ACS Combinatorial Science

RESEARCH ARTICLE

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Synthesis of a Stereochemically Diverse Library of Medium-Sized Lactams and Sultams via S_NAr Cycloetherification

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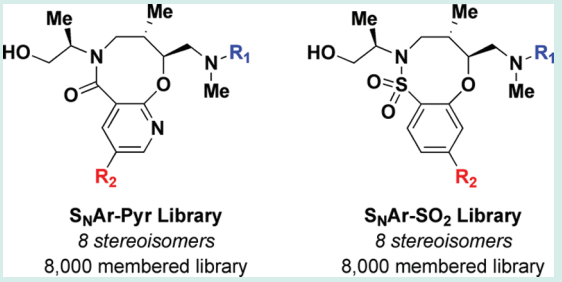
Supporting Information

ABSTRACT: We have implemented an aldol-based "build/couple/pair" (B/C/P) strategy for the synthesis of stereochemically diverse 8-membered lactam and sultam scaffolds via S_NAr cycloetherification. Each scaffold contains two handles, an amine and aryl bromide, for solid-phase diversification via N-capping and Pd-mediated cross coupling. A sparse matrix design strategy that achieves the dual objective of controlling physicochemical properties and selecting diverse library members was implemented. The production of two 8000-membered libraries is discussed including a full analysis of library purity and property distribution. Library diversity was evaluated in comparison to the Molecular Library Small Molecule Repository (MLSMR) through the use of a multifusion similarity (MFS) map and principal component analysis (PCA).



KEYWORDS: library design, diversity-oriented synthesis, physicochemical properties, diversity-ranking, maximum dissimilarity, sparse matrix

INTRODUCTION

Diversity-oriented synthesis (DOS) is a commonly employed strategy for the facile assembly of structurally diverse molecules rivaling the complexity of natural products.[1] A primary goal of DOS is the generation of compounds with both skeletal and stereochemical diversity. Recently, we described an aldol-based "build/couple/pair" (B/C/P) strategy for the generation of a stereochemically diverse set of medium- and large-sized rings via a common linear template.[2] Here, we take advantage of this aldol-based strategy for the synthesis of fused pyridines (**1**) and fused sultams (**2**) (Figure 1). In the *build* phase, a series of asymmetric *syn*- and *anti*-aldol reactions were applied to produce four stereoisomers of a Boc protected β-hydroxy-γ-amino acid (**3**). Both stereoisomers of PMB-protected alaninol (**4**) were also obtained to complement the aldol-derived acids. In the *couple* step, all 8 stereoisomeric amides were synthesized from the chiral acid and amine building blocks. The amide was subsequently reduced to generate a secondary amine (**5**). Finally, in the *pair* phase, we utilized an intramolecular S_NAr[3] as the key cyclization step to access either the S_NAr-Pyr lactam (**1**)[4] or the S_NAr-SO_2 sultam (**2**).[5] This work is based on our previous success with the S_NAr reaction for the synthesis of 8- and 9-membered lactams (**6** and **7**).[2] Two 8000-membered libraries were produced using solid-phase synthesis techniques. All 8 stereoisomers were prepared for each scaffold, providing not only structure−activity relationships (SAR) in primary screens, but also stereo/structure−activity relationships (SSAR). A sparse matrix library design strategy[6,7] was utilized to aid in the selection of diverse library members with built-in structural analogs and physicochemical properties suitable for high-throughput screening and downstream discovery.

Solution-Phase Synthesis of Library Scaffolds. The synthesis of S_NAr-Pyr scaffold **1** began with acylation of linear amine **5** using 5-bromo-2-chloronicotinoyl chloride **8**, which afforded amide **9a**−**d** in good yields (Table 1). The subsequent intramolecular S_NAr reaction showed strong stereochemical dependence. Amide **9a** was converted directly to **10a** in excellent yield (94%) upon treatment with TBAF in THF at 65 °C. However, application of these conditions to **9b** provided lactam **10b** in modest yield (71%). Fortunately, a two step protocol involving TBS-removal with CsF followed by cyclization with NaH in THF proved effective. Using this protocol, the *syn*-aldol derived substrates **9a** and **9b** were converted to **10a** and **10b**, respectively, in high yields (96−98%) without need for chromatographic purification. Meanwhile, S_NAr reaction of *anti*-aldol-derived substrates **9c** and **9d** proved challenging, as the two-step protocol led to formation of significant amount of oxazolidinone side-product (40−50%).[8] Use of the one-step deprotection/cyclization using TBAF in THF led to incomplete reaction even after 5 days and repeated addition of TBAF. Finally, the choice of solvent and the use of TBAF in DMF led to complete conversion of the S_NAr reaction with minimal oxazolidinone formation (10−15%). Under these conditions, the *anti*-aldol derived substrates **9c** and **9d** gave 84% and 80% of **10c** and **10d**, respectively. As our plan called for loading onto solid support

