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# Synthetic Studies on the Taxane Skeleton: Construction of Eight-Membered Carbocyclic Rings by the Intramolecular *B*-Alkyl Suzuki–Miyaura Cross-Coupling Reaction

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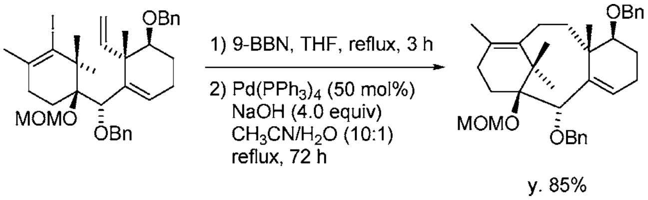
## ABSTRACT



**Construction of eight-membered carbocyclic rings via the intramolecular *B*-alkyl Suzuki–Miyaura cross-coupling reaction has been studied. This protocol proved its potency through the formation of the eight-membered ring possessing a quaternary carbon on its ring in high yield, affording promise of a new access to the eight-membered ring of Taxol.**

Palladium-mediated cross-coupling reactions have been utilized in organic synthesis because of their high efficiency and mild conditions. Among these reactions, the most utilized C−C bond-forming cross-coupling reactions are Mizoroki−Heck,[1] Stille,[2] and Suzuki−Miyaura reactions.[3] Because the Suzuki−Miyaura cross-coupling reaction is a powerful C−C bond-forming reaction under mild conditions, an increasing number of its variants have been reported.[4]

The *B*-alkyl Suzuki−Miyaura reaction, first reported by Suzuki and Miyaura in 1986, is an important variant, occurring between an alkyl borane and an aryl or vinyl halide, triflate, or enol phosphate.[5] The formation of five- and six-membered rings by the intramolecular *B*-alkyl Suzuki−Miyaura reaction has been reported to occur in a facile manner;[6] however, the closing of larger ring sizes by this

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[1] (a) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books, Sausalito, 1999.

[2] (a) Still, J. K. Angew. *Chem. Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Mitchell, T. N. *Synthesis* **1992**, 803−815.

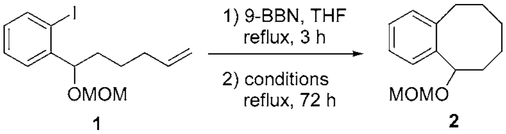
[3] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568.

[4] (a) Liu, S.-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, *23*, 2408−2409. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (c) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662−13663. (d) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910−3912. (e) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726−14727. (f) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341.

[5] (a) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369−6372. (b) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405−1408. (c) Oh-e, T.; Miyayra, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208.

10.1021/ol0481939 CCC: $27.50

**Table 1.** Intramolecular *B*-Alkyl Suzuki−Miyaura Cross-Coupling Reaction of **1**



| entry | Pd (mol %) | ligand (mol %) | base (equiv) | solvent | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $PdCl_2(dppf)$ (50) | $AsPh_3$ (100) | $Cs_2CO_3$ (2.0) | $THF/DMF/H_2O$ (6:3:1) | 32 |
| 2 | $PdCl_2(dppf)$ (50) | $AsPh_3$ (100) | $Tl_2CO_3$ (2.0) | $THF/DMF/H_2O$ (6:3:1) | 37 |
| 3 | $PdCl_2(dppf)$ (50) | $AsPh_3$ (100) | $Tl_2CO_3$ (2.0) | $CH_3CN/H_2O$ (10:1) | 41 |
| 4 | $PdCl_2(dppf)$ (50) | | $Tl_2CO_3$ (2.0) | $CH_3CN/H_2O$ (10:1) | 18 |
| 5 | $Pd(PPh_3)_4$ (50) | | $Tl_2CO_3$ (2.0) | $CH_3CN/H_2O$ (10:1) | 8 |
| 6 | $Pd(PPh_3)_4$ (50) | | NaOH (4.0) | $CH_3CN/H_2O$ (10:1) | 33 |
| 7 | $Pd(PPh_3)_4$ (50) | | CsF (4.0) | $CH_3CN/H_2O$ (10:1) | 51 |

[a] Isolated yields.

palladium-mediated reaction has been reported in either very poor yield or not at all.[7]

Eight-membered carbocyclic rings are difficult to construct because of entropy reasons, ring strain, the transannular interaction, and competing oligomerization processes; hence, their synthesis has been a challenging problem. Although the macrocyclization by the intramolecular *B*-alkyl Suzuki−Miyaura reaction has been reported, no examples of its application to the synthesis of eight-membered rings have been reported as far as we know.[8] We report herein our studies on the synthesis of eight-membered carbocyclic rings by the intramolecular *B*-alkyl Suzuki−Miyaura cross-coupling reaction and the promising result toward construction of a taxane skeleton.

