

# Palladium-Promoted Neutral 1,4-Brook Rearrangement/ Intramolecular Allylic Cyclization Cascade Reaction: A Strategy for the Construction of Vinyl Cyclobutanols

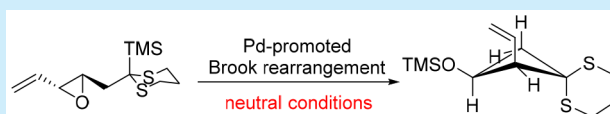
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## Supporting Information

**ABSTRACT:** A cascade reaction to build vinyl cyclobutanol rings through activation of vinyl epoxides by palladium, followed by 1,4-Brook rearrangement and intramolecular cyclization with a palladium complex of the resulting carbon anion, is described. Through this cascade reaction, several highly substituted cyclobutanol substrates were achieved in good yields with high stereoselectivities.

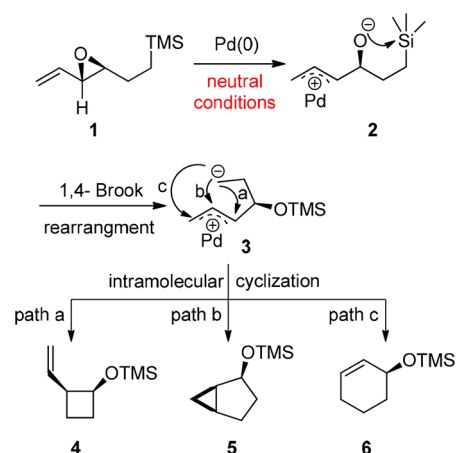


Substituted cyclobutanes are prevalent structures in numerous drugs and biologically active natural products,<sup>1</sup> such as melleolide, solanoeclepin A, marsupellin D, and plumisclerin A. The most widely used method for constructing cyclobutanes is [2 + 2] cycloadditions;<sup>2</sup> however, this reaction suffers from poor stereoselectivity. The undeniable benefits of cascade reactions are well established, having been recounted on numerous occasions.<sup>3</sup> However, designing cascade reactions with controllable product distributions, excellent molecular efficiencies, and high selectivities is still a grand challenge in chemistry. Our group has a long-standing interest in using cascade reactions for natural product syntheses<sup>4</sup> and designed several methodologies based on the Brook rearrangement.<sup>4e,f,6f,g</sup>

Based on these backgrounds, we hypothesized the cascade reaction outlined in Scheme 1. Palladium is known to activate vinyl epoxide **1** to generate complex **2**<sup>5</sup> with an oxygen anion and then undergo 1,4-silicon migration to further form carbon anion **3**,<sup>6</sup> which might attack the palladium complex to achieve this cascade reaction. The resulting  $\pi$ -allyl palladium complex can undergo intramolecular cyclization at three active sites, which subsequently afford vinyl cyclobutanol **4** (path a), bicyclo[3.1.0]hexane **5**<sup>4h,5b</sup> (path b), and cyclohexenol **6** (path c). Elegant works have been reported by Amos B. Smith's group involving anion relay chemistry (ARC) employing Brook rearrangements of various linchpins.<sup>7</sup> To the best of our knowledge, a Pd(0)-promoted Brook rearrangement of a linchpin has rarely been reported. Herein, we show the power of the palladium-promoted tandem [1,4]-Brook rearrangement/intramolecular allylic cyclization, which provides access to various functionalized vinyl cyclobutanols.

Then, *trans*-disubstituted vinyloxyepoxide **7a** derived from (*E*)-penta-2,4-dienoic acid<sup>8</sup> was prepared to test this hypothesis. Table 1 illustrates an abbreviated optimization of this cascade

## Scheme 1. Palladium-Promoted Brook Rearrangement/ Intramolecular Cyclization Cascade Reaction

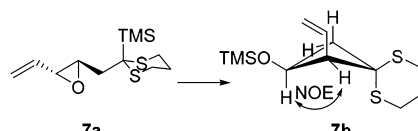


reaction. Initially, after screening several palladium catalysts and ligands, the best set of conditions included the Pd<sub>2</sub>(dba)<sub>3</sub>/dppe system with THF as a solvent at 60 °C (Table 1, entry 7). The relative configuration of **7b** was established by NOE experiments (see the Supporting Information for details). It is striking to note that the palladium-promoted cascade reaction even tolerated 1,3-dithiane functional groups.<sup>9</sup> We then turned our attention to investigate the solvent effects for the cascade annulations and found that THF was superior to other solvents (Table 1, entries 11–13).

