Heterocycles

DOI: 10.1002/anie.201007133

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

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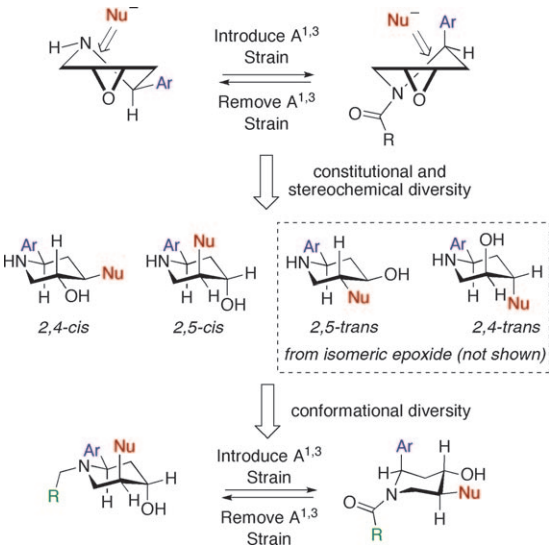
Screening approaches to probe molecules for drug discovery require access to high-quality, small-molecule libraries. One contemporary challenge in providing such access is the construction of libraries that maximize the coverage of chemical (functional group), stereochemical, and spatial diversity in 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).

Herein we describe a conformational switching approach toward shape-diverse piperidine libraries in which the presence or absence of 1,3-allylic strain ($A^{1,3}$ strain)[3] is leveraged to 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 in Scheme 1 for a series of substituted 2-arylpiperidines. 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 because of the minimization of 1,3-diaxial interactions) or sp^2 (Ar preferring axial position because of $A^{1,3}$ 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- versus 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 compounds in the library could then be substituted at N by a different set of alkyl or acyl substituents, thus leading to a doubling of the library members through *conformational diversity*.



Scheme 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.

We chose to demonstrate this approach by preparing a library based on the triazole-containing piperidines shown in Scheme 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), thus 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 3. Four 2-aryl-1,2,3,6-tetrahydropyridines were constructed from substituted benzaldehydes[8] in two steps by bisallylation/N-acylation and subsequent ring-closing metathesis. 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] By using *m*-CPBA or methyl-

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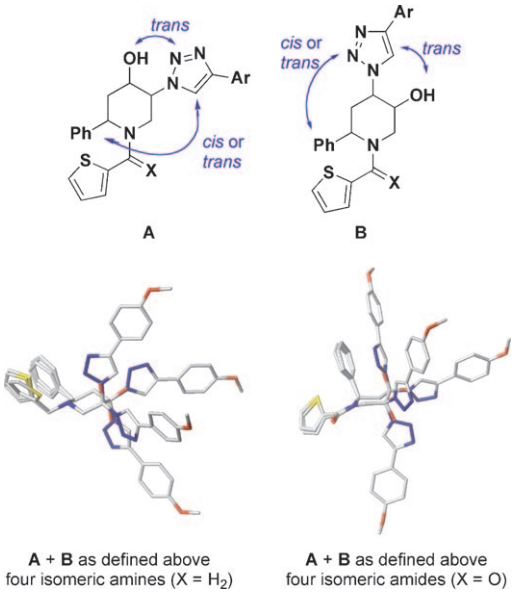
[**] This work was supported by the National Institute of General Medical Sciences (P50 69663).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007133.

