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$Pd(OAc)_2/P(^cC_6H_{11})_3$-Catalyzed Allylation of Aryl Halides with Homoallyl Alcohols via Retro-Allylation

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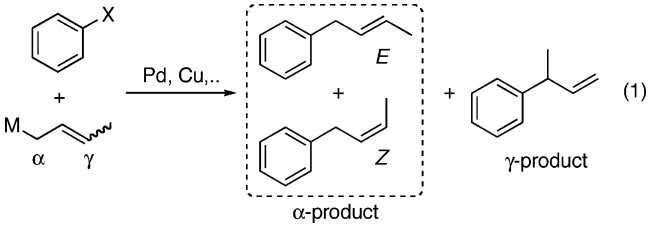
Abstract: Allylations of aryl halides take place upon treatment of tertiary homoallyl alcohols with aryl halides in the presence of cesium carbonate and a palladium catalyst. The allylation reaction would consist of the following steps: (1) oxidative addition of aryl halide to palladium, (2) ligand exchange between the halide and the homoallyl alcohol affording aryl(homoallyloxy)palladium, (3) retro-allylation of the palladium alkoxide to generate σ-allyl(aryl)palladium with concomitant liberation of the relevant ketone, and (4) productive reductive elimination. Since the retro-allylation step proceeds in a concerted fashion via a conformationally regulated six-membered cyclic transition state, the allylation reactions are highly regio- and stereospecific when homoallyl alcohols having a substituted allyl group are used. Whereas triarylphosphine is known to serve as a ligand for the palladium-catalyzed allyl transfer reactions, tricyclohexylphosphine proves to significantly expand the scopes of aryl halides to electron-rich aryl chlorides and of homoallyl alcohols to cyclic homoallyl alcohols. The new arylative ring-opening reactions of cyclic homoallyl alcohols allow for the synthesis of ketones having a branched or linear allylarene moiety at the remote terminus in regio- and stereospecific manners.

1. Introduction

Transition-metal-catalyzed cross-coupling reaction ranks as one of the most important reactions in organic synthesis and has been extensively investigated.[1] One thus tends to think that the cross-coupling strategy can construct arbitrary carbon−carbon bonds by optimizing reaction conditions. However, despite their seeming simplicity, the cross-coupling reactions of aryl halides with allylmetals represent rare combinations relative to those with arylmetals forming biaryls.[2−6] In light of the importance of allylation reactions in organic synthesis,[7] further studies on the rare cross-coupling reactions are necessary. However, there are many issues to be resolved, which include reaction efficiency and functional group compatibility.

The most critical problem is the regio- and stereoselectivity of the allylation when substituted allylmetals are employed (eq 1).[3b,e−i,4,5e,f,6] For instance, a cross-coupling reaction with a crotyl metal reagent takes place competitively at the α- and γ-positions of the crotyl group. In addition, the product coupled at the α-position usually consists of a mixture of *E* and *Z* isomers. In order that the cross-coupling allylation becomes a useful tool for modern organic synthesis, such regio- and stereochemical control of the allylation should be established.



As the pioneering solution to the problem, Hatanaka and Hiyama developed regioselective cross-coupling reactions of aryl halides with substituted allylfluorosilanes.[4] Monodentate triph-

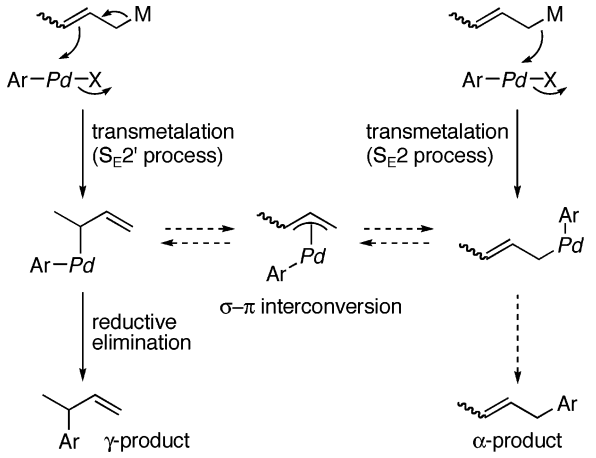
(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (c) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.: Springer: Berlin, 2002. (d) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

(2) Nickel- or copper-catalyzed reactions with an allyl Grignard reagent: (a) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958−1969. (b) Commercon, A.; Normant, J. F.; Villieras, J. *J. Organomet. Chem.* **1977**, *128*, 1−11. (c) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817−2825.

(3) Palladium-catalyzed reactions with allylstannanes: (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301−302. (b) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599−2602. (c) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630−4632. (d) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040. (e) Obora, Y.; Tsuji, Y.; Kobayashi, M.; Kawamura, T. *J. Org. Chem.* **1995**, *60*, 4647−4649. (f) Takemura, S.; Hirayama, A.; Tokunaga, J.; Kawamura, F.; Inagaki, K.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **1999**, *40*, 7501−7505. (g) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595−2598. (h) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2002**, 3620−3628. (i) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779−5789.

(4) Palladium-catalyzed reactions with allylfluorosilanes: (a) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075−7076. (b) Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 1279−1282. (c) Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511−6514. (d) Hatanaka, Y. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 581−592. (e) Hiyama, T.; Matsuhashi, H.; Fujita, A.; Tanaka, M.; Hirabayashi, K.; Shimizu, M.; Mori, A. *Organometallics* **1996**, *15*, 5762−5765. (f) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471−1478.