First, we investigated the intramolecular *B*-alkyl Suzuki−Miyaura reaction of a simple substrate **1**[9] (Table 1). As shown in Table 1, the reaction of **1** under Johnson's conditions[10] produced the cyclized product **2** but in 32% yield (entry 1). Hence, the reaction conditions were optimized by changing the base, solvent, and catalyst. By the use of $Tl_2CO_3$[8e] instead of $Cs_2CO_3$ under Johnson's conditions, the yield slightly increased (entry 2, 37%). When the solvent was changed to aqueous acetonitrile, the yield was further increased (entry 3, 41%); however, the reactions in the absence of $AsPh_3$ or with the use of $Pd(PPh_3)_4$ as catalyst gave lower yields (entries 4 and 5, 18% and 8%, respectively). We found that the conditions in entry 6, which afforded **2** in 33% yield, were comparable to Johnson's conditions; furthermore, the use of CsF[11] gratifyingly increased the yield to 51% (entry 7). Encouraged by these preliminary studies that disclosed the first synthesis of the eight-membered carbocyclic ring by the intramolecular *B*-alkyl Suzuki−Miyaura cross-coupling reaction, we next examined the reactions of more complex substrates**.** Thus, substrate **3**, prepared according to Danishefsky's procedure,[12] was subjected to the intramolecular *B*-alkyl Suzuki−Miyaura reaction (Table 2).

As shown in Table 2, the reaction of **3** under Johnson's conditions produced the deprotected product **5** in only 9% yield (entry 1). Hence, the reaction condition was optimized considering the results obtained in Table 1. Thus, $Pd(PPh_3)_4$ in aqueous acetonitrile gave a better yield (31%, entry 2), but $Tl_2CO_3$ did not improve the yield (22%, entry 3). Use of NaOH in aqueous acetonitrile did not improve the yield of **5** (14%, entry 4); furthermore, use of $Cs_2CO_3$, $Tl_2CO_3$, or NaOH in aqueous acetonitrile merely produced the deprotected product **5** (entries 1−5). Fortunately, when the reaction was carried out using less basic CsF, the desired **4** was obtained without formation of **5** (entries 6 and 7). In the use of CsF, aqueous acetonitrile as solvent was crucial for high yield again, affording **4** in 62% yield (entry 6). To our knowledge, the conditions for the intramolecular *B*-alkyl Suzuki−Miyaura reaction affording the eight-membered ring in good yield shown in Tables 1 and 2 have never been reported.

These optimization studies in Table 2 indicate the importance of the base and solvent in this reaction. Moreover, the yield was surmised to be reduced by hydrolysis of the cyclic carbonate group under the rather basic conditions because some unidentified byproducts formed in entries 1−5. Hence, other protective groups for the C1 and C2 hydroxyls stable

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(6) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321. (b) Miyaura, N.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1992**, *33*, 2571−2574. (c) Soderquist, J. A.; Leon, G.; Colberg, J. C.; Martinez, I. *Tetrahedron Lett.* **1995**, *36*, 3119−3122.

(7) (a) Kwochka, W. R.; Damrauer, R.; Schmidt, M. W.; Gordon, M. S. *Organometallics* **1994**, *13*, 3728−3732. (b) Smith, B. B.; Kwochka, W. R. *J. Org. Chem.* **1997**, *62*, 8589−8590. (c) Bracher, F.; Schulte, B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2619.

(8) (a) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687−2690. (b) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695−2698. (c) Gagnon, A.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1581−1584. (d) Bauer, M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 2205−2208. (e) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712−1713. (f) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313−10318.

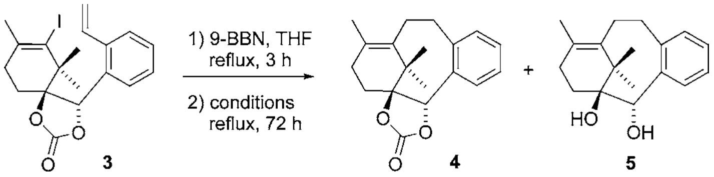
(9) 2-Iodobenzaldehyde was reacted with the Grignard reagent prepared from 5-bromo-1-pentene, and the resulting alcohol was protected with MOMCl (82%, 2 steps).

(10) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015.

