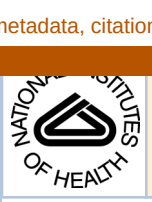

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1,3-Allylic Strain as a Strategic Diversification Element For Constructing Libraries of Substituted 2-Arylpiperidines

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Abstract

Flipping diversity—Minimization of 1,3-allylic strain is a recurring element in the design of a stereochemically- and spatially-diverse collection of 2-arylpiperidines. Here, stereochemically-diverse scaffolding is first constructed using $A^{1,3}$ strain to guide the regioselective addition of nucleophiles, which serve as handles for further substitution. *N*-substitution with alkyl and acyl substituents again leverages $A^{1,3}$ strain to direct each stereoisomer to two different conformer populations, doubling the number of library members.

Keywords

arylpiperidines; 1, 3-allylic strain; Fürst–Plattner; shape diversity; conformational diversity

Screening approaches to probe and drug discovery require access to high-quality small molecule libraries. One contemporary challenge in providing such access is the construction of libraries that maximize the coverage of chemical (functional group), stereochemical, and spatial diversity in a given chemotype.[1] Although the problem of functional group diversity has been addressed since the earliest days of combinatorial chemistry and parallel synthesis, the incorporation of stereochemical diversity and, more broadly, shape diversity has required the development of new strategies. These include the use of spatially diverse scaffolds or the pre-construction of stereochemically diverse building blocks that are then combined to afford final products ("build–couple–pair" [2] is an example of this).

In this paper, we describe a conformational switching approach toward shape-diverse piperidine libraries in which the presence or absence of 1,3-allylic strain[3] is leveraged to

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enhance both (1) scaffold diversity by regiodivergent opening of epoxide intermediates and (2) the conformational space of the final library through the simple expedient of changing the nature of nitrogen substitution.[4] The concept is illustrated Figure 1 for a series of 2-aryl substituted piperidines. For a given epoxide isomer, the conformation of the piperidine ring will depend on whether the N1 atom is sp^3 hybridized (Ar preferring an equatorial position due to minimization of 1,3-diaxial interactions) or sp^2 (Ar axial, due to $A^{1,3}$ strain in the equatorial isomer[5]). Nucleophilic addition to the epoxide would then take place according to the Fürst–Plattner principle[6] (trans–diaxial opening), leading to two *constitutional isomers* from this epoxide intermediate (2,4- vs. 2,5-cis Ar/Nu relationships). *Stereochemical diversity* would then follow by applying the same principles to the alternative epoxide diastereomer, affording the analogous 2,4- and 2,5-trans isomers. Once prepared – and likely following the downstream introduction of *functional group diversity* – the library could then be N-substituted by a different set of alkyl or acyl substituents, leading to a doubling of the library members through *conformational diversity*.

We chose to demonstrate this approach by preparing a library based on the triazole-containing piperidines shown in Figure 2 (selected because the arylpiperidine chemotype appears in a number of bioactive compounds and is therefore a desirable library scaffold for broad screening[7]). To a first approximation, the expected conformations in one such library are shown (four isomers bearing two different N-groups), demonstrating the range of conformational and configurational space covered by these compounds.

To demonstrate the value of 1,3-allylic strain in scaffold preparation, we first carried out the stereochemically- and constitutionally-differentiated scaffold syntheses shown in Scheme 1. Four 2-aryl-1,2,3,6-tetrahydropyridines were constructed from substituted benzaldehydes[8] in two steps via bisallylation/*N*-acylation followed by RCM. The *N*-acylated derivatives underwent highly stereoselective epoxidation reactions, presumably because the top faces as drawn were blocked by the aromatic groups in the most stable conformations.[5] Using *m*-CPBA or methyl(trifluoromethyl)dioxirane,[9] epoxidation from the less-hindered bottom alkene face afforded anti epoxides **3** (after DBU-mediated Fmoc removal) and **5**.[10] Alternatively, NBS/H_2O produced an uncharacterized bromohydrin intermediate,[11] resulting from trans-diaxial addition of H_2O to the bromonium ion formed on the less-hindered bottom alkene face. Treatment with base delivered the corresponding synepoxides **4** and **6**.[12]

Both NH and N-acylated epoxy piperidines were prepared as each was expected to react through the divergent conformations shown in Scheme 1 (b) to provide regioisomeric nucleophilic addition products according to the well-established Fürst–Plattner principle of trans–diaxial epoxide ring opening.[6a] In this way, allylic strain controlled both the stereochemical and regiochemical outcome of scaffold synthesis, delivering all four isomers of the *trans*-4,5-disubstituted 2-arylpiperidines desired for the targeted library. In only one stereochemical series was no selectivity obtained: epoxide **6** gave an essentially 1:1 mixture due to competing electronic and stereoelectronic preferences for this epoxide (see Supporting Information for details). However, even in this case, we were able to isolate >700 mg quantities of the desired NH azido alcohols in high purity (as was the case for all 16 of the desired scaffolds) for further diversification.

