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General Procedures for the Lithiation/Trapping of *N*-Boc Piperazines

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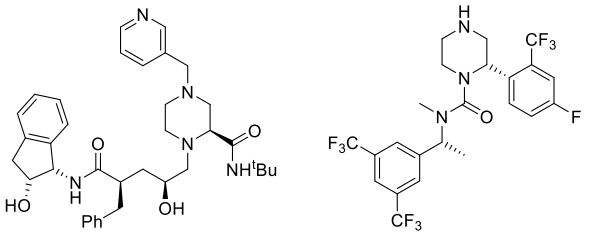
ABSTRACT: In order to provide α-substituted piperazines for early-stage medicinal chemistry studies, a simple, general synthetic approach is required. Here, we report the development of two general and simple procedures for the racemic lithiation/trapping of *N*-Boc piperazines. Optimum lithiation times have been determined using *in situ* IR spectroscopy and the previous complicated and diverse literature procedures have been simplified. Subsequent trapping with electrophiles delivered a wide range of α-functionalised *N*-Boc piperazines. The scope and limitations of the distal *N*-group has been investigated. The selective α- and β- arylation of *N*-Boc piperazines via lithiation/Negishi coupling is reported.

Piperazines are privileged groups within small molecule drugs. Of the 1175 drugs approved by the FDA between 1983 and 2012, 51 drugs contain the motif, making piperazine the 4th most common ring in drugs[1] and the 3rd most common nitrogen heterocycle.[2] Nevertheless, piperazines substituted at carbon are rare within small molecule therapeutics, with Indinavir[3] (an antiretroviral) and Vestipitant (a NK-1 antagonist currently in clinical trials) being notable examples (Figure 1).[4]

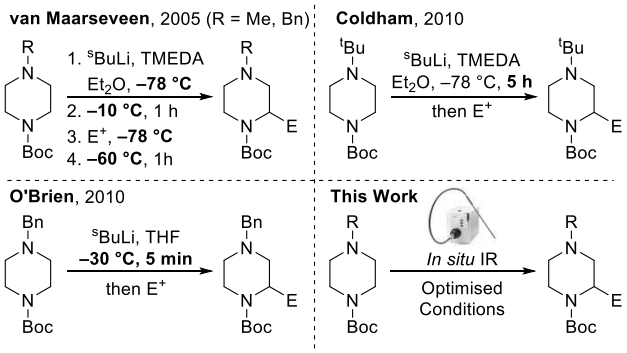
Figure 1. Structures of bio-active piperazines Indinavir and Vestipitant



Indinavir Vestipitant

The use of α-substituted piperazines in medicinal chemistry is somewhat limited by their poor commercial availability and the lack of simple methods for their synthesis. Available approaches include the formation of the piperazine ring, traditionally from amino acids (via ketopiperazines),[5] or more recently via Mitsunobu chemistry,[6] Pd-[7] or Au-catalysis,[8] photoredox catalysis,[9] or Bode's SnAP[10] and SLAP[11] reagents. The direct functionalization of the intact piperazine ring is an alternative strategy, allowing late stage introduction of the α-substituent. As an example, photoredox catalysis has been used for direct α-arylation and vinylation of *N*-aryl substituted piperazines but is limited to *N*-aryl substituents.[12] In 2016, we reported a route to a wide range of α-substituted piperazines *via* the enantioselective α-lithiation/trapping of *N*-Boc piperazines.[13,14] Although this previous study focused on the arguably more challenging asymmetric reaction, there remains a need to explore conditions for racemic lithiation/trapping for the following reasons. First, early-stage medicinal chemistry studies require rapid access to racemic products. Second, the racemic and asymmetric reactions do not always behave analogously. Third, the racemic lithiation/trapping of *N*-Boc piperazines is relatively under investigated and the few reports[15] have significant variation in the conditions used, involving very different reaction times and temperatures (Scheme 1). For example, van Maarseveen's conditions involved multiple warm/cool cycles.[15a] Subsequent reports by Coldham[15b] and ourselves[15c] employed either lengthy reaction times at −78 °C or short reaction times at elevated temperatures. Additional reports, focused on target synthesis, have used further modifications of these procedures.[15d-i]

Scheme 1. Direct Functionalization of *N*-Boc Piperazines via Lithiation/Trapping

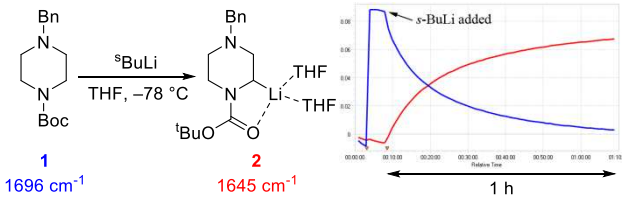


Due to the wide range of experimental conditions that have been reported to date and the need to have simple access to racemic products for medicinal chemistry studies, we set out to develop a general, unified and experimentally simple procedure for the direct functionalization of *N*-Boc piperazines via racemic lithiation/trapping (Scheme 1). Herein, we report our results and present two

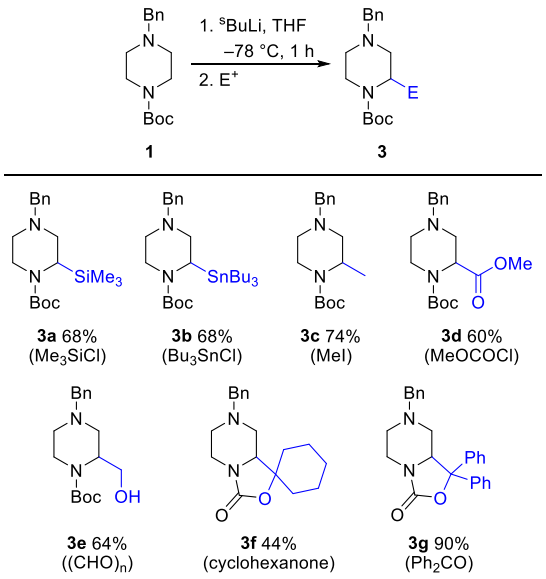
complementary, general procedures which were informed by *in situ* IR spectroscopic studies.

The simplest piperazine lithiation protocol involves the use of commercially available, orthogonally protected *N*-Boc-*N'*-benzyl piperazine **1** and diamine-free lithiation conditions, carried out at easily manageable (on a research scale) cryogenic conditions (–78 °C). Additionally, in our hands, we found that performing the reactions at –78 °C gave more reproducible yields than when using our previously published high-temperature (–30 °C) lithiation conditions.[15c] To assess the feasibility of such a system, we employed the use of *in situ* IR spectroscopy to identify the time taken for lithiation (by monitoring the change in $\nu_{C=O}$).[16] A solution of **1** in THF at –78 °C showed a $\nu_{C=O}$ peak at 1696 cm^{-1}. Upon addition of *s*-BuLi, lithiation of **1** proceeded to give lithiated intermediate **2** ($\nu_{C=O}$ peak at 1645 cm^{-1}) in 1 h (Scheme 2). In contrast to our previous *in situ* IR spectroscopic studies with *s*-BuLi/diamines in Et_2O, the pre-lithiation species was not detected.[16b]

Scheme 2. *In situ* IR Spectroscopic Monitoring of the *s*-BuLi/THF-mediated Lithiation of *N*-Boc Piperazine 1



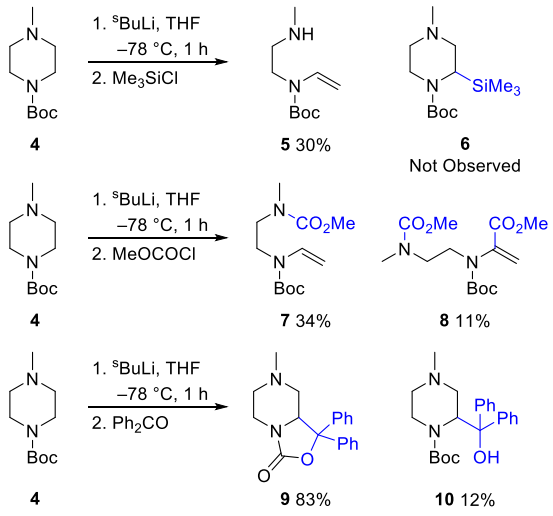
Scheme 3. Lithiation/Trapping of *N*-Boc-*N*-benzyl Piperazine 1



Having determined the time required for the diamine-free lithiation of **1**, the full lithiation/trapping process was investigated. Treatment of *N*-Boc-*N'*-benzyl piperazine **1** with 1.3 eq. of *s*-BuLi in THF at –78 °C for 1 h followed by addition of the electrophile gave α-substituted piperazines **3a-g** in 44–90% yields (Scheme 3). Good yields (60-74%) were obtained with Me_3SiCl, Bu_3SnCl, MeI, methyl chloroformate and paraformaldehyde. The use of cyclohexanone and benzophenone gave oxazolidinones **3f** and **3g** in 44% and 90% respectively, after cyclisation of the intermediate alkoxide on to the Boc group. The low yield of **3f** is probably due to the electrophile undergoing facile enolisation.

