ORGANIC LETTERS

2008
Vol. 10, No. 6
1047−1050

Enantioselective Arylative Cyclization of Allenyl Aldehydes with Arylboronic Acids under Pd(II)-diphosphine Catalysis

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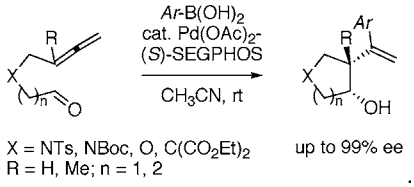
Received December 8, 2007

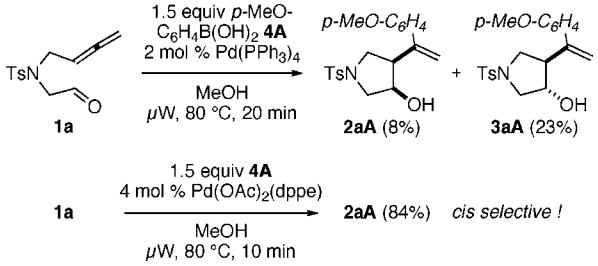
ABSTRACT



A $Pd(OAc)_2$–SEGPHOS combination catalyzes the first enantioselective arylative cyclization of allenyl aldehydes with arylboronic acids to provide *cis*-fused five- and six-membered cyclic homoallylic alcohols. The excellent diastereo- and enantioselectivity and the fact that the reaction proceeds at room temperature in the absence of any additives make the process highly practical.

Organoboron reagents are generally nontoxic, commercially available, stable, and compatible with various functional groups, and they are often employed for a wide variety of transition metal-catalyzed carbon−carbon bond formations.[1] Compared with organometallics such as Li, Mg, and Zn, the boron reagents are favorable for the alkylative cyclization reaction of unsaturated carbon−carbon bonds containing carbonyl groups to provide structurally complex cyclic compounds because their lower nucleophilicity causes no competitive 1,2-addition to the carbonyl groups.[2] In addition to the alkyne−aldehyde cyclization,[3] we have recently developed Pd^0/monophosphine-catalyzed alkylative cyclization of 3,4- and 4,5-dienals, leading to 3-substituted 3-cyclopentenols and cyclohexenols.[4] However, this catalyst turned out to be unsuitable for the cyclization of 5,6-dienal **1a** and provided five-membered cyclic alcohols **2aA** and **3aA** in poor yield and selectivity (Scheme 1, top). In our hands,

Scheme 1. $Pd(PPh_3)_4$- and $Pd(OAc)_2$(dppe)-Catalyzed Arylative Cyclization of Allenyl Aldehyde **1a**



reaction conditions for Pd^{2+}- or Rh^{1+}-catalyzed intermolecular coupling of allenes, aldehydes, and arylboronic acids[5]

(1) (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (c) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13−21. (d) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217−224.

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(3) (a) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406−1407. (b) Tsukamoto, H.; Ueno, T.; Kondo, Y. *Org. Lett.* **2007**, *9*, 3033−3036.

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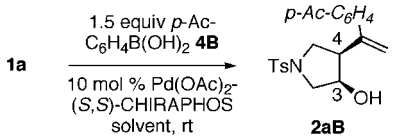
10.1021/ol702966j CCC: $40.75
Published on Web 02/23/2008

were not applicable to the intramolecular reaction. On the other hand, Lu's[6] and our groups[7] independently discovered that diphosphine-ligated Pd^{2+} catalysts promoted *cis*-selective arylative cyclization of alkyne-carbonyl compound through transmetalation of the Pd^{2+} catalysts with arylboronic acids and successive insertions of the alkyne and the intramolecular carbonyl group into the C−Pd bonds. Employment of $Pd(OAc)_2$(dppe)[8] instead of $Pd(PPh_3)_4$ for the cyclization of **1a** greatly improves the yield and selectivity to provide *cis*-addition product **2aA** exclusively (Scheme 1, bottom). The availability of chiral diphosphine ligands invokes development of its asymmetric process, which has never been achieved by these and other reagents.[9,10] Herein, we describe the first enantioselective arylative cyclization of 5,6- and 6,7-dienals with arylboronic acids under Pd^{2+}-diphosphine catalysis.

