H, CH₂Ph), 3.81 (d, *J* = 13.1 Hz, 1H, CH₂Ph), 3.77 (s, 3H, OMe for the first diastereoisomer), 3.75 (s, 3H, OMe for the second diastereoisomer) 3.33 – 3.18 (m, 2H, CH₂N), 3.18 – 2.98 (m, 1H, CH₂CC), 2.42 (dd, *J* = 16.5, 10.1 Hz, 1H, CH₂CC), 0.96 (s, 9H, *t*-Bu), 0.20 (app d, *J* = 3.5 Hz, 3H, Me), -0.03 (app d, *J* = 2.2 Hz, 3H, Me).

¹³C NMR (101 MHz, CDCl₃) δ 155.6, 137.5, 136.9, 129.2, 128.9, 128.8, 128.1, 128.0, 127.5, 124.1 (q, *J* = 284.5 Hz), 123.4 (q, *J* = 286.3 Hz), 86.2, 78.7 (first diastereoisomer), 78.7 (second diastereoisomer), 77.3 (m overlapping with chloroform signal), 74.4 (q, *J* = 32.4 Hz), 59.9, 57.1, 55.7, 53.5, 25.8, 24.0, 18.5, -3.2, -3.3.

IR $\nu_{\max}$ 2956 (w), 2854 (w), 2248 (w), 1720 (m), 1447 (m), 1360 (w), 1264 (w), 1172 (s), 1146 (m), 1099 (m), 915 (w), 864 (m).

HRMS calcd for C₃₀H₃₇F₆N₂O₃Si⁺ [M+H]⁺ 615.2472; found 615.2494.

***Tert*-butyl 3-benzyl-5-(2-fluorobenzyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (27)**

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and 1-bromo-2-fluorobenzene (**47**) (79 mg, 0.45 mmol, 1.5 equiv) at 70 °C. The crude oil (*dr* > 20:1 determined by integration in the ¹H NMR of the crude) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 85:15 to 40:60 Pentane:CH₂Cl₂) to afford the title compound **27** (108 mg, 0.246 mmol, 82 % yield) as a yellow oil.

R_f 0.40 (Pentane:CH₂Cl₂ 5:7).

¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.26 (m, 5H, ArH), 7.23 – 7.14 (m, 2H, ArH), 7.08 – 6.97 (m, 2H, ArH), 5.08 – 4.79 (m, 1H, CHCF₃), 4.32 – 4.17 (m, 1H, CHN), 3.88 (d, *J* = 13.4 Hz, 1H PhCH₂), 3.74 (d, *J* = 13.2 Hz, 1H, PhCH₂), 3.40 – 3.26 (m, 1H, NCH₂), 3.13 (dd, *J* = 11.6, 6.9 Hz, 1H, ArCH₂), 2.88 (dd, *J* = 11.6, 7.4 Hz, 1H, ArCH₂), 2.84 – 2.71 (m, 1H, NCH₂), 1.48 (s, 9H, Boc).

¹³C NMR (101 MHz, CDCl₃) δ 161.4 (d, *J* = 245.4 Hz), 154.6, 137.6, 131.8 (d, *J* = 4.9 Hz), 128.7, 128.6, 128.4 (d, *J* = 8.0 Hz), 127.8, 125.0 (d, *J* = 16.2 Hz), 124.41 (q, *J* = 284.4 Hz), 124.2 (d, *J* = 3.6 Hz), 115.4 (d, *J* = 22.1 Hz), 81.4, 77.2 (q, *J* = 33.1 Hz), 59.7, 57.0, 56.7, 34.0, 28.3.

IR $\nu_{\max}$ 3039 (w), 2824 (w), 1704 (s), 1490 (w), 1364 (s), 1286 (m), 1237 (m), 1155 (s), 907 (s).

HRMS (ESI) calcd for C₂₃H₂₇F₄N₂O₂⁺ [M+H]⁺ 439.2003; found 439.2004.

***Tert*-butyl 3-benzyl-5-(2-(trifluoromethoxy)benzyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (**28**)**

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.330 mmol, 1.1 equiv) and 1-bromo-2-(trifluoromethoxy)benzene (67 μ L, 0.45 mmol, 1.5 eq) at 70 °C. The crude oil (*dr* > 20:1 determined by integration in the crude ^{19}F NMR of the crude) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 85:15 to 50:50 Pentane: CH_2Cl_2) to afford the title compound **28** (122 mg, 0.242 mmol, 81 % yield) as a yellow oil.

R_f 0.45 (Pentane: CH_2Cl_2 5:7).

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.12 (m, 9H, ArH), 4.98 – 4.84 (m, 1H, CHCF_3), 4.30 – 4.16 (m, 1H, CHN), 3.87 (d, J = 13.0 Hz, 1H, CH_2Ph), 3.71 (d, J = 13.0 Hz, 1H, CH_2Ph), 3.31 – 3.20 (m, 1H, CH_2Ar), 3.11 – 3.01 (m, 1H, CH_2N), 2.92 – 2.80 (m, 2H, CH_2Ar and CH_2N), 1.43 (s, 9H, Boc).

^{13}C NMR (101 MHz, CDCl_3) δ 154.3, 147.8, 137.3, 131.9, 130.5, 128.6, 128.5, 127.9, 127.7, 126.7, 124.3 (q, J = 284.7 Hz), 120.5 (q, J = 257.5 Hz), 120.2, 81.3, 77.2 (m overlapping with chloroform signals), 59.7, 56.9, 56.5, 34.2, 28.1.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -56.89, -76.21.

