ORGANIC LETTERS

2004
Vol. 6, No. 12
1979−1982

Palladium-Catalyzed Ring Expansion Reaction of (*Z*)-1-(1,3-Butadienyl)cyclobutanols with Aryl Iodides. Stereospecific Synthesis of (*Z*)-2-(3-Aryl-1-propenyl)cyclopentanones

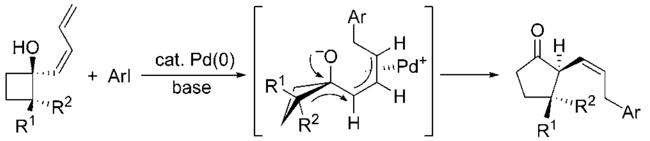
Masahiro Yoshida,* Kenji Sugimoto, and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

mihara@mail.pharm.tohoku.ac.jp

Received March 25, 2004

ABSTRACT



A novel type of cascade ring expansion process has been developed by the palladium-catalyzed reaction of (*Z*)-1-(1,3-butadienyl)cyclobutanols with aryl iodides. The reaction proceeds in a stereospecific manner to produce (*Z*)-2-(3-aryl-1-propenyl)cyclopentanones. It has also been found that regioselective α-arylation of alkenyl cyclopentanones proceeds to afford the α-arylated cyclopentanones.

Palladium-catalyzed reactions of unsaturated compounds with organic halides are one of the most important carbon−carbon bond formation reactions in organic synthesis, and a variety of synthetically useful products are obtained depending on the substrates.[1] It is known that conjugated 1,3-dienes react with aryl halides and nucleophiles by a cascade process.[2] Thus, regioselective insertion of a 1,3-diene into the arylpalladium species gives the π-allylpalladium intermediate, which regioselectively reacts with a nucleophile to produce the (*E*)-1,4-addition product.

Ring rearrangement of vinylcyclobutanol derivatives by transition metals is a valuable method for the construction of substituted five-membered ring systems.[3] The reaction is triggered by a release of the strain in four-membered ring systems, and this transformation has been successfully applied to the cascade process by introducing various unsaturated groups on the cyclobutane ring. The cascade ring expansion reaction of cyclobutanols having isopropenyl,[4] allenyl,[5] acetylenyl,[6] and propargyl[7] groups has been developed by us and other groups during the past decade. However, to the best of our knowledge, there are no examples of the reaction of 1,3-dienylcyclobutanols, which are expected to exhibit a different reactivity compared to that of the other unsaturated groups. Herein, we describe a preliminary result concerning the palladium-catalyzed insertion−ring expansion reaction of 1,3-dienylcyclobutanols with aryl iodides.

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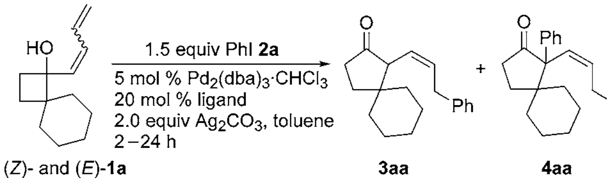
(1) (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley and Sons: New York, 1995. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(2) (a) Patel, B. A.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 5018. (b) Patel, B. A.; Kao, L. C.; Cortese, N. A.; Minkiewicz, J. V.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 918. (c) Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 3584. (d) Fischetti, W.; Mak, K. T.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948. (e) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807. (f) Uno, M.; Takahashi, T.; Takahashi, S. *Chem. Commun.* **1987**, 785. (g) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 1139. (h) Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882. (i) Larock, R. C.; Berrios-Pena, N. G.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447. (j) Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509. (k) Kagechika, K.; Ohshima T.; Shibasaki. M. *Tetrahedron* **1993**, *49*, 1773. (l) Ohshima, T.; Kagechika, K.; Adachi, A.; Sodeoka, M.; Shibasaki. M. *J. Am. Chem. Soc.* **1996**, *118*, 7108. (m) Flubacher, D.; Helmchen, G. *Tetrahedron Lett.* **1999**, *40*, 3867. (n) Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett.* **2003**, *5*, 3815.

