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Application of a Catalytic Asymmetric Povarov Reaction using Chiral Ureas to the Synthesis of a Tetrahydroquinoline Library

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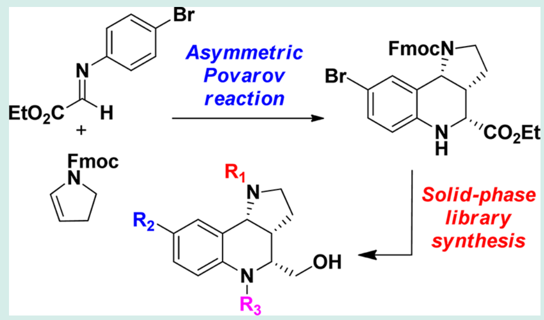
Supporting Information

ABSTRACT: A 2328-membered library of 2,3,4-trisubstituted tetrahydroquinolines was produced using a combination of solution- and solid-phase synthesis techniques. A tetrahydroquinoline (THQ) scaffold was prepared via an asymmetric Povarov reaction using cooperative catalysis to generate three contiguous stereogenic centers. A matrix of 4 stereoisomers of the THQ scaffold was prepared to enable the development of stereo/structure−activity relationships (SSAR) upon biological testing. A sparse matrix design strategy was employed to select library members to be synthesized with the goal of generating a diverse collection of tetrahydroquinolines with physicochemical properties suitable for downstream discovery.



KEYWORDS: *Povarov reaction, chiral urea, tetrahydroquinoline, asymmetric, solid-phase*

■ INTRODUCTION

The acid-catalyzed [4 + 2] cycloaddition of *N*-aryl imines and electron-rich olefins, known as the Povarov reaction,[1] is a powerful method for the synthesis of tetrahydroquinolines (THQ), a commonly occurring motif in a variety of natural products and biologically active compounds (Figure 1).[2] Up to three contiguous stereocenters can be generated simultaneously in the Povarov reaction, and enantioselective catalytic variants of this reaction have been identified recently.[3] As part of our ongoing efforts to develop new methods for producing collections of stereochemically and skeletally diverse small molecules,[4,5] we were interested in applying the chiral urea (**1**)/Brønsted acid cocatalyzed asymmetric Povarov reaction[3a] (Scheme 1) to the synthesis of a THQ-based library.

At the outset of the project we faced three synthetic challenges in the production of a diverse THQ-based library: (1) adaptation of the asymmetric Povarov reaction conditions to multigram scale, (2) development of a practical strategy for accessing a matrix of stereoisomers, and (3) optimization of solid-phase diversification reactions. In this paper, we describe successful solutions to these challenges in the context of the large-scale synthesis of a collection of stereoisomeric THQ scaffolds as well as the solid-phase production of a 2328-membered THQ library.

■ RESULTS AND DISCUSSION

Scaffold Design. In designing a THQ scaffold for library synthesis, we required two key features: 1) a primary alcohol for loading onto solid support and 2) chemical handles for introducing appendage diversity. With these features in mind, we began by selecting the imino Diels−Alder partners for the asymmetric Povarov reaction. Use of an imine glyoxolate **5**, obtained from condensation of aniline **6** and ethyl glyoxolate **7**, as the 4-π component,[6] was attractive for a number of reasons (Scheme 2). The use of glyoxolate ester derivatives would provide a low molecular weight scaffold bearing a functional handle for loading the products onto solid supports. In addition, the primary products of the Povarov reaction (**8**) contain an epimerizable stereogenic center that could allow further diversification of the scaffold. Finally, excellent enantio- and diastereoselectivities have been demonstrated in the urea-catalyzed asymmetric Povarov reaction of glyoxylate imines.[3a]

Various substituted anilines (4-methoxycarbonyl **6a**, 4-((*tert*-butyldimethylsilyl)oxy) **6b**, 4-bromo **6c**) were evaluated as imine precursors in the Povarov reaction with dihydrofuran as a model dienophile. The imine generated from **6a** was unstable and resulted in a low yield on large scale in the Povarov reaction. Meanwhile, reactions of **6b** were found to be poorly reproducible and became problematic with future protecting group manipulations. In contrast, **6c** offered good reactivity and reproducibility in the imine formation on large scale. Furthermore, the aryl bromide could be used as a diversity

