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Ligand-Free Suzuki–Miyaura Coupling with Sulfur-Modified Gold-Supported Palladium in the Synthesis of a Conformationally-Restricted Cyclopropane Compound Library with Three-Dimensional Diversity

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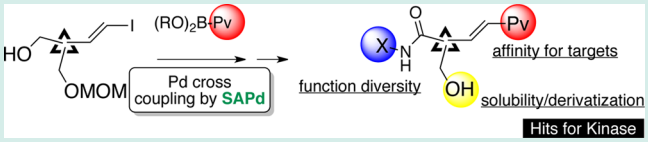
Supporting Information

ABSTRACT: A conformationally restricted privileged structure library with stereochemical diversity for a "fragment growth" methodology comprising 90 compounds was designed and systematically and efficiently synthesized using sulfur-modified Au-supported Pd (SAPd)-catalyzed ligand-free Suzuki–Miyaura coupling of vinyl iodide promoted by microwave and subsequent amidation in liquid-phase combinatorial chemistry as key reactions. Evaluation of the compounds with a 20-kinase panel indicated the usefulness of this "fragment growth" methodology for finding hit library compounds for fragment-based drug discovery.



KEYWORDS: *Suzuki–Miyaura coupling, privileged structure library, stereochemical diversity,*

INTRODUCTION

Fragment-based drug discovery (FBDD)[1,2] is a newly established method for hit finding; in essence, it bases its strength on the competent binding of small chemical entities to their targets. FBDD involves identifying small fragments, which, because of their small size, tend to bind with relatively low affinity, and then developing these to produce larger, higher-affinity ligands. The major advantage of FBDD over traditional high-throughput screening methods is that FBDD provides a more rapid and effective means of identifying ligands for a protein target. Identified fragment hits can be optimized by "linking," "merging," or "growth." Among them, "fragment growth" is thought to be more effective than linking or merging, because additional features can be added through iterative cycles to the hit fragment, leading to more potent compounds.[3] To identify valuable optimized compounds effectively by FBDD, privileged structures,[4,5] such as indoles, quinolines, purines, and benzimidazoles, are useful and historically yield several biologically active molecules that selectively modulate the activities of enzymes, G-protein coupled receptors, nuclear receptors, ion channels, and so on.[6] Here, we report our original "fragment growth" method for FBDD, based on the three-dimensional diversity-oriented strategy[7] using cyclopropane as the key unit to restrict the conformation of privileged molecules.

Although liquid-phase combinatorial synthesis is frequently used in medicinal chemical research, until our report there have been no known palladium catalysts that work repeatedly with low Pd-leaching (less than 1 ppm in the reaction mixture without purification). We recently developed a practical Pd material, sulfur-modified Au-supported Pd (SAPd),[8] which is, due to its lowest recorded Pd-releasing levels (less than 1 ppm in the reaction solvent, TON up to 2 760 000) and high recyclability (more than 10 cycles) in Suzuki–Miyaura coupling, one of the best Pd materials developed thus far. Because SAPd leaches extremely low levels of Pd into reaction mixtures, removal of residual Pd is unnecessary, even in the syntheses of pharmaceutical ingredients.

In the present study, as our original "fragment growth" method for FBDD, a conformationally restricted privileged structure library having not only functional diversity but also three-dimensional diversity[9] was designed and successfully synthesized using the ligand-free Suzuki–Miyaura coupling of

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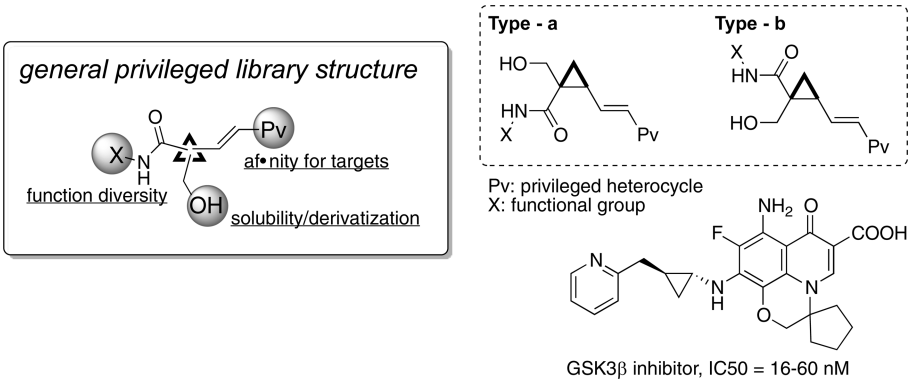