With an operationally simple lithiation/trapping procedure established, we chose to investigate the substrate scope and varied the expectedly innocuous distal *N*-substituent. Interestingly, our optimized diamine-free lithiation protocol gave varied results when applied to *N*-Boc-*N'*-methyl piperazine **4**. Lithiation under our standard conditions (*s*-BuLi, THF, –78 °C, 1 h) proceeded in the usual way, as shown by *in situ* IR monitoring (see Supporting Information) However, trapping with Me_3SiCl gave no α-silylated piperazine **6** (Scheme 4). The only product observed by ^1H NMR spectroscopy was the ring fragmented side-product **5**, which was isolated in 30% yield. As reported in our study into the asymmetric lithiation/trapping of *N*-Boc piperazines,[13] this side-product is formed by attack of the distal nitrogen on the electrophile, followed by ring fragmentation and N-Si bond cleavage upon work-up. Likewise, trapping with methyl chloroformate gave ring fragmented side-products **7** and **8** in 34% and 11% yields respectively. The latter formed from a subsequent Boc-directed vinylic lithiation (and trapping) event. In contrast, trapping with benzophenone gave α-substituted products **9** and **10** in 83% and 12% yields with no evidence of ring fragmented side-products. We suggest that ketones are less likely to interact with the distal nitrogen lone pair than Me_3SiCl and methyl chloroformate and so ring fragmentation did not occur.

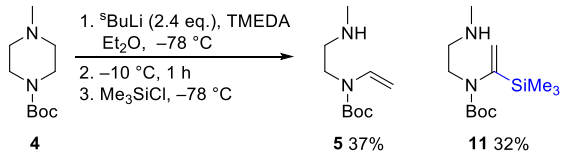
Scheme 4. Lithiation/Trapping of *N*-Boc-*N*-methyl Piperazine 4



Our unsuccessful trapping of lithiated *N*-Boc-*N'*-methyl piperazine **4** with Me_3SiCl was reminiscent of van Maarseveen *et al.*'s result. When lithiating **4** under different conditions they isolated only 5% of the desired α-silylated piperazine **6** when trapping with Me_3SiCl.[15a] To verify whether their low yield was in fact due to ring fragmentation, we repeated van Maarseveen's experiment. In our

hands, none of the desired product **6** was formed and the only fragmentation side-products **5** (isolated in 37% yield) and vinyl silane **11** (isolated in 32%) were observed (Scheme 5).

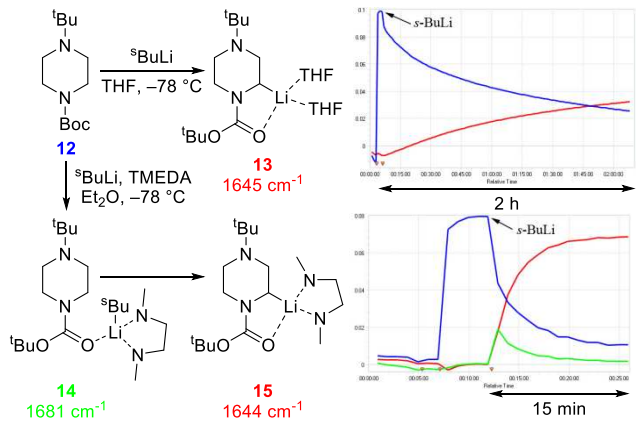
Scheme 5. Explanation of the Failure of the Lithiation/Trapping of 4 with Me_3SiCl



4 **5** 37% **11** 32%

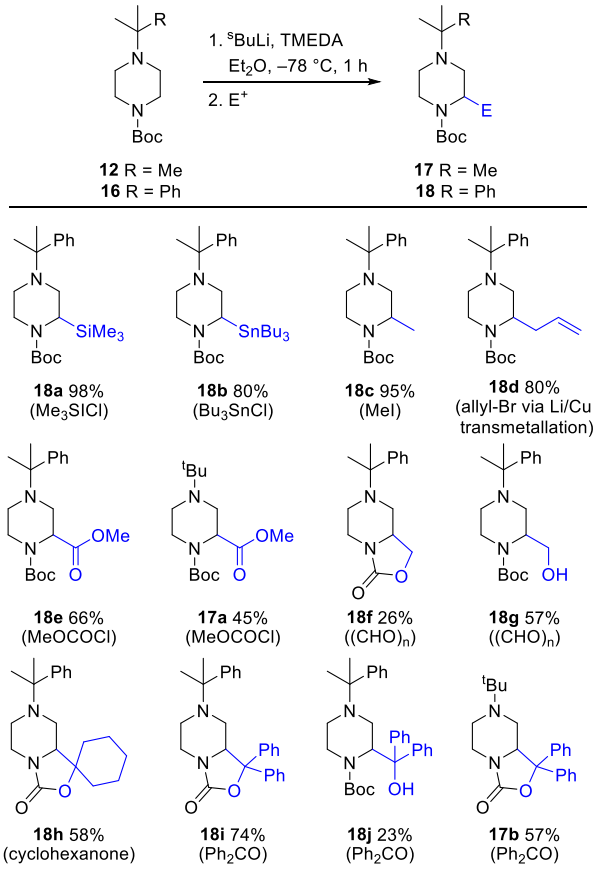
Thus, the use of a small distal *N*-substituent led to limitations with some electrophiles (Me_3SiCl and methyl chloroformate) due to ring fragmentation. In contrast increasing the size of the group led to a pronounced reduction in the *rate* of lithiation. Initial *in situ* IR studies with the previously reported[14,15b] *N*-Boc-*N*'-*tert*-butyl piperazine **12** showed that diamine-free lithiation was much slower than with *N*-Boc-*N*'-benzyl piperazine **1**.[13] Upon addition of *s*-BuLi to **12** in THF at –78 °C ($\nu_{C=O}$ 1694 cm^{-1}), lithiation proceeded to give lithiated intermediate **13** ($\nu_{C=O}$ 1645 cm^{-1}). However, after 2 h the reaction was incomplete (Scheme 6). Conversely, lithiation using *s*-BuLi/TMEDA in Et_2O at –78 °C was much faster: **12** ($\nu_{C=O}$ 1700 cm^{-1}) was converted in to lithiated intermediate **15** ($\nu_{C=O}$ 1644 cm^{-1}) *via* pre-lithiation complex **14** ($\nu_{C=O}$ 1681 cm^{-1})[17] within 15 min (Scheme 6).

Scheme 6. *In situ* IR Spectroscopic Monitoring of the Lithiation of *N*-Boc Piperazine 12



Due to the shorter lithiation time and associated operational ease, we opted to perform lithiation/trapping reactions of the sterically hindered *N*-Boc-*N*'-*tert*-butyl piperazine **12** and *N*-Boc-*N*'-cumyl piperazine **16** using *s*-BuLi/TMEDA in Et_2O at –78 °C for 1 h. Exposure of either **12** or **16** to these conditions followed by trapping led to α-substituted piperazines **17** and **18** in 45-98% yields (Scheme 7). Since we were unsuccessful in our attempts to cleave the *N*-*tert*-butyl group we focused mostly on cumyl protected piperazine **16** as it can be removed by hydrogenolysis.[13] Silylated, stannylated and methylated piperazines **18a**, **18b** and **18c** were isolated in 98%, 80% and 95% yield respectively. Transmetallation to copper followed by trapping with allyl bromide[15a,17] gave α-allyl piperazine **18d** in 80% yield. Lithiation/trapping of **16** and **12** with methyl chloroformate resulted in methyl esters **18e** and **17a** in 66% and 45% yields. Trapping **16** with paraformaldehyde gave a mixture of oxazolidinone **18f** and alcohol **18g** in 26% and 57% yield. Use of cyclohexanone gave solely oxazolidinone **18h** in 58% yield. Trapping of **16** with benzophenone gave **18i** and **18j** in a total yield of 97%, whereas trapping of **12** gave only oxazolidinone **17b** in 57% yield. Importantly, no ring fragmented side-products were observed in any case (due to the sterically demanding *N*-substituent), and the cumyl protecting group can be easily removed by hydrogenolysis.[13] Interestingly, for the same electrophile, the yields with *N*-Boc-*N*'-cumyl piperazine **16** (Scheme 7) were higher than when using *N*-Boc-*N*'-benzyl piperazine **1** (Scheme 3). It is possible that the larger protecting group prevents unwanted coordination of the distal nitrogen to the electrophiles.