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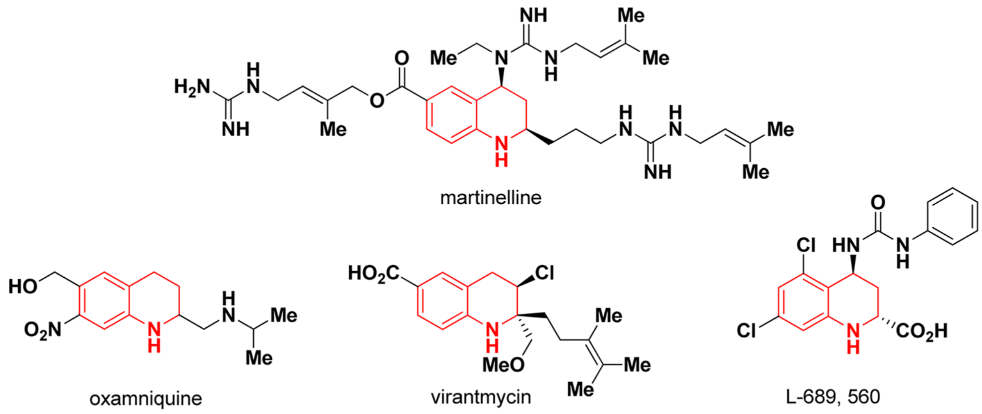
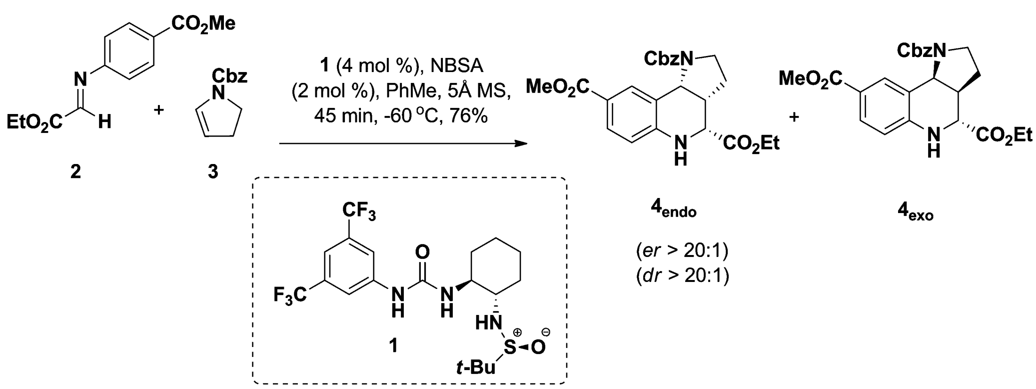
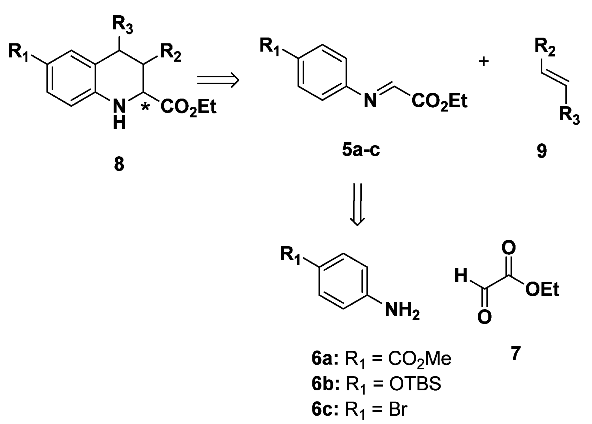


Figure 1. Examples of natural products and biologically active compounds featuring a tetrahydroquinoline core.

Scheme 1. Asymmetric Cocatalysis of the Povarov Reaction Using a Brønsted Acid and a Chiral Urea



Scheme 2. Retrosynthesis of THQ Scaffold 8



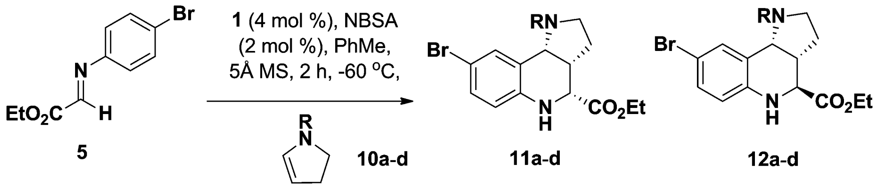
site on solid phase for cross coupling reactions.[7] It was found that the Povarov adduct could be recrystallized and thus confirming the absolute configuration of the cycloaddition product with endo stereochemistry.[8]

With the diene in hand, we moved on to study the dienophile partner **9**. We focused on dienophiles featuring a handle for solid-phase diversification, and those which showed good reactivity while retaining high levels of enantio- and diastereoselectivity in the Povarov reaction. As noted in previous reports, 2,3-dihydropyrrole derivative **10** is a versatile dienophile for the Povarov reaction.[3a,9,10] We conducted a study (Table 1) to determine the most suitable protecting group for the pyrrole nitrogen under Povarov reaction conditions. As expected, a noticeable difference in reactivity was observed based on the nature of the protecting group. For example, the nosylated pyrrole **10a** proved unreactive during the Povarov reaction mostly due to poor solubility in toluene at low temperatures (−60 °C) (entry 1). Meanwhile, use of Boc-protected pyrrole **10b** led to an overall decrease in yield (38%) and diastereoselectivity (from 9:1 to 7:3 *dr*) (entry 2). However, it was found that Fmoc and Cbz carbamates, **10c** and **10d** gave more suitable results with up to 80% isolated yield of the corresponding cycloadduct and with good levels of diastereoselectivity (9:1 *dr*) and enantioselectivity (up to 93:7 *er*). Thus, dienophile **10c** and **10d** were selected for the scale up of the THQ scaffolds for library production.

Large-Scale Reaction Optimization. Having selected **5c** as diene and **10c** and **10d** as dienophiles, we next evaluated the optimization for the asymmetric Povarov reaction on multigram scale to achieve high yield and optimal levels of enantio- and diasteroselectivity suitable for library production. In preliminary studies, we found that the manner in which the imine was generated was a critical parameter for obtaining consistent results on large scale.[11] The imine formed in situ was found to be extremely sensitive to nucleophilic attack with an excess of aniline leading to side product formation.[12] A practical procedure was developed involving formation of the imine via slow addition of aniline **6c** into glyoxolate **7** in toluene at 0 °C, followed by isolation of the crude imine via solvent removal in vacuo.[7]

Initially, when employing previously described conditions for the Povarov reaction[3a] (4 mol % of urea catalyst **1**, 2 mol % of *ortho*-nitrobenzenesulfonic acid (NBSA) as the Brønsted acid in toluene at −60 °C in presence of 5 Å MS, 1 mmol scale), we observed formation of the desired product **11** with good

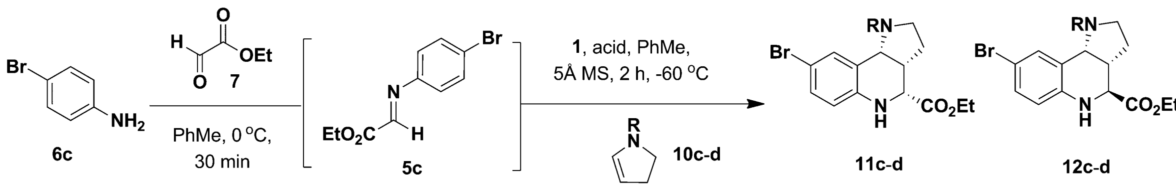
Table 1. Screening of Dienophiles for the Asymmetric Povarov Reaction



entry	R	product	dr^a	er^b	yield of **11** (%)^c
1	Ns, **10a**	**11a/12a**			NR
2	Boc, **10b**	**11b/12b**	7:3	95:5	32
3	Cbz, **10c**	**11c/12c**	9:1	93:7	58
4	Fmoc, **10d**	**11d/12d**	9:1	84:16	80

[a]Diastereoisomeric ratio *(dr)* was measured by UPLC with UV detection at 210 nm on the crude reaction mixture. [b]Enantiomeric ratio *(er)* was measured by SFC with UV detection at 210 nm after chromatography separation of the major diastereoisomer. [c]Isolated yield of **11** after silica gel chromatography.