IR ν_{max} 3067 (w), 2821 (w), 1710 (m), 1490 (w), 1455 (w), 1367 (m), 1258 (s), 1170 (s), 917 (w).

HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{F}_6\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 505.1920; found 505.1924.

***Tert*-butyl 3-benzyl-5-(2-bromobenzyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (**29**)**

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and 1,2-dibromobenzene (54 μ L, 0.45 mmol, 1.5 eq) at 70 °C. The crude oil (*dr* > 20:1 determined by integration in the ^{19}F NMR of the crude) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 85:15 to 50:50 Pentane: CH_2Cl_2) to afford the title compound **29** (95.0 mg, 0.190 mmol, 63 % yield) as a

yellow oil.

R_f 0.40 (Pentane: CH_2Cl_2 5:7).

^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, J = 7.9 Hz, 1H, ArH), 7.38 – 7.22 (m, 5H, ArH), 7.22 – 7.16 (m, 2H, ArH), 7.12 – 7.03 (m, 1H, ArH), 5.06 – 4.79 (m, 1H, CHCF_3), 4.45 – 4.29 (m, 1H, CHN), 4.02 – 3.83 (m, 1H, CH_2Ph), 3.77 – 3.66 (m, 1H, CH_2Ph), 3.44 – 3.22 (m, 1H, CH_2Ar), 3.22 – 3.05 (m, 1H, CH_2N), 3.00 – 2.88 (m, 1H, CH_2Ar), 2.88 – 2.75 (m, 1H, CH_2N), 1.40 (s, 9H, Boc).

^{13}C NMR (101 MHz, CDCl_3) δ 154.3, 137.6, 137.4, 132.7, 131.7, 128.6, 128.5, 128.1, 127.6, 127.4, 124.7, 124.3 (q, J = 284.7 Hz), 81.2, 77.2 (m overlapping with chloroform signals), 59.6, 56.4, 56.2, 39.9, 28.2.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -75.9.

IR ν_{max} 3065 (w), 2823 (w), 1709 (s), 1452 (w), 1365 (s), 1286 (m), 1170 (s), 914 (m).

HRMS (ESI) calcd for $C_{23}H_{27}^{79}BrF_3N_2O_2^+$ $[M+H]^+$ 499.1202; found 499.1193.

Methyl 3-benzyl-5-(2-bromo-4-formylbenzyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (30)

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and 3,4-dibromobenzaldehyde (158 mg, 0.600 mmol, 2.0 eq) at 70 °C. The crude oil (*dr* > 20:1 determined by integration in the crude 1H NMR of the crude) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 70:30 to 10:90 Pentane:Et₂O) to afford the title compound **30** (137 mg, 0.282 mmol, 94% yield) as a pale yellow oil.

R_f 0.30 (Pentane:Et₂O 1:1).

1H NMR (400 MHz, CDCl₃) δ 9.91 (s, 1H, CHO), 8.08 – 7.99 (m, 1H, ArH), 7.74 – 7.66 (m, 1H, ArH), 7.37 – 7.27 (m, 6H, ArH), 5.04 – 4.89 (m, 1H, CHCF₃), 4.46 – 4.34 (m, 1H, CHN), 3.91 (d, *J* = 13.3 Hz, 1H, CH₂Ph), 3.73 (d, *J* = 13.3 Hz, 1H, CH₂Ph), 3.64 (s, 3H, Me), 3.52 – 3.30 (m, 1H, CH₂Ar), 3.15 (dd, *J* = 11.6, 6.7 Hz, 1H, CH₂N), 3.01 (dd, *J* = 13.2, 8.0 Hz, 1H, CH₂Ar), 2.92 (dd, *J* = 11.6, 7.5 Hz, 1H, CH₂N).

^{13}C NMR (101 MHz, CDCl₃) δ 190.5, 155.9, 144.5, 137.2, 136.5, 133.9, 132.2, 128.7 (2C), 128.6, 128.0, 125.7, 124.2 (d, *J* = 284.0 Hz), 77.2 (m overlapping with chloroform signal), 59.7, 56.5 (2C), 53.3, 40.5.

IR ν_{max} 2973 (m), 1713 (s), 1598 (w), 1453 (m), 1369 (s), 1181 (s), 1139 (s), 1068 (m).

HRMS (ESI) calcd for $C_{21}H_{20}^{79}BrF_3N_2NaO_3^+$ $[M+Na]^+$ 507.0502; found 507.0500.

Tert-butyl 3-benzyl-5-(4-(methoxycarbonyl)benzyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (31)

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((tert-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.330 mmol, 1.1 equiv) and methyl 4-bromobenzoate (97 mg, 0.45 mmol, 1.5 equiv) at 70 °C. The crude oil (*dr* > 20 determined by integration in the crude 1H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 95:15 to 75:25 Pentane:Et₂O) affording the title compound **31** (107 mg, 0.224 mmol, 75 % yield) as a yellow oil.

R_f 0.35 (Pentane:Et₂O 4:1).