Figure 1. General scheme for our designed fragment structure and a medicinal example with cyclopropane.

vinyl iodides with SAPd as the key strategy. Throughout the study, SAPd proved to be an effective catalyst for liquid-phase combinatorial synthesis,[10] which is repeatedly used for synthesizing structurally diverse fragment molecules by Suzuki–Miyaura coupling of cyclopropylvinyl iodides with privileged heterocyclic boronic acids and without contamination. Furthermore, preliminary evaluation of the inhibitory effects of the library compounds on a panel of kinases suggested that the library for FBDD growth would be useful for finding hits with three-dimentional active structure information.

RESULTS AND DISCUSSION

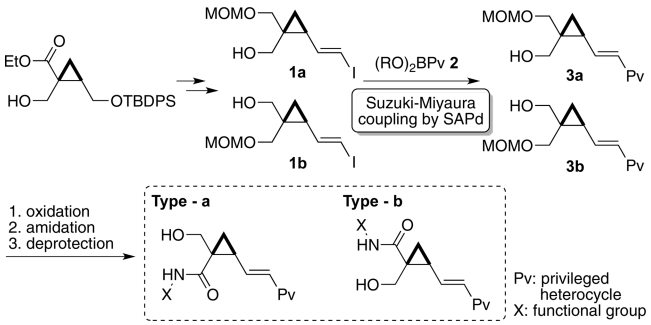
We have used cyclopropane as the key unit to design conformationally restricted analogs of bioactive ligands based on a spatial screening concept to search for unknown bioactive conformations of ligands.[11] These cyclopropane-containing compounds have three-dimensional structural diversity, which has allowed us to identify the appropriate conformations that produce bioactive compounds targeting a variety of biomolecules.

A small molecular library consisting of compounds with three-dimensional diversity would be expected to display a broader range of biological activities. However, most libraries used to date have been limited to aromatic heterocycles with an underrepresentation of chiral sp3-rich compounds. Recently a pioneering work on three-dimensionally diverse sp3-rich fragments using diversity-oriented synthesis was reported by Wong and co-workers, which included a variety of two-ring skeltones composed of a pyrrolidine and a saturated ring.[7] We hypothesized that combinational use, taking advantage of the small and rigid structural features of cyclopropane and the privileged structures, might provide the three-dimensionally diverse sp3-rich compounds with the privileged structures very effective in the fragment growing method.

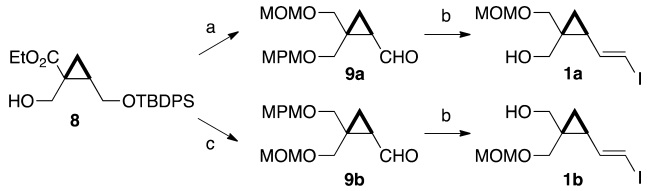
Thus, we designed a general structure having a vinylcyclopropane backbone, as shown in Figure 1. In the structure for FBDD growth, a privileged heterocyclic vinyl fragment, a functionalized carbamoyl fragment, and a hydroxymethyl fragment were attached to a vinylcyclopropane backbone, in which the relative location of these three fragments was effectively restricted due to the rigid cyclopropane ring. The structure for FBDD growth has the following advantages: (1) By changing the regiochemistry of these three groups on the cyclopropane ring, the library compounds can have remarkable three-dimensional diversity. (2) A variety of privileged heterocyclic fragments can be introduced by Suzuki–Miyaura coupling. (3) The use of the easy-forming amide linkage to introduce functional groups provides fragments with functional group diversity. (4) The hydroxymethyl group increases the solubility of the molecule in aqueous medium. (5) The hydroxymethyl group can be effectively used for further derivatization in the next "fragment growth" stage, and (6) the molecular weights of the library compounds are rather small. In the fragment growing approach, it is often difficult to find the site in hit fragments effective for the growing. The hydroxymethyl moiety can be extremely useful, when a hit is identified, because the presence of it hints at promotion of the facile elaboration or modifications of the hit for growing into a lead.