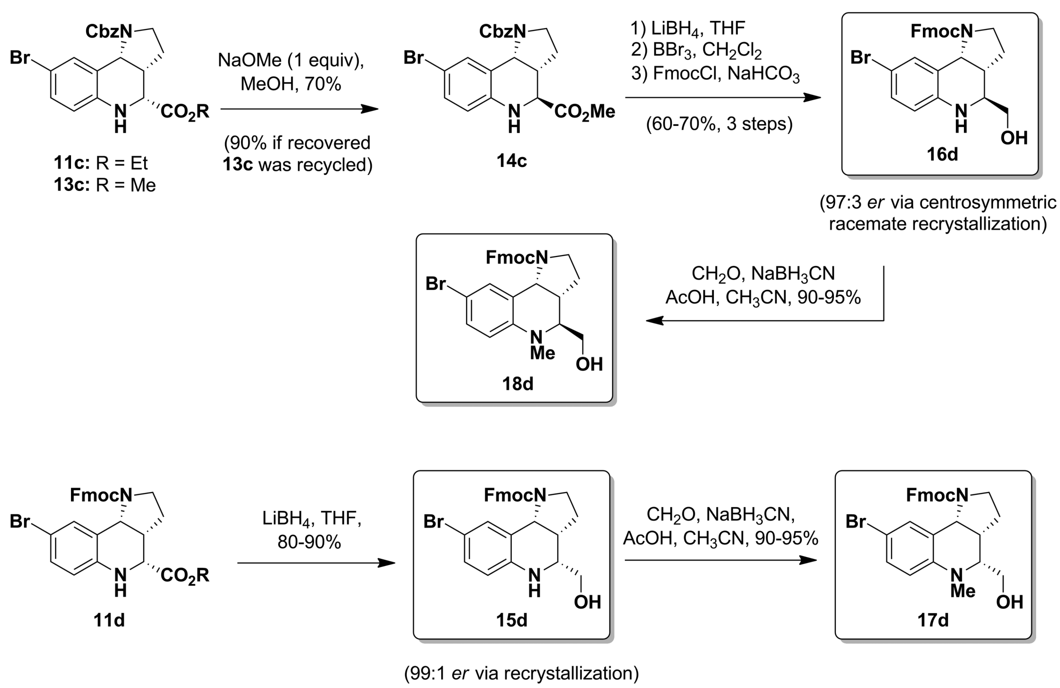
Table 2. Large Scale Reaction Optimization



entry	R	acid	acid (mol %)	cat. (mol %)	scale (mmol)	product	dr^a	er^b	yield of **11** (%)^c
1	Cbz, **10c**	NBSA	2	4	1	**11c/12c**	90:10	90:10	40
2	Cbz, **10c**	NBSA	2	4	25	**11c/12c**	90:10	93:7	58
3	Cbz, **10c**	PTSA	2	4	39	**11c/12c**	90:10	92:8	61
4	Cbz, **10c**	PTSA	1	2	39	**11c/12c**	89:11	89:11	58
5	Cbz, **10c**	PTSA	1	2	67	**11c/12c**	91:9	88:12	65
6	Fmoc, **10d**	PTSA	1	2	35	**11d/12d**	90:10	84:16	89

[a]Diastereoisomeric ratio *(dr)* was measured by UPLCwith UV detection at 210 nm on the crude reaction mixture. [b]Enantiomeric ratio *(er)* was measured by SFC with UV detection at 210 nm after chromatography separation of the major diastereoisomer. [c]Isolated yield of **11** after silica gel chromatography.

Scheme 3. Solution-Phase Synthesis of Library Scaffolds



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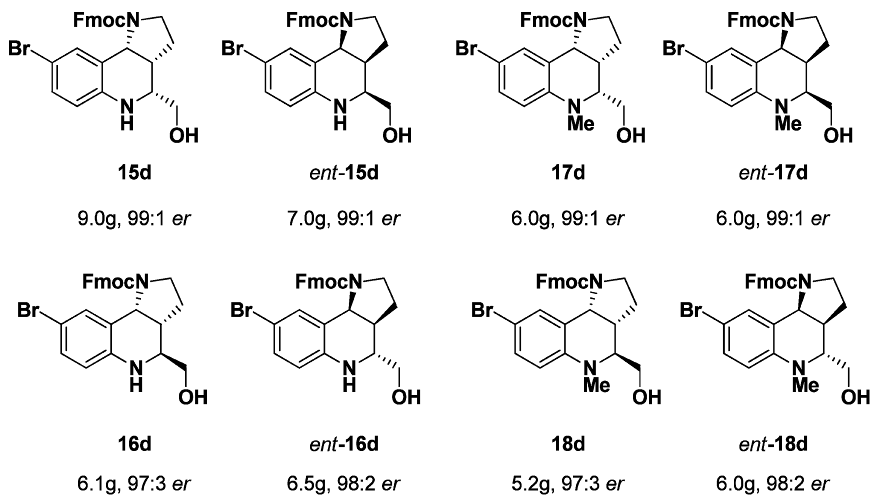
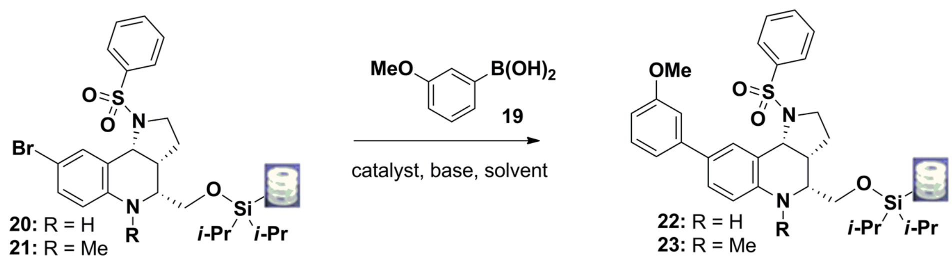