1H NMR (400 MHz, CDCl₃) δ 7.96 – 7.91 (m, 2H, ArH), 7.35 – 7.19 (m, 7H, ArH), 5.07 – 4.76 (m, 1H, CHCF₃), 4.23 – 4.04 (m, 1H, CHN), 3.89 (s, 3H, Me), 3.88 – 3.78 (m, 1H, CH₂Ph), 3.72 (d, *J* = 13.2 Hz, 1H, CH₂Ph), 3.51 – 3.31 (m, 1H, CH₂Ar), 3.07 (ddd, *J* = 11.6, 7.1, 1.4 Hz, 1H, CH₂N), 2.88 – 2.80 (m, 1H, CH₂N), 2.67 (dd, *J* = 13.0, 9.6 Hz, 1H, CH₂Ar), 1.48 (s, 9H, Boc).

^{13}C NMR (101 MHz, CDCl₃) δ 167.0, 154.3, 143.5, 137.4, 130.0, 129.3, 128.7 (2C), 128.6, 127.9, 124.4 (q, *J* = 284.8 Hz) 81.6, 77.1 (q, *J* = 33.1 Hz), 59.7, 58.0, 56.4, 52.1, 40.2, 28.3.

IR ν_{max} 3036 (w), 2943 (w), 2837 (w), 1711 (s), 1611 (w), 1445 (w), 1366 (s), 1280 (s), 1156 (s), 1115 (s), 965 (m), 874 (m).

HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{30}\text{F}_3\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 479.2152; found 479.2143.

***Tert*-butyl 3-benzyl-5-(4-cyanobenzyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (**32**)**

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv) and 4-bromobenzonitrile (82 mg, 0.45 mmol, 1.5 equiv) at 70 °C. The crude oil (>20:1 dr determined by integration of PhCH_2N peaks in the ^1H NMR) was purified by column chromatography on Biotage ((SNAP cartridge KP-SIL 25 g, 95:15 to 70:30 Pentane:Et₂O) affording the title compound **32** (114 mg, 0.256 mmol, 85 % yield) as a yellow oil.

R_f 0.30 (Pentane:Et₂O 4:1).

^1H NMR (400 MHz, CDCl₃) δ 7.58 – 7.46 (m, 2H, ArH), 7.36 – 7.17 (m, 7H, ArH), 4.96 – 4.82 (m, 1H, CHCF_3), 4.24 – 4.08 (m, 1H, CHN), 3.88 (d, J = 13.1 Hz, 1H, CH_2Ph), 3.73 (d, J = 13.1 Hz, 1H, CH_2Ph), 3.40 – 3.28 (m, 1H, CH_2Ar), 3.08 – 2.97 (m, 1H, CH_2N), 2.91 – 2.81 (m, 1H, CH_2N), 2.79 – 2.66 (m, 1H, CH_2Ar), 1.46 (s, 9H, Boc).

^{13}C NMR (101 MHz, CDCl₃) δ 154.1, 143.6, 137.2, 132.3, 130.0, 128.6 (2C), 127.8, 124.2 (q, J = 284.2 Hz), 118.9, 110.5, 81.6, 77.1 (m overlapping with chloroform signal), 59.6, 57.7, 56.3, 40.3, 28.2.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -76.2.

IR ν_{max} 2979 (s), 2898 (m), 1707 (m), 1376 (m), 1247 (w), 1166 (m), 1067 (s), 879 (w).

HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 446.2050; found 446.2060.

Methyl 3-benzyl-5-(3,5-bis(trifluoromethyl)benzyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (33**)**

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and 1-bromo-3,5-bis(trifluoromethyl)benzene (77 μl , 0.45 mmol, 1.5 equiv) at 70 °C. The crude oil ($dr > 20$ determined by integration in the crude ^{19}F NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 85:15 to 40:60 Pentane:CH₂Cl₂) affording the title compound **33** (152 mg, 0.295 mmol, 98 % yield) as a yellow oil.

R_f 0.50 (Pentane:CH₂Cl₂ 5:7).

^1H NMR (400 MHz, CDCl₃) δ 7.75 (s, 1H, ArH), 7.63 (s, 2H, ArH), 7.39 – 7.27 (m, 5H, ArH), 5.08 – 4.89 (m, 1H, CHCF_3), 4.29 – 4.13 (m, 1H, CHN), 3.92 (d, J = 13.4 Hz, 1H, CH_2Ph), 3.76 (d, J = 13.5 Hz, 2H, CH_2Ph), 3.73 (s, 3H, Me), 3.47 – 3.34 (m, 1H, CH_2Ar), 3.09 (dd, J = 11.6, 6.8 Hz, 1H, CH_2N), 2.98 – 2.91 (m, 1H, CH_2N), 2.88 (dd, J = 13.5, 8.7 Hz, 1H, CH_2Ar).

^{13}C NMR (101 MHz, CDCl_3) δ 155.8, 140.3, 137.1, 131.9 (q, $J = 33.2$ Hz), 129.5, 128.8, 128.7, 128.1, 124.2 (q, $J = 284.4$ Hz), 123.4 (q, $J = 272.7$ Hz), 121.04 – 120.63 (m), 77.2 (m overlapping with chloroform signals), 59.6, 58.0, 56.3, 53.4, 39.6.

^{19}F NMR (376 MHz, CDCl_3) δ -62.9, -76.5.

IR ν_{max} 2965 (w), 2901 (w), 1718 (m), 1451 (w), 1376 (m), 1282 (s), 1175 (s), 1137 (s), 906 (m).

HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{F}_9\text{N}_2\text{NaO}_2^+ [\text{M}+\text{Na}]^+$ 537.1195; found 537.1190.