The scaffolds were decorated by removal of the Boc group (if present) followed by either reductive alkylation or *N*-acylation, and finally, a Cu-induced triazole formation step (Scheme 2).[13] For this initial, speculative screening library, we chose a relatively small number of substituents that represent a range of aliphatic and aromatic diversity at the newly-introduced positions. The total number of compounds targeted in these steps, where R^1 and R^2 were one of the three substituents shown, was $16 \times 9 \times 2 = 288$ compounds.

Following parallel synthesis, the library was prepared for screening by mass-directed HPLC purification, yielding ultimately 268 compounds in >90% purity (UV) and >10 mg quantities. All compounds were characterized by high-resolution mass spectrometry.

A subset of 32 compounds (16 amines and the 16 corresponding amides), comprising four substitution patterns for each of the four stereochemical and constitutional isomers, was subjected to conformational analysis by ^{1}H NMR coupling constant analysis. The data revealed that each functionalized amino-piperidine isomer adopted the same conformation in solution, regardless of the substituents appended to the core. The same held true for the corresponding amides.

The conformational profiles of the 8 stereochemical families of the triazol-containing piperidines (4 amines and 4 amides) are shown in Figure 3.[14] Figure 3a shows overlays of each amino-piperidine (blue) paired with the corresponding amido-piperidine (green) counterpart, highlighting the conformational differences achieved through the introduction of 1,3-allylic strain. Three of the four families of amino-piperidines adopted chair forms placing the 2-aryl substituents equatorial. The 2,4-trans family of amino-piperidines exhibited a slight distortion from ideal chair conformation, while still placing the 2-aryl substituents in a pseudoequatorial. The corresponding 2,5-cis and 2,4-trans families of amido-piperidines adopted the opposite chair forms, placing the 2-aromatic substituents axial. However, rather than adopting chair forms placing all three non-hydrogen substituents (Ph, OH, triazole) in axial positions, the 2,5-trans amido-piperidines exhibited twist-like conformations, and the 2,4-cis amido-piperidines adopted boat conformations. Thus, each of the eight compounds in the family presents the piperidine substituents in a unique three-dimensional array. Taken together, these compounds (and by extension the entire library that they represent) comprise a shape-diverse collection with predictable three-dimensional shapes for use in biological screening and structure-activity relationship (SAR) development (Figure 3b).

Through these efforts, we have demonstrated a useful protocol for maximizing the stereochemical diversity in a piperidine library using a limited number of scaffolds and building blocks. This approach features the use of 1,3-allylic strain for controlling both the ring opening of epoxide precursors and, thus, constitutional isomerism, as well as the conformations of the final library members. In so doing, a library of 268 drug-like compounds having predictable conformations has been prepared. The compounds prepared in this work are being scrutinized by high-throughput screening whereas the concepts utilized in the present case are currently being applied to the construction of other heterocyclic libraries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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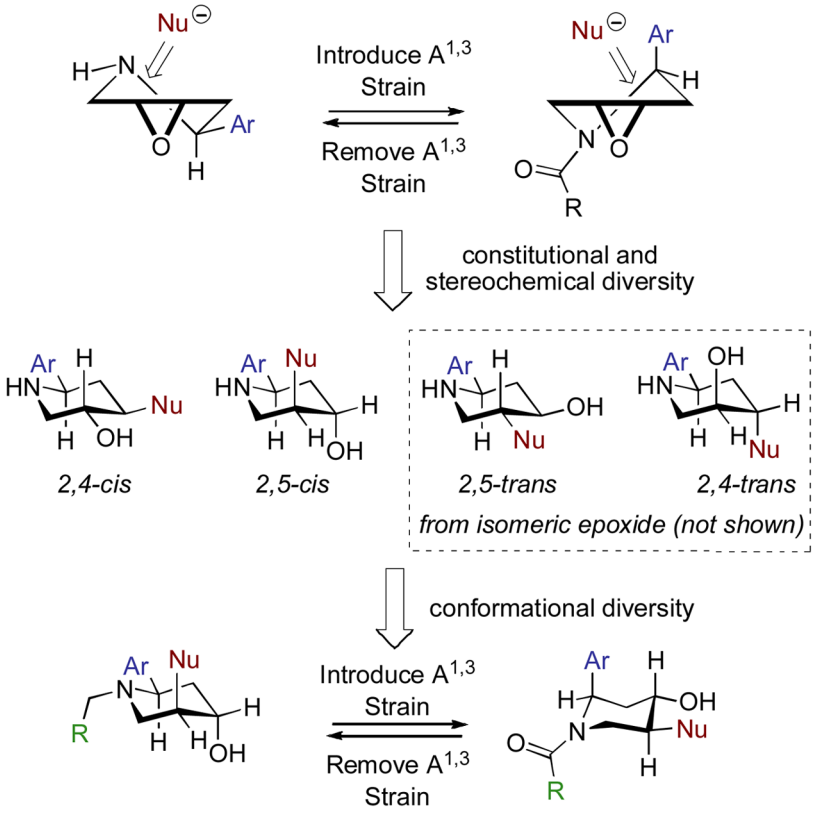