Scheme 7. Lithiation/Trapping of *N*-Boc Piperazines 12 and 16



18a 98% (Me_3SiCl) **18b** 80% (Bu_3SnCl) **18c** 95% (MeI) **18d** 80% (allyl-Br via Li/Cu transmetallation)

18e 66% (MeOCOCl) **17a** 45% (MeOCOCl) **18f** 26% $((CHO)_n)$ **18g** 57% $((CHO)_n)$

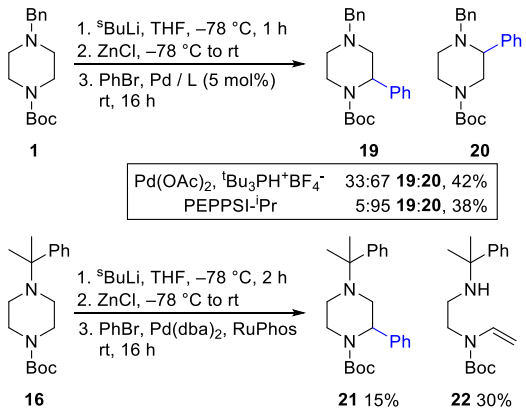
18h 58% (cyclohexanone) **18i** 74% (Ph_2CO) **18j** 23% (Ph_2CO) **17b** 57% (Ph_2CO)

One of the most useful extensions to the lithiation/trapping of *N*-Boc heterocycles for synthetic applications is the α-arylation methodology developed by Campos and co-workers.[18] This process proceeds via Li/Zn transmetallation and subsequent Negishi cross-coupling and has been well studied using *N*-Boc pyrrolidine[19] and piperidine.[16b,20] In 2010, our group reported the only example with an *N*-Boc piperazine.[15c] Therefore we decided to explore the arylation reaction using our diamine free

conditions, since TMEDA was known to hinder the Negishi coupling.

After lithiation, *N*-Boc-*N*'-benzyl piperazine **1** underwent Li/Zn transmetallation with $ZnCl_2$, prior to Negishi coupling with bromobenzene, catalysed by $Pd(OAc)_2$ and $tBu_3PH^+BF_4^-$. Surprisingly, a 33:67 mixture of inseparable regioisomers **19** and **20** was obtained in a combined 42% yield (Scheme 8). Formation of the unexpected regioisomer **20** presumably occurs through a β-hydride elimination/insertion sequence of the intermediate organopalladium species.[20c,21] This result corrects our previous incorrect report that only **19** was formed.[15c] A catalyst/ligand screen was performed in an attempt to selectively form either α- or β-arylated *N*-Boc piperazines (see Supporting Information for full details). Use of PEPPSI-*i*Pr[22] resulted in near complete selectivity for β-arylation with a 5:95 mixture of **19** and **20** being isolated in a moderate 38% yield (Scheme 8).

Scheme 8. Arylation of *N*-Boc piperazines 1 and 16



Submitting *N*-Boc-*N*'-cumyl piperazine **16** to arylation catalyzed by $Pd(dba)_2$ and RuPhos resulted in formation of only the α-arylated piperazine **21** in 15% yield, along with ring-fragmentation side-product **22** which was isolated in 30% yield (Scheme 8). Thus, selective synthesis of both the α- and β-arylated piperazines can be achieved through substrate control by varying the distal nitrogen protecting group and catalyst system. These initial preliminary results are encouraging and could warrant further investigation.

In conclusion, we have developed unifying, simple and general procedures for the racemic lithiation/trapping of *N*-Boc piperazines. *In situ* IR spectroscopic methods were used to determine the optimum conditions for lithiation of substrates with both sterically small (benzyl) and large (cumyl) substituents. The previous complicated and diverse literature procedures have been simplified, resulting an easy diamine-free lithiation/trapping of *N*-Boc-*N*-benzyl piperazine **1** and a slightly more complicated but higher yielding lithiation/trapping of *N*-Boc-*N*-cumyl piperazine **16**. These methods represent much needed simple and general approaches for the direct racemic functionalization of piperazines, and will find use in early-stage medicinal chemistry programmes. Additionally, the selective formation of both α- and β-arylated piperazines has been discovered.

Experimental Section

All-non aqueous reactions were carried out under oxygen free Ar or N_2 using flame-dried glassware. Et_2O and THF were freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use. TMEDA was distilled over CaH_2 before use. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C and was purchased in Winchester quantities. Water is distilled water.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Boiling points give for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer or a Perkin Elmer UATR Two FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. *In situ* ReactIR™ infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC10 spectrometer with a silicon-tipped (SiComp) probe.

Diamine Free Lithiation/Trapping of *N*-Boc-*N*'-Benzyl Piperazine 1. *s*-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N*'-Benzyl Piperazine **1** (1.0-3.0 mmol, 1.0 eq.) in THF (0.14 M) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then the electrophile (2.0 eq.) was added dropwise, as a solution in THF (1 mL) if necessary. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL), 20% $NaOH_{(aq)}$ (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which was purified by flash column chromatography on silica gel.

tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate (**3a**). *N*-Boc-*N*'-benzyl piperazine **1** (276 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and Me_3SiCl (254 µL, 2.0 mmol) gave, after purification (SiO_2, 9:1 petrol-EtOAc), substituted piperazine **3a** (236 mg, 68%) as a colourless oil; R_F (9:1 petrol-EtOAc) 0.4; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.32-7.30 (m, 4H), 7.27-7.22 (m, 1H) 4.20 (br s,

0.6H), 3.80 (br s, 0.4H), 3.61-3.55 (m, 1H), 3.44 (d, *J* = 13.0 Hz, 1H), 3.40 (d, *J* = 13.0 Hz, 1H), 3.05 (br s, 0.4H), 2.92 (br s, 0.6H), 2.80 (d, *J* = 12.0 Hz, 1H), 2.72 (m, 0.6H), 2.64 (br s, 0.4H), 2.24 (br s, 1H), 1.93 (td, *J* = 12.0, 3.0 Hz, 1H), 1.46 (s, 9H), 0.12 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7, 138.3, 129.1, 128.1, 127.0, 79.1, 63.4, 54.3, 53.2, 45.3, 41.4, 28.4, –0.8; IR ($CHCl_3$) 2977, 2804, 1673 (C=O), 1454, 1420, 1366, 1296, 1168, 1111, 1027, 840 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{33}N_2O_2Si$ $(M+H)^+$ 349.2306, found 349.2297 (+1.7 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

tert-Butyl 4-benzyl-2-(tributylstannyl)piperazine-1-carboxylate (**3b**). *N*-Boc-*N*'-benzyl piperazine **1** (276 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and Bu_3SnCl (542 µL, 2.0 mmol) gave, after purification (SiO_2, 19:1 petrol-EtOAc), substituted piperazine **3b** (387 mg, 68%) as a colourless oil; R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.38-7.21 (m, 5H), 4.13 (s, 0.5H), 4.03 (br d, *J* = 13.0 Hz, 0.5H), 3.80-3.16 (m, 4H), 2.82-2.37 (m, 3H), 2.21 (br s, 0.5H), 1.96-1.80 (m, 0.5H), 1.55-1.35 (m, 15H), 1.35-1.23 (m, 6H), 0.99-0.78 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.6, 154.2, 138.2, 129.4, 128.3, 127.2, 79.5, 79.4, 63.3, 58.1, 53.2, 53.0, 46.5, 45.5, 44.8, 42.6, 29.3, 29.3, 28.5, 27.9, 27.7, 13.8, 11.1, 10.4; IR ($CHCl_3$) 2961, 2911, 2881, 2827, 1647 (C=O), 1433, 1395, 1395, 1344, 1278, 1231, 1151, 1088, 1055, 1007, 850, 688 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{51}N_2O_2Sn$ $(M+H)^+$ 567.2972, found 567.2945 (+3.9 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