This effort began by investigating solvent effects on the asymmetric arylative cyclization of **1a** with *p*-acetylphenylboronic acid (**4B**) in the presence of $Pd(OAc)_2$-(*S*,*S*)-CHIRAPHOS complex as a catalyst (Table 1). In contrast to the cyclization reactions recently developed by us,[3,4,7] the reaction proceeds even at room temperature and is retarded by use of protic solvents (entries 1−5 vs 6). The solvent also affects the enantioselectivity of the cyclization, with reaction in CH_3CN leading to formation of (3*R*,4*R*)-**2aB** in 45% ee (entry 5). To improve the enantioselectivity, further ligand screening of chiral diphosphines shown in Figure 1 were conducted.

Table 1. Solvent Effects on Asymmetric Arylative Cyclization of **1a** with **4B** Using $Pd(OAc)_2$-(*S*,*S*)-CHIRAPHOS Complex



entry	solvent	time (h)	yield (%)	ee (%)[a]
1	CH_2Cl_2	1	quant	13
2	1,4-dioxane	2	quant	−10
3	THF	2	99	12
4	DMF	2	96	38
5	CH_3CN	3	88	45
6[b]	*t*-BuOH	34	84	24

[a] The ee values were determined by chiral HPLC, and the major enantiomer was determined by Mosher's method as (3*R*,4*R*) except for entry 2. [b] Reaction at 50 °C.

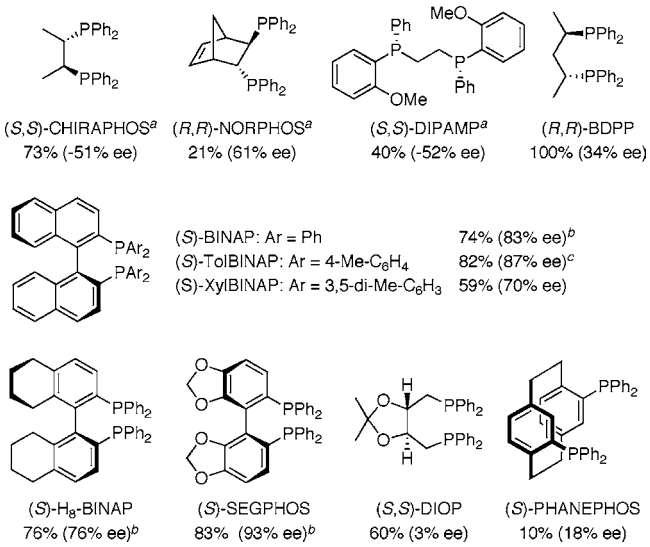


Figure 1. Chiral diphosphine ligands screened in the asymmetric cyclization of **1a** with **4A**. Reaction with 1.5 equiv of **4A**, 10 mol % of $Pd(OAc)_2$ and diphosphine at rt. Major enantiomer was (3*S*,4*S*)-**2aA** except for CHIRAPHOS and DIPAMP. (a) Reaction at 0 °C. (b) Phenylated product **2aF** was also obtained in 22, 17, and 5% yield for BINAP, H_8-BINAP, and SEGPHOS, respectively. (c) *p*-Methylphenylated product **2aC** was also obtained in 19% yield.

Employment of C2-tethered CHIRAPHOS, NORPHOS, DIPAMP, C3-tethered BDPP, C4-tethered DIOP, and PHANEPHOS with $Pd(OAc)_2$ for the cyclization of **1a** with *p*-methoxyphenylboronic acid (**4A**) gives **2aA** in poor to moderate enantioselectivity (Figure 1). In contrast to these diphosphine ligands, BINAP and its analogues[11] containing an axially chiral biaryl structure dramatically improve the enantioselectivity of the cyclization. However, the use of BINAP and TolBINAP as the ligands is accompanied by the formation of a considerable amount of phenylated product **2aF** and *p*-methylphenylated product **2aC** (Table 2), respectively. These byproducts should be generated by aryl−aryl exchange[12] between *p*-methoxyphenyl group and the diphosphine bound to the Pd center prior to the allene insertion step. (*S*)-SEGPHOS turns out to be the best ligand to afford

(5) (a) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221−2224. (b) Hopkins, C. D.; Guan, L.; Malinakova, H. C. *J. Org. Chem.* **2005**, *70*, 6848−6862. (c) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2006**, *8*, 5971−5974. (d) Bai, T.; Ma, S.; Jia, G. *Tetrahedron* **2007**, *63*, 6210−6215.