Received: February 1, 2011
Revised: April 12, 2011
Published: April 28, 2011

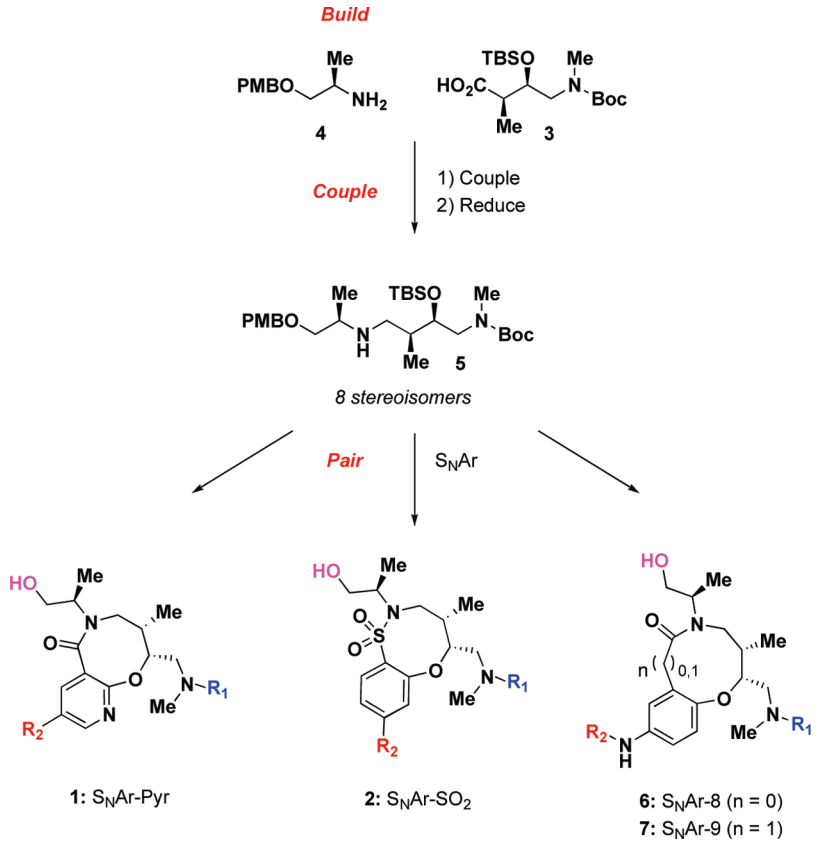


Figure 1. Synthesis of medium-sized ring scaffolds from a common linear intermediate.

(SynPhaseLanterns)[9] using an acid-labile silicon linker, the Boc protecting group was exchanged for Fmoc, and subsequent DDQ-mediated PMB removal led to the isolation of primary alcohol **1** (Scheme 1). S_NAr-Pyr scaffolds **1a**−**d** (and the corresponding enantiomers *ent*-**1a**−**d**) were prepared in 15−20 g quantities using this 5-step sequence starting from linear amine **5**.

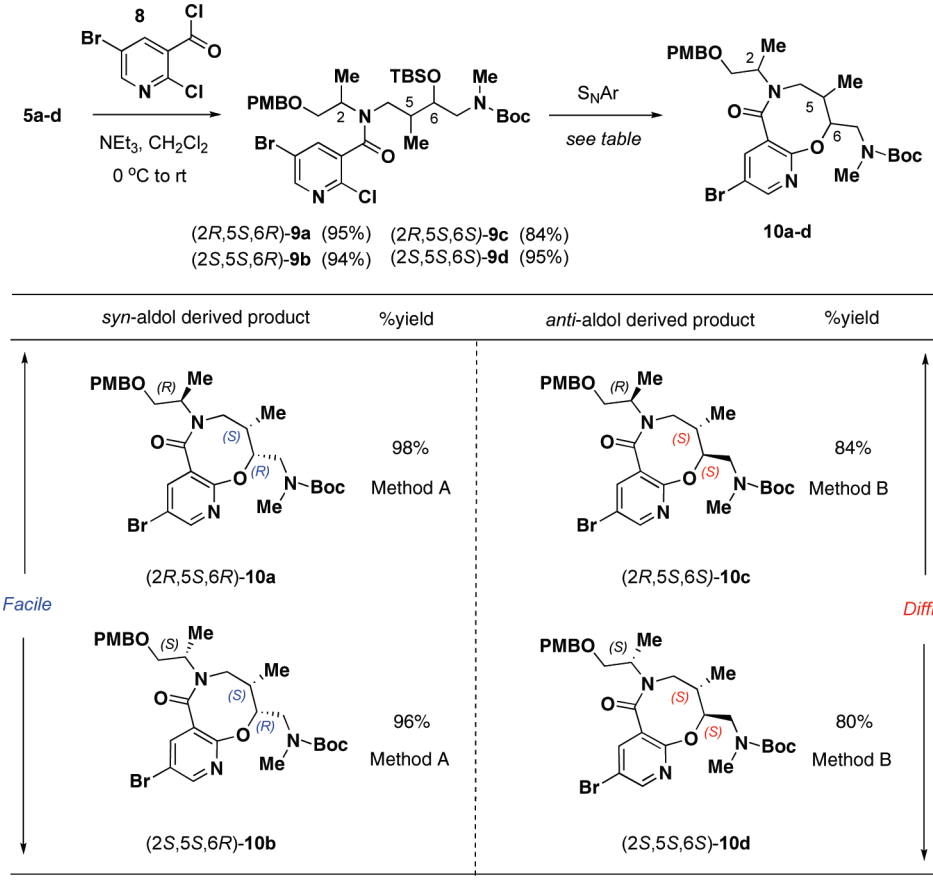
A similar approach as described above was utilized in the synthesis of fused bicyclic sultams.[5] All stereoisomers of the common linear intermediate **5** were coupled with 4-bromo-2-fluorobenzene sulfonyl chloride **12** in good yield to give the S_NAr precursor **13** (Table 2). Similar to the fused pyridine systems, the success of the S_NAr reaction involving sulfonamides **13** varied depending on the relative stereochemistry of the adjacent stereocenters. Meanwhile, sulfonamides **13c** and **13d**, derived from the *syn*-aldol reaction, were easily converted in excellent yield to sultams **14a** and **14b**, respectively, by treatment with CsF in DMF at 85 °C. Sulfonamides **13c** and **13d**, both derived from the *anti*-aldol, were converted to sultams **14c** and **14d** utilizing the two-step approach that was employed for substrates **9a** and **9b**. First, treatment with CsF gave a mixture of uncyclized TBS deprotected material along with desired **14**. Treatment of the mixture with NaH gave complete conversion to **14c** and **14d**, respectively, in good yield over the two steps. It is important to note, independent of the protocol used, the product could be isolated in sufficient purity without silica gel purification. This is in contrast to the S_NAr-Pyr substrates, where the use of TBAF required silica gel purification. Completing the synthetic sequence required the exchange of the Boc group for Fmoc followed by DDQ-mediated PMB removal to afford the desired S_NAr-SO_2 scaffolds **2a**−**d** (and the corresponding enantiomers *ent*-**2a**−**d**) in good yield in 15−20 g quantities (Scheme 2).