tert-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (**3c**). *N*-Boc-*N*'-benzyl piperazine **1** (829 mg, 3.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 3.0 mL, 3.9 mmol) and MeI (374 µL, 6.0 mmol) gave, after purification (SiO_2, 9:1 petrol-EtOAc), substituted piperazine **3c** (645 mg, 74%) as a colourless oil; R_F (7:3 petrol-EtOAc) 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.26-7.22 (m, 1H), 4.18 (br s, 1H), 3.80 (br d, *J* = 12.5 Hz, 1H), 3.53 (d, *J* = 13.0 Hz, 1H), 3.40 (d, *J* = 13.0 Hz, 1H), 3.11 (td, *J* = 12.5, 3.5 Hz, 1H), 2.77-2.73 (m, 1H), 2.59 (dt, *J* = 11.0, 1.5 Hz, 1H), 2.12 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.00 (ddd, *J* = 12.5, 11.5, 3.5 Hz, 1H), 1.45 (s, 9H), 1.24 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.8, 138.4, 128.7, 128.2, 127.0, 79.3, 62.8, 57.3, 53.2, 47.0, 39.1, 28.4, 15.9; IR (ATR) 2973, 1688 (C=O), 1452, 1407, 1392, 1364, 1341, 1322, 1305, 1279, 1247, 1223, 1158, 1107, 1059, 1039, 1028, 740, 700 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{27}N_2O_2$ $(M+H)^+$ 291.2067, found 291.2072 (–1.0 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

1-*tert*-Butyl 2-methyl 4-benzylpiperazine-1,2-dicarboxylate (**3d**). *N*-Boc-*N*'-benzyl piperazine **1** (276 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and MeOCOCl (155 µL, 2.0 mmol) gave, after purification (SiO_2, 9:1 to 7:3 petrol-EtOAc), substituted piperazine **3d** (200 mg, 60%) as a colourless oil; R_F (7:3 petrol-EtOAc) 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.32-7.24 (m, 5H), 4.71 (br s, 0.55H), 4.54 (br s, 0.45H), 3.85 (br d, *J* = 13.0 Hz, 0.55H), 3.77-3.75 (m, 0.45H), 3.73 (s, 1.35H), 3.71 (s, 1.65H), 3.58 (d, *J* = 13.0 Hz, 0.45H), 3.58 (d, *J* = 13.0 Hz, 0.55H), 3.45 (d, *J* = 13.0 Hz, 0.55H), 3.41 (d, *J* = 13.0 Hz, 0.45H), 3.34-3.27 (m, 1.55H), 3.18 (td, *J* = 13.0, 3.0 Hz, 0.45H), 2.79 (br d, *J* = 11.0 Hz, 0.45H), 2.74 (d, *J* = 11.0 Hz, 0.55H), 2.18 (td, *J* = 11.0, 4.0 Hz, 1H), 2.11 (br d, *J* = 11.0 Hz, 0.55H), 2.11 (br d, *J* = 11.0 Hz, 0.45H), 1.47 (s, 4.9H), 1.42 (s, 4.1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.3, 171.1, 155.8, 155.3, 137.6, 128.7, 128.1, 127.2, 80.2, 62.3, 55.5, 54.3, 53.5, 52.4, 52.3, 51.9, 42.0, 41.0, 28.3; IR ($CHCl_3$) 2979, 1744 (C=O, CO_2Me), 1691 (C=O, Boc), 1408, 1366, 1301, 1169, 1119, 1046, 976, 867 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{27}N_2O_4$ $(M+H)^+$ 335.1965, found 335.1974 (–2.7 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

tert-Butyl 4-benzyl-2-(hydroxymethyl)piperazine-1-carboxylate (**3e**). *N*-Boc-*N*'-benzyl piperazine **1** (276 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and paraformaldehyde (60 mg, 2.0 mmol) gave, after purification (SiO_2, 7:3 to 1:1 petrol-EtOAc), substituted piperazine **3e** (197 mg, 64%) as a colourless oil; R_F (1:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 4.07 (br s, 1H), 3.96-3.81 (m, 3H), 3.51 (d, *J* = 13.0 Hz, 1H), 3.47 (d, *J* = 13.0 Hz, 1H), 3.40 (br s, 1H), 2.98 (dt, *J* = 11.5, 2.0 Hz, 1H), 2.83 (br d, *J* = 10.0 Hz, 1H), 2.31 (ddd, *J* = 11.5, 4.0, 1.0 Hz, 1H), 2.09 (ddd, *J* = 12.5, 11.5, 4.0 Hz, 1H), 1.45 (s, 3H), OH not resolved; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1, 137.0, 129.0, 128.5, 127.5, 80.0, 66.7, 63.0, 55.1, 52.5, 51.1, 41.4, 28.4; IR ($CHCl_3$) 3280 (OH), 2971, 2913, 2781 1658 (C=O), 1433, 1390, 1345, 1302, 1197, 1152, 1103, 1060, 1035, 997, 743 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{27}N_2O_3$ $(M+H)^+$ 307.2016, found 307.2023 (–2.2 ppm error). Spectroscopic data consistent with those reported in the literature.[23]

7-Benzyl-hexahydrospiro[[1,3]oxazolo[3,4-a]piperazine-1,1'-cyclohexane]-3-one (**3f**). *N*-Boc-*N*'-benzyl piperazine **1** (276 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and cyclohexanone (207 µL, 2.0 mmol) gave, after purification (SiO_2, 1:1 petrol-EtOAc), oxazolidinone **3f** (131 mg, 44%) as a white solid; R_F (1:1 petrol-EtOAc) 0.1; mp 64-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 3.76 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.61-3.49 (m, 2H), 3.39 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.05 (td, *J* = 12.5, 3.5 Hz, 1H), 2.77-2.73 (m, 2H), 2.05-1.97 (m, 2H), 1.89-1.20 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.4, 137.3, 128.8, 128.3, 127.3, 80.7, 63.0, 61.7, 52.8, 51.7, 41.0, 36.7, 30.7, 28.3, 25.0, 21.9; IR ($CHCl_3$) 2896, 1710 (C=O), 1428, 1331, 1286, 1074, 1025, 961, 890, 745 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{25}N_2O_2$ $(M+H)^+$ 301.1905, found 301.1911 (+1.6 ppm error).

7-Benzyl-1,1-diphenyl-hexahydro-1H-[1,3]oxazolo[3,4-a]piperazin-3-one (**3g**). *N*-Boc-*N*'-benzyl piperazine **1** (415 mg, 1.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.5 mL, 1.95 mmol) and benzophenone (547 mg, 3.0 mmol) in THF (1 mL) gave, after purification (SiO_2, 4:1 to 7:3 petrol-EtOAc), substituted piperazine **3g** (520 mg, 90%) as a white solid, R_F (7:3 petrol-EtOAc) 0.2; mp 146-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.40-7.21 (m, 13H), 4.54 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.80 (ddd, *J* = 13.0, 3.5, 1.5 Hz, 1H), 3.50 (d, *J* = 13.0 Hz, 1H), 3.31 (d, *J* = 13.0 Hz,