***Tert*-butyl 3-benzyl-5-(3,5-bis(trifluoromethyl)benzyl)-5-methyl-2-(trifluoromethyl)imidazolidine-1-carboxylate (**34**)**

Following General Procedure **C**, the title compound was prepared from *N*-benzyl-2-methylprop-2-en-1-amine (**45**) (48.4 mg, 0.300 mmol) and 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.33 mmol, 1.1 equiv), 1-bromo-3,5-bis(trifluoromethyl)benzene (77 μl , 0.45 mmol, 1.5 equiv) at 70 $^\circ\text{C}$. The crude oil ($dr > 20$ determined by integration in the crude ^1H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 90:10 to 60:40 Pentane: CH_2Cl_2) affording the title compound **34** (152 mg, 0.266 mmol, 89 % yield) as a yellow oil.

R_f 0.70 (Pentane: CH_2Cl_2 5:7).

^1H NMR (400 MHz, CDCl_3) δ 7.75 (s, 1H, ArH), 7.63 (s, 2H, ArH), 7.37 – 7.25 (m, 5H, ArH), 5.04 – 4.91 (m, 1H, CHCF_3), 4.01 (d, $J = 13.6$ Hz, 1H, CH_2Ph), 3.85 (d, $J = 13.6$ Hz, 1H, CH_2Ph), 3.63 – 3.47 (m, 1H, CH_2Ar), 3.14 (d, $J = 10.4$ Hz, 1H, CH_2N), 2.93 (d, $J = 13.7$ Hz, 1H, CH_2Ar), 2.69 (dd, $J = 10.3, 1.6$ Hz, 1H, CH_2N), 1.61 (s, 3H, Me), 1.53 (s, 9H, Boc).

^{13}C NMR (101 MHz, CDCl_3) δ 153.1, 139.4, 137.8, 131.3 (q, $J = 33.0$ Hz), 130.9, 128.7, 128.4, 127.8, 124.1 (q, $J = 292.5$ Hz), 123.6 (q, $J = 272.5$ Hz), 120.7 (m), 81.9, 76.4 (q, $J = 31.3$ Hz), 64.0, 58.6, 56.5, 42.5, 28.2, 25.2.

IR ν_{max} 2986 (w), 2865 (w), 1704 (m), 1461 (w), 1365 (m), 1277 (s), 1166 (s), 1132 (s), 904 (m).

HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{28}\text{F}_9\text{N}_2\text{O}_2^+ [\text{M}+\text{H}]^+$ 571.2002; found 571.1998.

***Tert*-butyl 3-benzyl-5-((3-fluoropyridin-2-yl)methyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (**35**)**

Following General Procedure **D** with DPEPhos (19 mg, 0.036 mmol) as ligand, the title compound was prepared from *N*-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.330 mmol, 1.1 equiv) and 2-bromo-3-fluoropyridine (79 mg, 0.45 mmol, 1.5 equiv) at 70 $^\circ\text{C}$. The crude oil ($>20:1$ dr determined by integration of PhCH_2N peaks in the ^1H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 96:4 to 75:25 Pentane:EtOAc) affording the title compound **35** (88 mg, 0.20 mmol, 67 % yield) as a yellow oil.

R_f 0.25 (Pentane:EtOAc 5:1).

¹H NMR (400 MHz, CDCl₃) δ 8.2 (dt, *J* = 4.7, 1.5 Hz, 1H, HetAr*H*), 7.26 – 7.16 (m, 6H, Ar*H*), 7.08 – 7.02 (m, 1H, HetAr*H*), 5.01 – 4.67 (m, 1H, CF₃CH), 4.54 – 4.23 (m, 1H, NCH), 3.79 – 3.67 (m, 2H, PhCH₂), 3.53 – 3.43 (m, 1H, HetArCH₂), 3.18 – 3.09 (m, 1H, NCH₂), 3.09 – 2.98 (m, 1H, NCH₂), 2.97 – 2.87 (m, 1H, HetArCH₂), 1.39 (s, 9H, Boc).

¹³C NMR (101 MHz, CDCl₃) δ 158.1 (d, *J* = 256.8 Hz), 154.5, 146.9 (d, *J* = 15.6 Hz), 145.0 (d, *J* = 5.4 Hz), 137.6, 128.8, 128.6, 127.8, 124.3 (q, *J* = 284.5 Hz), 122.9, 122.5 (d, *J* = 19.4 Hz), 81.4, 77.2 (q, *J* = 33.2 Hz), 59.9, 57.2, 55.6, 35.7, 28.3.

IR ν_{max} 3068 (w), 2827 (w), 1707 (s), 1454 (m), 1366 (s), 1285 (m), 1248 (m), 1173 (s), 964 (w), 909 (s).

HRMS (ESI) calcd for C₂₂H₂₆F₄N₃O₂⁺ [M+H]⁺ 440.1956; found 440.1951.

Methyl 3-benzyl-5-((2-chloropyrimidin-5-yl)methyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (36)

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and 5-bromo-2-chloropyrimidine (87.0 mg, 0.450 mmol, 1.5 equiv) at 70 °C. The crude oil (>20:1 dr determined by integration of PhCH₂N peaks in the ¹H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 80:20 to 20:80 Pentane:Et₂O) affording the title compound **36** (112 mg, 0.270 mmol, 90 % yield) as a yellow oil.

R_f 0.25 (Pentane: Et₂O 5:1).

¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 2H, HetAr*H*), 7.39 – 7.24 (m, 5H, Ar*H*), 5.05 – 4.86 (m, 1H, CF₃CH), 4.16 (q, *J* = 7.4 Hz, 1H, NCH), 3.94 (d, *J* = 13.3 Hz, 1H, PhCH₂), 3.75 (d, *J* = 13.2 Hz, 1H, PhCH₂), 3.70 (s, 3H, Me), 3.17 (dd, *J* = 14.1, 5.9 Hz, 1H, HetArCH₂), 3.07 – 2.94 (m, 2H, NCH₂), 2.76 (dd, *J* = 14.0, 7.7 Hz, 1H, HetArCH₂).

¹³C NMR (101 MHz, CDCl₃) δ 160.0, 155.6 (2C), 136.8, 129.7, 128.8, 128.6, 128.1, 124.1 (d, *J* = 284.4 Hz), 77.2 (q, *J* = 33.6 Hz), 59.5, 57.6, 56.1, 53.5, 33.8.

IR ν_{max} 2965 (m), 2908 (w), 1713 (s), 1579 (w), 1549 (w), 1448 (m), 1393 (s), 1362 (s), 1283 (m), 1239 (m), 1141 (s), 1072 (m), 985 (w), 912 (w), 852 (w).

HRMS (ESI) calcd for C₁₈H₁₈ClF₃N₄NaO₂⁺ [M+Na]⁺ 437.0963; found 437.0958.

Methyl 3-benzyl-5-((5-nitrofuran-2-yl)methyl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (37)

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and 2-bromo-5-nitrofuran (86 mg, 0.45 mmol, 1.5 equiv) at 70 °C. The crude oil (>20:1 dr determined by integration of PhCH₂N peaks in the ¹H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 80:20 to 40:60 Pentane:Et₂O) affording the title compound **37** (101 mg, 0.244 mmol, 81 % yield) as a yellow oil.

R_f 0.20 (Pentane: Et₂O 2:1).

¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H, ArH), 7.21 (d, *J* = 3.6 Hz, 1H, HetArH), 6.31 (d, *J* = 3.6 Hz, 1H, HetArH), 5.06 – 4.86 (m, 1H, CF₃CH), 4.38 – 4.26 (m, 1H, NCH), 3.92 (d, *J* = 13.6 Hz, 1H, PhCH₂), 3.77 (d, *J* = 13.2 Hz, 1H, PhCH₂), 3.71 (s, 3H, Me), 3.32 (d, *J* = 12.3 Hz, 1H, HetArCH₂), 3.21 – 3.05 (m, 2H, NCH₂), 2.88 (dd, *J* = 15.0, 8.1 Hz, 1H, HetArCH₂).

¹³C NMR (101 MHz, CDCl₃) δ 156.2, 155.6, 151.9, 136.9, 128.8, 128.7, 128.0, 124.1 (q, *J* = 284.3 Hz), 112.8, 111.3, 77.1 (m overlapping with chloroform signal), 59.6, 56.6, 55.5, 53.5, 32.8.

IR ν_{max} 3141 (w), 2983 (w), 2962 (w), 2902 (w), 1711 (m), 1591 (w), 1529 (w), 1498 (m), 1448 (w), 1359 (m), 1330 (w), 1285 (w), 1236 (w), 1145 (m), 1074 (w), 1025 (w), 908 (s).

HRMS (ESI) calcd for C₁₈H₁₈F₃N₃NaO₅⁺ [*M*+Na]⁺ 436.1091; found 436.1081.

Methyl 5-((5-benzoylthiophen-2-yl)methyl)-3-benzyl-2-(trifluoromethyl)imidazolidine-1-carboxylate (38)

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 2,2,2-trifluoro-1-((methoxycarbonyl)amino)ethyl acetate (**2aa**) (71 mg, 0.33 mmol, 1.1 equiv) and (5-bromothiophen-2-yl)(phenyl)methanone (120 mg, 0.450 mmol, 1.5 equiv) at 70 °C. The crude oil (>20:1 dr determined by integration of PhCH₂N peaks in the ¹H NMR) was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 90:20 to 50:50 Pentane:Et₂O) affording the title compound **38** (120 mg, 0.246 mmol, 82 % yield, 95 % purity) as a yellow oil.

R_f 0.50 (Pentane: Et₂O 1:1).

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.78 (m, 2H, ArH), 7.62 – 7.54 (m, 1H, ArH), 7.52 – 7.43 (m, 3H, ArH), 7.38 – 7.22 (m, 5H, ArH), 6.92 – 6.80 (m, 1H, ArH), 5.16 – 4.79 (m, 1H, CF₃CH), 4.33 – 4.12 (m, 1H, NCH), 3.88 (d, *J* = 13.5 Hz, 1H, PhCH₂), 3.78 (d, *J* = 13.5 Hz, 1H, PhCH₂), 3.78 (s, 3H, Me), 3.70 – 3.45 (m, 1H, ArCH₂), 3.21 – 3.12 (m, 1H, NCH₂), 3.07 (dd, *J* = 11.9, 7.4 Hz, 1H, NCH₂), 2.94 (dd, *J* = 14.3, 9.8 Hz, 1H, ArCH₂).

¹³C NMR (101 MHz, CDCl₃) δ 188.0, 155.7, 149.8, 142.5, 138.1, 137.0, 135.4, 132.3, 129.2, 128.7, 128.7, 128.5, 128.0, 127.3, 124.1 (d, *J* = 284.5 Hz), 77.1 (q overlapping with chloroform signal), 59.8, 58.0, 56.8, 53.5, 35.1.