Library Design. With the S_NAr-Pyr and S_NAr-SO_2 scaffolds in hand, a sparse matrix design strategy was implemented to select library members to be synthesized.[6] A virtual library was constructed for each scaffold incorporating all possible building block combinations at R_1 (amine) and R_2 (aryl bromide) using a master list of reagents (R_1 = sulfonyl chlorides, isocyanates, acids and aldehydes; R_2 = boronic acids and alkynes). Physicochemical property filters were then applied to eliminate building block combinations that led to products with undesirable physicochemical properties. Property filters included the following: MW ≤625, ALogP −1 to 5, H-bond acceptors and donors ≤ 10, rotatable bonds ≤ 10, and TPSA ≤ 140. To increase the percentage of "Lipinski compliant" products, a "75/25" rule was also implemented where 75% of all library members had MW <500. A total of 1000 compounds per scaffold were selected from the remaining set using chemical similarity principles, maximizing diversity but retaining near neighbors for built-in SAR. The reagents selected for library production are shown below (Charts 1 and 2). The same set of reagents was used for each stereoisomer thereby maintaining the ability to generate SSAR for each building block combination.

Solid-Phase Library Production. The construction of the S_NAr-Pyr and S_NAr-SO_2 libraries is outlined in Scheme 3. Scaffolds **1a**−**d** and **2a**−**d** (and the corresponding enantiomers) were loaded onto silicon-functionalized PS-SynPhase Lanterns (L-series) activated with TfOH in the presence of 2,6-lutidine (average loading level = 18 umol/Lantern).[9,10] The first diversity site, a secondary amine, was then revealed under standard conditions required for Fmoc removal (20% piperidine in DMF), and amines **16a**−**d** and **17a**−**d** were capped with the selected

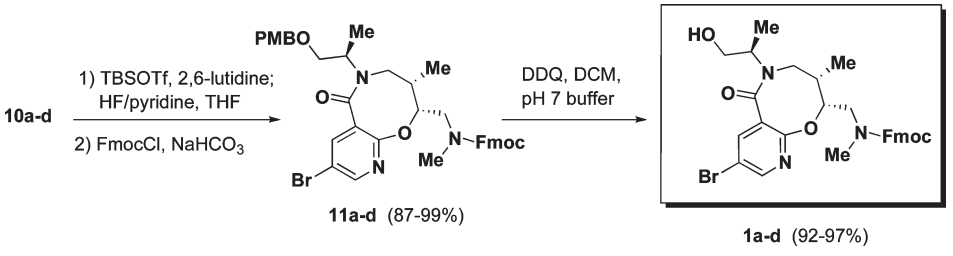
dx.doi.org/10.1021/co2000218 |*ACS Comb. Sci.* 2011, 13, 365–374

Table 1. S_NAr Cyclization to Form Lactams 10a−d[a]



[a] Method A: (a) CsF (5 equiv), DMF, 85 °C; (b) NaH (5 equiv), THF, 0 °C to rt; Method B: TBAF (5 equiv), DMF, 65 °C.

Scheme 1. Preparation of Final S_NAr-Pyr Scaffold 1

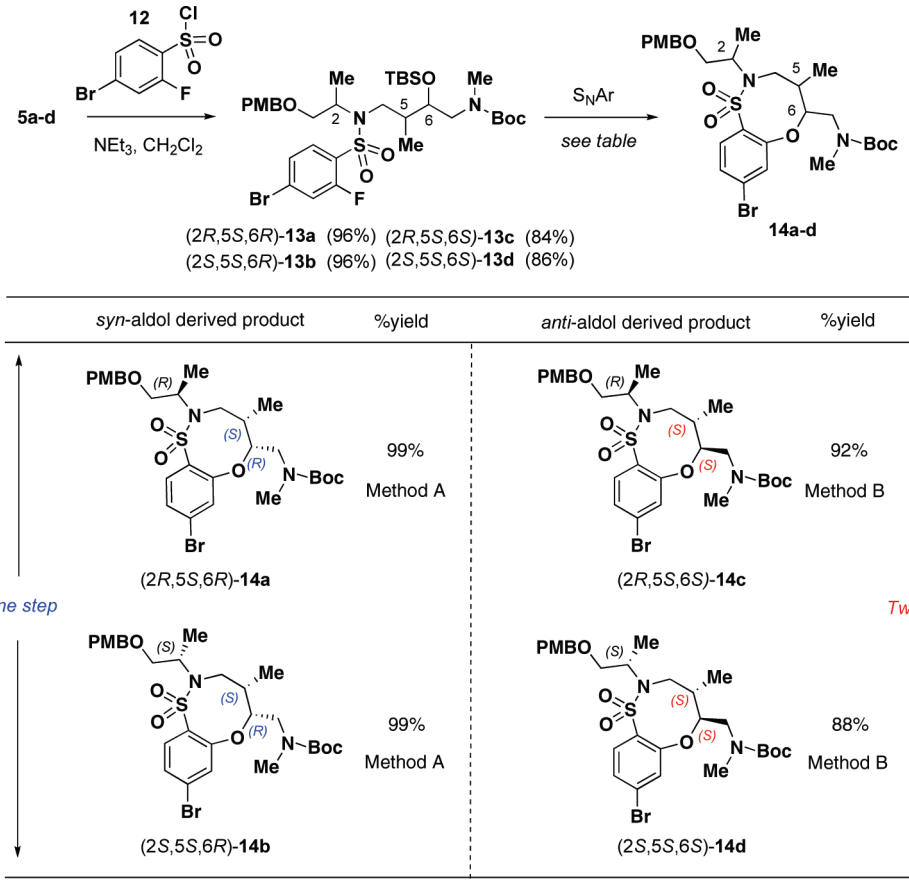


electrophiles (sulfonyl chlorides *1*−*11*, isocyanates *12*−*26*, carboxylic acids *27*−*50*, and aldehydes *51*−*71*) or skipped (*72*) to yield compounds **18a**−**d**{*1*−*72*} and **19a**−**d**{*1*−*72*}. Next, Sonogashira and Suzuki cross-coupling reactions were carried out to introduce appendage diversity at R_2. For the Sonogashira reaction, the Lantern-bound aryl bromides were heated at 60 °C in DMF overnight in the presence of DIEA, CuI, $Pd(PPh_3)_2Cl_2$, and the selected alkynes {*1*−*24*}. Meanwhile, for the Suzuki reaction, the Lanterns were heated at 60 °C in EtOH for 5 days in the presence of Et_3N, $Pd(PPh_3)_2Cl_2$ and boronic acids {*25*−*44*}. Removal of residual Pd and Cu was achieved by washing the Lanterns with 0.1 M NaCN. Finally, cleavage with HF-pyridine in THF afforded library members **20a**−**d**{*1*−*72*,*1*−*45*} and **21a**−**d**{*1*−*72*,*1*−*45*} with an average yield of 90 and 91%, respectively.[11]