1H), 3.09 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H), 2.70-2.66 (m, 1H), 2.55 (ddd, *J* = 11.0, 3.5, 1.5 Hz, 1H), 1.93 (td, *J* = 12.0, 3.5 Hz, 1H), 1.57 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.5, 142.7, 139.1, 137.6, 129.1, 128.8, 128.7, 128.6, 128.5, 128.1, 127.6, 126.2, 126.0, 85.3, 62.9, 61.1, 55.7, 50.7, 41.5; IR ($CHCl_3$) 3020, 2400, 1751 (C=O), 1422, 1215, 929, 759, 669 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_2$ $(M+H)^+$ 385.1911, found 385.1899 (+3.6 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

tert-Butyl 4-methylpiperazine-1-carboxylate (**4**). A solution of di-*tert*-butyl dicarbonate (21.6 g, 99.2 mmol, 1.1 eq.) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of *N*-methyl piperazine (10 mL, 90.2 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred for at rt for 16 h. Water (100 mL) and 20% $NaOH_{(aq)}$ (100 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave *N*-Boc-*N*′-methyl piperazine **4** (16.5 g, 92%) as a colourless oil, R_F (9:1 CH_2Cl_2-MeOH) 0.2; bp 105-110 °C / 0.9 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (t, *J* = 5.0 Hz, 4H), 2.29 (t, *J* = 5.0 Hz, 4H), 2.24 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6, 79.5, 54.7, 46.1, 43.5, 28.3. Spectroscopic data consistent with those reported in the literature.[24]

tert-Butyl *N*-ethenyl-*N*-[2-(methylamino)ethyl]carbamate (**5**). *N*-Boc-*N*′-methyl piperazine **4** (200 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and Me_3SiCl (254 µL, 2.0 mmol) gave, after purification (SiO_2, 9:1 CH_2Cl_2-MeOH), vinyl carbamate **5** (60 mg, 30%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (br s, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 4.21 (br s, 1H), 3.65 (br s, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.47 (s, 3H), 2.11 (br s, 1H), 1.49 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.9, 132.9, 90.8, 81.3, 48.2, 41.9, 36.0, 28.2; IR ($CHCl_3$) 3513 (NH), 2978, 1698 (C=O), 1629, 1456, 1368, 1152, 862, 759 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{21}N_2O_2$ $(M+H)^+$ 201.1598, found 201.1595 (+2.0 ppm error).

tert-Butyl *N*-ethenyl-*N*-{2-[(methoxycarbonyl)(methyl)amino]ethyl}carbamate (**7**) and methyl 2-{[(*tert*-butoxy)carbonyl]({2-[(methoxycarbonyl)(methyl)amino]ethyl})amino}prop-2-enoate (**8**). *N*-Boc-*N*′-methyl piperazine **4** (200 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and MeOCOCl (155 µL, 2.0 mmol) gave, after purification (SiO_2, 9:1 CH_2Cl_2-MeOH), vinyl carbamate **7** (88 mg, 34%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.11 (dd, *J* =15.0, 10.0 Hz, 0.5H), 6.95 (dd, *J* = 15.0, 10.0 Hz, 0.5H), 4.48 (m, 0.5H), 4.46-4.18 (m, 1.5H), 3.69 (s, 3H), 3.69-3.57 (m, 2H), 3.39-3.35 (m, 2H), 2.93 (s, 1.5H), 2.91 (s, 1.5H), 1.50 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 156.6, 152.9, 152.5, 132.9, 132.6, 91.1, 90.6, 81.4, 81.2, 52.6, 52.5, 45.9, 45.6, 41.2, 40.4, 35.5, 28.1; IR ($CHCl_3$) 2983, 1697 (C=O), 1630 (C=O), 1486, 1423, 1393, 1368, 1233, 1216, 1155, 575 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{22}N_2NaO_4$ $(M+Na)^+$ 281.1476, found 281.1472 (–1.0 ppm error); and vinyl carbamate **8** (35 mg, 11%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.92 (br s, 1H), 5.56 (br s, 0.5H), 5.40 (br s, 0.5H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.67 (s, 3H), 3.62-3.55 (m, 2H), 3.48-3.45 (m, 2H), 3.95 (s, 1.5H), 3.94 (s, 1.5H), 1.41 (br s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 166.2, 157.0, 156.7, 153.7, 153.6, 140.5, 140.0, 117.7, 81.4, 81.2, 52.6, 52.5, 52.3, 52.2, 47.9, 47.1, 35.2, 34.8, 28.0; IR ($CHCl_3$) 3023, 1734 (C=O, CO_2Me), 1699 (C=O, Boc), 1486, 1439, 1395, 1369, 1236, 1161, 765; HRMS (ESI) *m/z* calcd for $C_{14}H_{24}N_2NaO_6$ $(M+Na)^+$ 339.1527, found 339.1526 (+0.2 ppm error).

7-Methyl-1,1-diphenyl-hexahydro-1H-[1,3]oxazolo[3,4-a]pyrazin-3-one (**9**) and *tert*-butyl 2-(hydroxydiphenylmethyl)-4-methylpiperazine-1-carboxylate (**10**). *N*-Boc-*N*′-methyl piperazine **4** (200 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) and benzophenone (364 mg, 2.0 mmol) in THF (1 mL) gave, after purification (SiO_2, 98:2 to 95:5 CH_2Cl_2-MeOH), oxazolidinone **9** (263 mg, 83%) as a white solid, R_F (19:1 CH_2Cl_2-MeOH) 0.4; mp 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.37-7.23 (m, 8H), 4.50 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.83 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H), 3.12 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H), 2.68-2.64 (m, 1H), 2.43 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H), 2.18 (s, 3H), 1.93 (td, *J* = 12.0, 3.5 Hz, 1H), 1.43 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8, 142.2, 138.6, 128.5, 128.3, 128.2, 127.8, 125.8, 125.6, 85.1, 60.9, 56.9, 53.2, 46.3, 41.5; IR ($CHCl_3$) 2948, 2804, 1751 (C=O), 1450, 1409, 1360, 1301, 1255, 1138, 1032, 988, 757 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_2O_2$ $(M+H)^+$ 309.1598, found 309.1599 (+0.1 ppm error) and alcohol **10** (45 mg, 12%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.70-7.07 (m, 10H), 5.23 (br d, *J* = 4.0 Hz, 0.5H), 4.90 (br d, *J* = 4.0 Hz, 0.5H), 4.17-4.11 (m, 0.5H), 3.86-3.72 (m, 1.5H), 2.97-2.92 (m, 1H), 2.87-2.84 (m, 0.5H), 2.78-2.76 (m, 0.5H), 2.28 (dd, *J* = 12.0, 4.0 Hz, 0.5H), 2.24 (dd, *J* = 12.0, 4.0 Hz, 0.5H), 2.17 (s, 1.5H), 2.14 (s, 1.5H), 2.10-1.98 (m, 1H), 1.25 (s, 4.5H), 1.21 (s, 4.5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.6, 154.2, 147.7, 147.2, 145.0, 144.7, 128.3, 128.1, 127.5, 127.3, 126.7, 126.6, 126.5 126.3, 126.1, 126.0, 83.5, 83.4, 79.8, 79.7, 56.6, 55.8, 55.2, 54.4, 54.3, 53.5, 45.8, 45.7, 41.4, 40.3, 28.2, 28.0; IR ($CHCl_3$) 3680 (OH), 3019, 2980, 2855, 2807, 1681 (C=O), 1461, 1417, 1367, 1350, 1304, 1287, 1215, 1169, 1146, 1027, 765 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_3$ $(M+H)^+$ 383.2329, found 383.2317 (+3.6 ppm error).

tert-Butyl *N*-ethenyl-*N*-[2-(methylamino)ethyl]carbamate (**5**) and *tert*-butyl *N*-[2-(methylamino)ethyl]-*N*-[1-(trimethylsilyl)ethenyl]carbamate (**11**). *s*-BuLi (1.85 mL of a 1.3 M solution in hexanes, 2.4 mmol) was added dropwise to a stirred solution of *N*-Boc-*N*′-methyl piperazine **4** (200 mg, 1.0 mmol) and TMEDA (360 µL, 2.4 mmol) in Et_2O (7 mL) at –78 °C under Ar. The resulting solution was warmed to –10 °C and stirred for 1 h. The solution was cooled to –78 °C then Me_3SiCl (305 µL, 2.4 mmol) was added dropwise. The reaction mixture was warmed to –60

°C, stirred for 1 h then allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and 20% $NaOH_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography (SiO_2, 9:1 CH_2Cl_2-MeOH) gave vinyl carbamate **5** (75 mg, 37%) as a pale yellow oil and silane **11** (86 mg, 32%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (br s, 1H), 5.13 (br s, 1H), 3.59 (t, *J* = 7.0 Hz, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.53 (br s, 1H), 2.49 (s, 3H), 1.47 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.4, 153.3, 112.7 (br), 80.6, 49.5, 46.7, 35.6, 28.5, 0.5; IR ($CHCl_3$) 2972, 1656 (C=O), 1432, 1372, 1346, 1228, 1197, 1136, 831, 742 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{29}N_2O_2Si$ $(M+H)^+$ 273.1993, found 273.2000 (–1.9 ppm error).

