Rapid Assembly of Saturated Nitrogen Heterocycles in One-Pot: Diazo–Heterocycle 'Stitching' by N–H Insertion and Cyclization

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Abstract: Methods that provide rapid access to new heterocyclic structures in biologically relevant chemical space provide important opportunities in drug discovery. Here, a strategy is described for the preparation of 2,2-disubstituted azetidines, pyrrolidines, piperidines and azepanes bearing ester and diverse aryl substituents. A one-pot rhodium catalyzed N–H insertion and cyclization sequence uses diazo compounds to stitch together linear 1,*m*-haloamines (*m* = 2 to 5) to rapidly assemble 4-, 5-, 6- and 7-membered saturated nitrogen heterocycles in excellent yields. Over fifty examples are demonstrated, including with diazo compounds derived from biologically active compounds. The products can be functionalized to afford α,α-disubstituted amino acids and applied to fragment synthesis.

Innovative organic synthesis is essential to meet the requirement of the pharmaceutical industry to access new biologically relevant chemical space.[1] New processes should allow the reliable and rapid molecular assembly of diverse analogues and enable late-stage functionalization. Saturated heterocyclic structures are of particularly high importance for application in drug discovery, [2] and controlled construction of saturated heterocycles bearing functionalizable vectors remains a significant synthetic challenge. Examples of heterocycle assembly strategies applicable to different ring sizes are scarce. Notable exceptions include Aggarwal's vinyl sulfonium salts for the generation of 3- to 7-membered saturated heterocycles (Figure 1a i).[3] More recently, Bode has developed SnAP reagents that have been applied to the synthesis of saturated heterocycles providing 5- to 7-membered rings with varied substituents (Figure 1a ii).[4]

Pyrrolidines and piperidines are abundant motifs in nature and the pharmaceutical industry (Figure 1b).[5] 4-Membered azetidines and 7-membered azepanes have been less exploited, but offer design opportunities for medicinal chemists.[6] All have been the focus of enormous synthetic effort in recent years.[7] α-Quaternary N-heterocycles, in particular 2-aryl proline derivatives, are highly valuable and have been utilized in pharmaceuticals and lead compounds.[8] The synthesis of these derivatives remains difficult and lengthy, and scope is limited, especially for the installation of electron-rich aromatic groups and access to 4-, 6- or 7-membered analogues.[9]

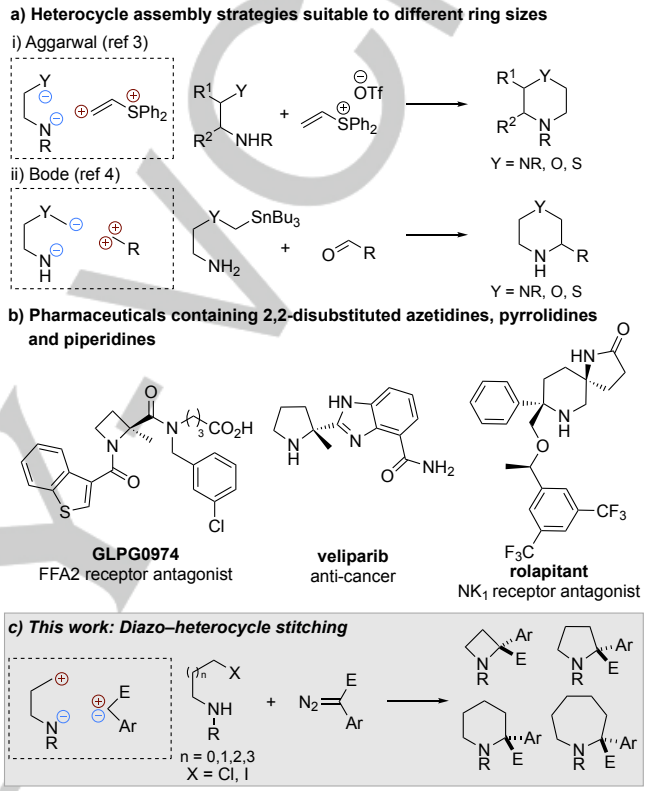

Figure 1. General strategies for the synthesis of saturated nitrogen heterocycles and examples of 2,2-disubstituted saturated nitrogen heterocycles in the pharmaceutical industry.