10.1021/ol049438k CCC: \$27.50

Our initial studies focused on reactions of 1,3-dienylcyclobutanol **1a** with iodobenzene (**2a**) (Table 1). When (*Z*)-**1a** is reacted with **2a** in the presence of 10 mol % Pd(PPh$_3$)$_4$ and Ag$_2$CO$_3$ in toluene at 60 °C, the reaction is complete within 2 h to afford a aryl-substituted cyclopentanone **3aa** along with further α-arylated product **4aa** in 77% yield with a ratio of 1.7:1 (entry 1). Interestingly, the geometries of the obtained products **3aa** and **4aa** are determined as *Z*, and the corresponding (*E*)-products are not observed. The products **3aa** and **4aa** are not produced at all when K$_2$CO$_3$ and Cs$_2$CO$_3$ are used instead of Ag$_2$CO$_3$ as a base. The reactions using PCy$_3$ and P(*o*-Tol)$_3$ with Pd$_2$(dba)$_3$•CHCl$_3$ also successfully proceed to give **3aa** and **4aa** in 55% and 85% yield, respectively (entries 2 and 3). The reactivity has been decreased when bidentate ligands such as dppe and dppf are used (entries 4 ad 5). It is clear from the studies of the reaction temperature in the presence of P(*o*-Tol)$_3$ that the yield has been improved to 98% by carrying out the reaction at 45 °C, and **3aa** is produced with high selectivity at room temperature (entries 6 and 7). On the other hand, the reaction does not proceed when the (*E*)-isomer **1a** is used as a substrate (entry 8).

Table 1. Palladium-Catalyzed Reaction of Dienylcyclobutanols (*Z*)- and (*E*)-**1a** with Iodobenzene (**2a**)[a]

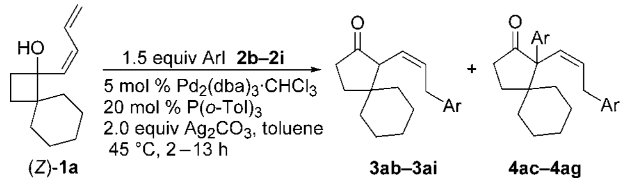


entry	substrate	ligand	temp (°C)	yield (%)[a]	**3aa**:**4aa**[b,c]
1	(*Z*)-**1a**	PPh$_3$[d]	60	77	1.7:1
2	(*Z*)-**1a**	PCy$_3$	60	55	1.7:1
3	(*Z*)-**1a**	P(*o*-Tol)$_3$	60	85	1.8:1
4	(*Z*)-**1a**	dppe	60	2 (66)	**3aa** only
5	(*Z*)-**1a**	dppf	60	8 (25)	**3aa** only
6	(*Z*)-**1a**	P(*o*-Tol)$_3$	45	98	5.5:1
7	(*Z*)-**1a**	P(*o*-Tol)$_3$	25	87 (94)	14:1
8	(*E*)-**1a**	P(*o*-Tol)$_3$	60	nr	

[a] The yields in parentheses are based on recovered starting material. [b] The configurations of **3aa** and **4aa** were determined by NOESY and ^{1}H NMR coupling constants of olefinic protons. [c] The ratios were determined by the isolation of each products. [d] 10 mol % Pd(PPh$_3$)$_4$ was used as a palladium catalyst.

Some results of palladium-catalyzed reactions of (*Z*)-**1a** with various aryl iodides **2b**−**i** are summarized in Table 2.

Table 2. Palladium-Catalyzed Reaction of Dienylcyclobutanols (*Z*)-**1a** with Aryl Iodides **2b**−**i**[a]



entry	Ar	product	yield (%)[a]	**3**:**4**[a]
1	2-methoxyphenyl (**2b**)	**3ab**	80	**3ab** only
2	4-methoxyphenyl (**2c**)	**3ac**/**4ac**	77	8.6:1
3	2-tolyl (**2d**)	**3ad**/**4ad**	91	6.0:1
4	4-tolyl (**2e**)	**3ae**/**4ae**	88	4.2:1
5	1-naphthyl (**2f**)	**3af**/**4af**	62	9.3:1
6	4-nitrophenyl (**2g**)	**3ag**	86	**3ag** only
7	4-acetylphenyl (**2h**)	**3ah**	57	**3ah** only
8	2-bromophenyl (**2i**)	**3ai**	73	**3ai** only

[a] Products ratios were determined by isolation of the each products.