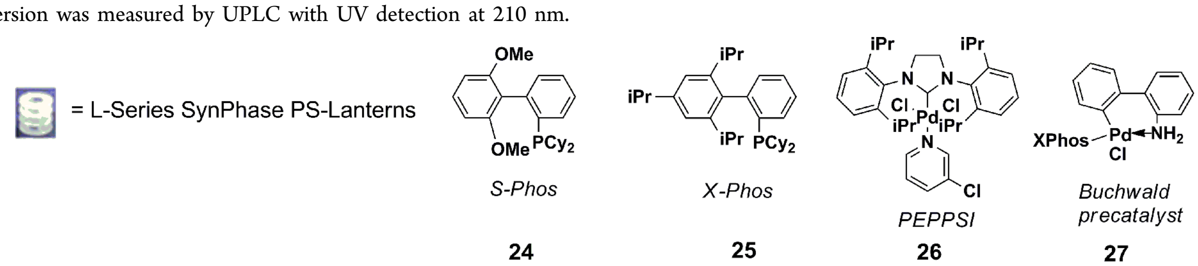
Figure 2. Matrix of four stereoisomers for the NH and NMe THQ scaffolds.

Table 3. Solid-Phase Suzuki Feasibility Studies



entry	SM	catalyst	base	T (°C)	solvent	product	conv (%)[a]	SM (%)[a]	byproduct (%)[a]
1	**20**	$PdCl_2(PPh_2)_3$	TEA	60	EtOH	**22**	60	12	18
2	**20**	$Pd(dba)_2$, $P(t\text{-}Bu)_3$	K_3PO_4	60	PhMe	**22**	70	5	25
3	**20**	PEPPSI	$CsCO_3$	60	1,4 dioxane	**22**	78	9	13
4	**20**	$Pd(dba)_2$, S-Phos	K_3PO_4	60	PhMe	**22**	73	0	27
5	**20**	Buchwald precatalyst	K_3PO_4	rt	THF	**22**	100	0	0
6	**21**	Buchwald precatalyst	K_3PO_4	rt	THF	**23**	100	0	0

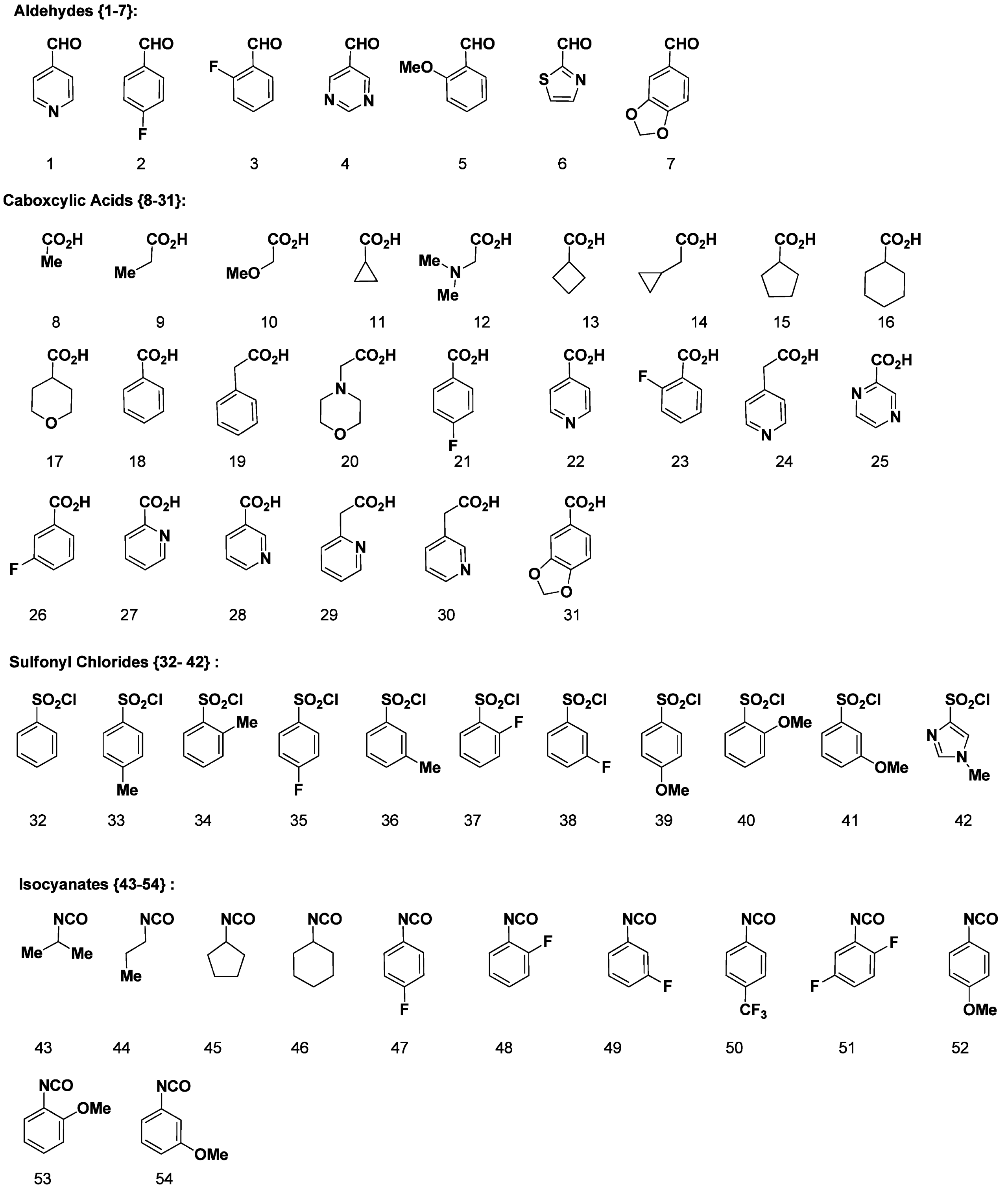
[a]Conversion was measured by UPLC with UV detection at 210 nm.