In this study, we planned to construct a racemic small library for FBDD growth comprising type-a and type-b structures,

Scheme 1. General Scheme for the Synthesis of the Designed Privileged Library Compounds



Scheme 2. Preparation of Vinyl Iodides 1a and 1b[a]



[a](a) (1) 4-MeOC$_6$H$_4$CH$_2$OC(=NH)CCl$_3$, PPTS, CH$_2$Cl$_2$, 24 h, 57%; (2) LiBH$_4$, THF, reflux, 18 h; (3) MOMCl, ^{i}Pr$_2$EtN, CH$_2$Cl$_2$, 24 h; (4) Bu$_4$NF, THF, 3 h; (5) Dess-Martin periodinane, CH$_2$Cl$_2$, 0 °C, 2 h, 79% (5 steps). (b) (1) CHI$_3$, CrCl$_2$, THF, 0 °C, 4 h; (2) DDQ, CH$_2$Cl$_2$, 5 h, 79% (2 steps from **9a**), 69% (2 steps from **9b**). (c) (1) MOMCl, ^{i}Pr$_2$EtN, CH$_2$Cl$_2$, 24 h; (2) LiBH$_4$, THF, reflux, 18 h; (3) 4-MeOC$_6$H$_4$CH$_2$OC(=NH)CCl$_3$, PPTS, CH$_2$Cl$_2$, 24 h; (4) Bu$_4$NF, THF, 3 h; (5) Dess-Martin periodinane, CH$_2$Cl$_2$, 0 °C, 2 h, 56% (5 steps).

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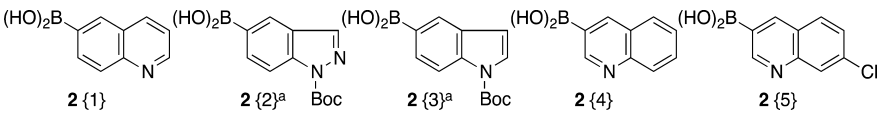

Figure 2. Diversity reagents **2**{*1*–*5*}. (a) Boc group is removed in the final product **7**.

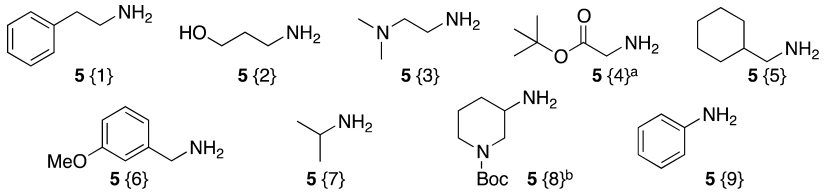

Figure 3. Diversity reagents **5**{*1*–*9*}. (a) *tert*-Butyl group is removed in the final product **7**. (b) Boc group is removed in the final product **7**.

Table 1. SAPd Catalyzed Suzuki–Miyaura Coupling of 1 and 2[a]

entry	vinyl iodide **1**	boronic acid **2**	product **3**	yield (%)[b]
1	**1a**	**2**{*1*}	**3a**{*1*}	78 (48)
2	**1a**	**2**{*2*}	**3a**{*2*}	40[c,d] (33)
3	**1a**	**2**{*3*}	**3a**{*3*}	88[c] (53)
4	**1a**	**2**{*4*}	**3a**{*4*}	82 (73)
5	**1a**	**2**{*5*}	**3a**{*5*}	50[c,d] (7)
6	**1b**	**2**{*1*}	**3b**{*1*}	87 (48)
7	**1b**	**2**{*2*}	**3b**{*2*}	7 (39)
8	**1b**	**2**{*3*}	**3b**{*3*}	66 (58)
9	**1b**	**2**{*4*}	**3b**{*4*}	55 (41)
10	**1b**	**2**{*5*}	**3b**{*5*}	57 (37)