With the optimized conditions in hand, we next explored the substrate scope of this cascade reaction (Table 2). All the

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Table 1. Optimization of the Reaction Conditions



| entry <sup>a</sup> | Pd source   | ligand              | temp (°C) | solvent                         | 7b yield (%) <sup>b</sup> |
|--------------------|---|---------------------|-----------|---------------------------------|---------------------------|
| 1                  | Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> | dppe <sup>c</sup>   | rt        | THF                             | n.r.                      |
| 2                  | Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> | dppe <sup>c</sup>   | 60        | THF                             | 39                        |
| 3                  | Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> | dppe <sup>c</sup>   | 80        | THF                             | 33                        |
| 4                  | PdCl <sub>2</sub>                                     | dppe <sup>c</sup>   | 60        | THF                             | trace                     |
| 5                  | Pd(PPh <sub>3</sub> ) <sub>4</sub>                    | –                   | 60        | THF                             | trace                     |
| 6                  | Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> | dppe                | 60        | THF                             | 60                        |
| 7                  | Pd <sub>2</sub> (dba) <sub>3</sub>                    | dppe                | 60        | THF                             | 72                        |
| 8                  | Pd <sub>2</sub> (dba) <sub>3</sub>                    | dppf                | 60        | THF                             | 54                        |
| 9                  | Pd <sub>2</sub> (dba) <sub>3</sub>                    | TMEDA               | 60        | THF                             | complex                   |
| 10                 | Pd <sub>2</sub> (dba) <sub>3</sub>                    | P(OPh) <sub>3</sub> | 60        | THF                             | complex                   |
| 11                 | Pd <sub>2</sub> (dba) <sub>3</sub>                    | dppe                | 60        | toluene                         | 34                        |
| 12                 | Pd <sub>2</sub> (dba) <sub>3</sub>                    | dppe                | 60        | CH <sub>2</sub> Cl <sub>2</sub> | trace                     |
| 13                 | Pd <sub>2</sub> (dba) <sub>3</sub>                    | dppe                | 60        | Et <sub>2</sub> O               | 55                        |
| 14                 | Pd <sub>2</sub> (dba) <sub>3</sub>                    | –                   | 60        | THF                             | n.r.                      |

<sup>a</sup>Reaction conditions: vinyl epoxide silane **7a** (0.2 mmol), Pd source (10 mol %), ligand (25 mol %), Ar, 24 h. <sup>b</sup>Yields of isolated products.

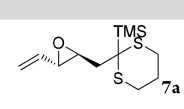
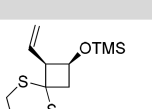
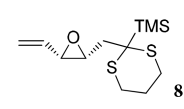
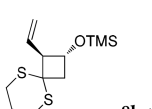
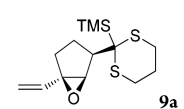
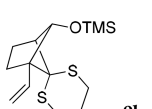
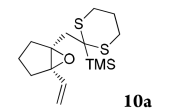
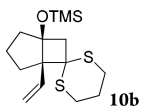
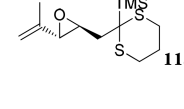
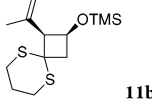
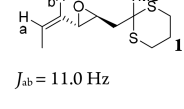
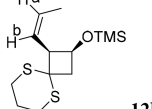
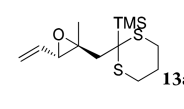
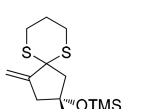
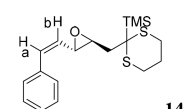
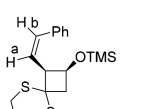
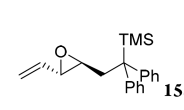
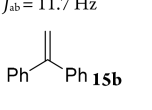
<sup>c</sup>The amount of ligand used was 20 mol %. dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1'-bis(diphenylphosphino)ferrocene, TMEDA = tetramethylethylenediamine.