(6) (a) Song, J.; Shen, Q.; Xu, F.; Lu, X. *Org. Lett.* **2007**, *9*, 2947−2950. (b) Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131−5133.

(7) Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *9*, 4227−4230.

(8) (a) Marson, A.; van Oort, A. B.; Mul, W. P. *Eur. J. Inorg. Chem.* **2002**, 3028−3031. (b) Bianchini, C.; Meli, A.; Oberhauser, W. *Organometallics* **2003**, *22*, 4281−4285.

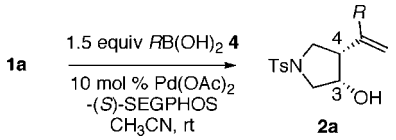
(9) Pd^0-catalyzed arylative cyclization with aryl iodides and distannane or In: (a) Ha, Y.-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143−1146. (b) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376−4379. See also silylative and stannylative cyclization: (c) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343−345. (d) Yu, C.-M.; Youn, J.; Lee, M.-K. *Org. Lett.* **2005**, *7*, 3733−3736.

(10) Ni^0-catalyzed alkylative cyclization with organozinc reagents: (a) Montgomery, J.; Song, M. *Org. Lett.* **2002**, *4*, 4009−4011. (b) Song, M.; Montgomery, J. *Tetrahedron* **2005**, *61*, 11440−11448. (c) Kang, S.-K.; Yoon, S.-K. *Chem. Commun.* **2002**, 2634−2635.

(11) (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350. (b) Akutagawa, S. *Appl. Catal., A* **1995**, *128*, 171−207. (c) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801−1836.

(12) (a) Macgregor, S. A. *Chem. Soc. Rev.* **2007**, *36*, 67−76. (b) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313−6315. (c) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12−13. (e) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441−12453.

Table 2. Asymmetric Arylative Cyclization of **1a** with **4B-K** Using $Pd(OAc)_2$/SEGPHOS Catalytic System



entry	R	2a	time (h)	yield (%)	ee (%)[a]
1	*p*-Me−C_6H_4 **4C**	**2aC**	7	90	97
2	*m*-Me−C_6H_4 **4D**	**2aD**	10	93	97
3	*o*-Me−C_6H_4 **4E**	**2aE**	48	83	95
4	C_6H_5 **4F**	**2aF**	6	90	97
5	*p*-Br−C_6H_4 **4G**	**2aG**	4	92	97
6	*p*-Ac−C_6H_4 **4B**	**2aB**	3	quant	98
7[b]	*p*-Ac−C_6H_4 **4B**	**2aB**	12	96	98
8	*m*-NO_2-C_6H_4 **4H**	**2aH**	4	85	97
9	2-thiophene **4I**	**2aI**	4	85	89
10	3-thiophene **4J**	**2aJ**	4	78	95
11[c,d]	(*E*)-*β*-styrene **4K**	**2aK**	4	58	81

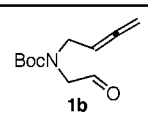
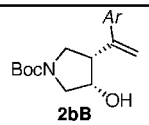
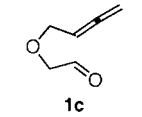
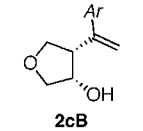
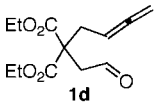
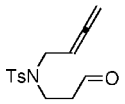
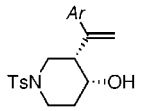
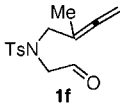
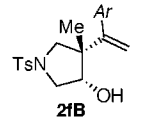
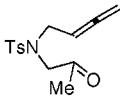
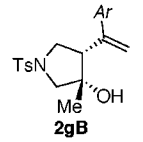
[a] The ee values were determined by chiral HPLC. [b] Reaction with 3 mol % of catalysts. [c] Reaction with 20 mol % of catalysts. [d] *Trans* isomer **3aK** was also obtained in 7% yield (56% ee).

