Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 04 Dec 2007.

To cite this article: Young-Ger Suh, Young-Choon Lee, Jung-Ae Ko, Soon-Ai Kim, Jee-Young Kim, Jae-Kyung Jung, Seung-Yong Seo & Kee-Ho Lee (2000) Palladium-Catalyzed Diastereoselective Cyclization of the Allylic Precursors. A Concise Synthetic Route to 3-Azabicyclo[3.3.0]Octane and Hydroisoindole Skeletons, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:16, 3053-3060, DOI: 10.1080/00397910008087454

To link to this article: http://dx.doi.org/10.1080/00397910008087454

SYNTHETIC COMMUNICATIONS, 30(16), 3053–3060 (2000)

PALLADIUM-CATALYZED DIASTEREOSELECTIVE CYCLIZATION OF THE ALLYLIC PRECURSORS. A CONCISE SYNTHETIC ROUTE TO 3-AZABICYCLO[3.3.0]OCTANE AND HYDROISOINDOLE SKELETONS

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Abstract: A useful variant of palladium-catalyzed 1,2-diastereoselective cyclization of the allylic precursors based on the steric nature of the anion stabilizing groups has been developed. The 1,1,2-trisubstituted cycloalkane products have also been efficiently transformed into the azabicyclic systems.

Palladium catalyzed cyclization has been utilized as one of the most powerful synthetic tools for carbocycle construction due to its highly versatile selectivities.[1] In particular, the 1,2-diastereoselectivity between the newly formed stereogenic center possessing vinyl group and the adjacent chiral centers has been extensively explored.[2] However, the synthetically useful 1,2-diastereocontrol between the new stereogenic center and the nucleophilic carbon possessing two different anion stabilizing groups has not attracted much attention[3] because its synthetic utilities are limited by the difficult stereocontrol at the nucleophilic carbon as well as the ultimate loss of the established stereochemistry upon removal of anion stabilizing groups.

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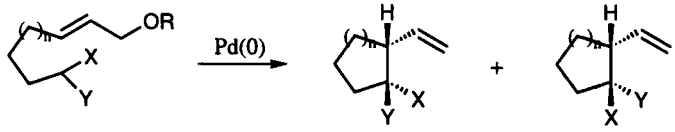
Since we have recently reported a new palladium-catalyzed stereoselective cyclization[4] which provides both 1,2-diastereocontrol and 1,3-asymmetric induction, we have further searched for an alternative route to the 1,2-diastereoselective cyclization by employing an acyclic allylic precursors instead of our previous lactone bearing allylic carbonates. We herein describe a convenient acyclic version of the palladium-catalyzed 1,2-diastereoselective cyclization of the allylic carbonates established via systematic studies on the nucleophilic carbon units. In addition, the extended applications of this procedure to the syntheses of 3-azabicyclo[3.3.0]octane and hydroisoindole skeletons are also reported.

Our basic strategy relies on the 1,2-diastereoselective C-C bond formation induced by the steric nature of the anion stabilizing groups at the nucleophilic carbon as shown in Scheme 1.