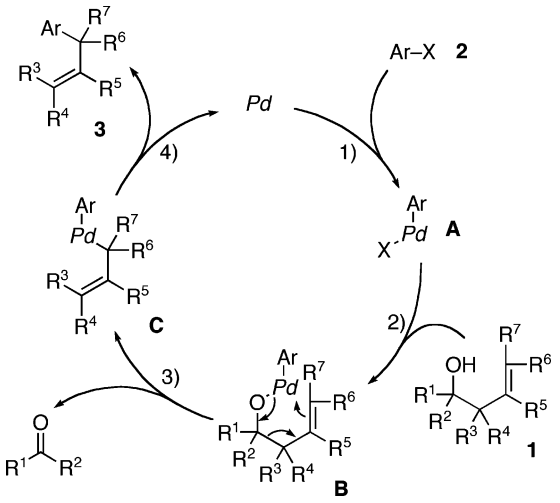
Scheme 1



enylphosphine led to γ-selectivity,[4a] and bidentate 1,3-bis(diphenylphosphino)propane, to α.[4c] However, the excellent example highlights the difficulty in achieving the cross-coupling allylation from the viewpoint of modern organic synthesis. Specifically, the reactions required heating in sealed tubes and the use of relatively labile allylfluorosilanes and lacked universal stereochemical control of the (*E*)- and (*Z*)-α-products. A regiocontrolled coupling reaction of tributylcrotylstannane with 1-iodonaphthalene was reported.[3e] Use of triphenylarsine as a ligand provided the corresponding (*E*)-α-product, whereas triphenylphosphine yielded the γ-product.[8] Unfortunately, the generality and the efficiency of the reaction are unsatisfactory, and no procedure to obtain (*Z*)-α-product was disclosed. Very recently, a γ-selective cross-coupling reaction with potassium (*E*)-crotyltrifluoroborate was reported, wherein no α-selectivity was attained.[5e,f,9]

The γ-selectivity observed in the reactions of crotylfluorosilanes and of crotyltrifluoroborate was explained by the following hypotheses (Scheme 1):[4a,5e] (1) the transmetalations between the crotylmetals and arylpalladium halides proceed in an S$_E$2′ process,[10] and (2) aryl(1-methyl-2-propenyl)palladiums, a σ-allylpalladium[11] formed by the transmetalations, predominantly undergo rapid reductive elimination of 1-methyl-2-propenylarenes without suffering from conceivable $\sigma-\pi$ interconversion that can lead to the α-product. The hypotheses clearly suggest

Scheme 2



that one should simply prepare and use the corresponding well-defined allyl metals to obtain the desired products selectively. In spite of the intelligible idea, preparation of allyl metals having an arbitrary substitution pattern is generally difficult. Moreover, there remains a possibility that the transmetalation would proceed unexpectedly in an S$_E$2 fashion, which can heavily depend on the structure and electronic factors of allyl metals used.[10]

We have recently communicated the use of homoallyl alcohols as the allyl sources in the palladium-catalyzed allylations of organic halides instead of allyl metal reagents.[12] Scheme 2 illustrates our proposed mechanism. After oxidative addition yielding **A** (step 1), ligand exchange with homoallyl alcohol **1** would take place to afford alkoxy(aryl)palladium **B** (step 2). Retro-allylation reaction of **B**,[13−15] the key step of our strategy, occurred, providing σ-allyl(aryl)palladium **C** (step 3). Since the retro-allylation proceeds in a concerted fashion via a conformationally regulated six-membered cyclic transition state and the reductive elimination from **C** (step 4) is faster than the isomerization of **C** to π-allyl(aryl)palladium (see Scheme 1), the stereo- and regiochemical information of homoallyl alcohol **1** is transferred to **C** and then to the allylated product **3**. In contrast to allyl metals, homoallyl alcohols are not sensitive to

(5) Palladium-catalyzed reactions with allylboron reagents: (a) Kalinin, V. N.; Denisov, F. S.; Bubnov, Y. N. *Mendeleev Commun.* **1996**, *6*, 206−207. (b) Fürstner, A.; Siedel, G. *Synlett* **1998**, 161−162. (c) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459−2465. (d) Kotha, S.; Behera, M.; Shah, V. R. *Synlett* **2005**, 1877−1880. (e) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704−705. (f) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 1368−1369.

(6) Palladium-catalyzed reactions with allylindiums: (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201−3204. (b) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265−8268.

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

(8) Ligand effect on the regiochemistry of such couplings is discussed in detail: (a) Kurosawa, H.; Shiba, K.; Hirako, K.; Kakiuchi, K.; Ikeda, I. *J. Chem. Soc., Chem. Commun.* **1994**, 1099−1100. (b) Kurosawa, H.; Shiba, K.; Hirako, K.; Ikeda, I. *Inorg. Chim. Acta* **1996**, *250*, 149−154. (c) Kurosawa, H.; Ogoshi, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 973−984.

(9) γ-Selective Pd-catalyzed reactions of allylboronic acids with iodoarenes have been reported very recently. However, a different mechanism which includes a carbopalladation process is believed to operate in the reactions. Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150−8151.