Diazo compounds have found significant application in heterocycle synthesis,[10,11] with X–H and C–H insertion reactions being used to effect cyclization.[12] In 2014, as part of our fragment-oriented synthesis program, we reported the use of diazo compounds in an O–H insertion to construct the cyclization precursor for preparation of diverse 2,2-disubstituted oxetane derivatives.[13] In 2015, Sun cyclized homopropargylic amines with Rh and Cu carbenes to form various alkylidine pyrrolidines.[14,15] Hu and Moody recently independently demonstrated N–H insertion to β-aminoketones followed by intramolecular aldol to access pyrrolidines.[16] We envisaged using diazo compounds as a stitch to form 4-, 5-, 6- and 7-membered N-heterocycles, all involving the same strategic disconnection.

Here we report a broad strategy for the preparation of 2,2-disubstituted azetidines, pyrrolidines, piperidines and azepanes from diazo compounds and linear 1,*m*-haloamines (*m* = 2–5; Figure 1d). A one-pot Rh-catalyzed N–H insertion and intramolecular alkylation is applied to a range of heterocyclic ring sizes (4–7), and also to the late-stage functionalization of

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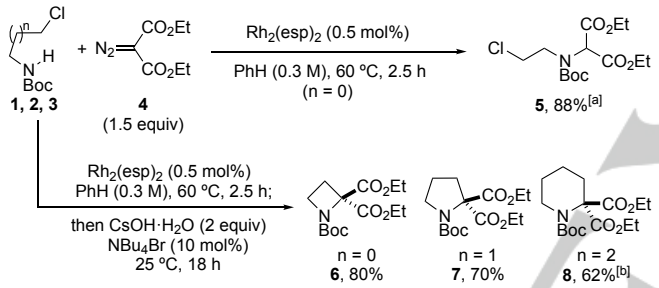
bioactive compounds. These heterocyclic motifs are targeted as fragments and building blocks for screening or further elaboration. The installation of common, easily-removable protecting groups allows facile further derivatization, including the formation of unnatural amino acids.

To implement our strategy we first undertook extensive optimization of reaction conditions for the N–H insertion of diethyl diazomalonate **4** into protected 1,2-haloamines, targeting the azetidine product (Scheme 1). Investigation of different *N*-protecting groups, leaving groups, catalysts and other parameters led us to conditions using *N*-Boc-2-chloroethylamine **1**, using a $Rh_2(esp)_2$ catalyst in benzene at 80 ºC (See SI for further details). Further optimization using a design of experiment (DOE) approach allowed the reduction of temperature, time and equivalents of diazo reagent, providing an 88% yield of Boc-amine **5** as a potential cyclization precursor. This species could indeed be cyclized with various bases to form azetidine **6**, and we were delighted to find that the process could be effected in one-pot. Addition of CsOH and tetrabutylammonium bromide to the reaction mixture following N–H insertion directly yielded the azetidine product **6** in high yield.