[a]MW1 conditions: **1a** or **1b** (0.084 mmol), SAPd (14 × 12 mm), ethanol (1 mL), DMF (1 mL) microwave heating (300 W, single-mode), 90 °C, 45 min, then MW2 conditions; boronic acid **2** (1.5 equiv), K_2CO_3 (2 equiv), toluene (1.5 mL) microwave heating (500 W, multimode), 100 °C, 1 h. [b]Numbers in parentheses indicate the yield using a conventional homogeneous catalyst; boronic acid **2** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), $CsCO_3$ (2 equiv), DMF, rt - reflux, 3–24 h. [c]0.25 mL of H_2O was added in multimode microwave heating. [d]DMF was used as a solvent and reaction time was 30 min in single-mode microwave heating.

Table 2. Preparation of Carboxylic Acids 4 from Alcohol 3 by Oxidation

entry	alcohol **3**	yield in DMP oxidation (%)	yield in Pinnich oxidation (%)
1	**3a**{*1*}	90	82
2	**3a**{*2*}	81	77
3	**3a**{*3*}	64	91
4	**3a**{*4*}	67	83
5	**3a**{*5*}	70	26[a]
6	**3b**{*1*}	95	82
7	**3b**{*2*}	80	95
8	**3b**{*3*}	72	91
9	**3b**{*4*}	97	91
10	**3b**{*5*}	84	90

[a]The carboxylic acid produced was unstable and decreased the yield.

which are two regioisomers included in the general structure. The synthetic strategies for the library compounds for FBDD growth are shown in Figure 1. Introduction of the key privileged heterocycles was planned by SAPd-promoted ligand-free Suzuki–Miyaura coupling between the cyclopropylvinyl iodides **1** as substrates, which were prepared from a known cyclopropane derivative, and the privileged heterocyclic boric acids **2**. Then, various functional groups were introduced by condensation with the amines X-NH_2 (Scheme 1).

When polymer-supported Pd is used, the reaction suffers from contamination problems, and troublesome washing is needed due to the strong absorption of the starting material and/or the product to the polymer. In dramatic contrast, SAPd has a much smaller surface area and absorbs many fewer organic compounds, including starting materials or products, compared with polymer-supported Pd, due to its low affinity for organic molecules. Moreover, the Au mesh, used as the support for Pd in SAPd, is malleable and easy to handle with a pair of tweezers. Although combinatorial synthesis is an important methodology in medicinal chemistry and is widely used for drug development, there has been no practical solid-supported Pd that could be repeatedly used for the synthesis of different kinds of coupled products.[12] Considering the above-mentioned advantages, SAPd may indeed be an ideal solid catalyst for combinatorial Suzuki–Miyaura coupling for medicinal chemical research studies. Consequently, we tried liquid-phase combinatorial Suzuki–Miyaura coupling of cyclopropylvinyl iodides with SAPd by changing the privileged heterocyclic boronic acids **2**.

The coupling substrates, cyclopropylvinyl iodides **1a** and **1b**, were synthesized according to Scheme 2. Thus, the known cyclopropane derivative **8**[13] was converted into the cyclopropane aldehyde **9a** or **9b** via protecting group manipulation, reduction, and oxidation, of which Takai coupling gave the cyclopropylvinyl iodides **1a** and **1b**.