enantio- (9:1 *er*) and diastereoselectivity (9:1 *dr*) albeit in modest yield (40%) (Table 2, entry 1). We hypothesized that residual amount of water from the Brønsted acid may hydrolyze the water-sensitive imine **5c**[10,13] and, therefore, affect the overall isolated yield of **11** on large scale. After studying the effect of other Brønsted acids in the Povarov reaction, we found that the use of anhydrous *p*-toluenesulfonic acid (PTSA)[14] gave comparable results (yield and enantio- and diastereoselectivity) to NBSA (Table 2, entries 2 and 3). Anhydrous PTSA was found to be easy to use and could be stored for several weeks at room temperature in a desiccator. Thus, for practical reasons we decided to use PTSA for the remainder of our optimization experiments. This modification enable us to conduct the asymmetric Povarov reaction on large scale with up to 66 mmol of **5** (17 g) in presence of **10c** as the dienophile to give moderate yield and good enantiomeric ratio (65%, 88:12 *er*, entry 5). Similar yield and enantioselectivity of **11d** was obtained when **10d** was used as dienophile in the Povarov reaction. In addition, **11d** could be easily purified via crystallization to give almost enantiomeric pure material. Gratifyingly, we observed no erosion of reactivity when using lower catalyst and Brønsted acid loading (2 mol % of urea catalyst and 1 mol % of PTSA (entries 3 and 4)). Similar results were obtained in the Povarov reaction when the enantiomer of the urea catalyst **1** was employed.[15]

Epimerization Studies. To obtain stereochemical diversity, a practical method to epimerize the stereogenic center adjacent to the ester was sought to convert the endo diastereomer **11c** into the thermodynamically favored exo diastereoisomer **12c**. Although there was precedent for a similar epimerization strategy via the corresponding aldehyde in the synthesis of the natural product martinelline,[16] we were hoping to develop a

Chart 1. Building Blocks for Amine Capping



synthetic sequence to access **12c** directly and on large scale. After extensive screening of epimerization conditions,[17] it was found that treatment with 0.1 M solution of sodium methoxide in methanol at 60 °C afforded the desired epimer as the methyl ester (**14c**) in 70% yield (Scheme 3). The endo methyl ester **13c** that was recovered after purification could be resubjected to the same conditions to provide **14c** in 90% overall yield over two cycles.

Library Scaffold Preparation. For solid-phase library production, a protecting group manipulation was required to replace the incompatible Cbz group with Fmoc. To streamline the preparation of the final cores, we decided to utilize Fmoc-pyrrole **10d** as the dienophile to generate endo diastereoisomers and Cbz-pyrrole **10c** to generate the remaining exo diastereoisomers. After Povarov cycloaddition using Fmoc-pyrrole **10d** with either **1** or its enantiomer, cycloadduct **11d** was reduced using $LiBH_4$ to afford the corresponding primary

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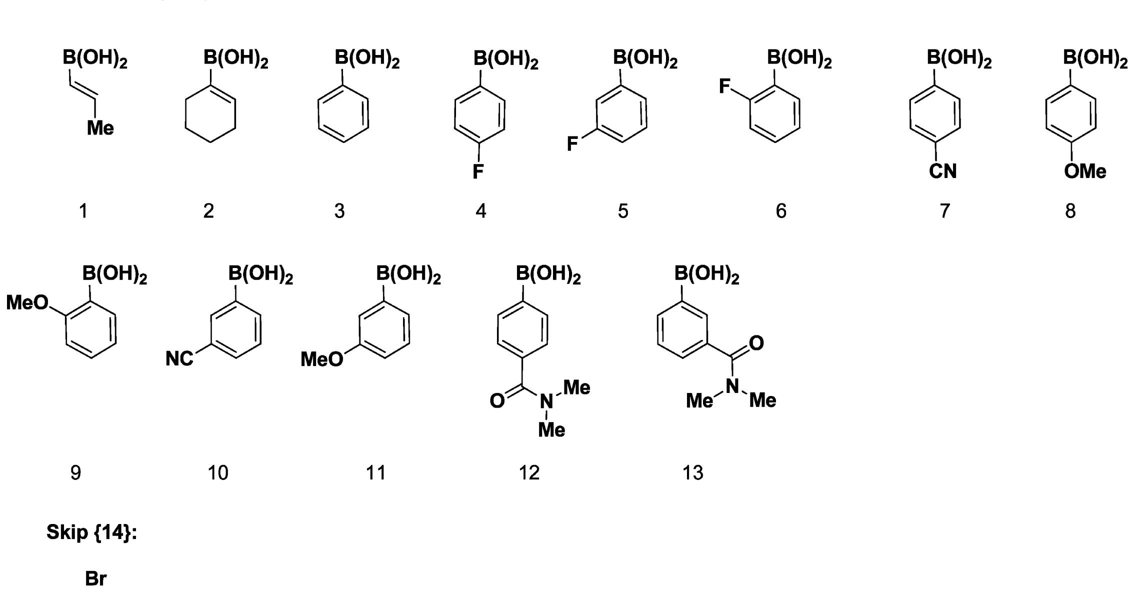
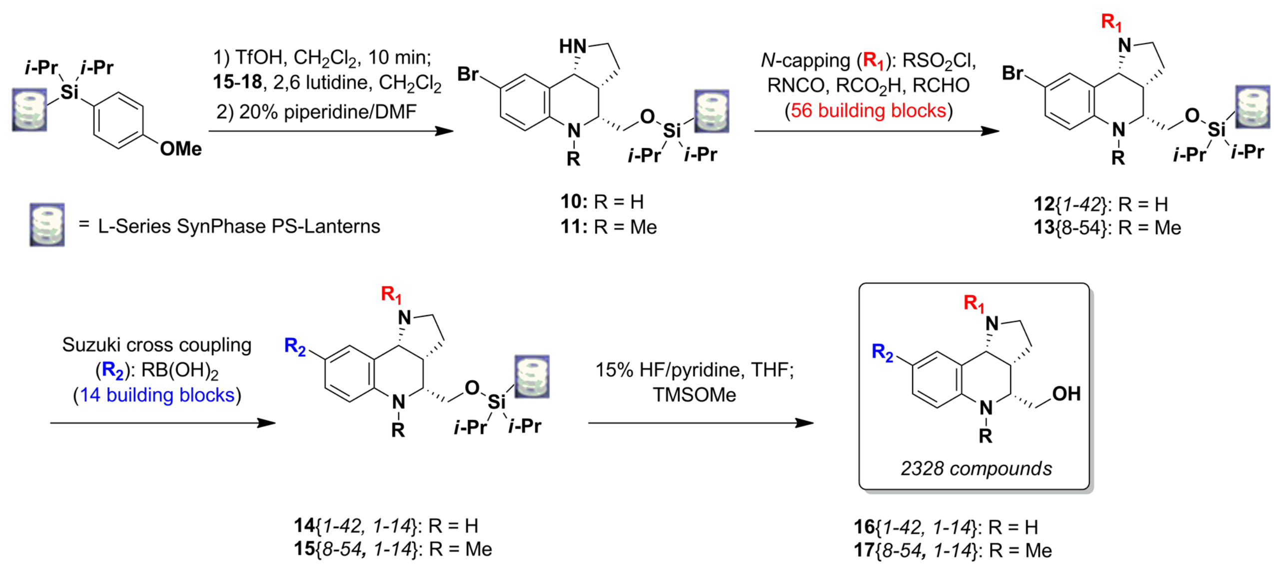
Chart 2. Building Block for Cross Coupling