(10) (a) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Tetrahedron* **1989**, *45*, 1067−1078. (b) Roberts, R. M. G. *J. Organomet. Chem.* **1969**, *18*, 307−319.

(11) Chemistry of σ-allylpalladiums: (a) Numata, S.; Okawara, R.; Kurosawa, H. *Inorg. Chem.* **1977**, *16*, 1737−1741. (b) Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026−7033. (c) García-Iglesias, M.; Buñuel, E.; Cárdenas, D. J. *Organometallics* **2006**, *25*, 3611−3618.

(12) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210−2211.

(13) Zirconium-mediated reactions: (a) Fujita, K.; Yorimitsu, H.; Oshima, K. *Chem. Rec.* **2004**, *4*, 110−119. (b) Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2004**, *69*, 3302−3307. Gallium-mediated reactions: (c) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2005**, *7*, 3577−3579. (d) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Organomet. Chem.* **2007**, *692*, 505−513. Rhodium-catalyzed reactions: (e) Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 2515−2517.

(14) Retro-allylations from lithium, magnesium, tin, and zinc alkoxides were observed: (a) Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134−2139. (b) Gerard, F.; Miginiac, P. *Bull. Chim. Soc. Fr.* **1974**, 2527−2533. (c) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186−195. (d) Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1978**, *162*, 37−44. (e) Yanagisawa, A.; Aoki, T.; Arai, T. *Synlett* **2006**, 2071−2074. Ruthenium-catalyzed deallylation was reported: (e) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587−5588. Rhodium-catalyzed deallylation was reported: (f) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9642−9643.

(15) Palladium-catalyzed reactions of organic halides with tertiary alcohols via β-carbon elimination were reported. Arylation with arylmethanols: (a) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407−10408. Via ring opening of cyclobutanols: (b) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010−11011. (c) Larock, R. C.; Reddy, C. K. *Org. Lett.* **2000**, *2*, 3325−3327. Alkynylation with propargylic alcohols: (d) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910−1913.

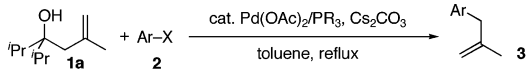
air and moisture. Any homoallyl alcohols are practically available, which would in principle allow for introducing allyl groups of various substitution patterns.

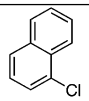
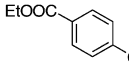
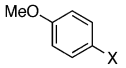
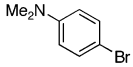
Despite the potential utility of our strategy, we noticed that the scope of our allylation reaction is limited. Specifically, some aryl bromides and most aryl chlorides did not undergo smooth allylation under the standard conditions. In addition, cyclic homoallyl alcohols are not good substrates, probably because they are so rigid that the interaction between the palladium center and the double bond is insufficient at the transition state of the palladium-mediated retro-allylation. The uniqueness of our allylation reaction promoted us to overcome these limitations. Here we report a much more efficient protocol. The improved protocol, which utilizes tricyclohexylphosphine as a ligand, now allows us to use a wider variety of aryl halides as well as to perform arylative ring-opening reactions of unstrained cyclic homoallyl alcohols.

2. Results and Discussion

2.1. Scope of Organic Halides and Ligand Effect. In the previous report,[12] we performed the reactions in most cases under the catalysis of 5 mol % of palladium acetate and 20 mol % of triarylphosphine. After screening of catalysts,[16] we found that a combination of 5 mol % of palladium acetate and *10 mol %* of tricyclohexylphosphine proved to be the best catalyst. Treatment of 1-chloronaphthalene (**2a**) with **1a**[17] in the presence of cesium carbonate and the $Pd(OAc)_2$/tri(*p*-tolyl)-phosphine (1:4 molar ratio) catalyst in refluxing toluene afforded 1-methallylnaphthalene (**3a**) in only 6% yield (Table 1, entry 1). On the other hand, the use of tricyclohexylphosphine[18] ($Pd(OAc)_2/PCy_3 = 1:2$) dramatically enhanced the catalytic activity (entry 2). It is worth noting that the $Pd(OAc)_2/PCy_3$ ratio is important to attain high yields. Use of a 1:4 ratio resulted in a very poor yield (6%) and recovery of 72% of **2a**. Tricyclohexylphosphine also promoted the methallylations of 4-bromobiphenyl (**2b**) and 2-bromonaphthalene (**2c**), wherein $P(p\text{-tol})_3$ failed to serve to attain satisfactory yields (entries 3−6). The bulkier PCy_3 would increase steric hindrance around the palladium center of the alkoxy(aryl)palladium **B**. PCy_3 would thus prevent the vacant coordination site that is responsible for the indispensable interaction with the double bond of **1a** from being occupied through the coordination of an additional PCy_3 and/or the dimerization of the palladium complex.[19] 2-Bromopyridine (**2d**) was converted to 2-methallylpyridine (**3d**) in moderate yield, the remainder being **2d** untouched (entry 7). Electron-deficient aryl chloride **2e** smoothly underwent the methallylation reaction (entry 8). Although the reaction of electron-rich *p*-bromoanisole (**2f**) with $P(p\text{-tol})_3$ resulted in a lower yield of coupling product **3f**, PCy_3 is the better ligand (entries 9 and 10). The reactions of electron-rich, much less reactive *p*-chloroanisole (**2g**) and *p*-bromo-*N*,*N*-dimethylaniline (**2h**) proceeded smoothly with the aid of PCy_3 (entries 11 and 12). Tri(*tert*-butyl)phosphine was also a highly effective ligand (entry 13). In this case, a catalyst prepared from equimolar amounts of $Pd(OAc)_2$ and P^tBu_3 was essential to attain high catalytic activity; otherwise the yields were poor (entry 14). Thus electron-rich trialkylphosphines have significantly expanded the scope of organic halides. Attempted methallylations of alkenyl halides resulted in poor to fair yields. The highest yield was observed when α-bromostyrene (**2i**) reacted with the aid of (*R*)-MONOPHOS ligand[20] (entry 15). Tricyclohexylphosphine did not work well in the reaction of **2i** (entry 16).