All library products were analyzed by ultraperformance liquid chromatography, and compound purity was assessed by UV detection at 210 nm. An overview of compound purity for the S_NAr-Pyr and S_NAr-SO_2 libraries with respect to building blocks and stereochemistry is provided in Figures 2 and 3. The average purity of the S_NAr-Pyr library was 85%, with 89% of the library being >75% pure, while the average purity of the S_NAr-SO_2 library was 85%, with 91% of the library being >75% pure. (See Figures S5 and S6, Supporting Information). In general, all building blocks performed well during the library production with the exception of certain reagent combinations. For example, compounds containing the dimethylisoxazole urea (**18a**−**d**{*25*} and **19a**−**d**{*25*}) performed poorly in the subsequent Suzuki reaction, presumably because of reduction of the N−O bond, as an M + 2 impurity was observed by LCMS for

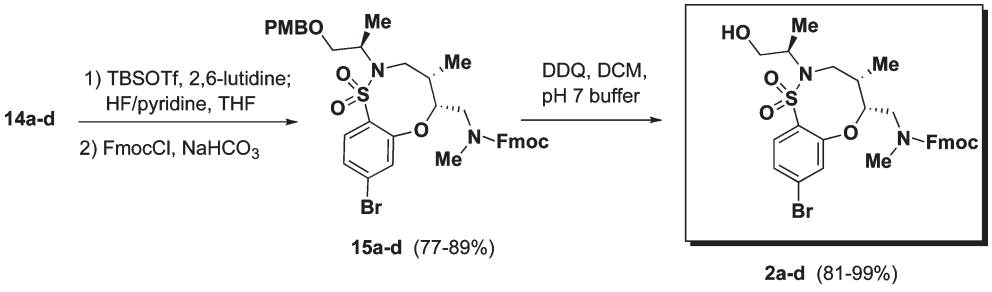
dx.doi.org/10.1021/co2000218 |*ACS Comb. Sci.* 2011, 13, 365–374

Table 2. S_NAr Cyclization to Form Sultams 14a−d[a]



[a] Method A: CsF (5 equiv), DMF, 85 °C; Method B: (a) CsF (5 equiv), DMF, 85 °C; (b) NaH (1 equiv), THF, 0 °C to rt.

Scheme 2. Preparation of Final S_NAr-SO_2 Scaffold 2



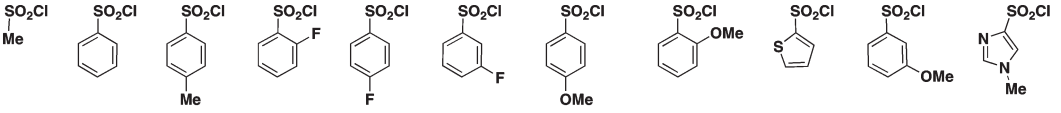
this reagent combination. Meanwhile products of reductive alkylation with 3-pyridyl benzaldehyde **18a−d**{*68*} and **19a−d**{*68*} performed poorly in the subsequent Sonogashira reaction. The success of the cross-coupling reaction in the presence of a free amine at R_1 to produce library members **20a−d**{*72,1−44*} and **21a−d**{*72,1−44*} was highly variable depending on the nature of the boronic acid and alkyne but in general was problematic. Surprisingly, the use of acetaldehyde for reductive alkylation at R_1 resulted in compounds (**20a−d**{*2,1−72*} and **21a−d**{*2,1−72*}) of low purity for both libraries.

Library Analysis. The S_NAr-Pyr and S_NAr-SO_2 libraries originate from the same linear intermediate (**5**, Figure 1) and vary in the pairing stage giving rise to different molecular architectures. The S_NAr-Pyr and S_NAr-SO_2 scaffolds have differences in their physicochemical properties such as molecular weight (372/407), ALogP (1.2/1.5), and TPSA, (75/87) that ultimately influence product selection (Table 3). As evident in Figures 2 and 3 the selected building block combinations vary significantly for these two scaffolds. For example, products are spread evenly in the S_NAr-Pyr library (Figure 2), as compared to the S_NAr-SO_2 library (Figure 3) for which small aliphatic building block combinations are favored (e.g., acids *27−34* and aldehydes *51−54*). Analysis of the S_NAr-Pyr and S_NAr-SO_2 libraries reveals that the property profile for each library was within the intended range for the library

dx.doi.org/10.1021/co2000218 |*ACS Comb. Sci.* 2011, 13, 365–374

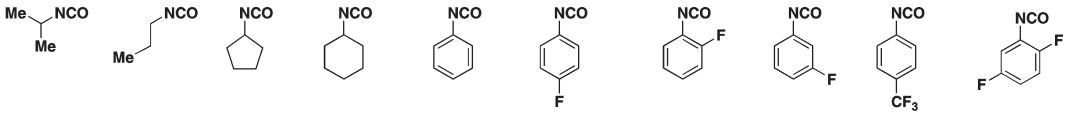
Chart 1. Building Blocks {*1*−*72*} Used for Amine Capping at R_1

Sulfonyl Chlorides {1-11}:

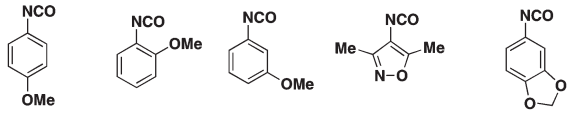


1 *2* *3* *4* *5* *6* *7* *8* *9* *10* *11*

Isocyanates {12-26}:

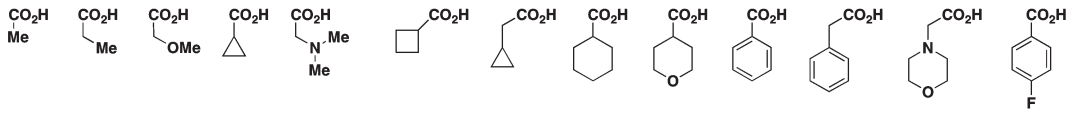


12 *13* *14* *15* *16* *17* *18* *19* *20* *21*

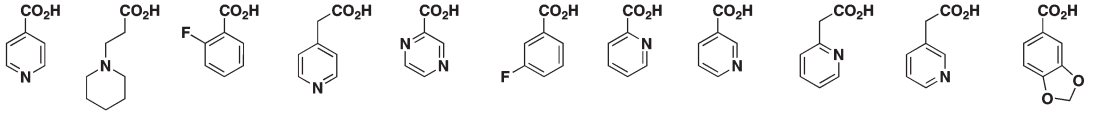


22 *23* *24* *25* *26*

Carboxylic Acids {27-50}:

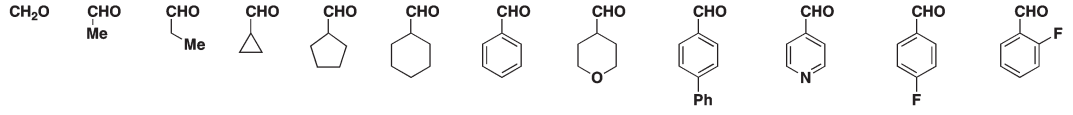


27 *28* *29* *30* *31* *32* *33* *34* *35* *36* *37* *38* *39*

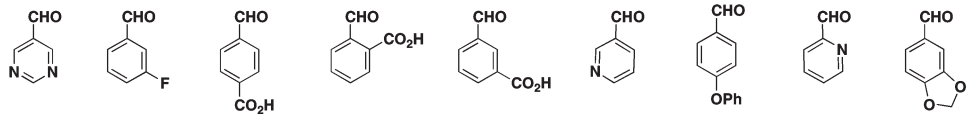


40 *41* *42* *43* *44* *45* *46* *47* *48* *49* *50*

Aldehydes {*51-71*}:



51 *52* *53* *54* *55* *56* *57* *58* *59* *60* *61* *62*



63 *64* *65* *66* *67* *68* *69* *70* *71*

Skip {*72*}:

H

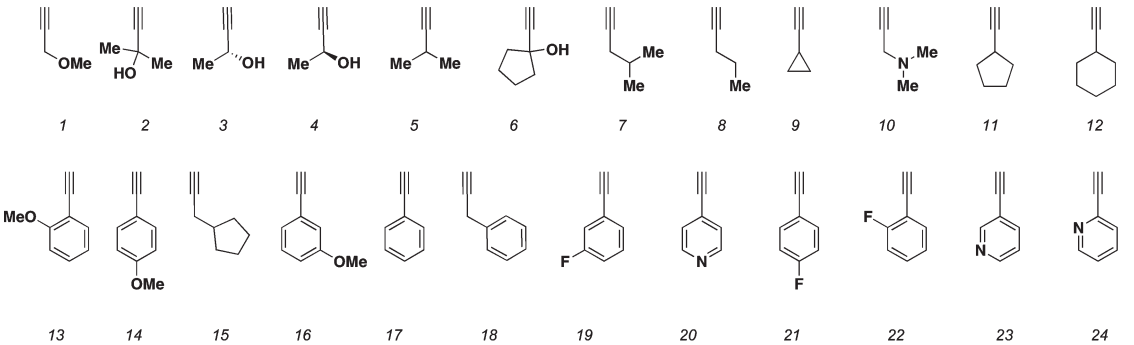
design (MW ≤ 625, ALogP −1 to 5, H-bond acceptors and donors ≤ 10, rotatable bonds ≤ 10, and TPSA ≤ 140). Not surprisingly, S_NAr-SO_2 library members have higher mean values for MW and TPSA because of inherent differences between the initial scaffolds.

The structural diversity of library members resulting from S_NAr-Pyr and S_NAr-SO_2 pathways was analyzed in comparison to the NIH Molecular Library Small Molecule Repository (MLSMR) as we intended to submit a subset of these compounds to the collection at the time of the analysis. We employed multifusion similarity (MFS) maps for the comparison of each collection using extended connectivity fingerprints (ECFP_4) for molecular representation and Tanimoto coefficient as the

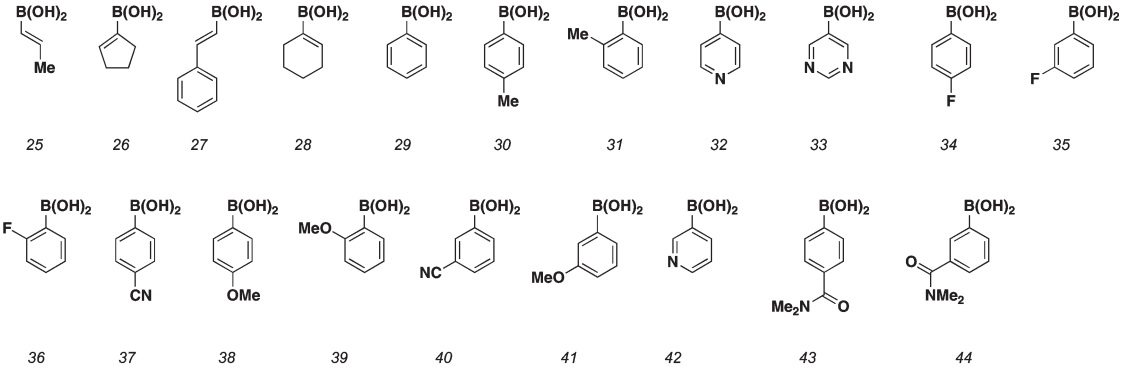
dx.doi.org/10.1021/co2000218 |*ACS Comb. Sci.* 2011, 13, 365–374