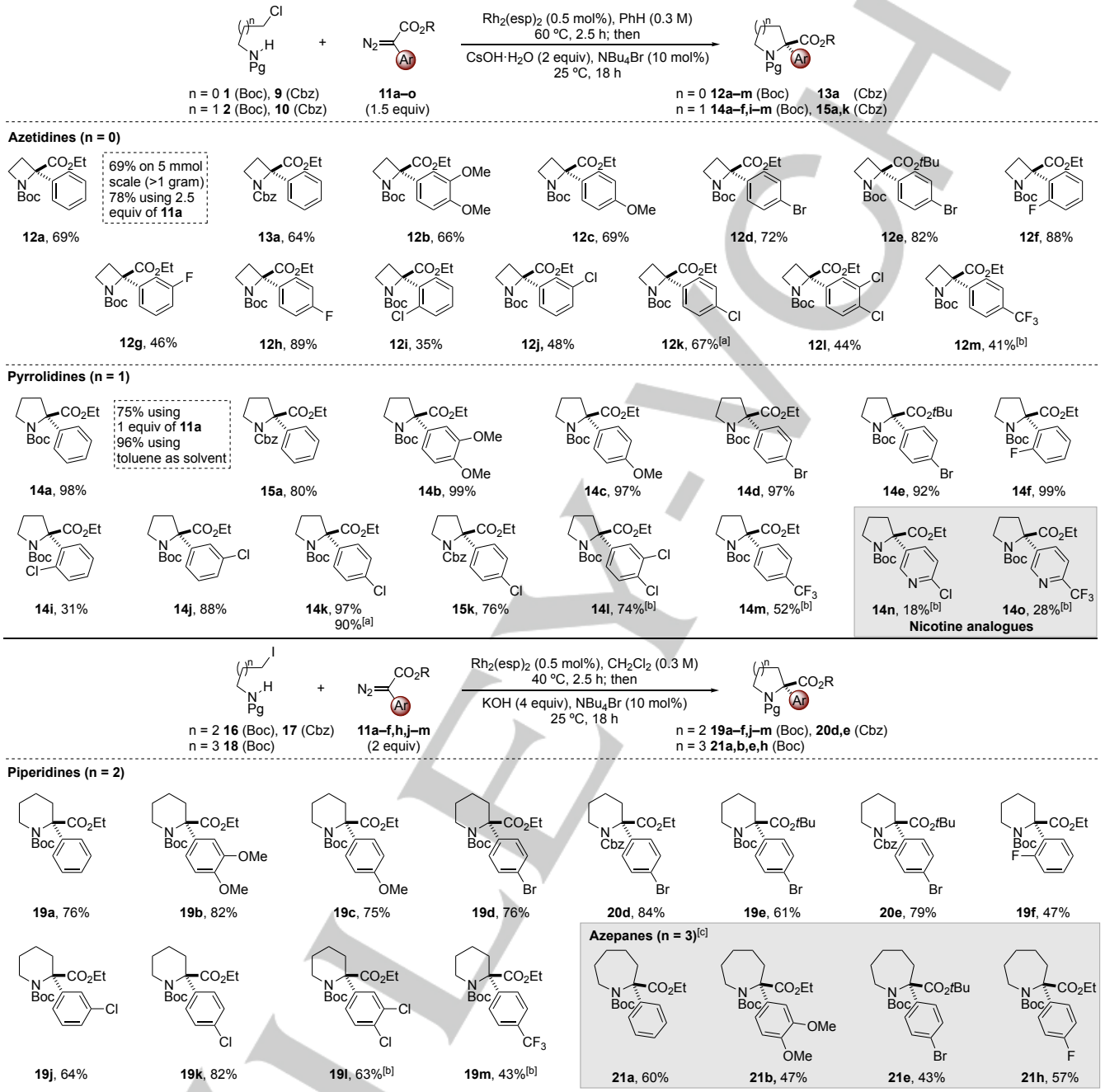
Scheme 1. Synthesis of 2,2-disubstituted azetidines, pyrrolidines and piperidines. [a] Yield determined by ^{1}H NMR spectroscopy relative to 1,3,5-trimethoxybenzene as an internal standard. [b] 2 equiv of diazo, CH_2Cl_2, 40 ºC, 4 equiv of CsOH.

Importantly, the same process was applicable to the homologous 1,3- and 1,4-chloroamine starting materials **2** and **3** to provide the pyrrolidine and piperidine products (**7** and **8**), just by extending the chain length. Notably, these reactions were performed without the requirement for a slow addition of the diazo compound.

Next, aryl-ester diazo compounds were examined to form different N-heterocycles bearing varied aromatic components, suitable for fragment synthesis (Scheme 2). Pleasingly, the use of the same optimized conditions was successful using *N*-Boc-2-chloroethylamine **1**, to provide azetidine **12a** in 69% yield on 0.5 mmol scale. The same yield was obtained on ten times the scale to afford > 1 g of the product. The yield could be increased to 78% by increasing the excess of diazo compound from 1.5 to 2.5 equiv. Using a Cbz protecting group gave a similar yield to afford azetidine **13a**. High yields were obtained for azetidines bearing electron-rich aromatic rings (**12b-c**). High yields were also achieved when changing the ester group from ethyl to *tert*-butyl (**12d** vs. **12e**). Halogens were well tolerated, providing handles for further functionalization (**12d-l**), though more electron-deficient aryl groups gave slightly lower yields. The subtle influence of the electronic character of the aromatic ring on the yield of the reaction is demonstrated by changing the position of the fluorine atom on the aromatic group in **12f-h**, where the presence of π-conjugation gave very high yields. Very electron deficient aryl groups, such as the 4-trifluoromethylphenyl moiety, could be installed using a slow addition of the diazo compound.

Exactly the same conditions were applied to generate 2-aryl proline analogues. These pyrrolidine rings were prepared in up to quantitative yields over the one-pot, two-step process. The 2-Ph *N*-Boc derivative **14a** was obtained in 98% yield. The reaction could be performed using 1 equiv of diazo **11a** and still obtain 75% yield. Toluene could be used in place of benzene to achieve the same high yield (96%). The yields were uniformly excellent, except for more hindered diazo compounds (**11i**), and highly electron-deficient diazo compounds, such as **11m**. Pyridine containing diazo compounds were suitable to generate nicotine analogues **14n** and **14o,** albeit in low overall yield.

