

Palladium–Indium-Mediated Arylative Cyclization of Allenyl-Aldehydes and -Ketones

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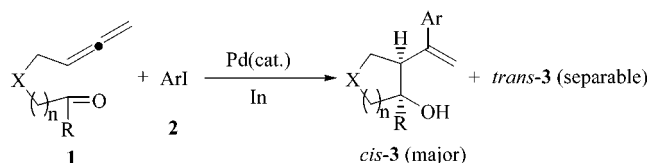
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Abstract: The arylative cyclization of allenyl-aldehydes and -ketones to form homoallylic cyclopentanol and cyclohexanol by the palladium-catalyzed and indium-mediated Babier allylation is described.

Over the past decade, indium has emerged as a useful metal for carbonyl allylation because of its environmentally benign properties coupled with its high chemo-, regio-, and diastereoselectivity, especially in aqueous media.¹ The indium-mediated carbonyl allylation is an aldol-type reaction where allylindium(I) species are usually generated from allylic bromides or iodides with indium in a polar solvent. The transformation of π -allylpalladium electrophilic species to a nucleophilic allyl species, which was used for carbonyl allylation, has been described.² This charge reversal was accomplished by reacting a π -allylpalladium intermediate followed by treatment of a low-valent metal compound indium to generate the corresponding allylic organometallic indium reagent.³ In 2000, Araki et al.⁴ developed reductive transmetalation of π -allylpalladium(II) species with indium(I) salts and expanded the use of allylic substrates in palladium-catalyzed allylation reactions. Recently,

Scheme 1



Scheme 2

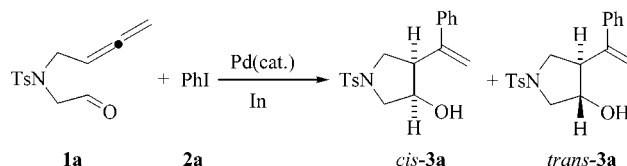


Table 1. Pd(0)–In-Mediated Arylative Cyclization of **1a** with **2a**^a

Entry	Catalyst (5 mol %) ^b	Time	Yield(%)	Cis/Trans ^c
1	Pd(OAc) ₂ +	2h	93	86/14
2	Pd(PPh ₃) ₄	3h	64	95/5
3	(π -allyl) ₂ Pd ₂ Cl ₂	7h	52	88/12
4	Pd ₂ (dba) ₃ ·CHCl ₃	7h	49	79/21
5	PdCl ₂ + dppf	14h	27	95/5

^a Reactions were run with **1a** (1.0 equiv) and **2a** (1.2 equiv) in DMF at 80 °C. ^b Ratio of Pd catalyst to ligand was 1:2. ^c Separated by SiO₂ column chromatography.

Grigg et al.⁵ reported a new allylation utilizing allenes and aryl iodides in the presence of palladium catalyst to form π -allylpalladium species, which transmetalate with indium and then are subjected to carbonyl addition with aldehydes to afford homoallylic alcohols in an intermolecular manner. In connection with our programs to utilize allenyl-aldehydes and -ketones in organic synthesis,⁶ we reasoned that with aryl iodides as electrophiles, arylative cyclization could be realized with allenyl-aldehydes and -ketones in an intramolecular manner, which allows three reactive functionalities to participate in the Pd/In coupling to form homoallylic cyclopentanol and cyclohexanol with incorporation of the quaternary centers for the allenyl-ketones. Here we report palladium(0)–indium-mediated arylative cyclization of allenyl-aldehydes and -ketones (Scheme 1).

To find suitable reaction conditions, a series of experiments was performed on the arylative cyclization of allenyl-aldehyde **1a** with iodobenzene (**2a**) to give the

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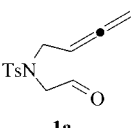
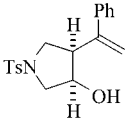
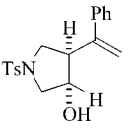
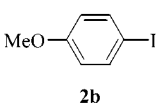
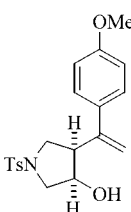
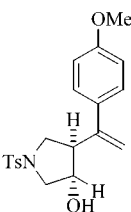

