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Readily Accessible sp³-Rich Cyclic Hydrazine Frameworks
Exploiting Nitrogen Fluxionality†

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Increased molecular complexity correlates with improved chances of success in the drug development process. Here, a strategy for the creation of sp³-rich, non-planar heterocyclic scaffolds suitable for drug discovery is described that obviates the need to generate multiple stereogenic centers with independent control. Asymmetric transfer hydrogenation using a tethered Ru-catalyst is used to efficiently produce a range of enantiopure cyclic hydrazine building blocks (up to 99% ee). Iterative C–N functionalization at the two nitrogen atoms of these compounds produces novel hydrazine and hydrazide based chemical libraries. Wide chemical diversification is possible through variation in the hydrazine structure, use of different functionalization chemistries and coupling partners, and controlled engagement of each nitrogen of the hydrazine in turn. Principal Moment of Inertia (PMI) analysis of this small hydrazine library reveals excellent shape diversity and three-dimensionality. NMR and crystallographic studies confirm these frameworks prefer to orient their substituents in a three-dimensional space under the control of a single stereogenic center through exploitation of the fluxional behavior of the two nitrogen atoms.

1. Introduction

Libraries of small molecules capable of exploring new areas of three-dimensional chemical space are of considerable value in drug discovery. There is growing evidence that molecular complexity, as measured by parameters such as the fraction of saturated carbon atoms (Fsp) and number of stereogenic centers, correlates with success rates in drug development.1 Despite these observations, analysis of current drug-like libraries such as the ChEMBL dataset reveals that they generally lack shape diversity and three-dimensionality.2

Hence, there is a need to create new stereochemically-rich compound libraries for use in drug-discovery programs that overcome these shortcomings. This is a challenging problem because it necessitates moving away from well-established synthetic methods (e.g. sp³-sp³ cross-couplings) toward chemistries that efficiently create non-planar scaffolds.3 In this Edge article, we report a way to create novel chemical libraries with considerable shape diversity without having to generate multiple stereogenic centers with independent control. The idea exploits the fluxional behavior of pyramidal nitrogen atoms within enantiopure cyclic hydrazines, to create new sp³-rich heterocyclic frameworks that display their chirality in an orchestrated way (Scheme 1).

This approach has a number of attractive features. Cyclic hydrazines and hydrazides are well represented in medicinal chemistry.4 They are found in many bioactive compounds including natural products (e.g. actinoramide A,5 sanglifehrin A6), proprietary lead compounds7 and approved drugs (e.g. cilazapril8) (Figure 1). Chemical libraries of 1 for discovery programs should be readily available by simple, late-stage diversification of 2 by iterative functionalization at each nitrogen atom. The availability of a plethora of C–N functionalization reactions combined with the high nucleophilicity of the hydrazine functional group make this disconnection highly attractive. By exploiting their dynamic behavior, it should be possible to display three substituents (R, R² and R³) attached to carbon and nitrogen very precisely in three-dimensional space. Of the four conformational isomers 1a-d that arise from pyramidal inversion, 1a is expected to be

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dominant. Typically, cyclic hydrazines adopt an anti-
configuration between the N-substituents to minimize non-
bonded interactions between the lone pairs.9 Thus, the
formation of 1b and 1c is expected to be disfavored.
Furthermore, non-bonding interactions between adjacent syn-
substituents should disfavor 1b-d relative to anti,anti-1a. Thus,
control over only one stereogenic center is needed to predict
productive, non-planar frameworks. Finally, further fine-
tuning of the substituent positioning should be possible by
variation of the ring size.

2. Results and discussion

2.1. Asymmetric synthesis of cyclic hydrazine frameworks

The first task was to identify an efficient, enantioselective
route to the hydrazine building blocks, i.e. 2 (Scheme 1). Key
requirements for such a synthesis were that it: (i) allow the
introduction of a variety of medicinally-relevant R substituents
with high levels of enantiocontrol; (ii) provide access to
different ring sizes; and (iii) yield differentially protected
groups. While several methods for the asymmetric synthesis of
cyclic hydrazines exist,10 none met our requirements.