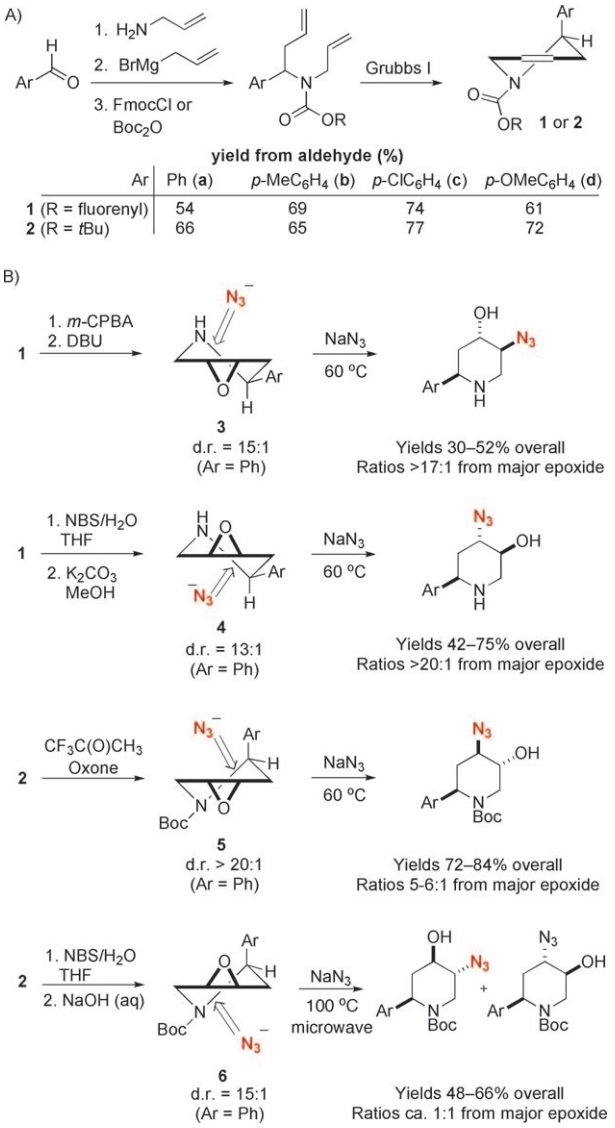


Scheme 2. Conformational diversity of targeted library containing sp^3 and sp^2 hybridized N-substituted versions of scaffolds **A** and **B**. In all, eight idealized conformers (four amines and four amides, all piperidines as chairlike conformation) are shown in the two overlays. Details, including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

(trifluoromethyl)dioxirane,[9] the 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 *syn*-epoxides **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 3b 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 because of competing electronic and stereoelectronic preferences for this epoxide (see the Supporting Information for details). However, even in this case, we were able to isolate more than 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.

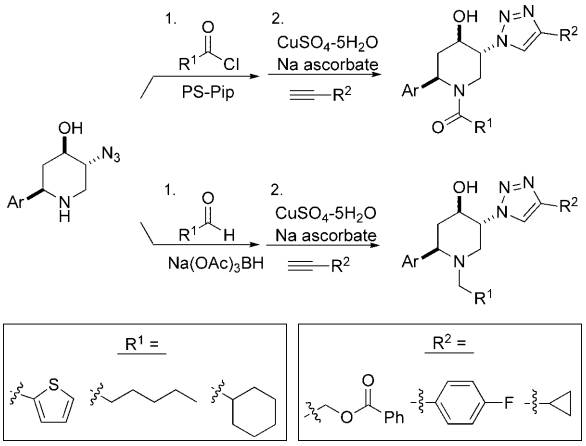
The scaffolds were decorated by removal of the Boc group (if present) and either subsequent reductive alkylation or N acylation, and finally, a copper-induced triazole formation step (Scheme 4).[13] For this initial, speculative screening library, we chose a relatively small number of substituents that represent a range of aliphatic and aromatic diversity at the newly introduced positions. The total number of compounds