(11) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

(12) Young, W. B.; Masters, J. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5228−5234.

**Table 2.** Intramolecular *B*-Alkyl Suzuki−Miyaura Cross-Coupling Reaction of **3**

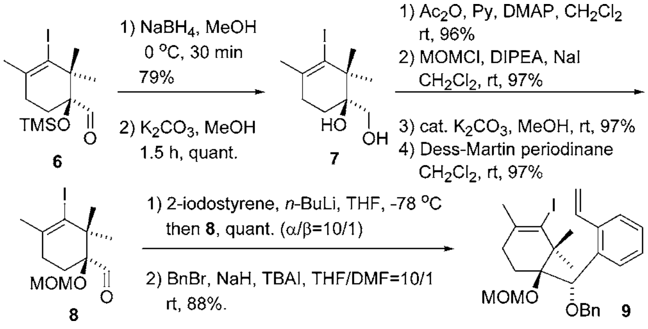


| entry | Pd (mol %) | ligand (mol %) | base (equiv) | solvent | product/yield (%)[a] |
|---|---|---|---|---|---|
| 1 | PdCl$_2$(dppf) (50) | AsPh$_3$ (100) | Cs$_2$CO$_3$ (2.0) | THF/DMF/H$_2$O (6:3:1) | **5**/9 |
| 2[b] | Pd(PPh$_3$)$_4$ (50) |  | Cs$_2$CO$_3$ (4.0) | CH$_3$CN//H$_2$O (5:1) | **5**/31 |
| 3 | Pd(PPh$_3$)$_4$ (50) |  | Tl$_2$CO$_3$ (2.0) | CH$_3$CN/H$_2$O (10:1) | **5**/22 |
| 4 | Pd(PPh$_3$)$_4$ (50) |  | NaOH (4.0) | CH$_3$CN/H$_2$O (10:1) | **5**/14 |
| 5 | Pd(PPh$_3$)$_4$ (50) |  | NaOH (4.0) | THF/H$_2$O (10:1) | **5**/36 |
| 6 | Pd(PPh$_3$)$_4$ (50) |  | CsF (4.0) | CH$_3$CN/H$_2$O (10:1) | **4**/62 |
| 7[c] | Pd(PPh$_3$)$_4$ (50) |  | CsF (4.0) | DMF/H$_2$O (5:1) | **4**/28 |

[a] Isolated yields. [b] Reaction time was 74 h. [c] Reaction temperature was 85 °C.

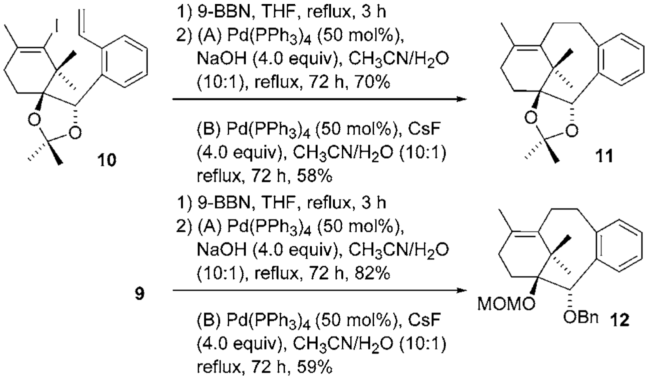
under the reaction conditions were examined. That is, acetonide **10** was prepared according to the literature,[13] and the substrate **9** having an MOM group at the C1 hydroxyl group and a benzyl group at the C2 hydroxyl group was prepared as shown in Scheme 1. Reduction of the known nonchiral aldehyde **6**[12] (79%) and removal of TMS gave **7** (quant). Selective acetylation (96%), protection of the tertiary alcohol with methoxymethyl ether (97%), removal of the acetyl group (97%), and Dess−Martin oxidation generated aldehyde **8** (97%). Treatment of 2-iodostylene with *n*-BuLi and then with **8** produced an inseparable mixture of diastereomers (quant, $\alpha/\beta = 10/1$), which was converted to separable benzyl ether **9** (88%).