substrates were achieved through substitution reactions with bromovinylepoxide and lithiated TMS-dithiane (see the Supporting Information for details). As outlined in Table 2, several vinyl cyclobutanols were accessed with reasonable yields and good diastereoselectivities through this method. The influence of the configuration of epoxide was also studied. The initial *trans*-disubstituted epoxide **7a** was converted efficiently to the corresponding **7b** in good yield with high diastereoselectivity (dr >20:1). *cis*-Disubstituted vinyl epoxide **8a** was also converted to the **8b** and **7b** in moderate yield with a diastereoselectivity ratio of 1.2:1.

The good diastereoselectivity of **7a** and the poor diastereoselectivity of **8a** can be explained as follows (Scheme 2). The palladium(0) catalyst coordinates to alkene **8a**, followed by oxidation addition and Brook rearrangement, forming the dithiane anion IV. Finally, the nucleophilic attack of the  $\pi$ -allyl unit on the face opposite to palladium and its attendant ligands resulted in the formation of the vinyl cyclobutanol **8b**. The steric interaction between the R substituent and  $\eta^3$ -allyl group of transition-state II would favor rotation around the C3–C4 bond resulting in transition-state I, which could be transformed to **7b**. The lack of steric interaction in the case of *trans*-vinylepoxide **7a** resulted in good diastereoselectivity.

To explore this scenario further, we next designed substrate **9a** to avoid the influence of the rotation around the C3–C4 bond. To our delight, the reaction worked well and smoothly afforded the bridge [2.1.1] bicyclic skeleton **9b** in moderate yield with high diastereoselectivity. In contrast, **10a** did not afford the corresponding bicyclic structure **10b**. We next examined a series of substrates with substitution on the olefin.

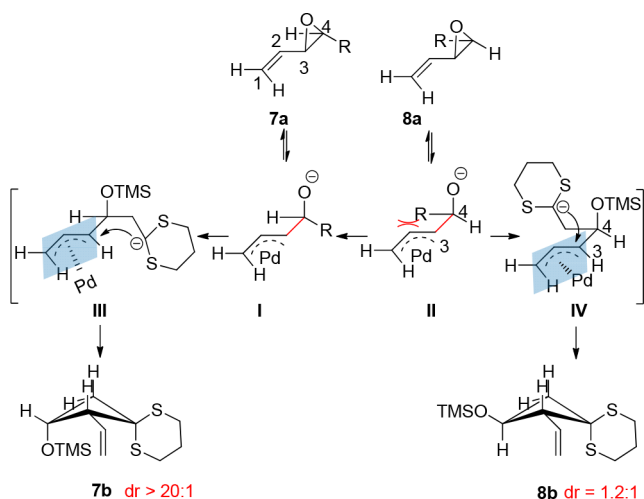
Table 2. Tandem Palladium-Catalyzed Brook Rearrangement/Intramolecular Allylic Cyclization for the Construction of Vinyl Cyclobutanols<sup>a</sup>

| entry          | substrate  | product   | yield (%) <sup>b</sup> |
|----------------|--|---|------------------------|
| 1              |                          |                          | 72                     |
| 2              |                          |                          | 60                     |
|                |  |   | dr = 1.2:1             |
| 3              |                          |                          | 55                     |
| 4              |                          |                          | n.r.                   |
| 5              |                          |                          | 67                     |
| 6              | <br>$J_{ab} = 11.0$ Hz | <br>$J_{ab} < 11.3$ Hz | 65                     |
| 7              |                        |                        | 72                     |
| 8 <sup>c</sup> | <br>$J_{ab} = 11.7$ Hz | <br>$J_{ab} = 11.7$ Hz | 67                     |
| 9 <sup>c</sup> |                        |                        | 75                     |