When SAPd was used as the catalyst in the Suzuki-Miyaura coupling of the vinyl iodide **1a** or **1b** and boronic acids **2**{*1*} with K_2CO_3 in EtOH under our previously reported best conditions,[8,10] the corresponding product was not yielded at all. Then, considering the reaction mechanism of SAPd in Suzuki–Miyaura coupling,[10] we hypothesized that the actual active Pd species were not sufficiently released from SAPd to promote the reaction under the above conditions and that microwave irradiation might accelerate the release of the Pd species. We examined the use of two kinds of microwaves, one for releasing the actual active Pd species (MW1) and another for promoting Suzuki–Miyaura coupling (MW2). After several experiments, we found the optimized conditions for MW 1 and MW 2. A mixture of the vinyl iodide **1a** or **1b** (0.17 mmol) and a mesh of SAPd (14 × 12 mm) in ethanol (1 mL) and DMF (1 mL) was irradiated with weaker microwaves (300 W, single-mode) at 90 °C for 45 min, and then the resulting mixture was added to a solution of a privileged heterocyclic boronic acid **2**{*1*}, {*2*}, {*3*}, {*4*}, or {*5*} (1.5 equiv; see Figures 2 and 3) and K_2CO_3 (2 equiv) in toluene (1.5 mL) and irradiated with a stronger

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Scheme 3. Synthesis of a Privileged Structure Library with Conformational Regstriction

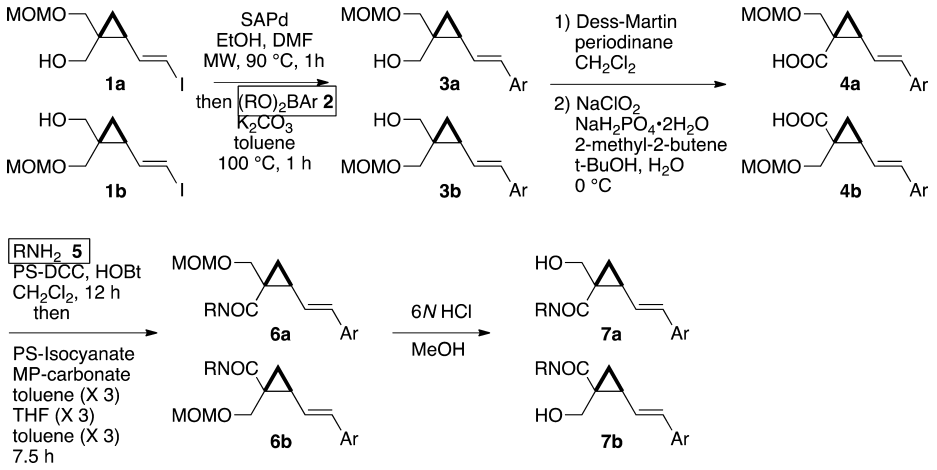

Table 3. Inhibitory Effects of 10 Selected Compounds on a Panel of 20 Different Kinases