Chart 2. Building Blocks {*1*−*45*} Used for Cross-Coupling Reactions at R_2

Alkynes {1-24}:



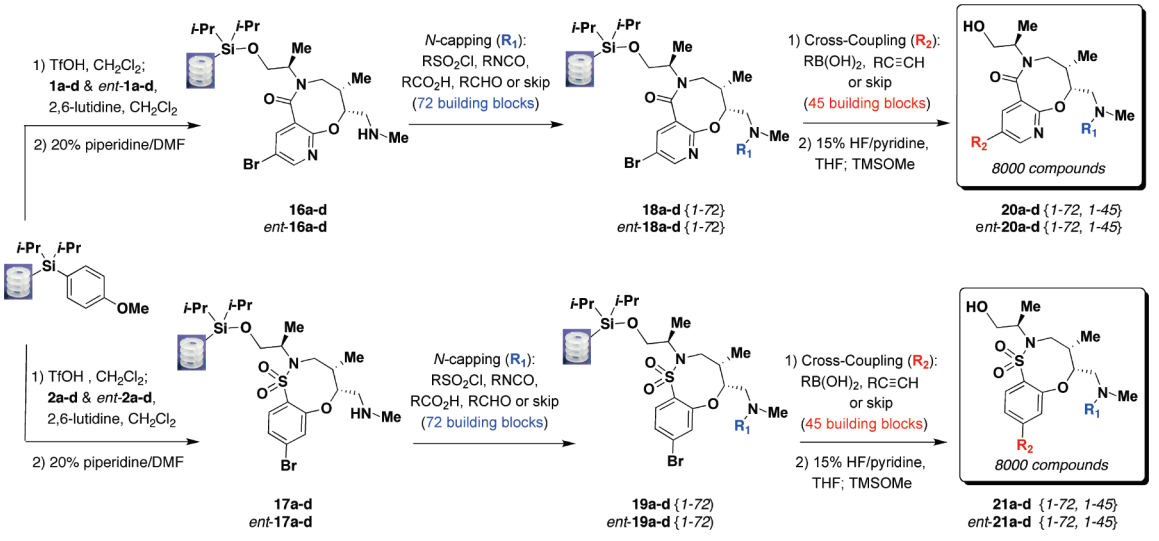
Boronic Acids {25-44}:



Skip {45}:

Br

Scheme 3. Solid-Phase Synthesis of S_NAr-Pyr and S_NAr-SO_2 Libraries on SynPhase Lanterns



similarity measure.[13] In this method, each molecule in the test set (S_NAr-Pyr and S_NAr-SO_2 library members) is compared to every molecule in the reference set (MLSMR) and the largest similarity score and the mean similarity score to the reference set is obtained.

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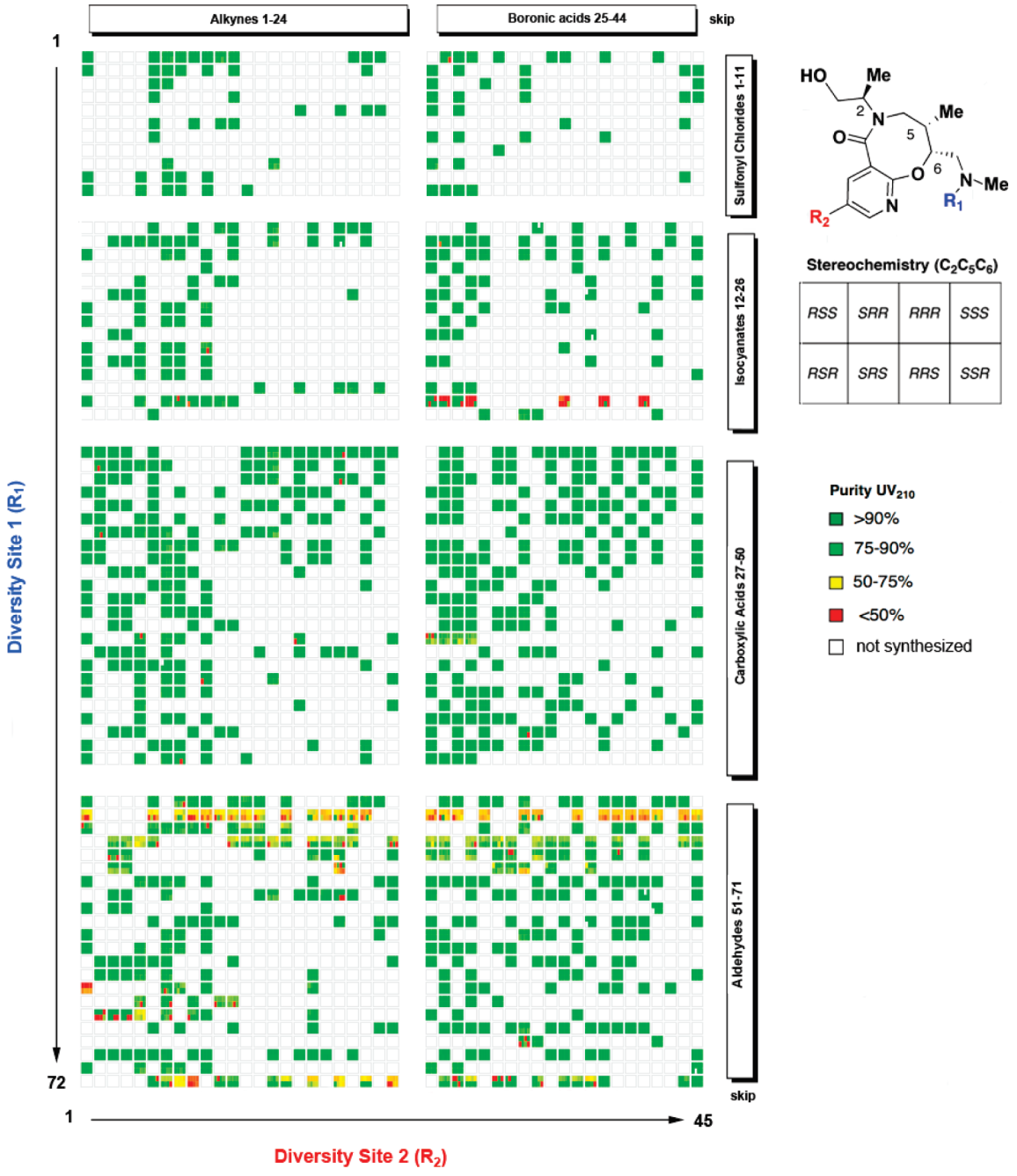