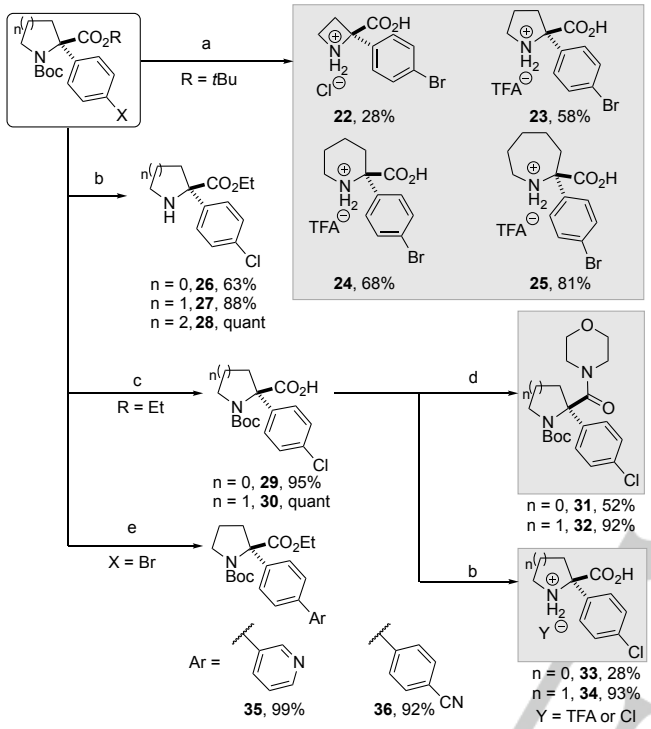
A modification in the reaction conditions was required for the synthesis of piperidine rings to improve the yield (see SI for further details).[17] Changing the leaving group to iodide and the base to KOH afforded high yields for electron-rich and electron-deficient aryl substituents from *N*-Boc-4-iodobutylamine **16**. The same procedure was also applied to the synthesis of 7-membered azepanes. Using CsOH as base for cyclization, azepanes **21** were synthesized in good yields without a conformational constraint required for the cyclization.



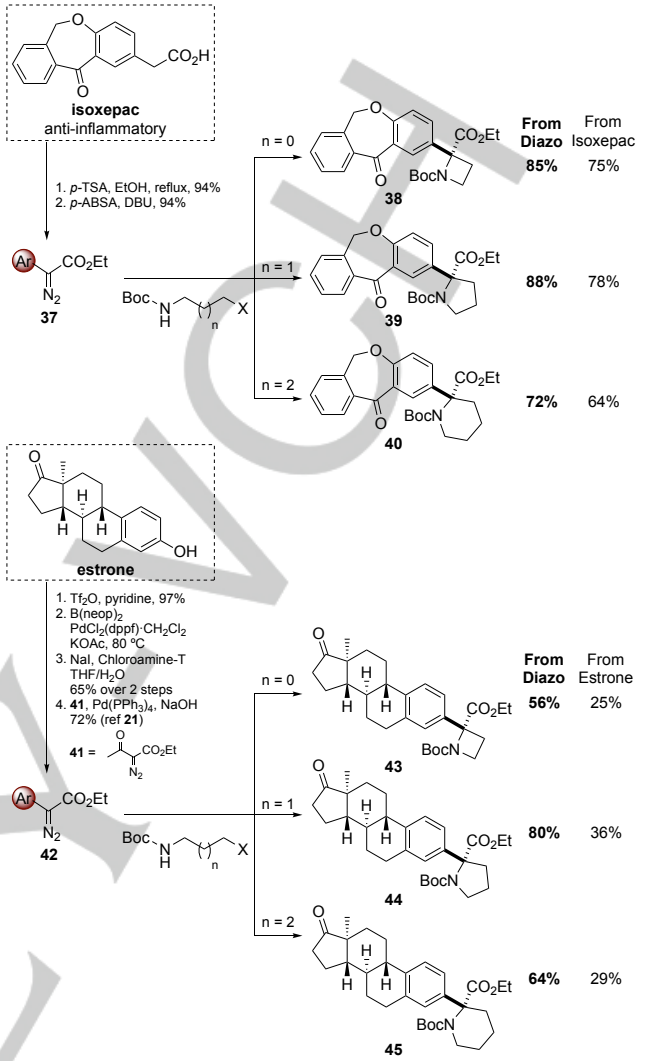
Scheme 2. Synthesis of 2,2-disubstituted azetidines, pyrrolidines, piperidines and azepanes. [a] 2.0–3.0 mmol scale. [b] Slow addition of 2.0 or 2.5 equiv of diazo compound over 1 h. [c] CsOH·H_2O instead of KOH.

