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Palladium-Catalyzed Tandem Cyclization of Allenyl-Aldehydes and -Ketones with Aryl Iodides and $Bu_3SnSnBu_3$

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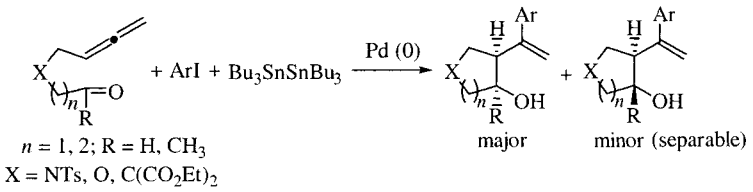
ABSTRACT



The arylative cyclization of allenyl-aldehydes with aryl iodides and hexa-*n*-butyldistannane to form substituted cyclopentanols and cyclohexanols by tandem palladium-catalyzed carbostannylation and allylation was achieved under mild conditions.

In the field of organic synthesis, it would be very desirable to facilitate two- and/or multistep bond formation in one pot using a single catalyst at a uniform temperature to achieve economically useful transformations, which should minimize the chemicals used and the waste produced, as well as the reaction time.[1,2] Jeong et al.[3] reported allylation/Pauson−Khand reaction with two artificial catalysts in a one-pot procedure and then Evans and Robinson[4] modified it in a tandem sequence with a Rh complex as the only catalyst. Recently, Shibasaki and co-workers[5] reported a one-pot synthesis of β-cyanohydrin from olefins with the multiaction of a Zr catalyst. In our ongoing studies to use allene substrates in organic reactions, we recently investigated the palladium-catalyzed tandem silastannylation/carbonyl allylation of allenyl-aldehydes and -ketones.[6] Our interest in the development of a new palladium-catalyzed allene chemistry led us to explore the palladium-catalyzed chemoselective arylative cyclization/allylation of allenyl-aldehydes and -ketones with aryl iodides and $Bu_3SnSnBu_3$, which allows three reactive functionalities to participate in the coupling sequence in a one-pot reaction.

It is thought that allenyl-aldehydes and -ketones are good substrates to form π-allylpalladium complexes through the reaction of the allene moiety with aryl iodides, which transmetalate with $Bu_3SnSnBu_3$ to give allylstannanes.[7] The allylstannanes thus formed in situ can be subjected to carbonyl allylation[8,9] in a tandem sequence using a single palladium catalyst and at a constant reaction temperature, as shown in Scheme 1.[10,11] We report here the palladium-

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 259−281. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1−16.

(2) (a) Hall, N. *Science* **1994**, *266*, 32−34. (b) Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115−136.

(3) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc*. **2000**, *122*, 10220−10221.

(4) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc*. **2001**, *123*, 4609−4610.

(5) Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 1256−1257.

(6) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2001**, *41*, 343−345.

(7) Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *Tetrahedron Lett*. **1999**, *40*, 6055−6058.

(8) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **1996**, 6641−6647.

(9) The condensation of allylic stannanes and aldehydes catalyzed by known palladium and platinum complexes is primarily limited to simple allylic stannanes and crotyl stannanes. See: (a) Nakamura, H.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, *122*, 11529−11530. (b) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **1996**, 1459−1460.

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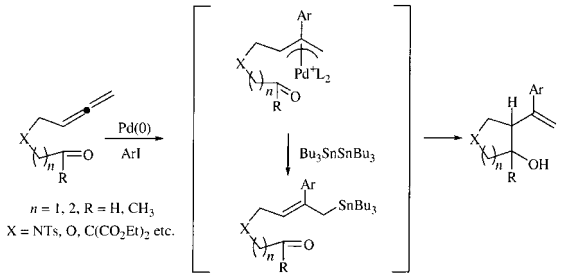
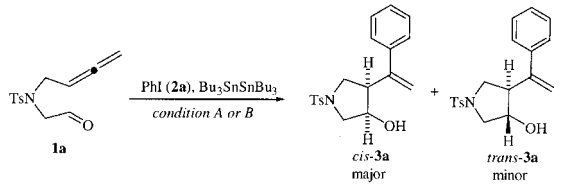
Scheme 1



catalyzed tandem arylative cyclization of allenyl-aldehydes and -ketones with aryl iodides and hexa-*n*-butyldistannane.