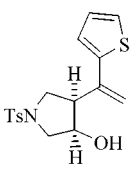
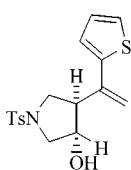
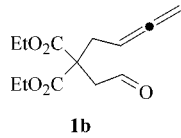
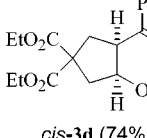
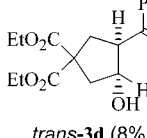
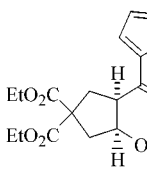
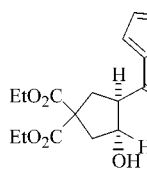
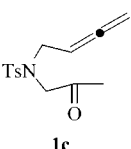
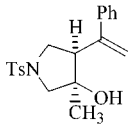
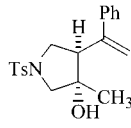
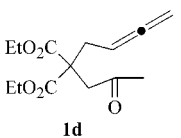
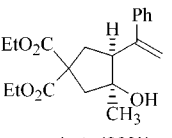
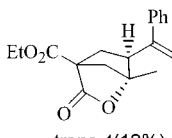
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Table 2. Pd(0)–In-Mediated Arylative Cyclization of δ -Allenyl-aldehydes and -Ketones^a

Entry	Substrate	Aryl Iodide	Time	Product	Total Yields(%) ^b
1		PhI 2a	2 h	 +  <i>cis</i> - 3a (80%) <i>trans</i> - 3a (13%)	93
2	1a		2 h	 +  <i>cis</i> - 3b (79%) <i>trans</i> - 3b (8%)	87
3	1a		3 h	 +  <i>cis</i> - 3c (84%) <i>trans</i> - 3c (4%)	88
4		2a	3 h	 +  <i>cis</i> - 3d (74%) <i>trans</i> - 3d (8%)	82
5	1b	2c	2 h	 +  <i>cis</i> - 3e (66%) <i>trans</i> - 3e (12%)	78
6		2a	7 h	 +  <i>cis</i> - 3f (75%) <i>trans</i> - 3f (5%)	80
7		2a	12h	 +  <i>cis</i> - 3g (68%) <i>trans</i> - 4 (12%)	80

^a Reactions were run with allenyl-aldehydes or -ketones (1.0 equiv) and aryl iodides (1.2 equiv) in DMF at 80 °C. ^b Yields are isolated yields.

coupled product **3a** under a palladium-catalyzed and indium-mediated reaction (Scheme 2).

The results are summarized in Table 1. Of the solvents tested (DMF, CH₃CN, toluene, 1,4-dioxane, and THF), DMF was the best choice. Among the catalysts tested (Pd(OAc)₂/tri(2-furyl)phosphine, Pd(PPh₃)₄, (π-allyl)₂Pd₂Cl₂, Pd₂(dba)₃·CHCl₃, and PdCl₂/dppf), the catalytic system Pd(OAc)₂/tri(2-furyl)phosphine was the most suitable (entry 1 in Table 1) in terms of the yields. The selectivity

was the best with Pd(PPh₃)₄ even if the yield was lower (64%) (entry 2 in Table 1).

However, the yield was better with Pd(OAc)₂ (5 mol %) and tri(2-furyl)phosphine catalyst systems.⁷ The *cis*-**3a** and *trans*-**3a** were separated by column chromatography, and the structures were clearly determined by comparison of NOESY spectrum analysis and X-ray

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Table 3. Pd(0)–In-Catalyzed Arylative Cyclization of ϵ -Allenyl-aldehydes and -Ketones^a

Entry	Substrate	Aryl Iodide	Time	Product	Total Yields(%)
1		2a	5h	 <i>cis</i> - 3h (78%) + <i>trans</i> - 3h (14%)	92
2	1e	2c	3h	 <i>cis</i> - 3i (71%) + <i>trans</i> - 3i (12%)	83
3		2a	3h	 <i>cis</i> - 3j (74%) + <i>trans</i> - 3j (8%)	82
4		2c	1h	 <i>cis</i> - 3k (68%) + <i>trans</i> - 3k (16%)	84
5		2b	20h	 <i>cis</i> - 3l (67%) + <i>trans</i> - 3l (15%)	82
6		2a	7h	 <i>cis</i> - 3m (63%) + <i>trans</i> - 3m (12%)	75

^a Reactions were run with allenyl-aldehydes or -ketones (1.0 equiv) and aryl iodides (1.2 equiv) in DMF at 80 °C.

crystallographic data of *cis*-**3a** (See Supporting Information).