	% Inhibition at 10 μM										IC_{50}
Kinase	7a	7b	7a	7b	7a	7b	7a	7b	7a	7b	(nM)
	{1,5}	{1,5}	{2,5}	{2,5}	{3,5}	{3,5}	{4,5}	{4,5}	{5,5}	{5,5}	staurosporin
ABL	- 6.6	- 4.1	- 6.6	- 5.3	- 5.0	-7.7	6.1	33.8	- 1.6	- 5.8	1,300
CSK	- 9.6	- 4.0	- 9.9	- 8.9	- 5.9	-10.5	- 2.8	- 2.8	- 7.9	- 6.8	1,500
EGFR	- 4.6	1.8	1.4	9.4	- 4.9	-4.9	- 1.1	- 1.9	0.1	- 0.7	4,000
EPHA2	- 5.8	- 6.1	- 5.4	- 0.8	- 5.3	-5.8	- 2.5	- 4.0	- 6.8	- 4.1	530
EPHB4	- 4.9	- 6.6	- 4.4	- 1.6	- 6.4	-5.3	- 3.6	0.8	- 5.8	- 5.0	1,500
FGFR1	- 6.7	- 1.5	1.5	1.5	- 5.8	-4.7	- 0.8	4.7	- 2.4	- 6.1	12
FLT3	- 3.8	4.3	7.3	11.8	0.6	11.7	21.5	56.7	- 0.5	- 4.1	0.34
IGF1R	- 4.7	- 0.9	1.6	0.0	- 6.8	2.2	- 2.1	- 0.1	0.2	- 2.9	150
ITK	- 3.8	4.5	1.1	2.4	- 1.6	-3.1	5.0	26.4	3.8	- 0.2	200
JAK3	- 5.2	0.5	10.3	14.9	- 4.1	-5.8	43.8	17.4	- 1.1	- 4.9	25
KDR	- 4.5	0.6	0.0	7.5	- 5.2	-5.7	19.9	73.0	- 0.9	- 4.1	18
LCK	- 4.3	33.7	2.9	10.9	- 2.5	-7.6	9.0	20.3	- 1.7	- 3.8	14
MET	- 6.6	- 2.4	- 3.1	1.3	- 6.7	-8.6	9.4	29.9	- 0.5	- 6.2	730
PDGFRα	- 0.6	10.2	0.3	10.0	- 3.7	-8.4	40.6	59.1	0.1	- 4.1	1.4
PYK2	- 7.0	- 9.8	6.4	- 2.2	-10.2	-9.1	- 4.9	- 1.0	- 8.3	- 8.5	4.9
SRC	- 7.0	- 0.4	0.9	0.3	- 3.5	-6.8	2.3	4.4	- 3.7	- 6.9	2.4
SYK	- 4.5	- 5.7	- 4.7	0.9	5.0	1.2	- 0.7	12.8	-11.1	- 6.6	0.63
TIE2	- 3.6	- 4.6	- 1.5	- 1.4	- 2.0	-5.1	- 3.6	0.6	- 4.0	- 4.4	190
TRKA	- 2.9	1.0	54.5	10.4	4.8	-0.6	49.2	49.4	2.1	- 3.6	0.64
TYRO3	- 7.2	- 0.8	2.4	5.6	- 7.4	-6.4	1.8	14.7	3.0	- 2.6	2.9

microwave (500 W, multimode) at 100 °C for 1 h. After the usual aqueous workup, the corresponding product **3** was obtained in high purity[14] as shown in Table 1. The SAPd was removed from the reaction mixture and used repeatedly for the reaction with substrates **1a** or **1b** and various boronic acids **2**. These results demonstrated that SAPd was an effective Pd catalyst for this kind of combinatorial synthesis without any contamination of other products or starting materials.

Successive oxidations of **3** with Dess-Martin periodinane (DMP) and under Pinnich conditions gave the corresponding carboxylic acids **4** (Table 2).

With carboxylic acids **4** in hand, we prepared the corresponding fragments by liquid-phase combinatorial chemistry. Thus, amine **5**, 1-hydroxybenzotriazole (HOBt), and polymer-bound carbodiimide resin[15,16] were added to a solution of **4** in dichloromethane (Scheme 3), and the mixture was stirred overnight at ambient temperature. After scavenging the excess amine with PS-isocyanate and then HOBt,[17] and then any remaining carboxylic acid with macroporous polymer-bound carbonate resin (MP-carbonate),[18] filtration and evaporation of the resulting mixture yielded the desired products **6** in high yields and purities. Acidic treatment of **6** led to production of the corresponding library compounds **7** in good to quantitative yields. Thus, we successfully constructed a small library comprising 90 library compounds for FBDD growth (45 type-a compounds and 45 type-b compounds), with molecular weights ranging from 314 to 422.