Substitution with methoxy and methyl groups in the *ortho* and *para* positions exhibits similar reactivity to give the corresponding products **3ab**−**ae** in good yields with a small amount of α-arylated products **4ac**−**ae** (entries 1−4). The reaction using 1-iodonaphthalene (**2f**) also proceeds to afford **3af** and **4af** in 63% yield with a ratio of 9.3:1 (entry 5). In the reactions with nitro- and acetyl-substituted aryl iodides **2g** and **2h**, the corresponding products **3ag** and **3ah** are obtained as the sole products, respectively (entries 6 and 7). When 2-bromoiodobenzene (**2i**) is used, the 2-bromophenyl-substituted cyclopentanone **3ai** is chemoselectively produced without the influence of a bromo atom (entry 8).

We next examined the reactions of various 1,3-dienylcyclobutanols **1b**−**d** with **2a** (Table 3). A substrate (*Z*)-**1b** having a dipentyl group on the cyclobutane ring is successfully transformed to **3ba** in 89% yield (entry 1). A *trans*-**3ca** is obtained as the sole product by the reaction of *trans*-(*Z*)-**1c** (entry 2). On the other hand, the reaction of the diastereomer *cis*-(*Z*)-**1c** exclusively provides *cis*-**3ca** (entry 3). It is ascertained from these results that the ring expansion process proceeds in a stereospecific manner.[8] Substrate (*Z*)-**1d**, substituted with a methyl group at the 3-position on the

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(3) (a) Boontanonda, P.; Grigg, R. *J. Chem. Soc., Chem. Commun.* **1977**, 583. (b) Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503. (c) Demuth, M.; Pandey, B.; Wietfeld, B.; Said, H.; Viader, J. *Helv. Chim. Acta* **1988**, *71*, 1392. (d) de Almeida Barbosa, L.-C.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 177. (e) Kim, S.; Uh, K. H.; Lee, S.; Park, J. H. *Tetrahedron Lett.* **1991**, *32*, 3395. (f) Nemoto, H.; Miyata, J.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10363. (g) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2329. (h) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74. (i) Nemoto, H.; Miyata, J.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1933. (j) Nemoto, H.; Takahashi, E.; Ihara, M. *Org. Lett.* **1999**, *1*, 517. (k) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645.

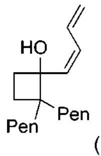
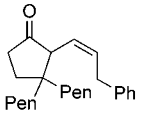
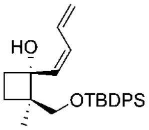
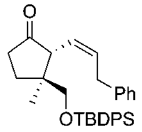
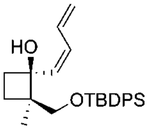
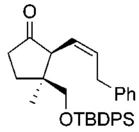
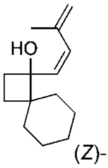
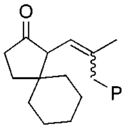
(4) (a) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Synlett* **1994**, 599. (b) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850. (c) Nemoto, H.; Yoshida, M.; Fukumoto, K.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 907. (d) Yoshida, M.; Ismail, M. A.-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2629.

(5) (a) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450. (b) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 5089. (c) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron* **2002**, *58*, 7839. (d) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 3877.

(6) (a) Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908. (b) Mitchell, D.; Liebeskind L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291. (c) Larock, R. C.; Reddy, Ch. K. *Org. Lett.* **2000**, *2*, 3325. (d) Larock, R. C.; Reddy, Ch. K. *J. Org. Chem.* **2002**, *67*, 2027. (e) Yoshida, M.; Sugimoto, K.; Ihara, M. *ARKIVOC* **2003**, *xiii*, 35.

(7) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583.

Table 3. Reactions Using Various 1-(1,3-Dienyl)cyclobutanols **1b**−**d** with Iodobenzene (**2a**)[a]

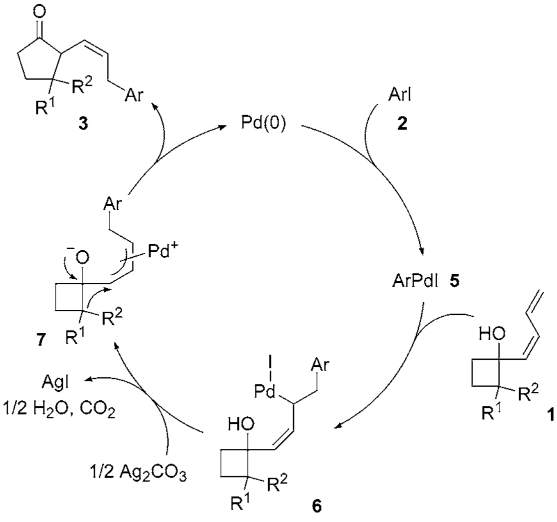
entry	substrate	product	yield (%)
1[b]	 (*Z*)-**1b**	 **3ba**	89
2	 *trans*-(*Z*)-**1c**	 *trans*-**3ca**	64
3	 *cis*-(*Z*)-**1c**	 *cis*-**3ca**	53
4	 (*Z*)-**1d**	 **3da**	82 ($Z:E = 5.3:1$)