Scheme 1



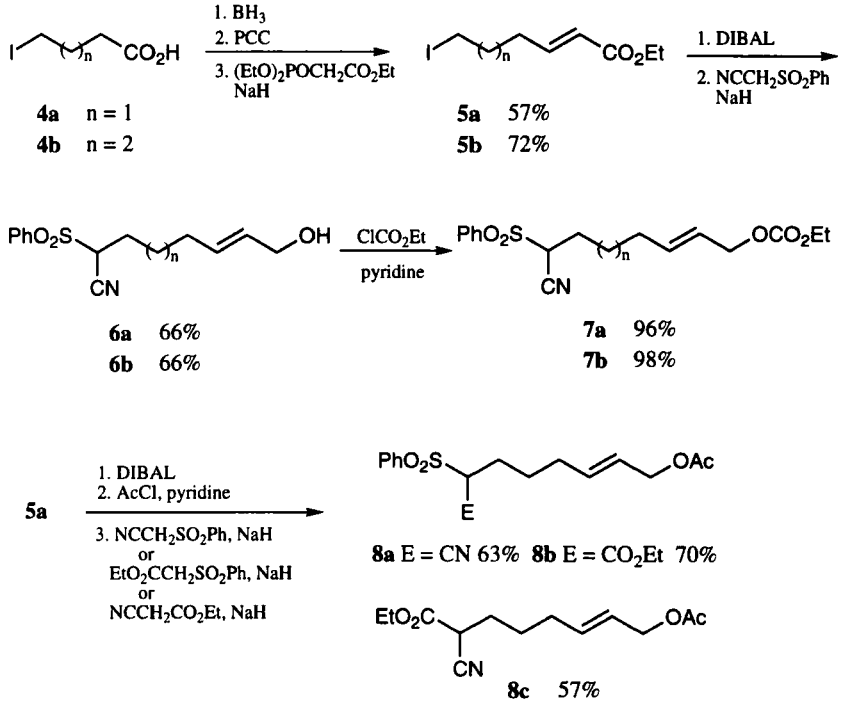
1 **2** **3**

n = 1, 2

X, Y = SO_2Ph, CO_2Et, CN

The three standard anion stabilizing groups which are readily convertible to other functional groups were initially examined for the 1,2-diastereoselective cyclizations. The corresponding allylic cyclization precursors were straightforwardly prepared from ω-iodoacids as shown in Scheme 2. Two carbon extension of 4-iodobutyric acid (**4a**) or 5-iodopentanoic acid (**4b**), displacement of the iodide with the requisite anion stabilizing groups and then ethoxycarbonylation or acylation provides a variety of cyclization precursors.

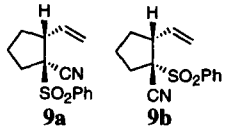
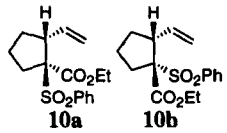
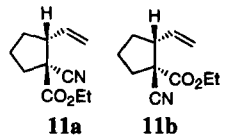
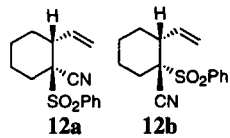
Scheme 2



First, allylic precursors **7a** and **8a-8c** (entry 1-4) were subjectd to the optimized cyclization conditions[5] for the 1,1,2-trisubstituted cyclopentanes and the Table 1 summarize the results. The allylic precursors **7a** and **8a** with (phenylsulfonyl) acetonitrile as a nucleophilic carbon unit provided the best diastereoselectivities in favor of the desired diastereomer **9a**.[6] However, the allylic carbonate **7a** was superior to the allylic acetate **8a** in terms of the chemical yield. The allylic precursors **8b** and **8c** with (phenylsulfonyl)acetate and cyanoacetate afforded the low or no diastereoselectivity respectively. The allylic carbonate precursors with (phenylsulfonyl)acetate or cyanoacetate which are not shown in Table 1 consistently provided the elimination products under a variety of reaction conditions. Cyclization of the allylic carbonate **7b** (entry 5) with the best anion

stabilizing group of (phenylsulfonyl)acetonitrile was also conducted to afford the good diastereoselectivity in favor of the desired trisubstituted cyclohexane **12a**.

Table 1. Effects of the anion stabilizing group on the cyclization of acyclic allylic precursors[a]

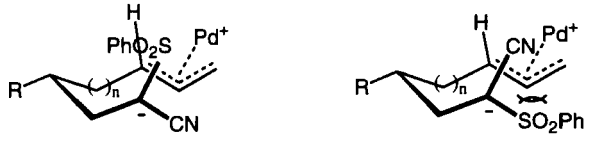
Entry	Allylic precursor	Catalyst	Yield(%)[b]	Products (Ratio)
1	**7a**	$Pd(dppe)_2$	80	 **9a** **9b** (5.2 : 1)
2	**8a**	$Pd(Ph_3P)_4$	25	(5.0 : 1)
3	**8b**	$Pd(Ph_3P)_4$	74	 **10a** **10b** (4.0 : 1)
4	**8c**	$Pd(Ph_3P)_4$	40	 **11a** **11b** (1.1 : 1)
5	**7b**	$Pd(dppe)_2$	76	 **12a** **12b** (7.1 : 1)

a. Reactions were performed at 0.1 to 0.05M concentration for 30 min to 2 h under reflux in THF.
b. Isolated yields.

The highest diastereoselectivities for the cyclization precursors possessing (phenylsulfonyl)acetonitrile is likely due to the least steric interactions between the nitrile group and the favored *syn*-π-allyl palladium complex[1b] as shown in the transition state A of Figure 1. The transition state B would suffer more steric

interaction between the bulkier phenylsulfonyl group and π-allyl palladium complex. This could be understood by the relatively low or no diastereoselectivities of the precursors **8b** and **8c** which have less steric differences between two anion stabilizing groups at the nucleophilic carbon.