Figure 1.
Use of $A^{1,3}$ strain to control constitutional (2,4- vs. 2,5-Ar/Nu relationship), stereochemical (cis vs. trans), and conformational diversity in piperidine libraries. *Functional group diversity* arises from variations in Ar, Nu, and R.

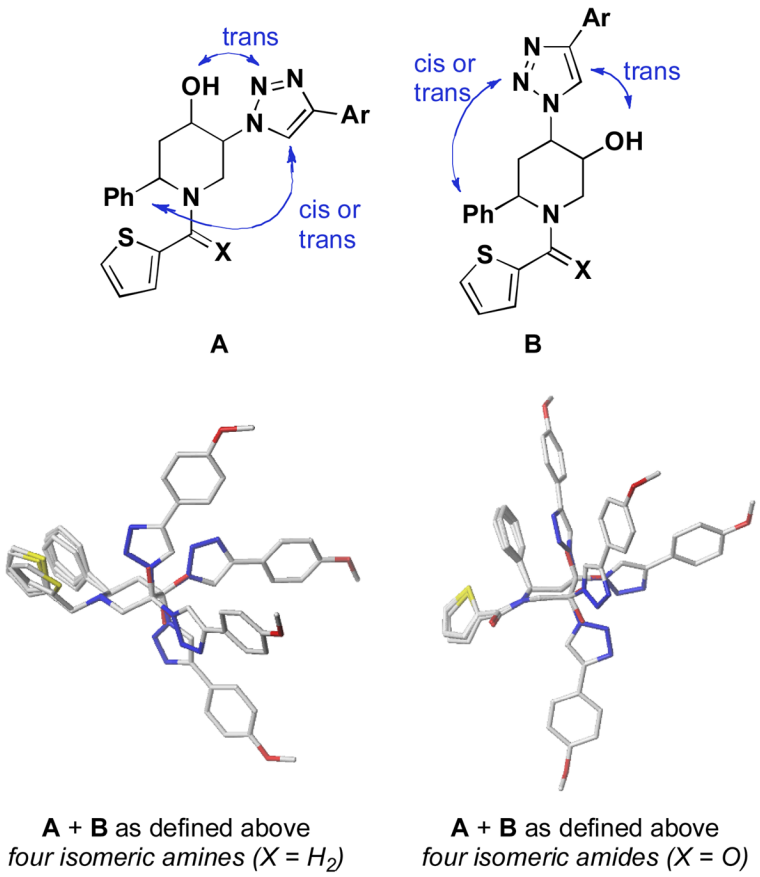


Figure 2.

Conformational diversity of targeted library containing sp^3 and sp^2 hybridized *N*-substituted versions of scaffolds **A** and **B**. In all, eight idealized conformers (four amines and four amides, all chair piperidines) are shown in the two overlays. Details, including the calculations of individual structures, are provided in Supporting Information.