[a] All reactions were carried out in the presence of 1.5 equiv of iodobenzene, 5 mol % $Pd_2(dba)_3$, 20 mol % P(*o*-Tol)3, and 2.0 equiv of Ag_2CO_3 in toluene at 45 °C for 3−6 h. [b] Pen = pentyl.

dienyl group, gives the (*Z*)- and (*E*)-**3da** as a 5.3:1 mixture in 82% yield (entry 4).

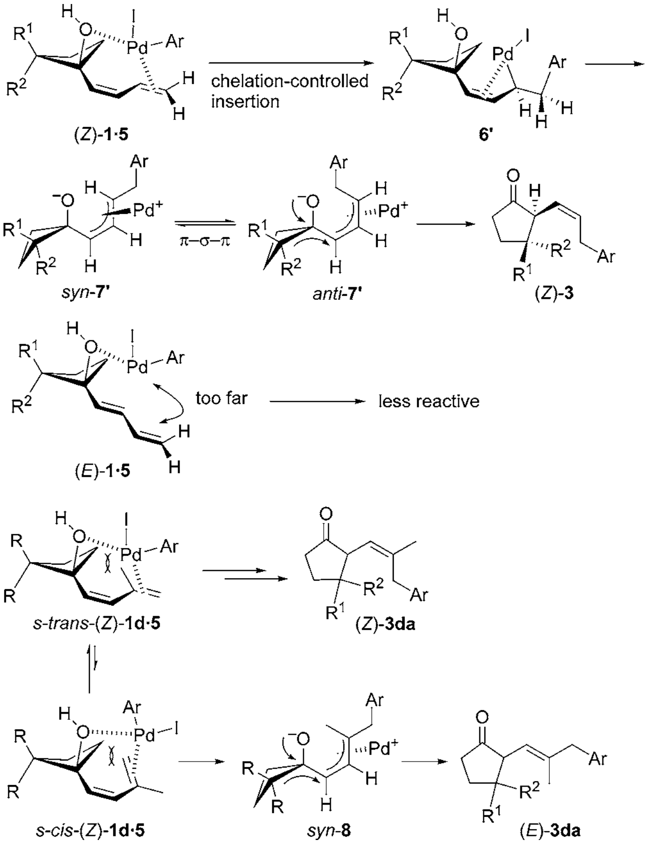
A plausible mechanism for the reaction is shown in Scheme 1. Regioselective insertion of the 1,3-dienyl moiety in **1** to an arylpalladium complex **5**, resulting from aryl iodide **2** with palladium(0), affords an allylpalladium species **6**. The complex **6** reacts with base to form a zwitterionic *π*-allylpalladium intermediate **7**,[9] which subsequently causes a ring rearrangement to produce a ring-expanded product **3** and regenerated palladium(0).

Scheme 1



Mechanistic rationalizations of the observed (*Z*)-specificity and diastereospecificity are described in Scheme 2. In case of the (*Z*)-substrate, coordination of both the olefin and hydroxyl groups in (*Z*)-**1** to arylpalladium **5** initially forms the intermediate (*Z*)-**1·5**, in which the dienyl group is located at the less hindered site to avoid a steric repulsion with substituents R^1 and R^2.[10] Regio- and diastereoselective insertion to palladium gives allylpalladium **6′**, which is successively transformed to *π*-allylpalladium *syn*-**7′**. It is expected that there is an equilibrium between *syn*- and *anti*-**7′**. The complex *syn*-**7′** interconverts by *π*-*σ*-*π* isomerization to the isomer *anti*-**7′**, which successively causes the concerted rearrangement of the cyclobutane ring on the opposite face of the palladium to produce (*Z*)-**3** in a stereospecific manner. A reason for the low reactivity of the (*E*)-substrate could be that the chelation-controlled insertion of the intermediate (*E*)-**1·5** is difficult because the distance between the hydroxy

Scheme 2



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[8] For studies about the diastereoselectivity in the ring expansion reaction of cyclobutanols, see refs 4b−d, 5b,c, and 7.