the maximum optical yield of (3*S*,4*S*)-**2aA** (93% ee)[13] and minimize the formation of **2aF**.[14]

Arylboronic acids with electron-donating (Table 2, entries 1−3) or -withdrawing (entries 5−8) groups serve as nucleophiles in this process, which leads to exclusive formation of cyclized products **2aB**−**H** in high yields and enantioselectivity.[15] In contrast to the Pd^0-catalyzed alkylative cyclization of 3,4- and 4,5-dienals,[4] electron-rich boronic acids require longer reaction times than their electron-deficient counterparts. The cyclization with *o*-methylphenylboronic acid (**4E**) is significantly slow but preserves high enantioselectivity (entry 3). The catalyst loading can be reduced from 10 to 3 mol % (entry 6 vs 7). These cyclization reactions also occur with heteroarylboronic acids **4I**−**J** (entries 9, 10). However, alkenylboronic acid **4K** provides the cyclized product **2aK** in lower yield, diastereo-, and enantioselectivity (entry 11).

Arylative cyclization reactions of allenyl aldehydes **1b**−**d** containing Boc-protected nitrogen, ether oxygen, and tertiary carbon with **4B** require longer times but provide homoallylic alcohols **2b**−**dB** in good yields with high ee values (Table 3, entries 1−3). Allenyl aldehyde **1e** with a longer tether also undergoes the stereoselective cyclization to give *cis*-fused six-membered cyclic alcohol **2eB** in excellent yield and enantioselectivity (entry 4). The use of 1,1-disubstituted allene-aldehyde **1f** leads to formation of enantiomerically

Table 3. Asymmetric Arylative Cyclization of **1b**−**g** with **4B**[a]

entry	substrate 1	product 2	time (h)	yield (%)	ee[b] (%)
1	 **1b**	 **2bB**	24	63	99
2	 **1c**	 **2cB**	24	76	96
3	 **1d**	 **2dB**	24	74	96
4[c]	 **1e**	 **2eB**	7	99	99
5[c]	 **1f**	 **2fB**	7	82	98
6[d]	 **1g**	 **2gB**	72	79	51

[a] Reaction with 1.5 equiv of **4B** and 20 mol % of $Pd(OAc)_2$ and (*S*)-SEGPHOS in CH_3CN at rt. Ar = C_6H_4-*p*-Ac. [b] The ee values were determined by chiral HPLC. [c] Reaction with 10 mol % of catalysts. [d] Reaction at 50 °C.

pure **2fB** containing a quaternary carbon center (entry 5). The cyclization of methyl ketone **1g** requires higher reaction temperature and decreases the optical yield of **2gB** (entry 6).

The plausible mechanism for the arylative cyclization is outlined in Scheme 2. Transmetalation of diphosphine-ligated Pd^{2+} catalyst **5** with arylboronic acid **4** leads to arylpalladium(II) intermediate **6**. Polar solvents such as acetonitrile would facilitate dissociation of an acetate anion from **6** to generate a cationic arylpalladium(II) **7**.[16] Regio- and stereoselective carbopalladation[17] of allene **1** with **7** from the less hindered side of distal allene *π*-system would produce *anti*-η^3-allylpalladium(II) **8a** kinetically. The *anti* isomer **8a** could

(13) The absolute configurations of major enantiomers were determined by Mosher's method. (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

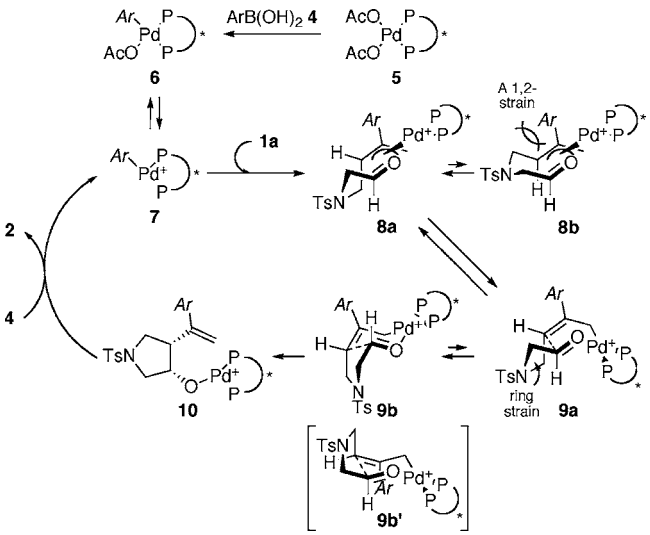
(14) SEGPHOS, having a narrower dihedral angle than BINAP, would accelerate the allene insertion into the Ar-Pd bond and minimize the aryl-aryl exchange. Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385−1393.