TMEDA mediated lithiation/trapping of *N*-Boc-*N*'-*tert*-butyl piperazine 12 and *N*-Boc-*N*'-cumyl piperazine 16. *s*-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (0.5-1.0 mmol, 1.0 eq.) and TMEDA (1.3 eq.) in Et_2O (0.14 M) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then the electrophile (2.0 eq.) was added dropwise, as a solution in THF (1 mL) if necessary. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL), 20% $NaOH_{(aq)}$ (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which was purified by flash column chromatography on silica gel.

tert-Butyl 4-(2-phenylpropan-2-yl)-2-(trimethylsilyl)piperazine-1-carboxylate (**18a**). *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol), TMEDA (97 µL, 0.65 mmol) and Me_3SiCl (127 µL, 1.0 mmol) gave, after purification (SiO_2, 9:1 petrol-Et_2O), substituted piperazine **18a** (184 mg, 98%) as a colourless oil; R_F (9:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.52-7.47 (m, 2H), 7.34-7.28 (m, 2H), 7.24-7.18 (m, 1H), 3.95 (br s, 0.6H), 3.72 (br s, 0.4H), 3.63-3.56 (br m, 1H), 2.95 (dt, *J* = 11.5, 2.0 Hz, 1H), 2.93 (br s, 0.4H), 2.84 (br s, 0.6H), 2.45 (br s, 2H), 2.03 (td, *J* = 11.5, 3.0 Hz, 1H), 1.43 (s, 9H), 1.35 (s, 6H), 0.13 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.5, 154.4, 148.4, 127.9, 126.3, 126.3, 79.1, 59.9, 47.1, 46.9, 46.5, 45.7, 44.7, 43.7, 42.0, 28.4, 26.7, 20.4, –0.6; IR ($CHCl_3$) 2965, 2931, 1645 (C=O), 1428, 1399, 1344, 1277, 1261, 1228, 1197, 1154, 1094, 916, 825, 749, 691 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{37}N_2O_2Si$ $(M+H)^+$ 377.2619, found 377.2601 (+4.3 ppm error).

tert-Butyl 4-(2-phenylpropan-2-yl)-2-(tributylstannyl)piperazine-1-carboxylate (**18b**). *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol), TMEDA (97 µL, 0.65 mmol) and Bu_3SnCl (271 µL, 1.0 mmol) gave, after purification (SiO_2, 19:1 petrol-Et_2O), substituted piperazine **18b** (260 mg, 81%) as a colourless oil; R_F (19:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.23-7.16 (m, 1H), 4.21-4.12 (m, 0.5H), 3.97 (br d, *J* = 12.0 Hz, 0.5H), 3.60-3.25 (m, 1.5H), 2.86-2.52 (m, 2.5H), 2.31 (br s, 1H), 2.06-1.84 (m, 1H), 1.55-1.37 (m, 15H), 1.33-1.22 (m, 12H), 0.95-0.83 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.6, 153.9, 148.3, 148.2, 128.0, 126.3, 79.3, 79.0, 60.0, 50.2, 46.9, 45.9, 45.6, 43.0, 29.2, 28.4, 27.9, 27.8, 27.6, 27.3, 26.8, 25.7, 22.1, 20.7, 13.7, 11.1, 10.4; IR ($CHCl_3$) 2971, 2913, 2881, 2827, 1645 (C=O), 1432, 1397, 1344, 1280, 1197, 1152, 1090, 1002, 947, 908, 849, 743, 691, 658 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{55}N_2O_2Sn$ $(M+H)^+$ 595.3285, found 595.3261 (+3.6 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

tert-Butyl 2-methyl-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate (**18c**). *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol), TMEDA (97 µL, 0.65 mmol) and MeI (62 µL, 1.0 mmol) gave, after purification (SiO_2, 8:2 petrol-Et_2O), substituted piperazine **18c** (152 mg, 95%) as a colourless oil; R_F (8:2 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.33-7.27 (m, 2H), 7.23-7.18 (m, 1H), 4.12 (br s, 1H), 3.75 (br d, *J* = 13.0 Hz, 1H), 3.04 (td, *J* = 12.5, 3.5 Hz, 1H), 2.76-2.67 (m, 1H), 2.52 (dt, *J* = 11.0, 2.0 Hz, 1H), 2.31 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.14 (td, *J* = 12.5, 3.5 Hz, 1H), 1.44 (s, 9H), 1.33 (s, 3H), 1.30 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.9, 149.2, 128.0, 126.3, 126.2, 79.3, 59.4, 50.8, 47.6, 46.5, 39.9, 28.5, 24.3, 23.6, 15.8; IR ($CHCl_3$) 2931, 1652 (C=O), 1427, 1393, 1345, 1300, 1263, 1214, 1152, 1093, 1005, 691 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}N_2O_2$ $(M+H)^+$ 319.2380, found 319.2369 (+3.5 ppm error).

tert-Butyl 4-(2-phenylpropan-2-yl)-2-(prop-2-en-1-yl)piperazine-1-carboxylate (**18d**). *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol) was added dropwise to a stirred solution of *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol) and (97 µL, 0.65 mmol) in Et_2O (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of CuCN.2LiCl (0.25 mmol, 0.5 eq.) in THF (0.5 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. Then, allyl bromide (87 µL, 1.0 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NaHCO_{3(aq)}$ was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (SiO_2, 8:2 petrol-Et_2O) gave substituted piperazine **18d** (138 mg, 80%) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.48 (m, 2H), 7.34-7.28 (m, 2H), 7.24-7.18 (m, 1H), 5.73-5.63 (m, 1H), 5.09-5.02 (m, 1H), 4.99-4.94 (m, 1H), 4.01 (br s, 1H), 3.80 (br s, 1H), 2.98 (t, *J* = 11.5 Hz, 1H), 2.67 (br s, 2H), 2.57- 2.37 (m, 2H), 2.26 (dd, *J* = 11.5, 3.5 Hz, 1H), 2.21-2.08 (m, 1H), 1.43 (s, 9H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.8, 148.9, 125.7, 128.0,

126.3, 126.0, 116.8, 79.3, 59.4, 52.0 (br), 48.0, 46.4, 39.6 (br), 34.5, 28.4, 24.5, 23.2; IR ($CHCl_3$) 2972, 2930, 2776, 1658 (C=O), 1397, 1344, 1305, 1197, 1153, 1092, 972, 950, 907, 761, 732, 691, 658 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}N_2O_2$ $(M+H)^+$ 345.2537, found 345.2526 (+3.1 ppm error).

1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (**18e**). *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol), TMEDA (97 µL, 0.65 mmol) and MeOCOCl (77 µL, 1.0 mmol) gave, after purification (SiO_2, 97:3-8:2 CH_2Cl_2-Et_2O), substituted piperazine **18e** (119 mg, 66%) as a pale yellow oil; R_F (19:1 CH_2Cl_2-Et_2O) 0.2; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.42–7.37 (m, 2H), 7.31–7.25 (m, 2H), 7.23–7.17 (m, 1H), 4.66 (br s, 0.55H), 4.50 (br s, 0.45H), 3.80 (d, *J* = 11.0 Hz, 0.55H), 3.72 (s, 1.35H), 3.70 (s, 1.65H), 3.72-3.69 (m, 0.45H), 3.35–3.19 (m, 1.55H), 3.13 (td, *J* = 12.0, 3.0 Hz, 0.45H), 2.74 (d, *J* = 10.5 Hz, 0.45H), 2.67 (d, *J* = 10.5 Hz, 0.55H), 2.37 (dd, *J* = 11.5, 3.5 Hz, 1HH), 2.18 (td, *J* = 11.5, 3.5 Hz, 1H), 1.46 (s, 5H), 1.41 (s, 4H), 1.31 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 171.6, 171.4, 156.0, 155.4, 148.4, 148.3, 127.9, 126.3, 125.9, 80.1, 59.2, 56.0, 54.9, 51.8, 47.8, 45.7, 42.7, 41.7, 28.3, 28.2, 24.0, 23.9, 23.7; IR ($CHCl_3$) 2972, 2933, 1718 (C=O, CO_2Me), 1662 (C=O, Boc), 1469, 1452, 1391, 1369, 1346, 1331, 1310, 1284, 1195, 1155, 1101, 1016, 951, 736, 692 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{31}N_2O_4$ $(M+H)^+$ 363.2278, found 363.2277 (0.0 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