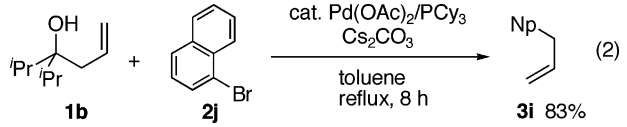
Table 1. $Pd(OAc)_2/PCy_3$-Catalyzed Methallylation of Aryl Halides **2** with Homoallyl Alcohol **1a** via Retro-Allylation[a]



entry	Ar–X	2	ligand	time/h	3	yield/%[b]
1		**2a**	$P(p\text{-tol})_3$	8	**3a**	6
2		**2a**	PCy_3	12	**3a**	79[c]
3		**2b**	$P(p\text{-tol})_3$	8	**3b**	(34)
4		**2b**	PCy_3	12	**3b**	83
5		**2c**	$P(p\text{-tol})_3$	8	**3c**	(<30)
6		**2c**	PCy_3	12	**3c**	86
7		**2d**	PCy_3	14	**3d**	56
8		**2e**	PCy_3	11	**3e**	79
9		**2f** (X = Br)	$P(p\text{-tol})_3$	8	**3f**	(29)
10		**2f** (X = Br)	PCy_3	24	**3f**	67
11		**2g** (X = Cl)	PCy_3	11	**3f**	70
12		**2h**	PCy_3	15	**3g**	80
13		**2h**	P^tBu_3	11	**3g**	(57)
14		**2h**	P^tBu_3[d]	11	**3g**	(12)[e]
15		**2i**	MP[f]	11	**3h**	45[g]
16		**2i**	PCy_3	11	**3h**	5

[a] A mixture of $Pd(OAc)_2$ (0.025 mmol), phosphine (0.10 mmol for $P(p\text{-tol})_3$ and PPh_3, 0.050 mmol for PCy_3 and (*R*)-MONOPHOS, 0.025 mmol for P^tBu_3), Cs_2CO_3 (0.72 mmol), **1a** (0.60 mmol), and **2** (0.50 mmol) was boiled in toluene (3.0 mL). [b] Isolated yields. Yields determined by ^1H NMR are in parentheses. [c] As a byproduct, 2-methallylnaphthalene was obtained in 8% yield. [d] 0.050 mmol of P^tBu_3 was used. [e] 74% of **2h** was recovered. [f] (*R*)-MONOPHOS, a monodentate phosphoramidite ligand, [(*R*)-(binaphthoxy)]$PNMe_2$. See reference 20. [g] Alcohol **1a** (1.0 mmol) and Cs_2CO_3 (1.2 mmol) were used.

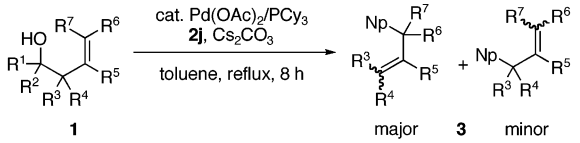
2.2. Homoallyl Alcohols as Regio- and Stereospecific Allyl Donors. Homoallyl alcohol **1b** effected allylation of **2j** to yield 1-allylnaphthalene (**3i**) in excellent yield (eq 2, Np = 1-naphthyl hereafter). The reaction of **1b** implies the generality of the allyl



transfer reaction in the $Pd(OAc)_2/PCy_3$ system. We thus examined the scope of homoallyl alcohols, focusing on the

(16) The results of the ligand screening experiments are in the Supporting Information.
(17) The preparations of homoallyl alcohols **1**, **6**, and **8** are described in the Supporting Information in detail.
(18) (a) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807−4810. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (c) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.
(19) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232−1233. (b) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533−1541.

Table 2. Regiospecific Allylation of 1-Halonaphthalene with Homoallyl Alcohols **1**[a]



entry	alcohol **1**	major **3**[b]	minor **3**[b]
1	**1c**	**3j** 92% (96%)	**3k** 0% (3%)
2	**1d**	**3l** 80%, *E*/*Z* = 63:37 (86%, *E*/*Z* = 46:54)	**3m** 5% (6%)
3[c]	**1e**	**3m** 48% (72%)	**3l** 0% (<6%, *E*/*Z* = 23:77)
4	**1f**	**3m** 11% (5%)	**3l** 0% (<1%)

[a] The reactions were performed under the conditions in Table 1, entry 1. [b] The yields obtained by using P(*p*-tol)$_3$ are in parentheses. The yields in parentheses were reported in the previous communication. See ref 12. [c] Substrate **1e** (1.0 mmol) and Cs_2CO_3 (1.2 mmol) were used. More than 30% of naphthalene was obtained.