Consequently, a new two-step approach to 2 was devised
based upon enantiocontrolled reduction of ketones 3 followed
by ring closure. By varying the linker length between the
ketone and hydrazine functional groups, the approach offers
access to a range of different ring sizes. In choosing a method
for the reduction, we were drawn to Ru-catalyzed asymmetric
transfer hydrogenation (ATH) which typically delivers high
levels of enantioselectivity, requires low catalyst loadings, has
asymmetric induction fits established models,13 indicating that
the hydrazine plays no active role in catalyst binding.

Next, the ATH of a broad range of ketones was examined using
the optimized conditions (Figure 2). Full details relating to the
synthesis of substrates 5a-v are provided in the Supporting
Information. High yields and enantioselectivities were
achieved in all cases, with variations in the arene, nitrogen
protecting groups and linker length well tolerated. The sense
of asymmetric induction in these transformations was made by
analogy to that seen for R-6a. For 2-substituted aryl derivatives
5c and 5g, and for 3,5-difluoro derivative 5p, poor levels of
stereoinduction were obtained using 7c as catalyst. In these
cases, use of 7f bearing an additional electron-rich methoxy

Figure 1. Representative examples of bioactive molecules containing cyclic hydrazine
and hydrazide frameworks (highlighted in red).
group on the arene significantly improved the enantioselectivity.\textsuperscript{13b}

Figure 2. Ru-catalyzed ATH of hydrazine-containing ketones. \textsuperscript{a} Using \textit{R},\textit{R}-7f. \textsuperscript{b} ee determined after cyclization to 8. \textsuperscript{b} Using \textit{R},\textit{R}-7c.

Ring closure of 6a-v using diethyl azodicarboxylate (DEAD) and triphenylphosphine under Mitsunobu conditions provided the corresponding cyclic hydrazines 8a-v in good to excellent yields (Figure 3). It is possible to replace DEAD with less hazardous diisopropyl azodicarboxylate (DIAD), as illustrated for highly electron-rich thiophene (73% ee) was detected. The chemistry can be performed in good to excellent yields (Figure 3). It is possible to replace DEAD with less hazardous diisopropyl azodicarboxylate (DIAD) and triphenylphosphine under Mitsunobu conditions provided the group on the arene significantly improved the enantioselectivity.\textsuperscript{13b}

2.2. Synthesis of sp\textsuperscript{3}-rich hydrazine libraries by N-functionalization

To determine if these orthogonally-protected cyclic hydrazines could be used to generate sp\textsuperscript{3}-rich heterocyclic libraries, we explored their functionalization. To make this study practicable, a subset of six cyclic hydrazines, namely 8b, 8j, 8k, and 8t, were used. The sequence involved: (i) deprotection of the Ts group from the less hindered nitrogen using Mg metal; (ii) functionalization of C-N bond formation to introduce a variety of \textit{R}\textsuperscript{2} fragments; (iii) acidic deprotection of the Boc group from the second nitrogen; and (iv) addition of the \textit{R}\textsuperscript{1} fragment using similar chemistries used in Step (ii) (Figure 4). The deprotection reactions were essentially quantitative and so product purification was only conducted after each C-N functionalization. Conventional acylation and reductive amination reactions could be conducted on either nitrogen in generally high yields across a range of ring sizes. However, high-throughput optimization was required to identify general conditions for the Pd-catalyzed Buchwald-Hartwig aroylations (for full details, see Supporting Information).\textsuperscript{14}
Information). For the introduction of the R² fragment at the least hindered nitrogen on 8i, XPhosPd(crotyl)Cl, NaOEtBu and toluene proved the most effective combination of catalyst, solvent and base. Cross-coupling of the more hindered nitrogen in the pyrazolidine ring was achieved with a BippyPhosPd(allyl)OTf catalyst to provide 10d and 10g in good yields. For other substrates differing in ring size and aryl group, Pd(OAc)₂ and Xanthphos proved to be an effective catalyst system. Using this strategy, 14 derivatives (10a-k, 10m-o) were produced bearing a diverse set of N- and C-substituents across different hydrazine ring sizes. Additionally, by omitting the toluene, 90 °C, 20 h. occurred during these functionalization sequences. (Produced bearing a diverse set of N- and C-substituents across different hydrazine ring sizes. Additionally, by omitting the toluene, 90 °C, 20 h. produced bearing a diverse set of N- and C-substituents across different hydrazine ring sizes. Additionally, by omitting the toluene, 90 °C, 20 h.