1-*tert*-Butyl 2-methyl 4-tert-butylpiperazine-1,2-dicarboxylate (**17a**). *N*-Boc-*N*'-*tert*-butyl piperazine **12** (242 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol), TMEDA (195 µL, 1.3 mmol) and MeOCOCl (155 µL, 2.0 mmol) gave, after purification (SiO_2, 7:3 petrol-EtOAc), substituted piperazine **17a** (135 mg, 45%) as a pale yellow oil; R_F (7:3 petrol-EtOAc) 0.4; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) *δ* 4.70 (br s, 0.5H), 4.53 (br s, 0.5H), 3.83 (br d, *J* = 12.5 Hz, 0.5H), 3.75-3.73 (m, 0.5H), 3.73 (s, 1.5H), 3.72 (s, 1.5H), 3.52-3.45 (m, 1H), 3.13 (td, *J* = 12.5, 3.5 Hz, 0.5H), 3.03 (td, *J* = 12.5, 3.5 Hz, 0.5H), 2.92 (br d, *J* = 11.0 Hz, 0.5H), 2.84 (br d, *J* = 11.0 Hz, 0.5H), 2.28-2.23 (m, 1H), 2.11 (td, *J* = 11.0, 3.5 Hz, 1H), 1.46 (s, 4.5H), 1.42 (s, 4.5H), 0.96 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 171.6, 171.3, 155.8, 155.4, 80.0, 56.3, 55.0, 53.3, 51.9, 47.6, 45.2, 42.9, 42.0, 28.3, 25.8; IR ($CHCl_3$) 2976, 1745 (C=O, CO_2Me), 1689 (C=O, Boc), 1455, 1393, 1367, 1304, 1253, 1170, 1119, 1041, 965, 865, 761 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}N_2O_4$ $(M+H)^+$ 301.2122, found 301.2122 (0.0 ppm error). Spectroscopic data consistent with those reported in the literature.[13]

7-(2-Phenylpropan-2-yl)-hexahydro-1H-[1,3]oxazolo[3,4-a]pyrazin-3-one (**18f**) and *tert*-butyl 2-(hydroxymethyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate (**18g**). *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol), TMEDA (97 µL, 0.65 mmol) and paraformaldehyde (30 mg, 1.0 mmol) in Et_2O (1 mL) gave, after purification (SiO_2, 7:3-1:1 petrol-EtOAc), oxazolidinone **18f** (34 mg, 26%) as a pale yellow oil, R_F (7:3 petrol-EtOAc) 0.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.47 (m, 2H), 7.35-7.29 (m, 2H), 7.26-7.20 (m, 1H), 4.32 (t, *J* = 8.0 Hz, 1H), 3.88-3.72 (m, 3H), 3.05 (td, *J* = 12.0, 3.5 Hz, 1H), 2.85-2.74 (m, 2H), 2.21 (td, *J* = 12.0, 3.5 Hz, 1H), 2.04 (t, *J* = 11.0 Hz, 1H), 1.34 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 157.0, 148.3, 128.2, 126.5, 125.9, 65.5, 60.2, 54.0, 51.3, 45.4, 42.0, 25.2, 23.1; IR ($CHCl_3$) 2973, 1720 (C=O), 1496, 1545, 1404, 1194, 1045, 914, 771, 725, 659, 617 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{21}N_2O_2$ $(M+H)^+$ 261.1598, found 261.1587 (+3.9 ppm error) and substituted piperazine **18g** (96 mg, 57%) as a pale yellow oil, R_F (7:3 petrol-EtOAc) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25-7.20 (m, 1H), 4.19-3.57 (m, 5H), 3.26 (br s, 1H), 2.94 (d, *J* = 11.0 Hz, 1H), 2.72 (br s, 1H), 2.41 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.19 (td, *J* = 11.5, 3.0 Hz, 1H), 1.44 (s, 9H), 1.38 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 155.0, 147.4, 128.3, 126.7, 125.9, 79.8, 65.4, 59.9, 52.0, 48.1, 46.2, 42.1, 28.5, 24.2, 22.7; IR ($CHCl_3$) 2972, 2933, 1655 (C=O), 1392, 1370, 1345, 1290, 1196, 1152, 1100, 995, 895, 767, 747, 728, 692, 658 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}N_2O_3$ $(M+H)^+$ 335.2329, found 335.2325 (+1.2 ppm error).

7-(2-Phenylpropan-2-yl)-hexahydrospiro[[1,3]oxazolo[3,4-a]pyrazine-1,1'-cyclohexane]-3-one (**18h**). *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol), TMEDA (97 µL, 0.65 mmol) and cyclohexanone (104 mg, 1.0 mmol) gave, after purification (SiO_2, 9:1-7:3 petrol-EtOAc), oxazolidinone **18h** (95 mg, 58%) as a pale yellow oil, R_F (8:2 petrol-EtOAc) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 3.73 (dd, *J* = 13.0, 2.0 Hz, 1H), 3.31 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.97 (td, *J* = 12.0, 3.5 Hz, 1H), 2.76-2.67 (m, 2H), 2.19-2.06 (m, 2H), 1.91-1.40 (m, 10H), 1.33 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.5, 148.5, 128.2, 126.4, 125.8, 80.8, 62.7, 60.3, 46.7, 45.4, 41.9, 36.8, 30.7, 25.0, 24.4, 24.1, 22.0, 21.9; IR ($CHCl_3$) 2972, 2930, 2895, 1708 (C=O), 1497, 1425, 1404, 1342, 1263, 1199, 1162, 913, 771, 726, 691, 658 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{29}N_2O_2$ $(M+H)^+$ 329.2224, found 329.2207 (+4.6 ppm error).

1,1-Diphenyl-7-(2-phenylpropan-2-yl)-hexahydro-1H-[1,3]oxazolo[3,4-a]pyrazin-3-one (**18i**) and *tert*-butyl 2-(hydroxydiphenylmethyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate (**18j**). *N*-Boc-*N*'-cumyl piperazine **16** (152 mg, 0.5 mmol), *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol), TMEDA (97 µL, 0.65 mmol) and benzophenone (182 mg, 1.0 mmol) gave, after purification (SiO_2, 9:1-8:2 petrol-EtOAc), oxazolidinone **18i** (152 mg, 74%) as a white solid, R_F (7:3 petrol-EtOAc) 0.1; mp 122-124 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.43 (m, 4H), 7.39–7.19 (m, 11H), 4.42 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.83–3.72 (m, 1H), 3.04 (td, *J* = 12.0, 4.0 Hz, 1H), 2.69–2.63 (m, 1H), 2.56 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H), 2.09 (td, *J* = 11.5, 3.5 Hz, 1H), 1.55 (t, *J* = 11.0 Hz, 1H), 1.24 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.2, 148.3, 142.5, 138.9, 128.5, 128.3, 128.2, 128.1, 127.8, 126.5, 125.9, 125.8, 125.7, 88.3, 62.4, 60.2, 49.3, 45.3, 42.5, 25.0, 23.3; IR ($CHCl_3$) 2963, 2931, 1723 (C=O), 1470, 1426, 1390, 1342, 1282, 1241, 1159, 1100, 1059, 1016, 971, 895, 690 cm^{-1}; HRMS (ESI) *m/z* calcd for

$C_{27}H_{29}N_2O_2$ $(M+H)^+$ 413.2224, found 413.2216 (+2.6 ppm error) and substituted piperazine **18j**, (55 mg, 23%) as a white solid, R_F (7:3 petrol-EtOAc) 0.2; mp 54-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 8.25 (s, 0.5H), 8.10 (s, 0.5H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.42-7.07 (m, 10H), 5.16 (d, *J* = 3.0 Hz, 0.5H), 4.84 (d, *J* = 3.0 Hz, 0.5H), 4.09 (dd, *J* = 13.5, 3.0 Hz, 0.5H), 3.82-3.62 (m, 1.5H), 3.27-3.16 (m, 1H), 2.69 (d, *J* = 11.0 Hz, 0.5H), 2.61 (d, *J* = 11.0 Hz, 0.5H), 2.46 (dd, *J* = 11.5, 4.0 Hz, 0.5H), 2.41 (dd, *J* = 11.5, 4.0 Hz, 0.5H), 2.25-2.09 (m, 1H), 1.32 (s, 1.5H), 1.29 (s, 1.5H), 1.24 (s, 1.5H), 1.22 (s, 4.5H), 1.16 (s, 1.5H), 1.15 (s, 4.5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.5, 154.2, 147.1, 146.5, 145.7, 145.5, 145.0, 144.7, 128.4, 128.1, 128.0, 127.6, 127.5, 127.3, 126.9, 126.9, 126.8, 126.7, 126.5, 126.4, 126.4, 126.2, 126.2, 126.0, 126.0, 83.9, 83.8, 79.6, 60.3, 60.3, 55.6, 54.0, 48.5, 47.5, 46.8, 46.7, 42.2, 41.2, 28.1, 27.9, 26.4, 26.3, 19.7, 19.6; IR ($CHCl_3$) 2961, 2934, 1655 (C=O), 1427, 1395, 1345, 1326, 1284, 1232, 1151, 1096, 1001, 957, 690, 628 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{39}N_2O_3$ $(M+H)^+$ 487.2955, found 487.2944 (+2.4 ppm error). Spectroscopic data of **18i** consistent with those reported in the literature.[13]