To find optimum conditions, *N*-tosyl branched *δ*-allenyl-aldehyde **1a** was used as a model compound, and a series of experiments was performed with iodobenzene (**2a**) (1.1 equiv) and $Bu_3SnSnBu_3$ (1.1 equiv). Of the catalysts $Pd_2(dba)_3$, $PdCl_2(CH_3CN)_2$, $Pd(OAc)_2$/tri(2-furyl)phosphine, and $(\pi\text{-allyl})_2Pd_2Cl_2$, $Pd_2(dba)_3$ gave the best yield. Among the solvents THF, CH_3CN, toluene, and DMF, THF gave the best results, although CH_3CN and DMF were also effective. The best conditions were determined to be $Pd_2(dba)_3$ (5 mol %), PhI, and $Bu_3SnSnBu_3$ in THF at reflux for 1 h (condition A) and $Pd_2(dba)_3$, PhI, and $Bu_3SnSnBu_3$ in THF at room temperature for 12 h (condition B), as summarized in Scheme 2. With both conditions A and B, two easily separable *cis*-

Scheme 2



and *trans*-isomers **3a** were obtained in respective yields of 75% (*cis*:*trans* = 70:30) and 78% (*cis*:*trans* = 72:28).

The results of the palladium-catalyzed tandem arylative cyclization of *δ*-allenyl-aldehydes and -ketones with aryl iodides and $Bu_3SnSnBu_3$ are summarized in Table 1. The *δ*-allenyl-aldehyde **1a** reacted with iodobenzene (**2a**) in the presence of $Pd_2(dba)_3$ (5 mol %) and $Bu_3SnSnBu_3$ (1.1 equiv) in THF at reflux for 1 h to give *cis*-**3a** and *trans*-**3a** in total yield of 75% (53:22) (entry 1 in Table 1).[12] Under the same conditions using the same catalyst at room temperature for 12 h, the reaction of **1a** with **2a** gave *cis*-**3a** (65%) and *trans*-

Table 1. Pd(0)-Catalyzed Tandem Arylative Cyclization of *δ*-Allenyl-Aldehydes and -Ketones

Entry	Substrate	Aryl Iodide	Conditions	Time	Product	Yield (%)
1	1a	PhI (2a)	A	1 h	cis-3a (53%) + trans-3a (22%)	75
			B	12 h	cis-3a(65%) + trans-3a(13%)	78
2	1a	2b	A	0.5 h	cis-3b (59%) + trans-3b (27%)	86
3	1a	2c	A	0.5 h	cis-3c (63%) + trans-3c (24%)	87
			B	10 h	cis-3c(52%) + trans-3c(26%)	78
4	1b	2a	A	1 h	cis-3d (62%) + trans-3d (29%)	91
5	1c	2a	A	8 h	cis-3e (78%) + trans-3e (5%)	83
6	1d	2c	A	1 h	cis-3f	94

3a (13%).[12] *cis*-**3a** and *trans*-**3a** were readily separated by column chromatography, and their stereochemistries were unambiguously determined by comparing the results of a NOESY spectrum analysis (see Supporting Information) and the X-ray crystallographic data of *cis*-**3a** (Figure 1). In the NOESY spectra of *cis*-**3a** and trans-**3a**, NOE cross-peaks between the protons at ring junctions and vinyl protons were investigated. In the spectrum of *trans*-**3a**, cross-peaks were observed between the protons at ring junctions and one of the vinyl protons. However, in the case of *cis*-**3a**, a cross-peak was not observed between the proton adjacent to the OH group and one of the vinyl protons, which confirmed that these were isomers (see Supporting Information). Under

(10) The intermolecular allylation of allenes with aldehydes via palladium-catalyzed hydrostannylation has been reported: Cheng, H.-M.; Cheng, C.-H. *Org. Lett*. **2000**, *2*, 3439−3442.

(11) Carbonyl allylation of allylic derivatives by charge-reversal of electrophilic *π*-allylpalladium intermediates: (a) Masuyama, Y.; Hayashi, R.; Otake, K.; Kurusu, Y. *J. Chem. Soc., Chem. Commun*. **1988**, 44−45. (b) Masuyama, Y.; Otake, K.; Kurusu, Y. *Tetrahedron Lett*. **1988**, *29*, 3563−3566. (c) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc*. **1992**, *114*, 2577−2586.