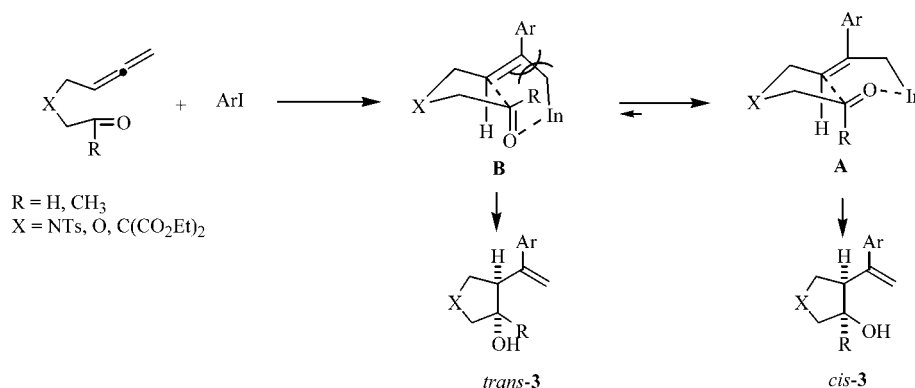
The results of arylative Pd(0)–In-mediated cyclization of δ -allenyl-aldehydes and -ketones are summarized in Table 2. The δ -allenyl-aldehyde **1a** reacted with iodo-benzene (**2a**) in the presence of Pd(OAc)₂ (5 mol %)/tri-(2-furyl)phosphine (10 mol %) and indium (1.2 equiv) in DMF at 80 °C for 2 h afforded *cis*-**3a** (80%) and *trans*-**3a** (13%) in 93% total yield (entry 1 in Table 2). Under the same conditions, *p*-methoxyiodobenzene (**2b**) and 2-iodothiophene (**2c**) were coupled with **1a** to provide separable *cis* and *trans* isomers **3b** and **3c** in 87 and 88% yields, respectively (entries 2 and 3). When the malonate-branched δ -allenyl-aldehyde **1b** was treated with iodo-benzene (**2a**) and 2-iodothiophene (**2c**), separable *cis* and *trans* isomers **3d** and **3e** were isolated in 82 and 78% yields, respectively (entries 4 and 5). This arylative

cyclization was applied to δ -allenyl-ketones, and quaternary centers by formation of 3°-cyclopentanol were successfully introduced. The δ -allenyl-ketone **1c** was smoothly coupled under the same conditions to afford readily separable *cis*- and *trans*-**3f** in 80% yields (entry 6).⁸ The stereochemistry was confirmed by NOE experiments in NMR. Accordingly, the malonate-branched δ -allenyl-ketone **1d** was treated with **2a** to provide separable *cis*-**3g** (68%) along with bicyclic lactone **4** (12%) in 80% yield (entry 7).⁸

This Pd(0)/In-mediated arylative cyclization was extended to synthesize six-membered cyclohexanol derivatives, and the results were summarized in Table 3. The ϵ -allenyl-aldehyde **1e** reacted with iodo-benzene (**2a**) in

(8) The *cis* and *trans* stereochemistry was deduced by NOE experiments.

Scheme 3



the presence of $\text{Pd}(\text{OAc})_2$ (5 mol %)/tri(2-furyl)phosphine (10 mol %) and indium in DMF at 80 °C for 5 h afforded separable *cis*- and *trans*-cyclohexanols *cis*-3h (78%) and *trans*-3h (14%) in 92% total yield (entry 1 in Table 3). Under the same conditions with 2-iodothiophene (**2c**) as an electrophile, *cis*-3i (71%) (see Supporting Information) and *trans*-3i (12%) were afforded in 83% yield (entry 2). The malonate-branched ϵ -allenyl-aldehyde **1f** reacted with iodobenzene (**2a**) under the same conditions for 3 h to provide a separable mixture of *cis*-3j (74%) and *trans*-3j (8%) in 82% yield (entry 3). For the ether-linked ϵ -allenyl-aldehyde **1g**, *cis*-3k (68%) and *trans*-3k (16%) were obtained in 84% yield (entry 4). This arylative cyclization was applied to ϵ -allenyl-ketones to form six-membered and 3°-cyclohexanols. The ϵ -allenyl-ketone **1h** was treated and smoothly coupled with *p*-methoxyiodobenzene (**2b**) under the same conditions for 20 h to furnish a mixture of separable *cis*-3l (67%) and *trans*-3l (15%) in 82% yield (entry 5).⁸ Finally, the malonate-branched ϵ -allenyl-ketone **1i** was coupled with iodobenzene (**2a**) to afford *cis*-3m (63%) and *trans*-3m (12%) in 75% yield (entry 6).⁸

The exact mechanism for the favored formation of the *cis* isomer as a major product over the *trans* isomer remained to be elucidated. Our explanation for the formation of *cis* isomers as the major products is as follows. It is reasoned that the aryl-substituted allylic indium species formed from allenes and aryl iodides in the presence of a palladium catalyst and indium undergo carbonyl allylation to give *cis*- or *trans*-cycloalkanols. The *cis* selectivity can be ascribed to the fact that the intermediates **A**, which lead to the *cis* isomers, are energetically more stable than **B** presumably because of the steric hindrance between the R and Ar groups (Scheme 3).

In summary, the tandem palladium-catalyzed and indium-mediated arylative cyclization of allenyl-aldehydes and -ketones to form homoallylic cyclopentanols and cyclohexanols was accomplished.