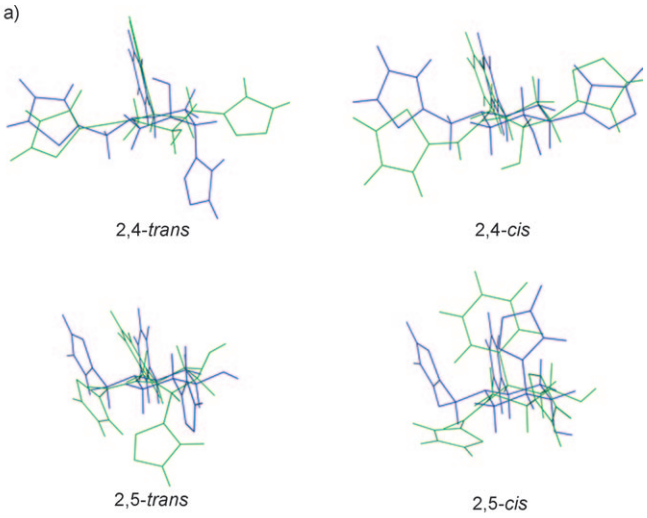
Scheme 3. Preparation of scaffold precursors by A) tetrahydropiperidine synthesis and B) stereoselective epoxidation reactions and allylic strain control of regiochemistry of epoxide ring opening (general reaction conditions for azidation: NaN_3, NH_4Cl, MeOH/H_2O (3:1), 60 °C). Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethyloxycarbonyl, *m*CPBA = *meta*-chloroperbenzoic acid, NBS = *N*-bromosuccinimide, THF = tetrahydrofuran.

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. After parallel synthesis, the library was prepared for screening by mass-directed HPLC purification, yielding ultimately 268 compounds in greater than 90 % purity (UV) and greater than 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 ^1H NMR spectroscopy using coupling constant analysis. The data revealed that each functionalized amino/piperidine



Scheme 4. Scaffold diversification. PS-Pip = polystyrene-based piperidine.



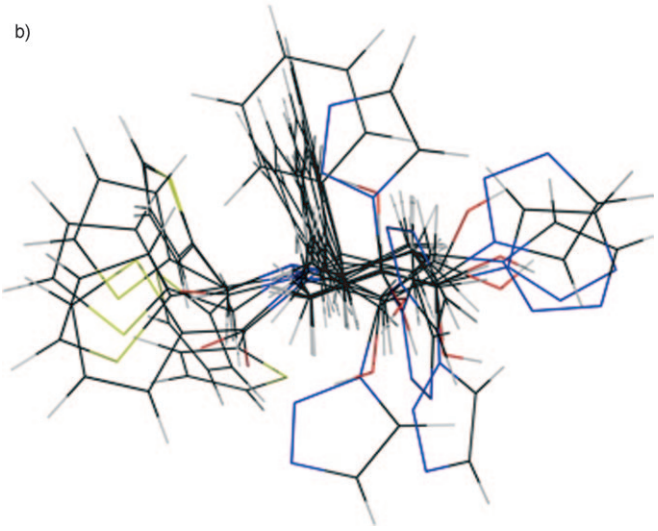


Figure 1. a) Overlays contrasting amino/piperidine conformation (blue) with the corresponding amido/piperidine conformation (green) for each isomeric pair (NMR). b) Overlay showing the chemical space occupied by the entire library. For each case: Ar = Ph, R^1 = 2-thiophene, $R^2 = CH_2OBz$. For individual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

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 eight stereochemical families of the triazole-containing piperidines (4 amines and 4 amides) are shown in Figure 1.[14] Figure 1 a 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 conformations, thus placing the 2-aryl substituents in the equatorial position. The 2,4-*trans* family of amino/piperidines exhibited a slight distortion from an ideal chair conformation, while still placing the 2-aryl substituents in a pseudoequatorial position. The corresponding 2,5-*cis* and 2,4-*trans* families of amido/piperidines adopted the opposite chair conformations, thus placing the 2-aryl substituents in the axial position. However, rather than adopting chair conformations and placing all three non-hydrogen substituents (Ph, OH, triazole) in axial positions, the 2,5-*trans* amido/piperidines exhibited twistlike 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 the development of structure–activity relationship (SAR) studies (Figure 1 b).

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 druglike 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.

Received: November 12, 2010
Revised: January 13, 2011
Published online: February 23, 2011

Keywords: compound libraries · heterocycles · strained molecules · synthetic methods

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[14] Details of the conformational analyses and depictions of the individual isomers are provided in the Supporting Information.