Scheme 4. Solid-Phase Synthesis of THQ Library on SynPhase Lanterns



alcohol **15d** (Scheme 3).[18] Scaffold **15d** could be easily recrystallized in a 9:1 mixture of benzene and dichloromethane to give enantioenriched compounds with excellent enantioselectivity (99:1 *er*). After epimerization of **11c** to **14c**, the exo Fmoc protected diastereoisomer was obtained via a stepwise processes involving (1) ester reduction using $LiBH_4$ and (2) protecting group exchange from the incompatible Cbz to Fmoc to afford **16d**. Recrystallization of **16d** afforded enrichment of enantiopure compound up to 97:3 *er*.

During initial feasibility studies, it was found that the THQ aniline had limited reactivity upon treatment with various electrophiles, such as acyl chlorides and sulfonyl chlorides, thus restricting its use as diversity site for solid-phase production. However, it was found that the aniline could be alkylated by reductive amination with a limited number of aldehydes. Formaldehyde was found to be the most reactive among the aldehydes tested. Scaffolds **15d** and **16d** were therefore methylated via reductive amination with excellent yields (90–95%) to give **17d** and **18d**. This strategy allowed us to generate eight different scaffolds, including both enantiomers of the NH and NMe endo and exo cores (Figure 2).

Solid-Phase Feasibility Studies. With the NH and NMe THQ-scaffolds in hand, we turned our attention to the development of solid-phase methods for the introduction of building blocks at the two diversity sites: (1) the secondary amine and (2) the aryl bromide. Solid-phase feasibility studies were conducted on SynPhase Lanterns (vide infra). Amine capping at the first diversity site for both the NH and NMe sublibraries involved screening with a variety of electrophiles, including isocyanates, sulfonyl chlorides, aldehydes, and acids. Bis-capping was observed with the use of isocyanates in the presence of the free aniline and therefore removed from the design of the NH sublibrary. While isocyanates performed well for the NMe sublibrary, the use of aldehydes was problematic resulting in significant decomposition during reductive alkylation conditions. Therefore, aldehydes were removed