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We selected five type-a library compounds for FBDD growth **7a**{*1,5*}, **7a**{*2,5*}, **7a**{*3,5*}, **7a**{*4,5*}, and **7a**{*5,5*}, with different heterocycles and the same cyclohexylcarbamoyl group, and the corresponding five type-b library compounds **7b**{*1,5*}, **7b**{*2,5*}, **7b**{*3,5*}, **7b**{*4,5*}, and **7b**{*5,5*} for preliminary evaluation with a 20-kinase[19,20] assay panel at 10-μM concentrations.[21] As summarized in Table 3, kinase activities were inhibited by the library compounds for FBDD growth, as expected. It is particularly noteworthy that the inhibitory effects changed depending on the regiochemistry (type-a or type-b), i.e., three-dimensional positioning of the three substituents on a cyclopropane ring. For example, although both **7a**{*4,5*} (type-a) and **7b**{*4,5*} (type-b) have the same quinoline-3-yl privileged structure and a cyclohexylcarbamoyl group, the two compounds fro FBDD growth inhibited a variety of kinases with different selectivities: typically, **7a**{*4,5*} (43.8%) > **7b**{*4,5*} (17.4%) against JAK3, and **7a**{*4,5*} (19.9%) < **7b**{*4,5*} (73.0%) against KDR. The compound **7a**{*2,5*} (type-a), having Cl-quinoline, selectively inhibited TRKA among the 20 kinases, but the corresponding type-b regioisomer **7b**{*2,5*} had insignificant inhibitory effects on the kinase.

As a result of this study, **7a**{*4,5*}, **7b**{*4,5*}, and **7a**{*2,5*} were identified as hits as inhibitors of JAC3, KDR, and TRKA, respectively. Thus, the three-dimensional diversity-oriented conformational restriction strategy using our heterogeneous Pd catalyst, SAPd, works effectively in the privileged structure library.

SUMMARY

A conformationally restricted privileged structure library for FBDD growth, having not only functional diversity but also three-dimensional diversity, was designed. SAPd-catalyzed ligand-free Suzuki−Miyaura coupling of vinyl iodides with heteroaromatic boronic acids, which was effectively promoted by microwave irradiation, was developed, resulting in the construction of the designed library for FBDD growth comprising 90 compounds. Biological evaluation with a kinase panel showed that the library is useful for finding hits to provide a further "fragment growth" stage.

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest.

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(9) The trisubstituted cyclopropane derivative is unique because it has three-dimentional diversity for FBDD. Also, our "fragment growth" method for FBDD is original, because it has not only functional diversity but also three-dimentional structural diversity.

(10) Our preliminary model example of combinatorial biaryl coupling: Hoshiya, N.; Shuto, S.; Arisawa, M. The Actual Active Species of the Sulfur-modified Gold-supported Palladium as a Highly Effective Palladium Reservoir in the Suzuki-Miyaura Coupling. *Adv. Synth. Catal.* **2011**, *353*, 743−748. In Suzuki−Miyaura coupling, vinyl iodides are usually less reactive than phenyl iodide, and this reported protocol does not work for Suzuki−Miyaura coupling of vinyl iodide with heterocyclic aromatic boronic acids.

(11) For example: (a) Kazuta, Y.; Matsuda, A.; Shuto, S. Development of Versatile *cis*- and *trans*-Dicarbon-Substituted Chiral Cyclopropane Units: Synthesis of (1*S*,2*R*)- and (1*R*,2*R*)-2-Aminomethyl-1-(1*H*-imidazol-4-yl)cyclopropanes and Their Enantiomers as Conformationally Restricted Analogues of Histamine. *J. Org. Chem.* **2002**, *67*, 1669−1677. (b) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. Cyclopropane-Based Conformational Restriction of Histamine. (1*S*,2*S*)-2-(2-Aminoethyl)-1-(1*H*-imidazol-4-yl)cyclopropane, a Highly Selective Agonist for the Histamine H_3 Receptor, Having a *cis*-Cyclopropane Structure. *J. Med. Chem.* **2003**, *46*, 1980−1988. (c) Watanabe, M.; Kazuta, Y.; Hayashi, H.; Yamada, S.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2006**, *49*, 5587−5596. (d) Watanabe, M.; Hirokawa, T.; Kobayashi, T.; Yoshida, A.; Ito, Y.; Yamada, S.; Orimoto, N.; Yamasaki, Y.; Arisawa, M.; Shuto, S. Investigation of the Bioactive Conformation of Histamine H_3 Receptor Antagonists by the Cyclopropylic Strain-Based Conformational Restriction Strategy. *J. Med. Chem.* **2010**, *53*, 3585−3593.