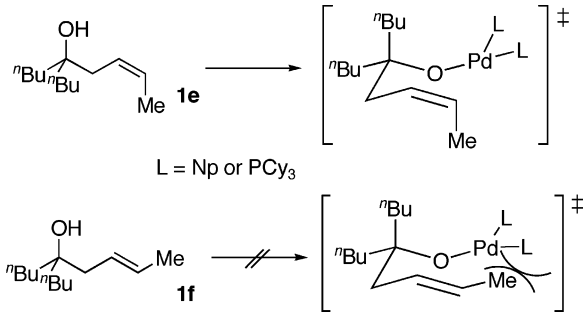
feasibility of regio- and stereocontrolled allylation in the present catalyst system.

2.2.1. Regiocontrol. To justify our idea depicted in Scheme 2, we prepared a variety of homoallyl alcohols having unsymmetrically substituted allyl moieties that are to be transferred.[17] As the data summarized in Table 2 clearly show, the reactions with the homoallyl alcohols indeed proceeded with high regiospecificity. In the reaction of **1c** (entry 1), the carbon−carbon bond formation took place at the terminal olefinic carbon of **1c** to provide trisubstituted alkene **3j** exclusively. No regioisomer **3k** was detected. Notably the **3j**/**3k** selectivity obtained by using PCy_3 was much better than that obtained by using P(*p*-tol)$_3$.[12] By changing P(*p*-tol)$_3$ to PCy_3, increasing the steric bulk around the palladium would accelerate the rate of the reductive elimination,[19] thereby avoiding undesirable isomerization of the initially formed σ-allylpalladium (Scheme 1). The formation of linear coupling product **3l** predominated over that of branched **3m** in the reaction of **1d** (entry 2). In contrast, the use of **1e** led to the opposite regioselectivity (entry 3). The regiospecificity is highly suggestive of the retro-allylation of **B** followed by rapid reductive elimination (Scheme 2).

It is worth noting that alcohol **1f**, the stereoisomer of **1e**, resisted the transformation (entry 4). The substituent R^6, located at the *trans* position to the hydroxylated moiety, would retard the reaction. We are tempted to assume that, on the transition state of the retro-allylation reaction, R^6 and one of the ligands on the palladium of square planer geometry would create so strong a repulsion that the palladium could not approach the carbon−carbon double bond (Scheme 3).

The substituents on the carbon−carbon double bonds proved to influence the efficiency of the allyl transfer reaction. In

Scheme 3



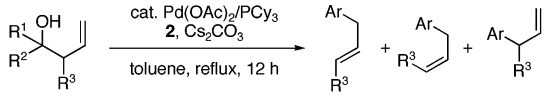
contrast, the substituents at the allylic positions had little effect on the efficiency. These facts strongly suggest that the reactions proceed via a retro-allylation process. From a mechanistic point of view, our carbon−carbon bond cleavage is completely different from the palladium-catalyzed β-carbon elimination.[15]

2.2.2. Stereocontrol of α-Products. Although the reactions of **1d** selectively yielded the linear coupling product **3l**, **3l** consisted of a 63:37 mixture of (*E*)- and (*Z*) isomers (Table 2, entry 2). We thus designed diastereomerically pure **1g**, having *tert*-butyl and methyl groups at the oxygenated carbon (Table 3). To our delight, **1g** realized stereospecific synthesis of (*E*)- and (*Z*)-**3l**. Treatment of **2j** with *threo*-**1g**[21] under the Pd(OAc)$_2$/PCy_3 catalysis afforded (*E*)-**3l** stereoselectively (entry 1). On the other hand, formation of (*Z*)-**3l** predominated over that of (*E*)-**3l** in the reaction of *erythro*-**1g** (entry 2). Electron-rich aryl chloride **2g** as well as electron-deficient **2e** also participated in stereospecific allylations (entries 3−6). The formations of (*Z*)-**3** from *erythro*-**1g** were always exclusive when PCy_3 was used.

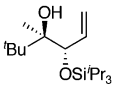
(20) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539−11540.

(21) For the *erythro*/*threo* nomenclature, see: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106−2108.

Table 3. Stereospecific Allylation of **2** with Diastereomerically Pure Homoallyl Alcohols **1g**−**1i**[a]