Figure 2. Purity analysis (UV 210 nm) for S_NAr-Pyr Library. Library members are displayed as blocks of 8 stereoisomers (see legend) and reagents used for solid-phase diversification are shown on the *x*- and *y*-axes. (See Charts 1 and 2 for detailed list of reagents).[12]

The resulting mean similarity (*x*-axis) and maximum similarity (*y*-axis) values are plotted in two dimensions as a scatter plot facilitating the visual characterization and comparison. Figure 4 shows the MFS map comparing S_NAr-Pyr and S_NAr-SO_2 libraries to the MLSMR. Each data point in the map depicts a compound from the test set and its location was influenced by the reference set. (The reference compounds themselves do not appear in the plot.) The maximum mean similarity of each library is 0.15 indicative of their overall structural diversity with respect to the MLSMR reference set. There are no compounds with maximum similarity equal to or greater than 0.45 in the MLSMR, which clearly illustrates the regions of chemical space unexplored by the MLSMR.

We also carried out a principal components analysis (PCA)[14] using 16 structural and physicochemical descriptors (including MW, ALogP, rotatable bonds, and TPSA) for the MLSMR and S_NAr-Pyr and S_NAr-SO_2 libraries. The PCA plot is shown in Figure 5. The DOS libraries property space is embedded in the MLSMR property space with ~75% of compounds being Lipinski compliant. This observation is particularly important because it dispels the common notion that DOS may not render compounds with good properties.[15] While occupying desirable property space we have covered new chemical space of structural diversity.

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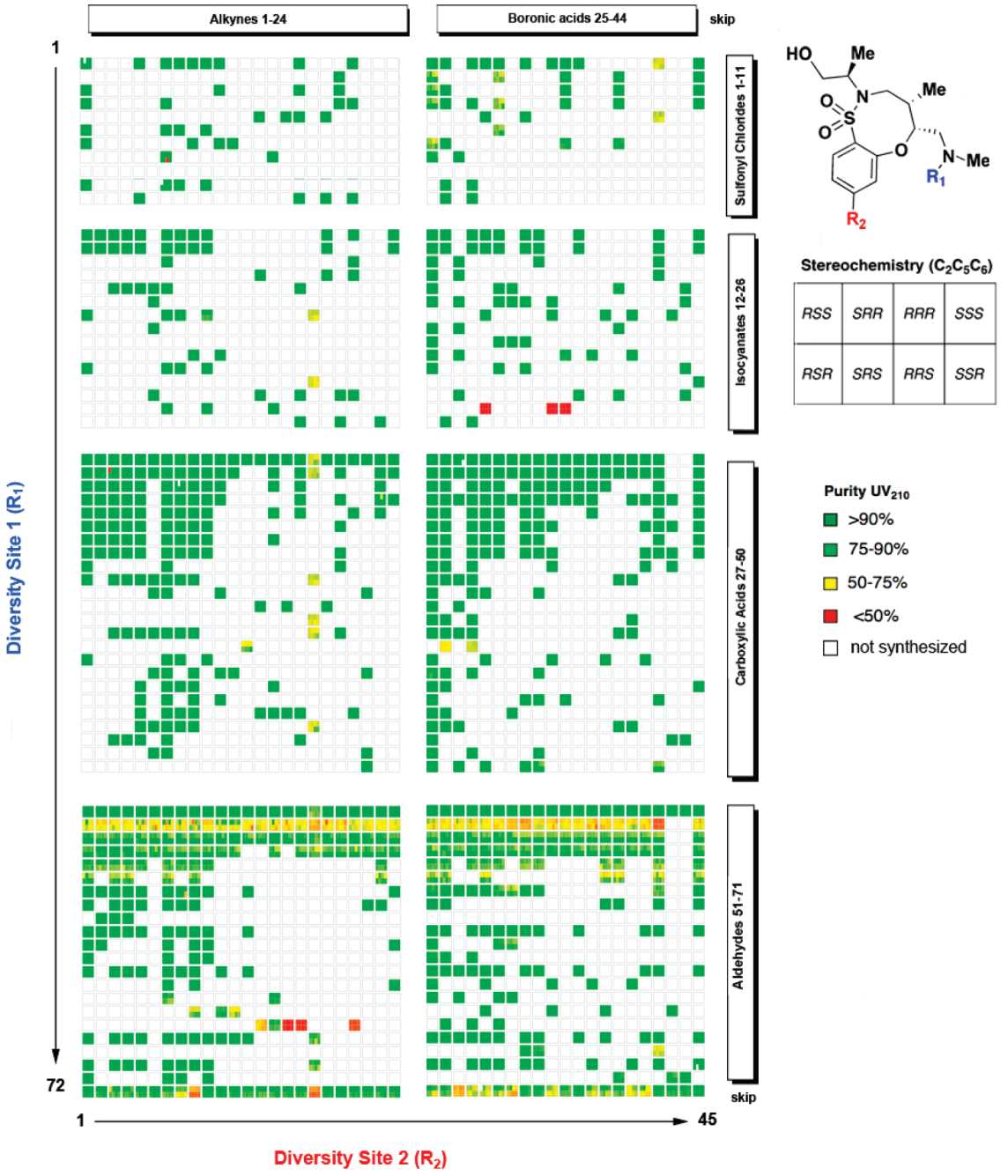