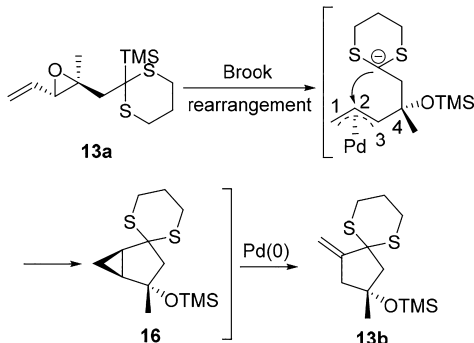
<sup>a</sup>Reaction conditions: vinyl epoxide silane (0.2 mmol), Pd<sub>2</sub>dba<sub>3</sub> (10 mol %), dppe (25 mol %), 2 mL of THF, 60 °C, 24 h. <sup>b</sup>Yields of isolated products. <sup>c</sup>Reaction time is 4 h.

The reaction worked well and smoothly afforded **11b**, **12b**, and **14b** in moderate yields with high diastereoselectivities. We then made a careful analysis of vinyl vicinal proton coupling constants of **12b** ( $J_{ab} < 11.3$  Hz) and **14b** ( $J_{ab} = 11.7$  Hz), which suggested the double bonds of **12b** and **14b** are in the *cis* configuration. Retention of olefin configuration of **12b** and **14b** can be explained by the high stability of the  $\pi$ -allylpalladium resulting from the neighboring-group effect of the hydroxy.<sup>10</sup> When **13a** was treated with the standard conditions, **13b** was obtained in good yield. Because of the steric interaction between the dithiane anion and the adjacent quaternary stereocenter at C4 (Scheme 3), the  $\pi$ -allyl palladium complex

Scheme 2. Transition-State Models to Rationalize the Diastereoselectivity of 7a and 8a



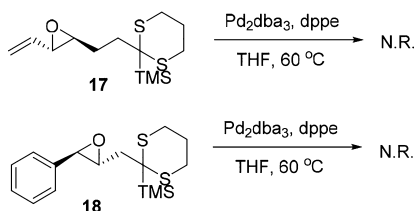
Scheme 3. Proposed Mechanism for the Formation of 13b



was attacked by the dithiane anion at C2, resulting in the formation of [3.1.0] **16**,<sup>4h,5a,b</sup> which was transformed into **13b** in situ through the palladium-catalyzed isomerization of cyclopropane.<sup>1f</sup> When **15a**, containing trimethylsilyldiphenylmethane in place of 2-TMS-1,3-dithiane, was treated with the standard conditions for 4 h, ethene-1,1-diylidibenzene **15b**, which might be formed by retroelectrocyclization of vinyl cyclobutanol,<sup>12</sup> was obtained in 75% yield.

To obtain detailed mechanistic insight for this transformation, some experiments were performed, as shown in Scheme 4. When **17** was treated with the standard conditions,

Scheme 4. Control Experiments



no 1,5-silyl migration occurred.<sup>13</sup> The moderate Lewis acidity of the palladium complex, which might catalyze the tandem reaction of vinyl epoxide as a Lewis acid, has been reported in the literature.<sup>14</sup> When **18** was treated with the standard conditions, [1,4]-Brook rearrangement did not occur, and the cyclization product was not detected. This result indicated that

the Lewis acidity of the palladium complex could not be recommended in this tandem reaction.

In conclusion, we developed a tandem palladium-promoted Brook rearrangement/intramolecular allylic cyclization reaction of vinyl epoxide silanes. The method provided access to several vinyl cyclobutanols in moderate to good yields with high diastereoselectivities. Moreover, the method involved the report of Pd(0)-promoted Brook rearrangement and initiated the Brook rearrangement under neutral conditions. We believe that this method will provide new insights into the Brook rearrangement. Furthermore, this method might be utilized to synthesize natural products and valuable drug molecules.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01381.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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