IR ν_{max} 3066 (w), 2960 (w), 2903 (w), 1714 (m), 1634 (m), 1448 (s), 1365 (m), 1288 (s), 1174 (m), 1143 (s), 909 (s).

HRMS (ESI) calcd for C₂₅H₂₄F₃N₂O₃S⁺ [*M*+H]⁺ 489.1454; found 489.1457.

***Tert*-butyl 3-benzyl-2-(trifluoromethyl)-5-(2-(trifluoromethyl)allyl)imidazolidine-1-carboxylate (**39**)**

yellow oil.

Following General Procedure **D**, the title compound was prepared from N-benzylprop-2-en-1-amine (**1**) (44.2 mg, 0.300 mmol), 1-((*tert*-butoxycarbonyl)amino)-2,2,2-trifluoroethyl acetate (**2a**) (85 mg, 0.330 mmol, 1.1 equiv) and 2-bromo-3,3,3-trifluoroprop-1-ene (79 mg, 0.45 mmol, 1.5 eq) at 70 °C. The crude oil (>20:1 dr determined by integration in the crude ¹H NMR) was purified by chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 85:15 to 40:60 Pentane:CH₂Cl₂) affording the title compound **39** (115 mg, 0.262 mmol, 87 % yield) as a

R_f 0.40 (Pentane:CH₂Cl₂ 5:7).

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.28 (m, 5H, ArH), 5.75 – 5.65 (m, 1H, CCH₂), 5.42 – 5.30 (m, 1H, CCH₂), 5.08 – 4.77 (m, 1H, CHCF₃), 4.21 – 4.01 (m, 1H, NCH), 3.90 (d, *J* = 13.4 Hz, 1H, PhCH₂), 3.77 (d, *J* = 13.2 Hz, 1H, PhCH₂), 3.10 – 2.94 (m, 3H, NCH₂ and CH₂CCF₃), 2.24 (dd, *J* = 14.4, 9.9 Hz, 1H, CH₂CCF₃), 1.48 (s, 9H, Boc).

¹³C NMR (101 MHz, CDCl₃) δ 154.3, 137.4, 135.1 (q, *J* = 30.7 Hz), 128.8 (2 signals), 128.0, 124.4 (q, *J* = 284.6 Hz), 123.6 (q, *J* = 273.6 Hz), 120.9, 81.8, 77.0 (q overlapping with chloroform signals), 59.8, 56.5, 55.3, 34.8, 28.9.

IR *v*_{max} 2979 (w), 1709 (m), 1454 (w), 1364 (m), 1288 (w), 1248 (w), 1169 (s), 1121 (s), 1072 (w), 876 (w).

HRMS (ESI) calcd for C₂₀H₂₄F₆N₂NaO₂⁺ [M+Na]⁺ 461.1634; found 461.1648.

8. Products transformations.

Tert-butyl 2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**14**)

Following a slightly modified procedure,²⁶ a solution of *tert*-butyl 3-(4-methoxybenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**10**) (111 mg, 0.200 mmol) in CH₂Cl₂ (0.35 mL) was slowly added to a solution of DDQ (54.5 mg, 0.240 mmol, 1.2 eq) in CH₂Cl₂ (1 mL) and water (0.080 mL) at 0 °C. The mixture was stirred at rt for 10 h and then poured into ice cold water (5 mL) and extracted with CH₂Cl₂ (2x10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 92:8 to 75:25 Pentane:Et₂O) to give the title compound **14** (82 mg, 0.19 mmol, 94 % yield) as a colorless oil.

1-(4-Methoxybenzyl)-2-(trifluoromethyl)-4-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine (**40**)

A solution of *tert*-butyl 3-(4-methoxybenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**10**) (111 mg, 0.200 mmol) in water:ethanol (1:1, 3 mL) was heated under microwave irradiation at 160 °C for 15 min. The volatiles were removed under reduced pressure and the residue to afford the title compound **40** as a pale yellow oil (88.2 mg, 0.194 mmol, 97 % yield, 95% purity, 1:1 dr by integration of the benzylic peaks in the ¹H NMR).

R_f 0.10 (EtOAc:Et₃N 99:1).

¹H NMR (400 MHz, Chloroform-*d*) 1:1 mixture of diastereoisomers A and B δ 7.26 – 7.19 (m, 4H, ArH A and B), 6.89 – 6.82 (m, 4H, ArH A and B), 4.18 – 4.08 (m, 3H, ArCH₂ B and CHCF₃ A and B), 3.99 (d, *J* = 13.0 Hz, 1H, ArCH₂ A), 3.80 (s, 6H, OMe A and B), 3.63 (d, *J* = 13.0 Hz, 1H, ArCH₂ A), 3.58 (d, *J* = 12.7 Hz, 1H, ArCH₂ B), 3.54 – 3.45 (m, 2H, NCH A and B), 3.00 (dd, *J* = 8.4, 5.2 Hz, 1H, NCH₂ B), 2.94 (dd, *J* = 10.4, 5.6 Hz, 1H, NCH₂ A), 2.83 (dd, *J* = 10.4,

²⁶ Lehmann, L.; Friebe M.; Brumby T.; Suelzle D.; Platzek J. (Schering Aktiengesellschaft) WO2004/87656 A1, 2004.