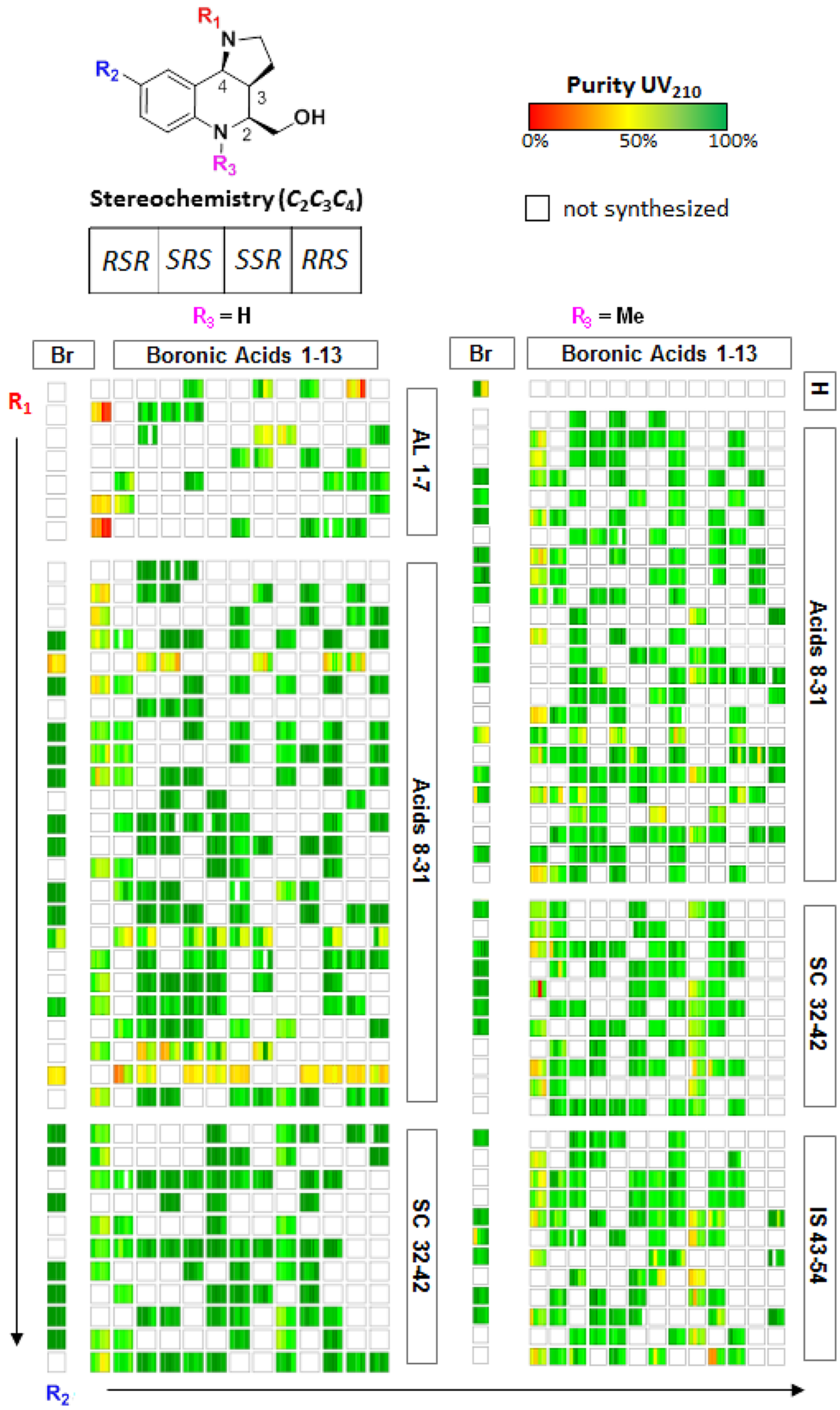


Figure 3. Purity analysis for THQ library (UPLC analysis with UV detection at 210 nm). Library members are displayed as blocks of 4 stereoisomers (see legend) for both the NH and NMe sublibraries. Reagents used for solid-phase diversification are shown on the *x*- and *y*-axes. (See Charts 1 and 2 for detailed list of reagents).

from the NMe sublibrary design. Acids and sulfonyl chlorides performed well for both sublibraries.

Next, the feasibility of Pd-mediated cross coupling reactions at the aryl bromide was investigated. Both Sonogashira and Suzuki cross couplings were explored. Initial screenings of the Sonogashira cross coupling led to poor conversion and produced a significant amount of side products. Therefore, we decided to focus solely on the Suzuki cross coupling for production purposes. Traditional Suzuki conditions on solid phase were attempted using 3-methoxybenzene boronic acid **19** and sulfonamides **20** and **21** as a model (Table 3, entry 1). Moderate conversion to the desired product was observed in addition to the formation of a significant amount of unknown byproducts,[19] possibly due to a rapid protodeboronation step[20] versus a slow oxidative insertion step. A variety of other conditions were screened including multiple ligands ($P(t\text{-}Bu)_3$, PEPPSI **26**,[21] S-Phos **24**, Pd catalyst ($PdCl_2(PPh_3)_2$), Pd-$(dba)_2$), bases (TEA, K_3PO_4, Cs_2CO_3) and solvents (EtOH,

Table 4. Property Analysis for the THQ Library

property[a]	NH scaffold[b] (n = 1)	NMe scaffold[b] (n = 1)	NH library (n = 1100)	NMe library (n = 1252)
MW	283	297	420	433
ALogP	1.4	1.9	2.9	3.4
TPSA	44	36	73	65
rot. bonds	1	1	3.9	3.7
HBA	3	3	4.4	4.2
HBD	3	2	2.0	1.3

[a]Physicochemical properties listed as mean values. [b]Property analysis of bare scaffolds, where R_1 and R_2 = H.

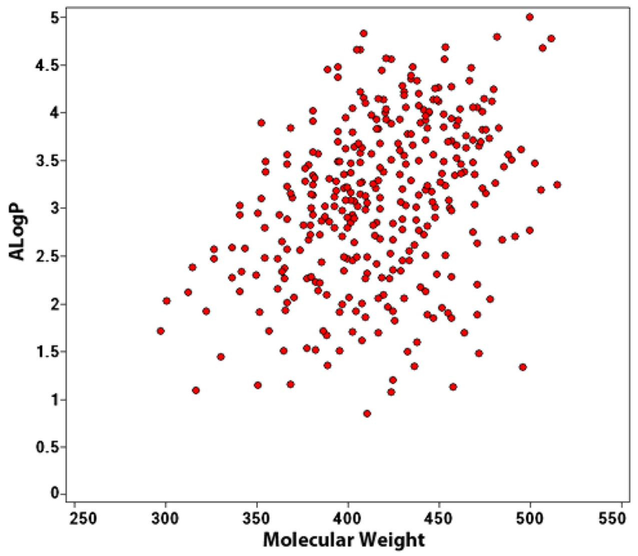


Figure 4. Molecular weight (MW) and ALogP distribution for THQ-library members.

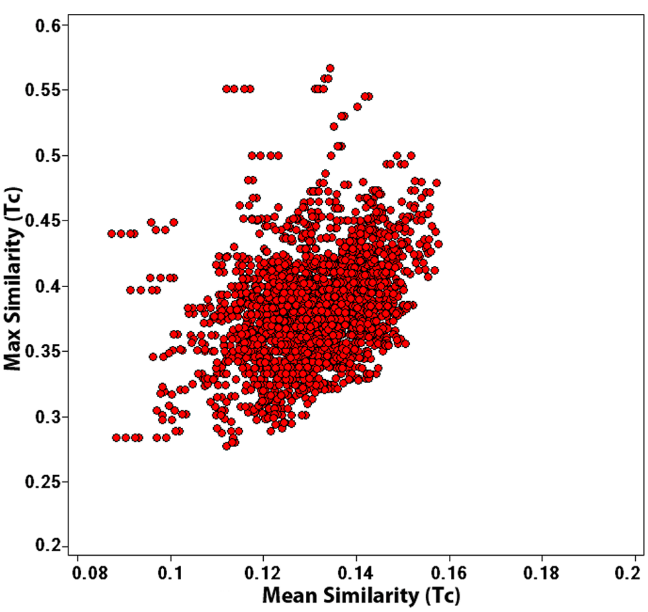


Figure 5. Multifusion similarity map comparing the THQ library (n = 2328) to the 2011 MLSMR (n = 335834). The reference set (MLSMR) is not shown on the map (see text for details).