7-*tert*-Butyl-1,1-diphenyl-hexahydro-1H-[1,3]oxazolo[3,4-a]pyrazin-3-one (**17b**). *N*-Boc-*N*′-*tert*-butyl piperazine **12** (242 mg, 1.0 mmol), *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol), TMEDA (195 µL, 1.3 mmol) and benzophenone (364 mg, 2.0 mmol) in Et_2O (1 mL) gave, after purification (SiO_2, 99:1-98:2 CH_2Cl_2-MeOH), oxazolidinone **17b** (200 mg, 57%), as a white solid, R_F (99:1 CH_2Cl_2-MeOH) 0.2; mp 193-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.53-7.50 (m, 2H), 7.39-7.24 (m, 8H), 4.43 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.85 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H), 3.08 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H), 2.92-2.88 (m, 1H), 2.62 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H), 2.06 (td, *J* = 12.0, 3.5 Hz, 1H), 1.51 (t, *J* = 11.0 Hz, 1H), 0.93 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.1, 142.4, 138.8, 128.5, 128.4, 128.2, 127.8, 126.0, 125.7, 85.4, 61.9, 54.3, 48.8, 44.8, 42.6, 26.0; IR ($CHCl_3$) 2975, 1750 (C=O), 1449, 1363, 1302, 1255, 1203, 1036, 984 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{26}N_2O_2$ $(M+H)^+$ 351.2067, found 351.2062 (+0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[17]

tert-Butyl 4-benzyl-2-phenylpiperazine-1-carboxylate (**19**) and *tert*-butyl 4-benzyl-3-phenylpiperazine-1-carboxylate (**20**). *s*-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc-*N*′-benzyl piperazine **1** (276 mg, 1.0 mmol) in THF (7 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, $ZnCl_2$ (1.0 M solution in Et_2O, 0.6 mL, 0.6 mmol) was added and the resulting solution was stirred at −78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (140 µL, 1.3 mmol) was added, followed by the addition of $Pd(OAc)_2$ (11 mg, 0.05 mmol) and $^tBu_3PHBF_4$ (18 mg, 0.06 mmol). The mixture was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the solution stirred at rt for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (20 mL). The filtrate was washed with H_2O (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (SiO_2, 19:1 petrol-EtOAc) gave a 33:67 mixture of substituted piperazines **19** and **20** (by ^{1}H NMR spectroscopy) (147 mg, 42%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.47 (m, 1.34H), 7.31-7.19 (m, 8.66H), 5.23 (br s, 0.33H), 4.10-3.89 (m, 1.67), 3.79 (d, *J* = 13.5 Hz, 0.67H), 3.57 (d, *J* = 13.0 Hz, 0.33H), 3.45 (d, *J* = 13.0 Hz, 0.33H), 3.30-3.27 (m, 1H), 3.03 (td, *J* = 12.5, 3.5 Hz, 0.33H), 3.02-2.76 (m, 3H), 2.41 (dd, *J* = 12.0, 4.0 Hz, 0.33H), 2.16 (td, *J* = 12.0, 3.5 Hz, 0.33H), 2.07 (td, *J* = 12.0, 3.0 Hz, 0.67H), 1.47 (s, 3H), 1.45 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{22}H_{29}N_2O_2$ $(M+H)^+$ 353.2224, found 353.2224 (0.0 ppm error). Spectroscopic data of **20** consistent with those reported in the literature.[25]

s-BuLi (1.3 M solution in hexanes, 1.0 mL, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc-*N*′-benzyl piperazine **1** (276 mg, 1.0 mmol) in THF (7 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, $ZnCl_2$ (1.0 M solution in Et_2O, 0.6 mL, 0.6 mmol) was added and the resulting solution was stirred at −78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (140 µL, 1.3 mmol) was added, followed by the addition of PEPPSI-^{i}Pr (34 mg, 0.05 mmol). The mixture was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the solution stirred at rt for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (20 mL). The filtrate was washed with H_2O (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (SiO_2, 19:1 petrol-EtOAc) gave a 5:95 mixture of substituted piperazines **19** and **20** (by ^{1}H NMR spectroscopy) (54 mg, 38%) as a colourless oil.

tert-Butyl 2-phenyl-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate (**21**) and *tert*-butyl *N*-ethenyl-*N*-{2-[(2-phenylpropan-2-yl)amino]ethyl}carbamate (**22**). *s*-BuLi (1.3 M solution in hexanes, 0.5 mL, 0.65 mmol) was added dropwise to a stirred solution of *N*-Boc-*N*′-cumyl piperazine **16** (152 mg, 0.5 mmol) in THF (4 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 2 h. Then, $ZnCl_2$ (1.0 M solution in Et_2O, 0.3 mL, 0.3 mmol) was added and the resulting solution was stirred at −78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (70 µL, 0.65 mmol) was added, followed by the addition of of $Pd(dba)_2$ (14 mg, 0.025 mmol) and RuPhos (12 mg, 0.025 mmol). The mixture was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the solution stirred at rt for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (20 mL). The filtrate was washed with H_2O (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (SiO_2, 85:15 petrol-Et_2O then 4:1 petrol:EtOAc) gave substituted piperazine **21** (29 mg, 15%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.17 (m, 10H), 5.17 (br s, 1H), 3.90 (d, *J* = 13.0 Hz, 1H), 3.26

(d, J = 12.0 Hz, 1H), 3.07 (td, J = 12.5, 3.5 Hz, 1H), 2.71 (d, J = 8.5 Hz, 1H), 2.63 (dd, J = 12.0, 4.0 Hz, 1H), 2.29 (td, J = 12.0, 3.5 Hz, 1H), 1.43 (s, 9H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2, 148.4, 140.9, 128.0, 127.9, 127.2, 126.4, 126.2, 79.7, 59.8, 54.2, 49.2, 46.4, 41.0, 28.4, 24.0, 23.3 (one Ph not resolved); IR (ATR) 2974, 1689 (C=O), 1494, 1448, 1412, 1390, 1364, 1295, 10251, 1230, 1164, 1113, 1029, 1012, 975, 956, 762, 697 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{33}N_2O_2$ $(M+H)^+$ 381.2537, found 381.2533 (+0.8 ppm error), and vinyl carbamate **22** (46 mg, 30%) as a pale yellow oil, R_F (4:1 petrol-Et_2O) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.5 Hz, 2H), 7.34-7.28 (m, 2H), 7.23-7.17 (m, 1H), 7.14-6.80 (br m, 1H), 4.16 (br s, 2H), 3.53 (br s, 2H), 2.51 (t, J = 7.0 Hz, 2H), 1.47-1.42 (br m, 15H) (NH not resolved); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.1, 147.8, 133.0, 128.3, 126.3, 125.8, 90.8, 81.2, 55.9, 43.6, 40.5, 29.7, 28.3; MS (ESI) m/z 305 $(M + H)^+$; IR (ATR) 2974, 2930, 1703 (C=O), 1625 (CH=CH_2), 1454, 1421, 1358, 1327, 1249, 1215, 1155, 1129, 1029, 835, 763, 699 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{28}N_2O_2$ $(M + H)^+$ 305.2224, found 305.2213 (+3.9 ppm error) and *N*-Boc piperazine **16** (80 mg, 53%).

ASSOCIATED CONTENT

Supporting Information. NMR spectra, *in situ* IR spectroscopic data, and arylation catalyst/ligand screen. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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