6.3 Hz, 1H, NCH₂ A), 2.63 (dd, *J* = 17.3, 5.4 Hz, 2H, CH₂CC B and NH), 2.52 – 2.39 (m, 4H, NCH₂ B CH₂CC B, CH₂CC A), 1.09 – 1.04 (m, 21H, TIPS B), 1.04 – 0.99 (m, 21H, TIPS A).

¹³C NMR (101 MHz, CDCl₃) 1:1 mixture of diastereoisomers δ 159.1, 159.0, 130.5, 130.3, 130.0, 129.9, 125.5 (q, *J* = 282.2 Hz), 125.1 (q, *J* = 282.0 Hz), 113.9 (2C), 105.7, 103.1, 84.7, 82.3, 77.7 (q overlapping with chloroform signal, *J* = 31.2 Hz), 77.6 (q overlapping with chloroform signal, *J* = 31.4 Hz), 58.9, 58.4, 57.5, 57.0, 55.6, 55.4 (2C), 55.3, 26.2, 22.6, 18.8, 18.7, 11.3, 11.3.

IR ν_{max} 2943 (s), 2866 (m), 2173 (w), 1614 (w), 1514 (m), 1464 (m), 1382 (w), 1289 (m), 1249 (s), 1156 (s), 1035 (m), 919 (w), 884 (m), 832 (w).

HRMS (ESI) calcd for C₂₄H₃₈F₃N₂O₃Si⁺ [M+H]⁺ 455.2700; found 455.2709.

***Tert*-butyl 3-(4-methoxybenzyl)-5-(prop-2-yn-1-yl)-2-(trifluoromethyl)imidazolidine-1-carboxylate (**41**)**

To a solution of *tert*-butyl 3-(4-methoxybenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**10**) (222 mg, 0.400 mmol) in THF (Volume: 5.5 mL) at 0 °C was added dropwise a 1N solution of TBAF (1.08 mL, 1.08 mmol, 2 equiv) in THF. The reaction mixture was stirred for 45 min at rt and then quenched by addition of a solution of sat. NH₄Cl and diluted with Et₂O (10 mL). The organic layer was washed with brine (2x2 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 93:7 to 85:15 Pentane:EtOAc) to give the title compound **41** (156 mg, 0.392 mmol, 98 % yield) as a pale yellow oil.

R_f 0.75 (Pentane:Et₂O 2:1).

¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.20 (m, 2H, ArH), 6.89 – 6.84 (m, 2H, ArH), 5.06 – 4.72 (m, 1H, CHCF₃), 4.14 – 3.86 (m, 1H, CHNBoc), 3.79 (s, 3H, Me), 3.74 (s, 2H, ArCH₂), 3.30 – 3.14 (m, 2H, CH₂N), 3.00 – 2.75 (m, 1H, CH₂CC), 2.24 (ddd, *J* = 16.3, 10.1, 2.7 Hz, 1H, CH₂CC), 1.93 (t, *J* = 2.7 Hz, 1H, CCH), 1.46 (s, 9H, Boc).

¹³C NMR (101 MHz, CDCl₃) δ 159.3, 154.1, 130.1, 129.3, 124.2 (q, *J* = 284.2 Hz), 114.0, 81.6, 80.3, 77.1 (q, *J* = 33.3 Hz), 70.2, 59.3, 56.7, 55.5, 55.3, 28.3, 23.6.

IR ν_{max} 3305 (w), 3006 (w), 2937 (w), 2838 (w), 2121 (w), 1707 (s), 1613 (w), 1514 (m), 1463 (w), 1366 (s), 1287 (m), 1249 (s), 1155 (s), 1031 (w), 872 (m).

HRMS (ESI) calcd for C₂₀H₂₆F₃N₂O₃⁺ [M+H]⁺ 399.1890; found 399.1889.

N1-(4-methoxybenzyl)-5-(triisopropylsilyl)pent-4-yne-1,2-diamine dihydrochloride (42)

A solution of *tert*-butyl 3-(4-methoxybenzyl)-2-(trifluoromethyl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)imidazolidine-1-carboxylate (**10**) (111 mg, 0.200 mmol) in MeOH (1 mL) at -40 °C was treated with a 4N HCl solution in CPME (0.125 mL, 0.500 mmol, 2.5 equiv). The reaction mixture was allowed to slowly warm up to rt over 5 h. Then nitrogen was bubbled in the reaction mixture and the volatiles were removed under reduced pressure. The residue was further dried by co-evaporation with toluene to afford a solid. The solid was triturated with an ice cold mixture of pentane and acetonitrile (4:1, 3x0.1 mL) to afford the title compound **42** (80 mg, 0.18 mmol, 89% yield) as a beige solid.

m.p.: 185-186 °C.

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.54 – 7.48 (m, 2H, *ArH*), 7.04 – 6.97 (m, 2H, *ArH*), 4.30 (d, *J* = 13.0 Hz, 1H, *ArCH*₂), 4.24 (d, *J* = 13.0 Hz, 1H, *ArCH*₂), 3.87 – 3.78 (m, 1H, *NCH*), 3.82 (s, 3H, OMe), 3.48 (dd, *J* = 13.8, 4.4 Hz, 1H, *NCH*₂), 3.41 (dd, *J* = 13.8, 7.5 Hz, 1H, *NCH*₂), 2.93 (dd, *J* = 17.5, 5.5 Hz, 1H, *CH*₂CC), 2.86 (dd, *J* = 17.5, 7.3 Hz, 1H, *CH*₂CC), 1.16 – 0.99 (m, 21H, TIPS).