PhMe, 1,4-dioxane, THF) in an attempt to increase the rate of oxidative insertion and potentially limit formation of side products without success (Table 3, entries 1−4). A recent publication from the Buchwald lab highlights the use of X-Phos ligand in a preformed catalyst.[22] The use of such a precatalyst was reported to increase the rate of boronic acid coupling versus its decomposition due to the use of milder reaction condition. Upon treatment with the Buchwald precatalyst **27** at room temperature, we were delighted to find formation of the desired cross coupling product in high conversion without the formation of undesired side products for both NH and NMe sublibraries (entries 5 and 6).

With this information in hand, a sparse matrix design strategy for each sublibrary was implemented to select library members to be synthesized. First, a virtual library was constructed for both sublibraries using 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).[23] This resulted in ∼2400 compounds per stereoisomer. Physicochemical property filters were then applied to eliminate building block combinations that led to products with undesirable properties. Property filters included the following: MW ≤ 500, ALogP −1 to 5, H-bond acceptors + donors ≤10, rotatable bonds ≤10 and TPSA ≤ 140. A total of 274 compounds per scaffold for the NH sublibrary and 310 compounds per scaffold for the NMe sublibrary were selected from the remaining set using chemical similarity principles, maximizing diversity but retaining near neighbors for built-in SAR.[22] 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. With the solid-phase feasibility studies complete, we turned our attention to library production. Immobilization of the scaffold onto solid support was achieved via activation of the SynPhase Lanterns (L-series) with triflic acid followed by treatment with scaffolds **15**−**18** in the presence of excess 2,6-luditine (Scheme 4).[24] The average loading levels obtained were 17.0 μmol/Lantern for the NH sublibrary and 13.3 μmol/Lantern for the NMe sublibrary. Removal of the Fmoc protecting group under standard conditions followed by capping with the appropriate electrophilic building blocks for NH and NMe sublibraries yielded compounds **12**{*1*−*42*} and **13**{*8*−*54*}. Subsequent Pd-mediated cross coupling utilizing the Suzuki reaction afforded compounds **14**{*1*−*42*, *1*−*14*} and **15**{*8*−*54*, *1*−*14*}. Once the reaction sequence was complete, the Lanterns were subjected to an aqueous sodium cyanide wash (1:1 1.0 M NaCN in water/THF solution) to remove any residual Pd. Release of the final compounds (**16**{*1*−*42*, *1*−*14*} and **17**{*8*−*54*, *1*−*14*}) from solid support was achieved via treatment with HF/pyridine. All library products were analyzed by ultraperformance liquid chromatography, and compound purity was assessed by UV detection at 210 nm. The average purity of the THQ NH library (1088 compounds) was 78%, with 71% of the library being >75% pure, while the average purity of the THQ NMe library (1240 compounds) was 75%, with 68% of the library being >75% pure. A full purity analysis is provided in Figure 3. Of note, certain nitrogen containing building blocks proved problematic during the amine capping for the NH sublibrary, including acids *12*, *24*, *29* and *30*, while the *trans*-1-propenylboronic acid (*1*) generally did not perform well for either sublibrary.

Library Analysis. Analysis of the THQ library (Table 4 and Figure 4) reveals that the calculated physicochemical property profile for the compound set is within the intended range for the library design (vide supra). Meanwhile, the structural diversity of the THQ library was analyzed in comparison to the NIH Molecular Library 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 (T_c) as the similarity measure.[25] In this method, each molecule in the test set (THQ library, n = 2328) is compared to every molecule in the reference set (2011 MLSMR, n = 335834), and the largest similarity score and the mean similarity score to the reference set is obtained. 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 5 shows the MFS map comparing the THQ library 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 on the plot.) The maxium mean similarity of the THQ library is 0.13 (T_c) indicative of the overall structural diversity with the respect to the MLSMR reference set. Furthermore, there are no compounds with maximal similarity equal or greater than 0.57 (T_c) in the MLSMR, illustrating that these compounds represent regions of unoccupied chemical space within this collection.

■ CONCLUSIONS

In summary, a 2328-membered library of tetrahydroquinolines was successfully prepared using the asymmetric Brønsted acid/urea-catayzed Povarov reaction[3a] as a key step. Adaptation of the Povarov reaction for large scale synthesis led to the use of anhydrous PTSA as the Brønsted acid in place of NBSA and optimization of the imie formation step. These modifications enabled the large scale (>5 g) preparation of 4 stereoisomers of two THQ scaffolds with two functional handles for solid-phase diversification. In silico library design followed by production on SynPhase Lanterns afforded a diverse library of functionalized tetrahydroquinolines with properties suitable for downstream discovery.

■ ASSOCIATED CONTENT

Supporting Information

Additional data and figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) This side product was identified as the aminal adduct.

(13) NBSA is commercially available only as the hydrate (containing x molecules of water). To remove residual amounts of water, NBSA was dissolved in a minimum amount of dry THF and azeotroped with toluene. This sequence was repeated three times until a dark brown viscous oil was obtained. The light sensitive oil was dried under high vacuum over $CaCl_2$ and stored in the dark.

(14) *p*-Toluenesulfonic acid was dehydrated by azeotropic distillation with toluene using a Dean−Stark apparatus. The residue was then crystallized from benzene.

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