2.3. Molecular shape and dynamics of sp²-rich hydrazine scaffolds.

The shapes of the cyclic hydrazines have been studied using a combination of computational and spectroscopic tools. To assess the three-dimensionality of 10a-q in the 17-member hydrazine library, the LLAMA package was used to compute and display their principal moments of inertia (PMI) (Figure 5). This tool randomly selects a number of 3D-conformers for each molecule, minimizes their energy and selects the lowest-energy one. The selected minimum energy conformers of 10a-q are provided in the Supporting Information. LLAMA then calculates the moments of inertia in the x, y and z axes. The PMI I1 coordinates are calculated by dividing inertia(x) by inertia(z). The I2 coordinates are calculated by dividing inertia(y) by inertia(z). This plot confirms that members of this small hydrazine library possess excellent shape diversity and three-dimensionality compared with conventional databases. The wide distribution of the heterocycle frameworks within this plot suggests that it is the nature of the appended substituents (R, R¹ and R²), rather than the size of the hydrazine ring, that has the greatest influence on their overall shape (Figure 5).

Next, the solution and solid-state structures of representative cyclic hydrazines and hydrazides were determined. A total of eight derivatives were studied by single crystal X-ray diffraction (XRD). The ORTEP depictions of 8d, 9m, 10a and 10b are given in Figure 6. For four-membered 8d and five-membered 10a and 10b, the anti,anti-configuration of the R, R¹ and R² substituents is apparent. For hexahydropyridazine 9m where the conformational flexibility of the ring becomes more important, the R group still exerts a strong influence leading to a highly non-planar structure in which the R, R¹ and R² substituents are displayed in a predictable way on opposite faces of the hydrazine ring. The crystallographic data also provide insight into the extent of pyramidalization of the two nitrogen atoms within the ring, a factor influencing both their shapes and fluxional behavior. The values for the pyramidalization of each nitrogen are given in Figure 6, with larger values indicating more sp²-character at the nitrogen center.
Next, the solution-state structure of 10b was determined in CD$_2$Cl$_2$ at 343 K by $^1$H NOESY spectroscopy (600 MHz). These conditions were used to produce a single set of well resolved signals. The solution structure was assigned on the basis of NOESY cross-peaks between the ortho-hydrogens of the phenyl ring (H-3) and the methylene hydrogens of the isobutyl group (H-9 and possibly H-10) consistent with these substituents being on the same side of the hydrazine ring (Figure 7b). Furthermore, the observation of a NOESY cross-peak between H-2 and H-8, and between H-6 and H-8 places all these atoms on the same side of the molecule and on the opposite face to the phenyl group (Figure 7c). On this basis we assign an anti,anti-configuration to 10b in solution (Figure 7a), similar to the solid-state structure (Figure 6).