(15) In contrast to **4A**, the boronic acids **4B**−**K** were exclusively incorporated into the products.

(16) The less polar solvent would make the acetate anion remain coordinated on the Pd^{2+} species and change the tetracoordinate intermediate **9b** into different intermediates unfavorable for the enantioselective cyclization (Table 1). We also observed that enantioselectivities of the cyclization of **1a** with **4B** using $Pd(CH_3CN)_2(BF_4)_2$ as a cationic Pd^{2+} source hardly depended on reaction solvents. Mikami, K.; Hatano, M.; Akiyama, K. *Top. Organomet. Chem.* **2005**, *14*, 279−321 and references therein.

(17) Regioselective carbopalladation of allenes usually produce C2-carbon-substituted *π*-allylpalladium(II): (a) Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867−1878. (b) Ma, S. *Pure Appl. Chem.* **2006**, *78*, 197−208. (c) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701−712. (d) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12−21. (e) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067−3125. (f) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111.

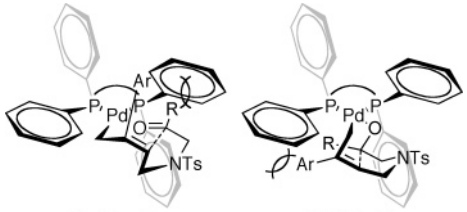
Scheme 2. Possible Mechanism for the Arylative Cyclization of **1a**



be converted to *syn* isomer **8b** through $\pi-\sigma-\pi$ isomerization, but the equilibrium would favor **8a** again due to its release from allylic 1,2-strain inherent in **8b**.[17a] Then, isomerization of η^3-allylpalladium(II) **8a** into η^1-allylpalladium(II) can form six-membered cyclic transition states **9a** and **9b**[18] for the intramolecular allylation of the carbonyl leading to *trans*- and *cis*-addition products, respectively. *Cis*-specific addition[9] indicates that the transition state **9b** is more favorable than **9a** having ring strain and this is transformed into the alkoxopalladium(II) **10**. Transmetalation of **10** (or protonation of **10** prior to the transmetalation) with **4** reproduces the arylpalladium(II) **7** along with the *cis*-addition product **2**. Furthermore, the stereochemical outcome would indicate that the enantioselectivity results from severe steric repulsion between the axial aryl group in **9b′** and an equatorial phenyl group in (*S*)-SEGPHOS, a factor which is not present in transition state **9b** (Scheme 3). A loss of

(18) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793.

Scheme 3. Transition States (TS) for **9b** and **9b′**



enantioselectivity with ketone **1g** could be attributed to a methyl group intruding into the phenyl ring of SEGPHOS in **9b** (R = Me).

In summary, we have developed the first enantioselective arylative cyclization reactions of allenyl aldehydes with arylboronic acids under Pd^{2+}-diphosphine catalysis. The excellent diastereo- and enantioselectivity and the fact that the reaction proceeds at room temperature in the absence of any additives make the process highly practical. Cyclic homoallylic alcohol products generated in these reactions should be useful intermediates in hetero- and carbocycle synthesis since they contain a rich array of preparatively important functional groups. Further studies probing the detailed mechanism and expanding the scope of the cyclization process are underway.

Acknowledgment. This work was partly supported by a Grant-in-Aid from the Japan Society for Promotion of Sciences (No.18790003) and Banyu Pharmaceutical Co., Ltd. Award in Synthetic Organic Chemistry, Japan. BINAP, TolBINAP, XylBINAP, H_8-BINAP, and SEGPHOS were supplied by Takasago International Corporation.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702966J