Figure 1



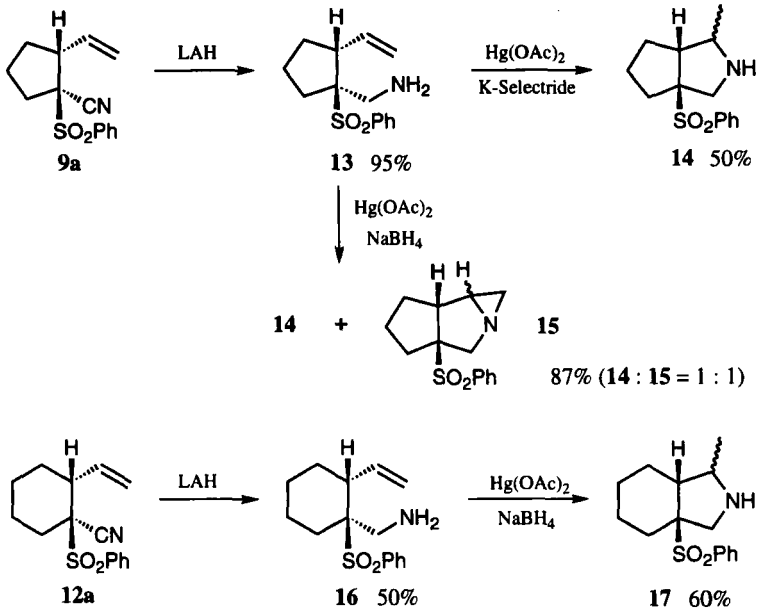
A B

R = H, n = 1 or 2

The standard cyclization procedure for the allylic carbonates **7a** and **7b** are as follows. To a solution of allylic carbonate (4 mmol) in THF (40 mL) was added $Pd(dppe)_2$ (0.08 mmol) in THF (5 mL) and the resulting solution was refluxed for one hour. The reaction mixture was filtered through a silica gel plug and concentrated. The residue was chromatographed on silica-gel with a mixture of ethyl acetate and hexane (1 : 1) to afford the pure cyclization product.[6]

The desired cyclization products **9a** and **12a** were further transformed into the 3-azabicyclo[3.3.0]octane **14**[7] and the hydroisoindole **17**[8] for the extended synthetic utilities of our diastereoselective cyclizations as well as the structural confirmation of the each diastereomers as shown in Scheme 3. Lithium aluminum hydride reduction of the nitrile **9a** followed by the intramolecular aminomercuration[9] ($Hg(OAc)_2$, THF then K-selectride) of the resulting amine afforded the 3-azabicyclo[3.3.0]octane **14** as an only regioisomer of 1 : 1 diastereomeric mixture.[10] It is noticeable that demercuration by sodium borohydride afforded 3-azabicyclo[3.3.0]octane **14** along with the azatricyclononane **15**.[11] The 1,1,2-trisubstituted cyclohexane **12a** also afforded the hydroisoindole **17** in 60 % yield by the same reaction sequence.

Scheme 3



In conclusion, we have developed a useful variant of palladium-catalyzed diastereoselective cyclization for the 1,1,2-trisubstituted cyclopentane and cyclohexane. The 1,2-diastereoselectivity presumably arises from the different steric effects of the anion stabilizing groups at the nucleophilic carbon. Moreover, the synthetic utilities of the 1,2-diastereocontrol have been extended by an efficient conversion of the 1,1,2-trisubstituted cycloalkanes to the useful bicyclic synthetic intermediates of 3-azabicyclo[3.3.0]octane and hydroisoindole.

Acknowledgements: This work was supported by grant (1999-2-215-001-3) from the Basic Research program of the KOSEF and partly by the Research Center for New Drug Development at Seoul National University.

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5. The optimized cyclization conditions for each allylic precursors were determined through our previous systematic studies on leaving groups, catalysts and solvents which are related to the reference 4.

6. The structures of each isomers were confirmed by the careful analysis of spectral data. The final structural confirmation of the desired isomer was inferred from the mercuricyclization of the amino-olefins **13** and **16**.

Spectral data for the cyclopentane **9a** as a representative cyclization product: IR (neat) 2220 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, J = 7.2 Hz), 7.77 (t, 1H, J = 7.2 Hz), 7.55 (m, 2H), 5.67 (ddd, 1H, J = 17.2, 9.6, 7.6 Hz),

5.00 (d, 1H, J = 9.6 Hz), 4.98 (d, 1H, J = 17.2 Hz), 3.27 (m, 1H), 2.59 (m, 1H), 1.81 - 1.52 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.2, 134.6, 130.7, 129.1, 118.3, 117.5, 117.3, 68.0, 44.6, 42.9, 31.8, 31.3, 25.3, 24.2, 19.3; Anal. Calcd for $C_{14}H_{15}N_1O_2S_1$: C, 64.34; H, 5.79; N, 5.34. Found: C, 64.71; H, 5.89; N, 5.29.

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Received in Japan 9/7/99