1 (*E*)-**3** (*Z*)-**3** branched **3**

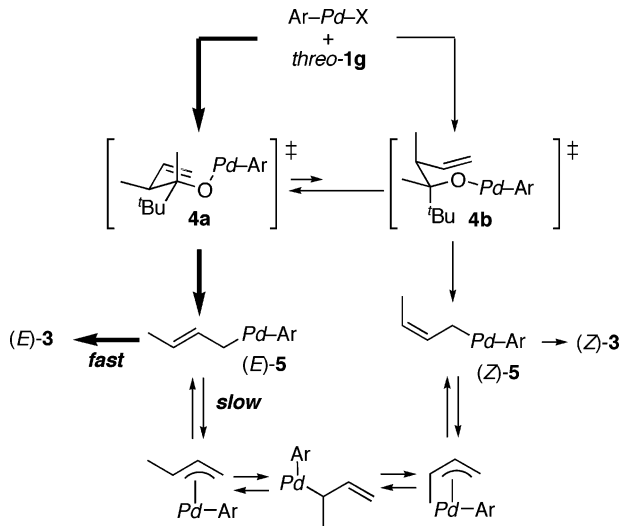
entry	**1**	**2**	(*E*)- and (*Z*)-**3**[b]	branched **3**
1	 *threo*-**1g**	**2j**	**3l**, 95%, *E*/*Z* = 97:3 (73%, *E*/*Z* = 98:2)	**3m**, 2%
2	 *erythro*-**1g**	**2j**	**3l**, 70%, *E*/*Z* = 0:100 (78%, *E*/*Z* = 4:96)	**3m**, 2%
3	*threo*-**1g**	**2e**	**3n**, 78%, *E*/*Z* = 95:5 (84%, *E*/*Z* = 97:3)	**3o**, 4%
4	*erythro*-**1g**	**2e**	**3n**, 73%, *E*/*Z* = 0:100 (74%, *E*/*Z* = 8:92)	**3o**, 6%[c]
5	*threo*-**1g**	**2g**	**3p**, 67%, *E*/*Z* = 96:4	**3q**, 4%
6	*erythro*-**1g**	**2g**	**3p**, 77%, *E*/*Z* = 0:100	**3q**, 3%
7	 *erythro*-**1h**	**2j**	**3r**, 88%, *E*/*Z* = 99:1 (89%, *E*/*Z* = 94:6)	**3s**, 0%
8	 *threo*-**1h**	**2j**	**3r**, 67%, *E*/*Z* = 0:100 (75%, *E*/*Z* = 4:96)	**3s**, 0%
9[d]	 *erythro*-**1i**	**2j**	**3t**, 87%, *E*/*Z* = 97:3 (84%, *E*/*Z* > 99:1)	**3u**, 0%

[a] The reactions were performed under the conditions in Table 1, entry 1. [b] The yields obtained by using P(*p*-tol)$_3$ and the corresponding aryl bromides are in parentheses. The yields in parentheses were reported in ref 12. [c] The branched product was contaminated with ethyl *p*-[(*E*)-1-methyl-1-propenyl]benzoate. [d] The alcohol **1i** used was a 9:1 mixture of *erythro*-**1i** and *threo*-**1i**.

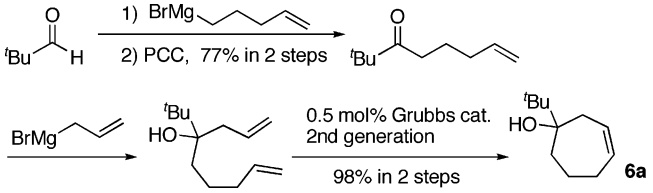
We rationalize the mechanism of the stereospecific allyl transfer reaction as follows (Scheme 4). Upon the retro-allylation reaction of *threo*-**1g**, a chairlike transition state **4a** that locates the *tert*-butyl group at the equatorial position would be most stable among possible transition states including another chairlike transition state **4b** and twist-boat transition states, on the basis of the conventional conformational analysis. Formation of aryl[(*E*)-crotyl]palladium (*E*)-**5** is thus favored. The intermediate probably undergoes reductive elimination so rapidly that its isomerization into π-allylpalladium and any other isomers is negligible. A similar explanation is applicable to the reaction of *erythro*-**1g**, where a chairlike transition state having the *tert*-butyl group at the equatorial position and the two methyl groups at the axial positions would be preferred.

The allyl transfer reaction was applied to stereospecific synthesis of vinyl ether **3r** starting from diastereomerically pure **1h** (Table 3, entries 7 and 8). Highly stereoselective

Scheme 4



Scheme 5



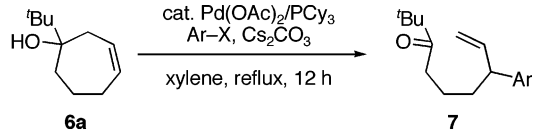
synthesis of silyl enolate (*E*)-**3t** also highlights the utility of the retro-allylation strategy (entry 9). Although **1i** consisted of the *erythro* and *threo* isomers in a ratio of 9:1, a slight excess (1.2 equiv) of **1i** allowed for the exclusive formation of (*E*)-**3t**.

2.3. Arylative Ring-Opening Reactions of Cyclic Homoallyl Alcohols. The allylation reactions mentioned so far are allyl transfer reactions from acyclic homoallyl alcohols **1a**−**1i**, which inherently accompany the loss of the corresponding ketone. We next considered cyclic homoallyl alcohols as substrates. Properly designed homoallyl alcohols can be transformed into σ-allyl-(aryl)palladium intermediates that have an intramolecular keto group. The reactions of such homoallyl alcohols proceed without loss of any carbon units.

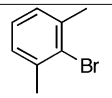
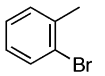
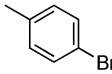
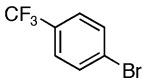
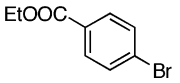
To begin with, cycloheptenol **6a** was prepared in four steps.[17] The synthesis consisted of (1) nucleophilic addition of 4-pentenylmagnesium bromide to pivalaldehyde, (2) oxidation with pyridinium chlorochromate, (3) nucleophilic allylation of the resulting ketone, and (4) ruthenium-catalyzed ring closing metathesis (Scheme 5). Each step was facile and robust, and thus endocyclic homoallyl alcohol **6a** was readily accessible.