To explore the fluxional behavior of the cyclic hydrazines, variable temperature $^1$H NMR studies were conducted using 10a and 10b. For 10a, the $^1$H NMR spectrum resolved into two sharp sets of signals at 233 K in CDCl$_3$, indicating the presence of two conformational isomers in a 56:44 ratio. In contrast, 10b exists predominately as a single conformational isomer at 233 K in CDCl$_3$, although small amounts of two additional isomers are seen (84:11:5). Evidently, the fluxional behavior is highly dependent on the nature of the N-substituents. This is consistent with changes in the extent of N-pyramidalization seen in the solid-state (Figure 6). Using the resolved methyl singlets of 10a, we were able to determine the barrier to interconversion of the two isomers at coalescence ($T_c$ = 258 K, $\Delta G^\ddagger = 54$ kJ mol$^{-1}$, see Supporting Information). The question arises as to whether the two isomers come from fluxionality at the hydrazine centers (Scheme 1), or from a process such as amide bond rotation within anti,anti-10a? On the available evidence, we suggest that only amide rotamers are being observed i.e. A and B (Scheme 2). First, whilst low temperature NOESY experiments did not allow us to fully deduce the solution-state structure of 10a, we did observe a NOESY cross-peak between the methine hydrogen at H-3 and the ortho-hydrogens of the COAr group for A but not B consistent with this assignment. Secondly, the measured interconversion barrier is more consistent with that of an amide bond rotation in similar systems. For example, both types of fluxionality operate concurrently in 11 with a lower barrier for rotation about the N–CO bond than ring inversion (box insert, Scheme 2). Finally, the near equal population of A and B is inconsistent with N-inversion as 1b-d are expected to be higher energy species due to unfavorable non-bonded interactions (Scheme 1). Although N-fluxionality is not operating in 10a, the observation of a third set of signals for 10b at low temperature, suggests that conformational isomers arising from N-inversion are accessible for some systems, albeit in low concentrations.

![Figure 6](https://example.com/f6.png)

**Figure 6.** Representative XRD structures of the cyclic hydrazines with measured values for the pyramidalization of the two ring nitrogens (N1 and N2).

![Figure 7](https://example.com/f7.png)

**Figure 7.** Solution-state structure of 10b derived by $^1$H-1H NOESY spectroscopy (600 MHz, CD$_2$Cl$_2$, 343 K): (a) anti,anti-representation of 10b with key NOEs indicated (red arrows). (b) Expansion of the NOESY spectrum highlighting cross-peaks between H-3 and H-9 and possibly H-10. (c) Expansion of the NOESY spectrum highlighting key cross-peaks between H-8 and H-2, and H-8 and H-6.

3. Conclusions

An efficient synthesis of differentially-protected cyclic hydrazines containing an adjacent stereogenic carbon atom has been devised using ATH as the key step. Commercially available tethered Ru-catalyst 7c, available in both enantiomeric forms, proved highly effective for the introduction of the asymmetric center by ketone reduction. In the few cases where low enantioselectivity was seen in the ATH, tethered catalyst 7f gave further improvements. The
methodology was used to make 22 different cyclic hydrazines in up to 99% ee, through variation in ring size (4- to 7-membered rings), C-3 substituents and nitrogen protecting groups. The chemistry is operationally simple and can be performed on a preparative scale. Chemical library construction is possible from these hydrazines by iterative C-N bond formation. Wide chemical diversification is possible through variation in the hydrazine structure, use of different functionalization chemistries and coupling partners, and controlled engagement of each nitrogen of the hydrazine in turn. Principal moment of inertia (PMI) analysis revealed excellent shape diversity and three-dimensionality within the assembled library, indicating their potential value in drug discovery. The preference for the molecules to adopt anti,anti-orientations of the three stereocenters was established using a combination of XRD and NMR spectroscopy. The fluxional behavior of these compounds was further explored by VT-NMR and low temperature NOESY experiments, from which useful insights have emerged about how the molecules sample chemical space. Future work will examine the feasibility of making larger chemical libraries based on these non-planar scaffolds and the exploitation of this chemistry in drug discovery programs.

Conflicts of interest

There are no conflicts to declare.

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Notes and references


14. CCDC 1944266 (6a), 1944267 (8d), 1944268 (8h), 1944269 (10a), 1944270 (10b), 1944271 (9m), 1944272 (10l), 1944273 (9i), and 1955341 (10o) contain the supplementary crystallographic data for this paper. These data are provided free of charge from the Cambridge Crystallographic Data Centre.

15. Double functionalization of four-membered diazetidines such as 8b has proven difficult in part because of low yields in the Pd-catalyzed cross-couplings. After *N*-deprotection, such substrates have more limited chemical stability.


18. The pyramidalization of the nitrogen atoms is defined as $360 - \sum$ where $\sum$ is the sum of the valence angles of the nitrogen atoms.