**Scheme 1**[a]



The intramolecular *B*-alkyl Suzuki−Miyaura cross-coupling reactions of **10** and **9** were carried out under the optimized conditions in Table 2. As shown in Scheme 2, the reactions of **10** and **9** under the conditions A (Pd(PPh$_3$)$_4$, 50 mol %; NaOH, 4.0 equiv; CH$_3$CN/H$_2$O, 10:1; reflux; 72 h) gave **11** and **12** in dramatically improved yields (70% and 82% yields, respectively). On the other hand, the reactions of **10** and **9** under the conditions B (Pd(PPh$_3$)$_4$, 50 mol %; CsF, 4.0 equiv; CH$_3$CN/H$_2$O, 10:1; reflux; 72 h) gave **11** and **12** in 58% and 59% yields, respectively. These results indicate that conditions A are the better conditions for these substrates. The protective groups were also shown to be important to increase the yield. Thus, the protective groups of the hydroxyls on the forming eight-membered ring should be stable under the basic conditions, and the acyclic protective groups such as in **9** are better than the cyclic ones such as carbonate or acetonide. The cyclic protective groups were surmised to restrict free rotation of the C1−C2 bond to enhance the ring closure; however, the transition state of the substrate possessing the cyclic protective group would be energetically unfavored as a result of the increasing strain.[14]

**Scheme 2**[a]



Finally, we examined the reaction of the more complex substrate **17** possessing a quaternary carbon on the forming eight-membered ring (Scheme 3). Previously reported chiral alcohol **13** (>99% ee)[15] was converted to **14** by hydro-

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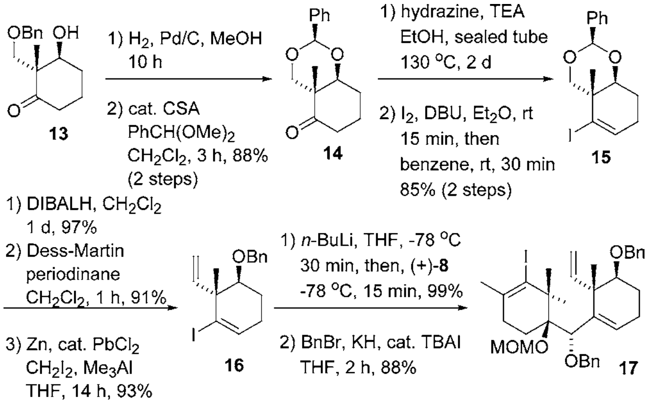
(13) Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 7253−7256.

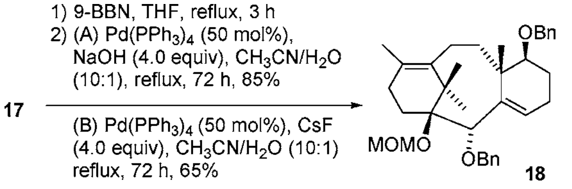
(14) For the similar results obtained, see: Miyamoto, S.; Doi, T.; Takahashi, T. *Synlett* **2002**, 97−99.

(15) Iwamoto, M.; Kawada, H.; Tanaka, T.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 7239−7243.

### Scheme 3[a]



### Scheme 4[a]



genolysis and the following benzylidene formation (88%, 2 steps). Ketone **14** was transformed to hydrazone, which was then treated with $I_2$ and DBU[16] to afford iodide **15** (85%, 2 steps). The selective reduction of the benzylidene group of **15** (97%), Dess−Martin oxidation (91%), and olefination by Takai's reagent[17] afforded **16** (93%). Coupling of the alkenyllithium derived from **16** with aldehyde (+)-**8**[18] afforded the desired product as a single diastereomer (99%), which was protected as a benzyl ether **17** (88%).

With **17** in hand, the intramolecular *B*-alkyl Suzuki−Miyaura cross-coupling reaction was executed under conditions A and B (Scheme 4). Gratifyingly, we succeeded in producing the cyclized product **18** in 85% yield under the conditions A. Because the product **18** possesses a 6−8−6 carbon skeleton required for the synthesis of Taxol, the intramolecular *B*-alkyl Suzuki−Miyaura reaction was found to be a promising method to construct the eight-membered ring of Taxol.

In summary, we have succeeded in constructing eight-membered rings via the intramolecular *B*-alkyl Suzuki−Miyaura cross-coupling reaction under new conditions. This protocol proved its potency through the formation of the eight-membered ring possessing a quaternary carbon on its ring in high yield. We are now developing this protocol to synthesize the more advanced synthetic intermediate possessing the tricyclic 6−8−6 carbon skeleton of Taxol. The further studies will be reported in due course.

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**Supporting Information Available:** Spectral data for all new compounds and experimental procedures for the reaction of **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147−162. (b) Grandi, M. J. D.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989−4992.

[17] (a) Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5581−5584. (b) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670.

[18] Iwamoto, M.; Miyano, M.; Utsugi, M.; Kawada, H.; Nakada, M. *Tetrahedron Lett.* **2004**, *45*, 8647−8651.