Figure 3. Purity analysis (UV 210 nm) for S_NAr-SO_2 Library. Library members are displayed as blocks of 8 stereoisomers (see legend) and reagents used for solid-phase diversification are shown on the *x*- and *y*-axes. (See Charts 1 and 2 for detailed list of reagents).[12]

Table 3. Property Analysis for S_NAr-Pyr and S_NAr-SO_2 Libraries

property	S_NAr-Pyr scaffold[a] (n = 1)	S_NAr-SO_2 scaffold[a] (n = 1)	S_NAr-Pyr library[b] (n = 7045)	S_NAr-SO_2 library[b] (n = 6690)
MW	372	407	484	504
ALogP	1.2	1.5	2.7	2.9
TPSA	75	87	95	105
rotatable bonds	4	4	7.3	7.2
HBA	5	5	6.1	6.0
HBD	2	2	1.3	1.3

[a] Property analysis of bare scaffolds, where R_1 and R_2 = H. [b] Property analysis (mean value) of all registered library samples passing QC requirements (purity >75%).

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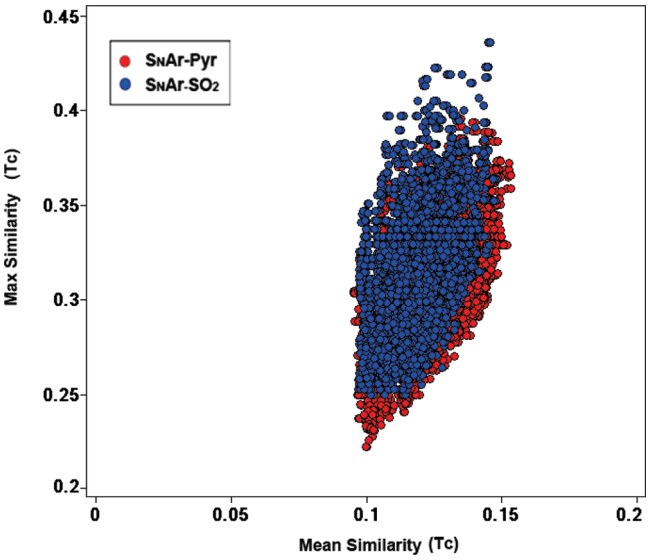

Figure 4. Multifusion similarity map comparing the S_NAr-Pyr (red) and S_NAr-SO_2 (blue) libraries to the MLSMR. The reference set (MLSMR) is not shown on the map (see text for details).

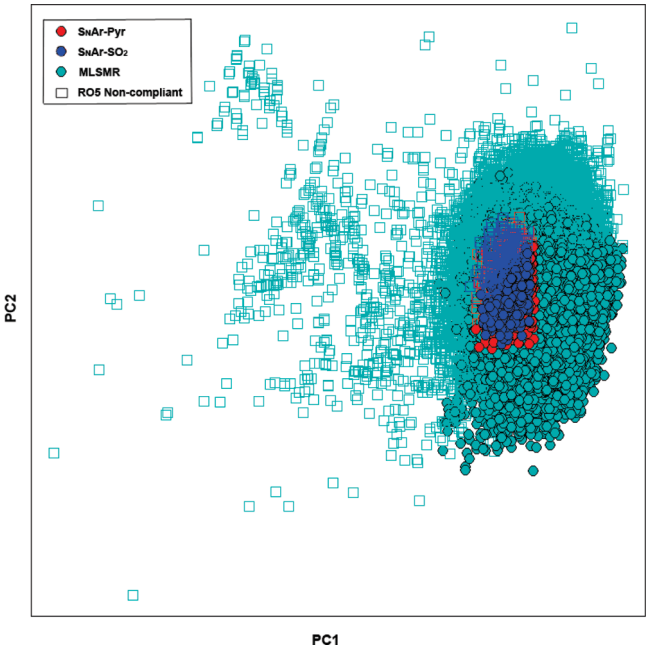

Figure 5. Principal component analysis of S_NAr-Pyr and S_NAr-SO_2 libraries compared to MLSMR. The 16 molecular descriptors used for PCA included molecular weight, ALogP, LogD, number of rotatable bonds, TPSA, number of nitrogen, oxygen, halogen, and sulfur atoms, hydrogen bond donors, and acceptors, aromatic rings, ring fusion degree, normalized number of ring systems, chiral centers, and fraction of sp^3.

CONCLUSION

In summary, we have implemented an aldol-based "build/couple/pair" (B/C/P) strategy for synthesis of stereochemically diverse 8-membered lactam and sultam scaffolds via S_NAr cycloetherification. A sparse matrix design strategy was implemented to select library members for synthesis to achieve a balance between diversity and built-in structural analogs. Analysis of final library members illustrates that the sparse matrix design achieved the intended outcome of structural diversity and favorable physicochemical properties. Screening of these compounds is currently underway in multiple biochemical and cell-based assays.

ASSOCIATED CONTENT

Supporting Information. Additional material as described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

This work was funded in part by the NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development (Broad Institute CMLD; P50 GM069721), as well as the NIH Genomics Based Drug Discovery U54 grants Discovery Pipeline RL1CA133834 (administratively linked to NIH Grants RL1HG004671, RL1GM084437, and UL1RR024924). We would like to thank Dr. Stephen Johnston for analytical support and Anita Vrcic for sorting, cleavage and formatting of library members.

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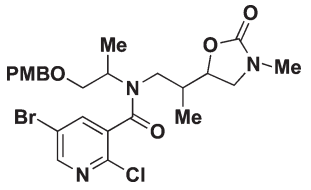
(8) Structure of oxazolidinone byproduct formed in the presence of NaH:



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(10) Lanterns were equipped with radio frequency transponders to enable tracking and sorting of library members.

(11) Average yield adjusted for purity. See Supporting Information (Figures S1−S4) for yield analysis.

(12) A detailed account of purity and yield for each library compound is provided as Supporting Information.

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