Experimental Section

General Methods. All reagents were obtained from commercial sources and used without further purification unless stated otherwise. Solvents for reactions were purified before use. IR spectra were recorded on a FT-IR spectrometer. ¹H NMR were conducted at 500 MHz in CDCl_3 , and chemical shifts are reported in δ units relative to the tetramethylsilane (TMS) signal at 0.00 ppm. Coupling constants (*J*) are reported in Hz. Melting points were determined in unsealed capillary tubes and are uncorrected. For thin-layer chromatography (TLC), precoated plates

(silica gel, 0.25 mm) were used. Silica gel (230–400 mesh) was used for column chromatography. The reported yields are for chromatographically pure isolated products.

General Procedure for the Palladium–Indium-Mediated Arylative Cyclization of Allenyl-Aldehydes and -Ketones. The following procedure is representative. To a stirred solution of δ -allenyl-aldehyde **1a** (100 mg 0.38 mmol), iodobenzene **2a** (92 mg, 0.45 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %), and tri(2-furyl)phosphine (10 mol %) in DMF (3 mL) was added indium (52 mg, 0.45 mmol). The reaction mixture was stirred at 80 °C for 2 h. Dilute hydrochloric acid (1 N) was added, and the reaction mixture was extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, and the crude product was separated by SiO_2 column chromatography (2:1 hexane/ethyl acetate) to afford the cyclized product *cis*-3a (103 mg, 80%) and *trans*-3a (17 mg, 13%).

4-(1-Phenyl-vinyl)-1-(toluene-4-sulfonyl)pyrrolidin-3-ol (*cis*-3a): white solid, mp 120 °C; TLC, SiO_2 , 1:2 EtOAc/hexanes, R_f = 0.41; ¹H NMR (500 MHz, CDCl_3) δ 2.43 (s, 3H), 3.27 (m, 1H), 3.38 (dd, 1H, *J* = 11.5, 0.6 Hz), 3.40 (dd, 1H, *J* = 11.4, 9.0 Hz), 3.60 (dd, 1H, *J* = 11.5, 4.2 Hz), 3.74 (dd, 1H, *J* = 9.0, 7.0 Hz), 4.16 (dd, 1H, *J* = 7.0, 4.6 Hz), 5.05 (dd, 1H, *J* = 1.5, 0.7 Hz), 5.45 (dd, 1H, *J* = 1.5, 0.7 Hz), 7.29 (m, 2H), 7.31 (m, 2H), 7.33 (m, 1H), 7.35 (d, 2H, *J* = 8.3), 7.76 (d, 2H, *J* = 8.3); ¹³C NMR (125 MHz, CDCl_3) δ 143.9, 143.7, 140.9, 134.5, 130.1, 129.1, 128.6, 127.9, 126.5, 116.5, 70.8, 56.2, 49.1, 48.9, 21.9; IR (KBr, cm^{-1}) 3576, 3056, 2984, 1428, 1339, 1266, 1161, 740; HRMS (EI) *m/z* 343.1229 (calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{S}$ 343.1242). (***trans*-3a**): TLC, SiO_2 , 1:2 EtOAc/hexanes, R_f = 0.39; ¹H NMR (500 MHz, CDCl_3) δ 2.44 (s, 3H), 3.16 (m, 1H), 3.22 (dd, 1H, *J* = 10.8, 4.1 Hz), 3.22 (dd, 1H, *J* = 10.1, 5.8 Hz), 3.60 (dd, 1H, *J* = 10.8, 5.5 Hz), 3.65 (dd, 1H, *J* = 10.1, 7.6 Hz), 4.17 (m, 1H), 5.06 (d, 1H, *J* = 1.2 Hz), 5.31 (s, 1H), 7.31 (m, 2H), 7.33 (d, 2H, *J* = 8.3), 7.34 (m, 2H), 7.35 (d, 2H, *J* = 8.3); ¹³C NMR (125 MHz, CDCl_3) δ 146.3, 143.7, 140.7, 133.7, 129.7, 128.5, 128.0, 127.6, 126.4, 113.4, 74.2, 54.1, 50.7, 50.6, 21.6; IR (neat, cm^{-1}) 3494, 3057, 2984, 1428, 1266, 1160, 740; HRMS (EI) *m/z* 343.1253 (calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{S}$ 343.1242).

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Supporting Information Available: Spectral and physical data of **3b–g**, **4**, **3h–m**, NOESY spectrum analysis coupled with molecular dynamics calculation data for *cis*-3a and *trans*-3a, NOE experiments for *cis*-3a and *trans*-3a, X-ray crystallographic data of *cis*-3a and *cis*-3i, and copies of ¹H and ¹³C NMR spectral data for **3a**, **3d**, *trans*-4, **3g**, **3h**, and **3k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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