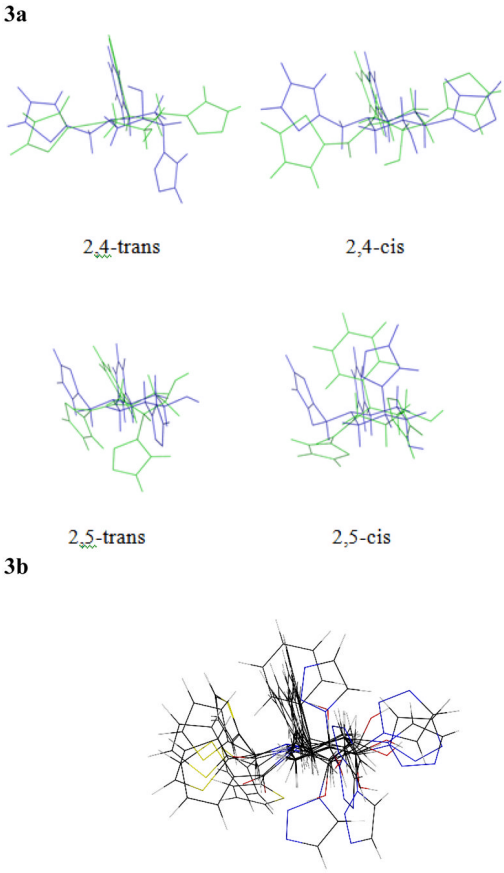
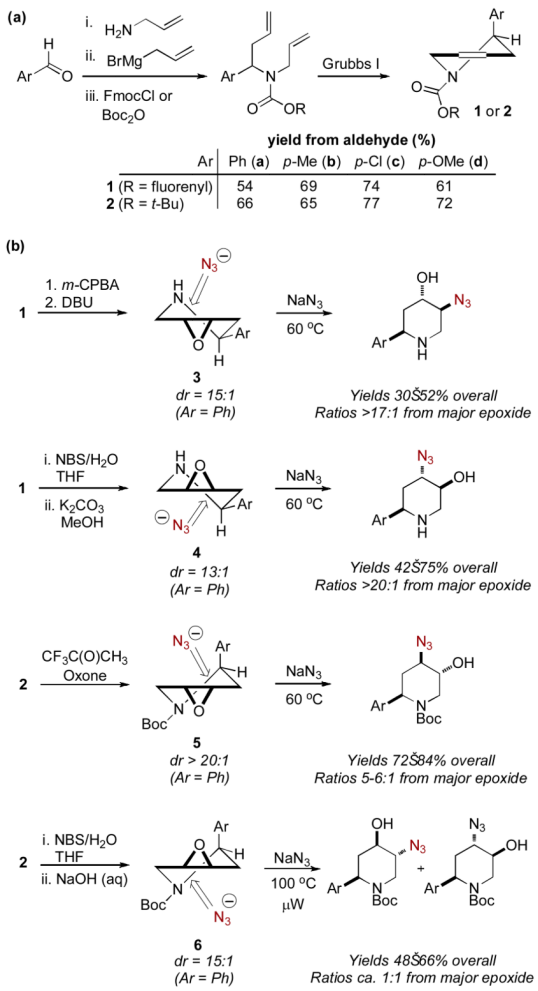


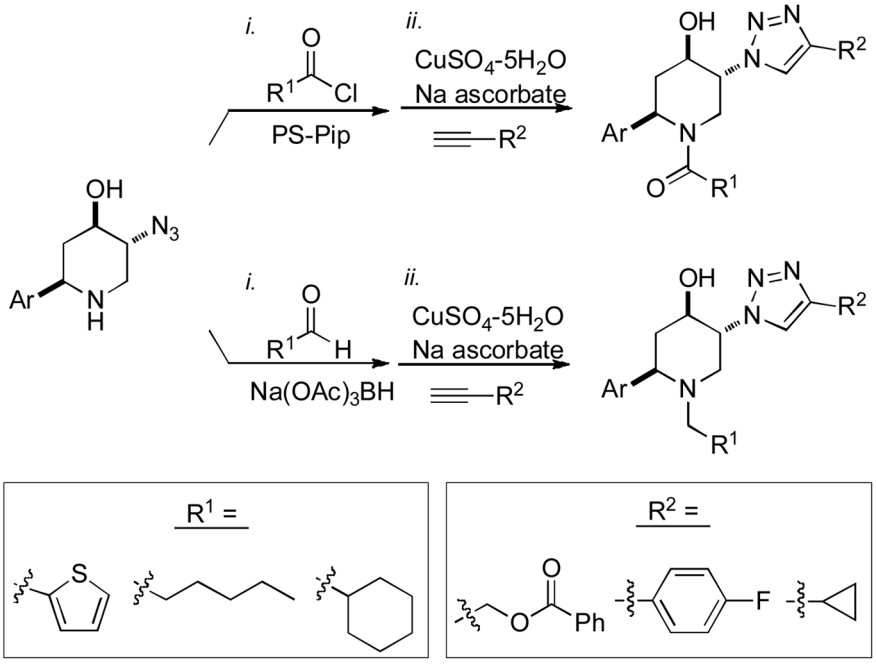
Figure 3.

(a) Overlays contrasting amino-piperidine conformation (blue) with the corresponding amido-piperidine conformation (green) for each isomeric pair (NMR). (b) Overlay showing the chemical space occupied by the entire library. For each case: Ar = Ph, R^1 = 2-thiphene, R^2 = CH_2OBz. For individual conformational analyses, see the Supporting Information.



Scheme 1.

Preparation of scaffold precursors via (a) tetrahydropiperidine synthesis and (b) stereoselective epoxidation reactions and allylic strain control of regiochemistry of epoxide ring opening (general conditions for azidation: NaN_3, NH_4Cl, $MeOH/H_2O$, 60 °C).



Scheme 2.
Scaffold diversification.