Cycloheptenol **6a** was subjected to the palladium-catalyzed reactions with various aryl bromides (Table 4). The arylative ring-opening reactions were regiospecific, providing terminal unsaturation. The reactions required a higher temperature in refluxing xylene. The more restricted conformation of **6a**, compared to that of acyclic homoallyl alcohols such as **1a**, would cause weaker interaction between the palladium and the double bond in the corresponding palladium alkoxide (Figure 1). Tricyclohexylphosphine, three equimolar amounts to palladium, was the best ligand, and triphenylphosphine did not serve (entry 5). The *tert*-butyl group of **6a** was essential to attain

Table 4. Arylative Ring-Opening Reactions of 1-*tert*-Butyl-3-cyclohepten-1-ol (**6a**)[a]



6a **7**

entry	Ar–X **2**	yield /%
1	 **2k**	**7a**, 80
2	 **2l**	**7b**, 68
3	 **2m**	**7c**, 70
4	 **2n**	**7d**, 65
5	**2n**	**7d**, <10[b]
6	 **2o**	**7e**, 64
7	 **2p**	**7f**, 46

[a] $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.075 mmol), Cs_2CO_3 (0.72 mmol), **6a** (0.60 mmol), and **2** (0.50 mmol) were used. [b] PPh_3 (0.10 mmol) was used instead of PCy_3 (0.075 mmol).

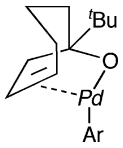
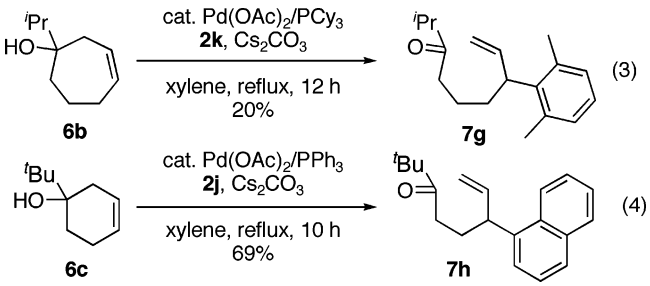


Figure 1. One of the possible modes of interaction between the palladium and the double bond of **6a**.

satisfactory yields. The reaction of the isopropyl analogue **6b** furnished the corresponding product in only 20% yield (eq 3). Cyclohexenol **6c** underwent the ring-opening, wherein PPh_3 was exceptionally the better ligand (eq 4).



We next prepared *erythro*- and *threo*-2-isopropenyl-1-methylcyclohexanol (**8a**).[17,21] Homoallyl alcohol **8a** was synthesized in four steps: (1) the reaction of cyclohexene oxide with di(isopropenyl)cuprate, (2) oxidation by PCC, and (3) methylation

Scheme 6

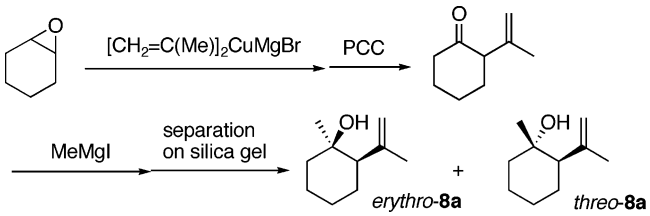
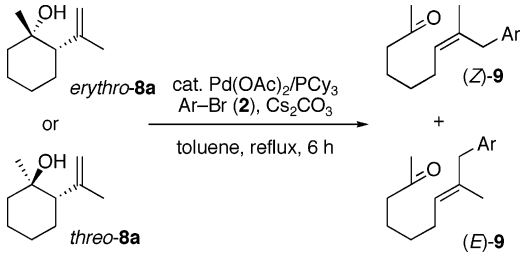


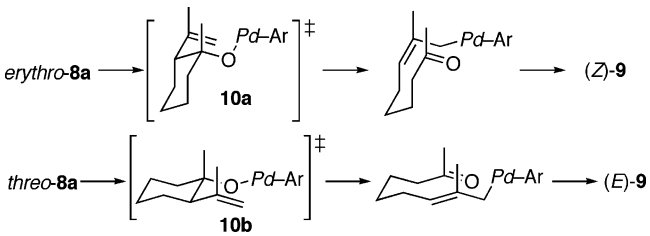
Table 5. Arylative Ring-opening Reactions of *erythro*- and *threo*-2-Isopropenyl-1-methylcyclohexanol (**8a**)[a]



entry	*erythro*/*threo*-**8a**	**2**	**9**	yield/% (*E*/*Z*)
1	*erythro*	**2k**	**9a**	76 (<1:99)
2	*erythro*	**2o**	**9b**	54 (<1:99)
3	*erythro*	**2p**	**9c**	81 (<1:99)
4	*erythro*	**2f**	**9d**	61[b] (<1:99)
5	*erythro*	**2m**	**9e**	64 (<5:95)
6	*erythro*	**2n**	**9f**	84 (<5:95)
7	*threo*	**2k**	**9a**	86 (>99:1)
8	*threo*	**2n**	**9f**	71 (>95:5)

[a] $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.075 mmol), Cs_2CO_3 (0.60 mmol), **8a** (0.50 mmol), and **2** (0.60 mmol) were used. [b] Performed for 22 h.