¹³C NMR (101 MHz, MeOD) δ 162.4, 132.9, 123.2, 115.7, 101.0, 87.8, 55.8, 52.8, 48.9 (overlapping with methanol signal), 48.8 (overlapping with methanol signal), 23.4, 19.0, 12.4.

IR ν_{max} 3408 (m), 3340 (m), 3282 (m), 2942 (w), 2864 (w), 2179 (w), 1614 (m), 1517 (s), 1463 (m), 1307 (w), 1254 (s), 1182 (m), 1078 (s), 1037 (s), 884 (m), 836 (m).

HRMS (ESI) calcd for C₂₁H₃₉N₂OSi [M+H]⁺ 375.2826; found 375.2816.

1-(Pyrrolidin-2-yl)-4-(triisopropylsilyl)but-3-yn-1-amine bis(2,2,2-trifluoroacetate) (43)

A solution of *tert*-butyl 3-(trifluoromethyl)-1-(3-(triisopropylsilyl)prop-2-yn-1-yl)pyrrolo[1,2-*c*]imidazole-2(3H)-carboxylate (**20**) (95.0 mg, 0.200 mmol) in DCM (2.5 mL) was treated with TFA (0.6 mL) at 0 °C and stirred at rt for 3 h and then dry methanol (1 mL) was added and the reaction was further stirred 1 h. The volatiles were removed under reduced pressure. The residue was further dried by co-evaporation with toluene to afford the pure title compound **43** (100 mg, 0.191 mmol, 96 % yield) as a light brown solid.

m.p.: 121-125 °C.

¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 7.99 (s, 5H, *NH*), 4.01 – 3.89 (m, 1H, *CHNH*₂), 3.83 – 3.74 (m, 1H, *CHNH*₃), 3.36 (dd, *J* = 8.7, 5.9 Hz, 2H, *CH*₂*NH*₂), 2.89 (dd, *J* = 18.3, 3.9 Hz, 1H, *CH*₂*CC*), 2.77 (dd, *J* = 18.3, 4.4 Hz, 1H, *CH*₂*CC*), 2.35 – 2.24 (m, 1H, *CH*₂*CHNH*₂), 2.18 – 2.06 (m, 1H, *CH*₂*CH*₂*NH*₂), 2.03 – 1.93 (m, partially overlapped with acetonitrile signal, 1H, *CH*₂*CH*₂*NH*₂), 1.87 – 1.73 (m, 1H, *CH*₂*CHNH*₂), 1.08 (s, 21H, TIPS).

¹³C NMR (101 MHz, CD₃CN) δ 162.8 (m), 117.5 (q, *J* = 292.7 Hz), 100.2, 87.7, 61.9, 51.7, 47.0, 29.2, 24.5, 23.8, 18.9, 11.9.

IR *v*_{max} 3518 (w), 2947 (w), 2868 (w), 2178 (w), 1672 (s), 1437 (w), 1191 (s), 1138 (s), 997 (w), 884 (w), 841 (w).

HRMS (ESI) calcd for C₁₇H₃₅N₂Si [M+H]⁺ 295.2564; found 295.2570.

N1-benzyl-3-(3,5-bis(trifluoromethyl)phenyl)-2-methylpropane-1,2-diamine bis(2,2,2-trifluoroacetate) (44**)**

A solution of *tert*-butyl 3-benzyl-5-(3,5-bis(trifluoromethyl)benzyl)-5-methyl-2-(trifluoromethyl)imidazolidine-1-carboxylate (**34**) (114 mg, 0.200 mmol) in DCM (2.5 mL) was treated with TFA (0.6 mL) at 0 °C and stirred at rt for 3 h and then dry methanol (1 mL) was added and the reaction was further stirred 1 h. The volatiles were removed under reduced pressure. The residue was further dried by co-evaporation with toluene to afford the pure title compound **44** (122 mg, 0.197 mmol, 99% yield) as a sticky yellow oil.

¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 8.85 (s, 5H, *NH*), 7.99 (s, 1H, *ArH*), 7.89 – 7.81 (m, 2H, *ArH*), 7.55 – 7.48 (m, 2H, *ArH*), 7.45 – 7.38 (m, 3H, *ArH*), 4.31 – 4.19 (m, 2H, *PhCH*₂), 3.39 (d, *J* = 14.0 Hz, 1H, *NCH*₂), 3.37 (d, *J* = 14.1 Hz, 1H, *ArCH*₂), 3.33 (d, *J* = 14.0 Hz, 1H, *NCH*₂), 3.17 (d, *J* = 14.1 Hz, 1H, *ArCH*₂), 1.44 (s, 3H, Me).

¹³C NMR (101 MHz, CD₃CN) δ 162.5 (q, *J* = 35.4 Hz), 137.0, 132.5 (q, *J* = 33.3 Hz), 132.4 (m), 131.3, 131.2, 130.5, 129.9, 124.4 (q, *J* = 272.0 Hz), 122.9 (m), 56.2, 53.5, 53.2, 42.9, 22.0.

IR *v*_{max} 3533 (w), 3043 (w), 2838 (w), 2584 (w), 1671 (m), 1463 (w), 1437 (w), 1381 (w), 1281 (m), 1176 (s), 1130 (s), 1030 (w), 903 (w), 840 (w).

HRMS (ESI) calcd for C₁₉H₂₁F₆N₂ [M+H]⁺ 391.1603; found 391.1606.

9. Spectra of new compounds (^1H NMR, ^{13}C NMR, IR)