(12) **Typical Procedure.** Method A. To a stirred solution of *δ*-allenyl-aldehyde **1a** (100 mg, 0.38 mmol), iodobenzene (**2a**) (86 mg, 0.42 mmol), and $Pd_2(dba)_3$ (5 mol %) in THF (3 mL) was added bis(tributyltin) (244 mg, 0.42 mmol). The reaction mixture was stirred at reflux for 1 h, and THF was evaporated in vacuo. The crude product was separated by column chromatography (hexane/ethyl acetate = 2:1) to give the cyclized products *cis*-**3a** (69 mg, 53%) and *trans*-**3a** (29 mg, 22%). Method B. To a stirred solution of *δ*-allenyl-aldehyde **1a** (100 mg, 0.38 mmol), iodobenzene (**2a**) (86 mg, 0.42 mmol), and $Pd_2(dba)_3$ (5 mol %) in THF (3 mL) was added bis(tributyltin) (244 mg, 0.42 mmol). The reaction mixture was stirred at room temperature for 12 h, and THF was evaporated in vacuo. The crude product was separated by column chromatography (hexane/ethyl acetate = 2:1) to give the cyclized products *cis*-**3a** (85 mg, 65%) and *trans*-**3a** (17 mg, 13%).

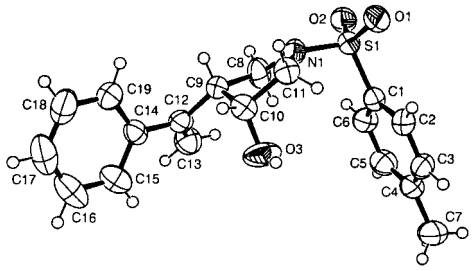
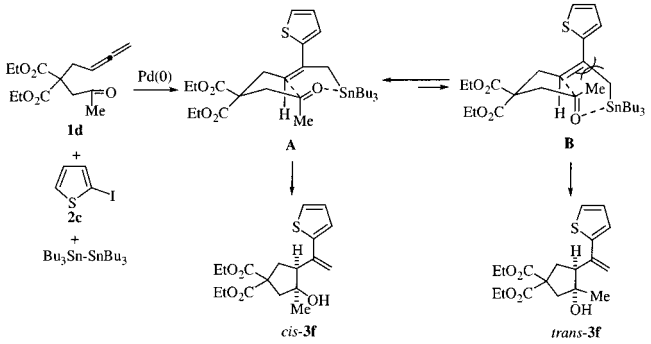


Figure 1. ORTEP drawing of *cis*-**3a**.

the same conditions, *p*-methoxyiodobenzene (**2b**) and 2-iodothiophene (**2c**) coupled with **1a** to provide separable *cis*- and *trans*-isomers **3b** and **3c** in 86% and 87% (entries 2 and 3). When the malonate branched δ-allenyl-aldehyde **1b** was treated with PhI (**2a**), a separable *cis*- and *trans*-isomer **3d** was isolated in 91% yield (entry 4). This arylative cyclization was applied to allenyl-ketones, and quaternary centers could be introduced by the formation of 3° cyclopentanol. To the best of our knowledge, this is first report of the palladium-catalyzed addition of allylstannanes to ketones. The δ-allenyl-ketone **1c** was coupled under the same conditions to give readily separable *cis*- and *trans*-**3e** in total yield of 83% (78:5). The stereochemistry was confirmed by NOE experiments in NMR. Notably, the malonate branched δ-allenyl-ketone **1d** was treated with **2c** to provide *cis*-**3f** as a sole product in 94% yield (entry 6).

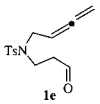
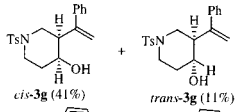
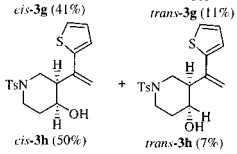
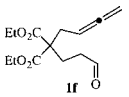
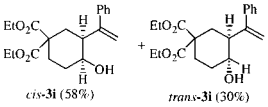
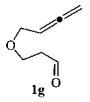
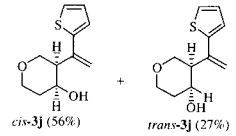
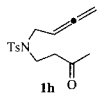
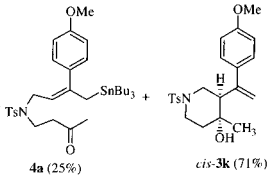
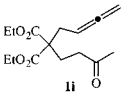
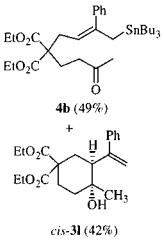
The exact mechanism for the formation of the *cis*-isomer as a major product over the *trans*-isomer remains to be elucidated. Our explanation for the formation of *cis*-**3f** as a sole product is as follows. Aryl-substituted allylstannanes are thought to be formed as intermediates **A** and **B**, which undergo carbonyl allylation to give *cis*- or *trans*-cyclopentanols. The *cis* selectivity of *cis*-**3f** can be ascribed to the fact that intermediate **A**, which leads to the *cis*-isomer, is energetically more stable than **B**, presumably because of steric hindrance between the methyl group and 2-thienyl group (Scheme 3).