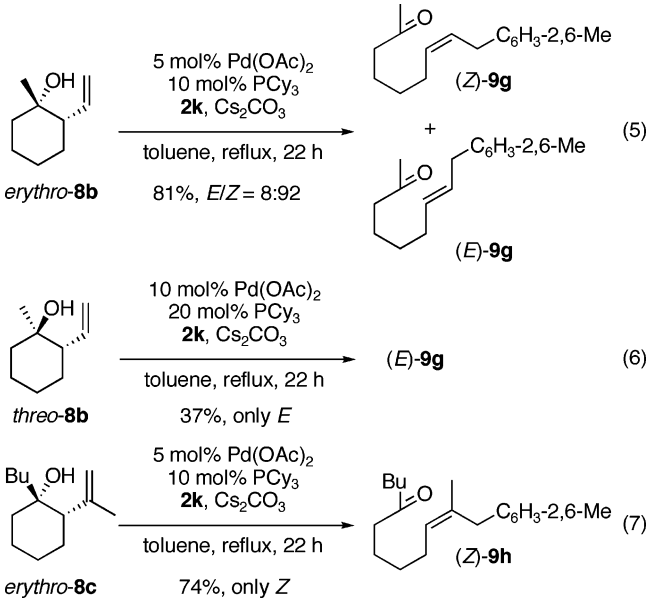
Scheme 7



of the resulting carbonyl group (Scheme 6). The methylation provided a mixture of *erythro*-**8a** and *threo*-**8a** in a ratio of 10:1, which was (4) chromatographed on silica gel to isolate each isomer.

Both of the isomers **8a** underwent smooth ring-opening with excellent regio- and stereospecificity (Table 5). The reactions represent novel synthesis of ketones involving extremely remote arylation. The high stereoselectivity would stem from bicyclic, decalin-like transition states **10** (Scheme 7).

Alcohol **8b** having a vinyl group underwent stereospecific ring-opening. In the reaction of *erythro*-**8b** (eq 5), slightly lower yet still satisfactory stereoselectivity was observed, compared to the reaction of *erythro*-**8a** (Table 5, entry 1). The stereoselectivity was perfect in the reaction of *threo*-**8b** albeit the conversion of *threo*-**8b** was low even with an increasing amount of the catalyst (eq 6). Synthesis of butyl ketone (*Z*)-**9h** was also successful starting from *erythro*-**8c** (eq 7).



3. Conclusion

Compared to the previous catalyst, the combination of palladium acetate and tricyclohexylphosphine proved to be much more effective for the palladium-catalyzed allylation of aryl halides with homoallyl alcohols. The scope of aryl halides has become wider, and most aryl halides including electron-rich aryl chlorides could participate. Moreover, the $Pd(OAc)_2/PCy_3$-catalyzed retro-allylation strategy is powerful enough to be applicable to arylative ring-opening reactions of cyclic homoallyl alcohols. The arylative ring-opening now allows for the regio- and stereospecific synthesis of ketones having a branched or linear allylarene unit at the remote terminus.

The retro-allylation system will be applicable to other transformations catalyzed by other transition metals, in which generation of the regio- and stereochemically defined σ-allyl complexes is important. In light of the importance of allylation reactions, retro-allylation can play key roles in developing highly selective organic reactions.

4. Experimental Section

4.1. Typical Procedure for $Pd(OAc)_2/PCy_3$-Catalyzed Allylation of Aryl Halides with Homoallyl Alcohol 1a: The reaction of entry 2 in Table 1 is representative. Cesium carbonate (0.23 g, 0.72 mmol) was placed in a 30-mL two-necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was dried in vacuo with heating with a hair dryer for 2 min. Palladium acetate (5.6 mg, 0.025 mmol) was added in the reaction flask. The flask was then filled with argon by using the standard Schlenk technique. Tricyclohexylphosphine (0.50 M in toluene, 0.10 mL, 0.050 mmol) and toluene (1.0 mL) were added, and the resulting mixture was stirred for 10 min at room temperature. Toluene (2.0 mL), homoallyl alcohol **1a** (0.10 g, 0.60 mmol), and 1-chloronaphthalene (**2a**, 0.081 g, 0.50 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 12 h. After the mixture was cooled to room temperature, water (20 mL) was added. The product was extracted with hexane (20 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification with hexane as an eluent gave 1-methallylnaphthalene (**3a**, 0.072 g, 0.40 mmol) in 79% yield.

4.2. Arylative Ring-Opening Reactions of Cyclic Homoallyl Alcohols: Palladium acetate (5.6 mg, 0.025 mmol), tricyclohexylphosphine (21 mg, 0.075 mmol), and cesium carbonate (235 mg, 0.72 mmol) were placed in a 30-mL reaction flask under argon. Xylene (5 mL) was added, and the whole mixture was stirred for 10 min to prepare the palladium catalyst. Substrates **6a** (101 mg, 0.60 mmol) and **2k** (0.069 mL, 0.50 mmol) were added to the mixture. The mixture was heated at reflux for 12 h. After the mixture was allowed to cool to ambient temperature, the product was extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to leave a yellow oil. Purification by silica gel column chromatography (hexane/ethyl acetate = 30:1) provided ketone **7a** (109 mg, 0.402 mmol) in 80% isolated yield.

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Supporting Information Available: Experimental details and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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