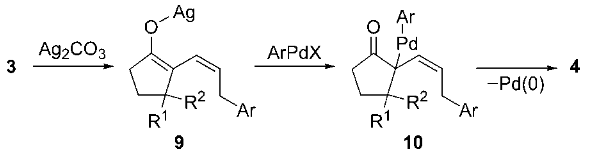
[9] As another possibility, the intermediate that palladium cation forms a bond to the alkoxide anion is also expected.

[10] The conformation of (*Z*)-**1·5** was predicted from the result of MOPAC 97/PM3 calculation of (*Z*)-**1a**.

group and the olefin becomes longer than that of (*Z*)-**1·5**. In the case of the methyl-substituted substrate (*Z*)-**1d**, it is expected that there is an equilibrium between the two intermediates *s-trans*- and *s-cis*-(*Z*)-**1d·5** by the allylic strain of the methyl group. As a result, (*E*)-**3da** has been provided as a minor product via *syn*-**8** along with the major production of (*Z*)-**3da**.

The formation of the α-arylated cyclopentanone **4** is explained by the palladium-catalyzed α-arylation of the resulting **3** (Scheme 3).[11] Thus, regioselective enolization of **3** with base affords the thermodynamically stable conjugated enolate **9**, followed by transmetalation with arylpalladium complex to produce **4** via the palladium enolate **10**.

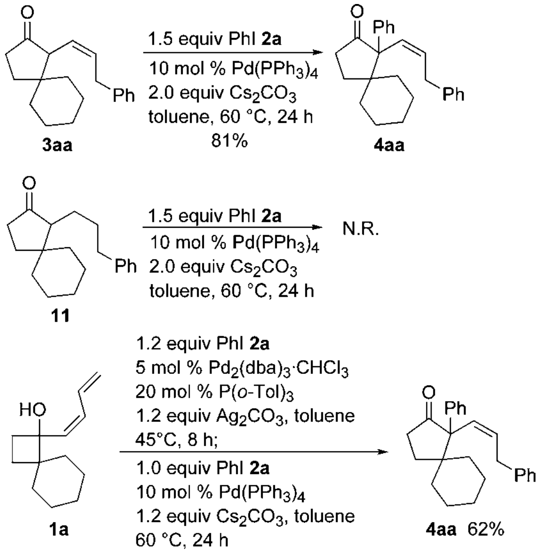
Scheme 3



To confirm the observed α-arylation process, several further experiments were carried out (Scheme 4). When **3aa** is reacted with **1a** in the presence of 10 mol % Pd(PPh_3)$_4$ and Cs_2CO_3, **4aa** is produced in 81% yield as a sole product. The result indicates that the α-arylated product **4** is formed from **3**, not directly from the substrate **1**. On the other hand, the reaction of **11** containing a saturated alkyl side chain does not proceed at all. Improvement of the direct production of **4aa** from **1a** has been performed by further addition of the reagents after the completion of the initial ring expansion reaction.

In conclusion, we have developed a novel type of palladium-catalyzed cascade insertion−ring expansion reaction of 1,3-dienylcyclobutanols with aryl iodides. Various substituted cyclopentanones having a (*Z*)-3-aryl-1-propenyl group can be synthesized in a stereospecific manner. It has also been found that regioselective α-arylation proceeds to afford the α-arylated cyclopentanones. The present results would provide a new method for the synthesis of highly functionalized cyclopentanones, and synthetic applications of the reaction are now in progress.

Scheme 4



Acknowledgment. This work was supported in part by Grant-in-Aid for Scientific Research on Priority Areas (A) “Exploitation of Multi Element Cyclic Molecules” from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Synthetic procedures and characterization data of the substrates **1a−d** and **11**; general experimental procedures and characterization data for products **3aa−ai**, **3ba−da**, **4aa**, and **4ac−af**; and procedure for determining the stereochemistry of *trans*-(*Z*)-**1c**, *cis*-(*Z*)-**1c**, *trans*-**3ca**, and *cis*-**3ca** by NOESY correlations. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.