Fragment-based drug discovery has become an established method for hit-discovery,[18] which has increased demand for novel fragments with appropriate properties that can also be further elaborated.[1] The products readily available by our approach presented attractive options for screening as related but topologically distinct structures with multiple potential binding sites for biological interactions, and without the requirement for additional substituents.[19] We next examined their derivatization. The free amino acids of each ring size **22**-**25** were generated, directly from the *N*–Boc *tert*-butyl ester derivatives **12e, 14e, 19e** and **21e** in a global deprotection, providing a very short route to these valuable derivatives (Scheme 3a). Alternatively, Boc deprotection was facile with diester and ester-aryl saturated nitrogen heterocycles to provide the free amines **26**-**28**.[20] Amides

31 and **32** could be formed by ester hydrolysis and amide coupling reactions in excellent yields over 2 steps (Scheme 3c and d). Boc deprotection provided an alternative route to free amino acids, here aryl chlorides **33** and **34**. Functionalization of the aromatic group by Suzuki–Miyaura cross-coupling provided (hetero)biaryls **35** and **36** in high yields, and another functionalizable vector (Scheme 3e).



Scheme 3. Functionalization of azetidine, pyrrolidine, piperidine and azepane scaffolds. a) n = 0: 4 N HCl in 1,4-dioxane, 0 to 25 ºC, 16–24 h. n = 1, 2 or 3: TFA:CH_2Cl_2 (1:1), 40 ºC, 16 h. b) n = 0: 4 N HCl in 1,4-dioxane, 0 to 25 ºC, 18 h. n = 1 or 2: TFA, CH_2Cl_2, 0 to 25 ºC, 15-18 h. c) NaOH (2 M aq.), EtOH, reflux, 3-5 h. d) DIPEA (3 equiv), HATU (1.2 equiv), morpholine (1.2 equiv), DMF, 40 ºC, 72 h. e) $ArB(OH)_2$ (1.3 equiv), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_3PO_4 (2 equiv), 1,4-dioxane:H_2O (4:1), 65 ºC, 18 h.



Scheme 4. Late-stage functionalization of bioactive compounds. Conditions as in Scheme 2. Steroid derivatives are assumed to be a 1:1 mixture of diastereoisomers.

Next we examined the potential of this approach for late-stage functionalization, aiming to stitch in different N-heterocycle components using diazo compounds generated from bioactive compounds. Starting from isoxepac, an anti-inflammatory pharmaceutical, esterification and diazo transfer provided diazo **37** on a gram scale in 88% overall yield. From **37**, the azetidine, pyrrolidine and piperidine analogues could be prepared in high yields (85%, 88%, 72% respectively for **38**–**40**). This represents a 4-step sequence to install three distinct heterocycles onto an existing pharmaceutical framework with only one chromatographic purification. With known diazo **42**,[21] generated from estrone, good yields were obtained for the synthesis of the 4-, 5- and 6-membered rings **43**–**45**. Yields over 25% were obtained in all cases across the overall 6-step synthetic sequence.

In summary, we have developed an efficient one-pot procedure for the rapid assembly of 2,2-disubstituted azetidines, pyrrolidines, piperidines and azepanes from simple acyclic precursors in very high yields. The products offer different 3-dimensional character and sit within underexplored fragment and lead-like chemical space. This methodology tolerates aryl groups bearing electron-withdrawing and electron-donating substituents on the diazo precursor and allows for the late-stage functionalization of bioactive natural products and pharmaceutical compounds. The products can be efficiently elaborated to provide non-planar fragments and building blocks, including unnatural amino acids. Attempts to expand this methodology towards a wider range of saturated heterocycles and enantioselective synthesis are ongoing.

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Keywords: Nitrogen Heterocycles • Amino Acids • Rhodium Catalysis • Cyclization • Fragment Synthesis

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Layout 1:

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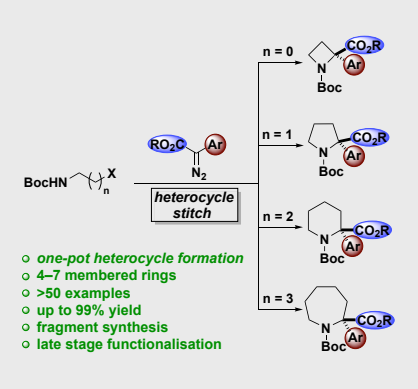
A stitch in time saves…steps. 2,2-Disubstituted azetidines, pyrrolidines, piperidines and azepanes are all constructed in one-pot from diazo compounds. Rh-catalysed N–H insertion and cyclization sequence couples diazo compounds and linear 1,*m*-haloamines (*m* = 2 to 5). Novel α,α-disubstituted amino acids, fragment synthesis, as well as, late-stage functionalization is demonstrated.



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