Scheme 3



This palladium-catalyzed tandem cyclization was extended to synthesize six-membered cyclohexanol derivatives, and

Table 2. Pd(0)-Catalyzed Tandem Arylative Cyclization of ϵ-Allenyl-Aldehydes and -Ketones

Entry	Substrate	Aryl Iodide	Conditions	Time	Product	Yield (%)
1		**2a**	B	15 h	 *cis*-**3g** (41%) + *trans*-**3g** (11%)	52
2	**1e**	**2b**	B	15 h	 *cis*-**3h** (50%) + *trans*-**3h** (7%)	57
3		**2a**	A	1 h	 *cis*-**3i** (58%) + *trans*-**3i** (30%)	88
4		**2c**	B	15 h	 *cis*-**3j** (56%) + *trans*-**3j** (27%)	83
5		**2b**	A	10 h	 **4a** (25%) + *cis*-**3k** (71%)	96
6		**2a**	A	18 h	 **4b** (49%) + *cis*-**3l** (42%)	91

the results are summarized in Table 2. The ϵ-allenyl-aldehyde **1e** reacted with iodobenzene (**2a**) in the presence $Pd_2(dba)_3$ (5 mol %) and $Bu_3SnSnBu_3$ (1.1 equiv) in THF at room temperature for 15 h to give readily separable *cis*- and *trans*-cyclohexanols *cis*-**3g** and *trans*-**3g** in a total yield of 52% (41:11) (entry 1 in Table 1). The *cis* stereochemistry of *cis*-**3g** was unambiguously assigned on the basis of X-ray crystallographic data (Figure 2). Under the same conditions with 2-iodothiophene (**2c**) as an electrophile *cis*-**3h** and *trans*-**3h** were obtained in a total yield of 57% (50:7) (entry 2).

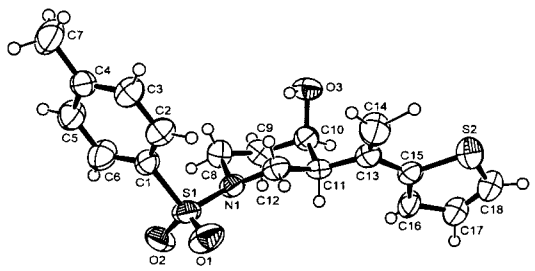


Figure 2. ORTEP drawing of *cis*-**3g**.

The malonate branched ϵ-allenyl-aldehyde **1f** reacted with PhI(**2a**) under the same conditions using the same catalyst at reflux for 1 h to give a separable mixture of *cis*-**3i** (58%) and *trans*-**3i** (30%) in a total yield of 88% (entry 3). For the ether-linked ϵ-allenyl-aldehyde **1g** *cis*-**3j** and *trans*-**3j** were obtained in a total yield of 83% (56:27) (entry 4). This arylative cyclization was applied to allenyl-ketones to form six-membered 3° cyclohexanols. The ϵ-allenyl-ketone **1h** smoothly coupled with *p*-methoxyiodobenzene (**2b**) under the same conditions to give the cyclized cyclohexanol *cis*-**3k**[13] in 71% yield together with a simple addition product **4a** in 25% yield (entry 5). Finally, when the malonate branched ϵ-allenyl-ketone **1i** was cyclized with iodobenzene (**2a**) to give *cis*-**3l** in 42% yield along with the uncyclized and simple addition product **4b** in 49% yield (entry 6).

(13) The *cis* and *trans* stereochemistry was deduced on the basis of the results of NOE experiments.

In summary, the palladium-catalyzed tandem arylative cyclization of allenyl-aldehydes and -ketones with aryl iodides and $Bu_3SnSnBu_3$ to form substituted cyclopentanols and cyclohexanols was achieved.

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Supporting Information Available: The characterization data for **3a**−**l**, **4a**, and **4b**, NOESY spectrum analysis coupled with molecular dynamics calculation data for *cis*-**3a** and *trans*-**3a**, NOE experiments for *cis*-**3a** and *trans*-**3a**, and X-ray crystallographic data for *cis*-**3a** and *cis*-**3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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