(12) Previously reported combinatorial Suzuki-Miyaura coupling: Uozumi, Y.; Nakai, Y. An Amphiphilic Resin-Supported Palladium Catalyst for High-Throughput Cross-Coupling in Water. *Org. Lett.* **2002**, *4*, 2997−3000.
(13) Kato, H.; Ishigame, T.; Oshima, N.; Hoshiya, N.; Shimawaki, K.; Arisawa, M.; Shuto, S. One-Pot Ring-Closing Metathesis (RCM)/Oxidation by an Assisted Tandem Ruthenium Catalysis for the Synthesis of 2-Quinolones. *Adv. Synth. Catal.* **2011**, *353*, 2676−2680.
(14) Because reactivity of vinyl iodides is rather low compared with aryl halides in Suzuki−Miyaura coupling, the reaction was occasionally not completed, and therefore, purification by column chromatography was needed. The products were pure enough in ^{1}H NMR spectra. See the Supporting Information.
(15) PS-Carbodiimide, 100−200 mesh, Argonaut Technologies.
(16) Parlow, J. J.; Mischke, D. A; Woodward, S. S. Utility of Complementary Molecular Reactivity and Molecular Recognition (CMR/R) Technology and Polymer-Supported Reagents in the Solution-Phase Synthesis of Heterocyclic Carboxamides. *J. Org. Chem.* **1997**, *62*, 5908−5919.
(17) Weidner, J. J; Parlow, J. J.; Flynn, D. L. Polymer-assisted solution phase synthesis: a general method for sequestration of byproducts formed from activated acyl-transfer reactants. *Tetrahedron Lett.* **1999**, *40*, 239−242.
(18) MP-Carbonate, 18−52 mesh, Argonaut Technologies.
(19) ABL, ABL tyrosine kinase. CSK, tyrosine-protein kinase CSK. EGFR, the epidermal growth factor receptor (EGFR) subfamily of tyrosine kinases, ephrin type-A receptor 2. EPHB4, ephrin type-B receptor 4. FGFR1, fibroblast growth factor receptor 1. FLT3, Fms-like tyrosine kinase 3. IGF1R, Insulin-like growth factor 1 receptor. ITK, IL2-inducible T-cell kinase. JAK3, Janus kinase 3. KDR, kinase insert domain receptor. LCK, lymphocyte-specific protein tyrosine kinase. MET, Mesenchymal-epithelial transition factor. PDGFR alpha, platelet-derived growth factor receptor A. PYK2, protein tyrosine kinase 2. SRC, Src protein-tyrosine kinase. SYK, Spleen tyrosine kinase. TIE2, endothelium-specific receptor tyrosine kinase. TRKA, neurotrophic tyrosine kinase receptor type 1. TYRO3, tyrosine-protein kinase receptor TYRO3.
(20) An example of unselective kinase inhibitor: (a) Oduor, R. O; Ojo, K. K.; Williams, G. P.; Bertelli, F.; Mills, J.; Maes, L.; Pryde, D. C.; Parkinson, T.; Van Voorhis, W. C.; Holler, T. P. TDR Targets: a chemogenomics resource for neglected diseases. *PLoS Neglected Trop. Dis.* **2011**, *5*, e1017. (b) Tückmantel, S.; Greul, J. N.; Janning, P.; Brockmeyer, A.; Grütter, C.; Simard, J. R.; Gutbrod, O.; Beck, M. E.; Tietjen, K.; Rauh, D.; Schreier, P. H. Identification of *Ustilago maydis* Aurora Kinase As a Novel Antifungal Target. *ACS Chem. Biol.* **2011**, *6*, 926−933.
(21) All test samples were dissolved in DMSO and diluted with assay buffer (20 mM HEPES, 0.01% Triton X-100, 2 mM DTT, pH 7.5) and diluted to 10 uM concentration with substrate/ATP/Mg or Mn solution. Test sample solution was incubated for 1 or 5 h. Termination buffer solution (Quickscout Screening Assist MSA) was added and checked inhibition %.
(22) We put the selected 10 compounds to preliminary evaluation with a 20-kinase assay in order to demonstrate that the library is actually effective.