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One-Pot Sequential Cu-Catalyzed Reduction and Pd-Catalyzed Arylation of Silyl Enol Ethers

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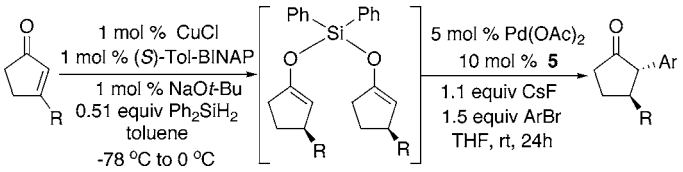
ABSTRACT



Enantiomerically enriched β-substituted diphenylsilyl enol ethers, which can be prepared from Cu-catalyzed asymmetric conjugate reduction, are utilized in the Pd-catalyzed arylation of various aryl bromides. This new method provides a simple route to α-arylated cycloalkanones with excellent levels of enantiomeric and diastereomeric purity. The isolation of the intermediate, diphenylsilyl enol ethers is not necessary; the procedure can be carried out in one-pot.

The palladium-catalyzed α-arylation of ketones has provided a general way to prepare α-arylated ketones.[1] In particular, the use of bulky, electron-rich phosphine ligands not only increased the rate of α-arylation but also allowed the use of aryl chlorides as substrates. The usual process, however, has several drawbacks. For example, arylation generally occurs preferentially at the less hindered of the two enolizable α-positions. Thus, it is often necessary to block one α-carbon in many instances to prevent multiple arylations of the substrate.[2] Another limitation is that for asymmetric ketone arylations, tertiary stereogenic centers formed after arylation at a methylene position contain a more acidic proton than that in the starting material, and therefore the product undergoes racemization under the reaction conditions. In many instances, reactions involving ketones and/or aryl halides bearing a base-sensitive functional group afford the desired products in low yield. As a result of these limitations, cyclopentanones, for example, remain one of the most difficult classes of ketones to arylate in affordable yield.[1c,2] The α-arylation of these ketones is potentially an attractive tool for preparing α-aryl cyclopentanones, a structural motif that often appears in natural products or important intermediates in their synthesis.[3] Thus, the Pd-catalyzed arylation of the corresponding silyl enol ether of ketones, which appears to overcome the disadvantages of direct ketone arylation, was reexamined. Simple fluoride sources, which serve as silicon activators, replace the need for a strong base.

Previously, Kuwajima described palladium-catalyzed coupling reactions of silyl enol ethers with aryl halides to afford

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(1) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (c) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (e) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (f) Satoh, T.; Kawamura, Y; Miura, M; Nomura, M. *Angew, Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (g) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (h) Terao, Y; Kametani, Y; Wakui, H; Satoh, T.; Miura, M; Nomura, M. *Tetrahedron* **2001**, *57*, 5967. (i) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209. For a recent review on Pd-catalyzed α-arylation of carbonyl compounds and nitriles, see: (j) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(2) For examples where α′-protected cyclopentanones were used for Pd-catalyzed arylation or vinylation, see: (a) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (b) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M., Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.

(3) (a) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290. (b) Srikrishna, A.; Reddy, T. J. *Tetrahedron* **1998**, *54*, 8133.

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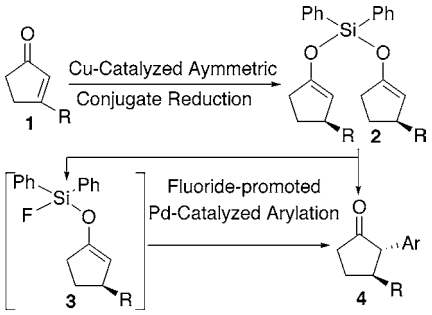
α-aryl ketones.[4] In his report, trimethylsilyl enol ethers of methyl ketones were coupled with aryl bromides using catalytic $PdCl_2(o\text{-}Tolyl_3P)_2$ in the presence of $n\text{-}Bu_3SnF$ as an additive. The organotin enolate generated in situ from the corresponding silyl enol ether was the proposed reactive species. Similarly, the use of an organotin enolate for the α-arylation of ketones was reported by Kosugi and Migita.[5] In this case, the tributyltin enolates were generated in situ from enol acetates. These methods, however, had poor substrate scope, encompassing only methyl ketones. Thus, internal ketones such as cycloalkanones were unreactive under the reaction conditions. Additionally, the use of the tin additive detracts from the attractiveness of the method.

In this report, we describe a room temperature, Pd-catalyzed method for the arylation of silyl enol ethers of cyclopentanones in the presence of CsF. We utilized enantiomerically enriched diphenylsilyl enol ethers **2**, which can be prepared from the Cu-catalyzed asymmetric conjugate reduction of cyclopentenones,[6,7] as cyclopentanone enolate equivalents. This protocol provides a new means to access various α-arylated cyclopentanones with excellent levels of enantiomeric and diastereomeric purity (Scheme 1). In addition,

Scheme 1

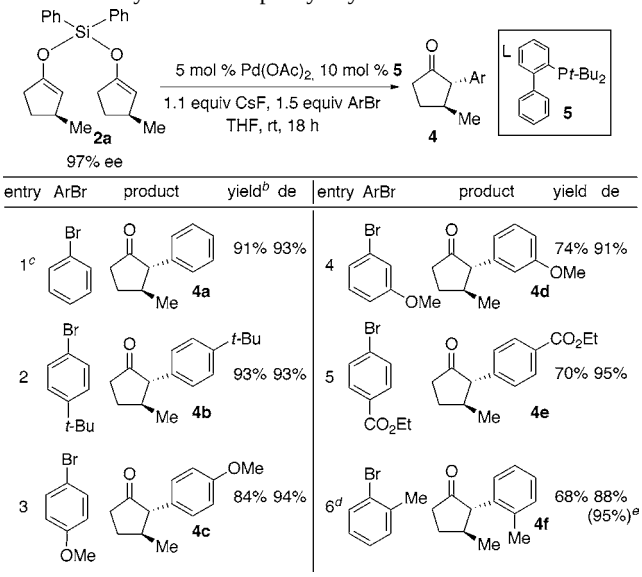


this process can be carried out in a one-pot procedure without the need for isolation of the intermediate, diphenylsilyl enol ethers.

Arylation of Diphenylsilyl Enol Ethers. A recent report describing the use of organosilanols or organosiloxanes as reactive nucleophilic partners in Pd-catalyzed coupling reactions[8,9] drew our attention to the use of **2** in the Pd-catalyzed arylation process (Scheme 1). We anticipated that under the Pd-catalyzed coupling conditions, **2** would be approximately as reactive as those siloxanes reported[8,9] and the fluorodiphenyl siloxane **3**, a possible transient intermediate generated in situ, would be also reactive due to the increased Lewis acidity of the silicon center.[10]

Initial experiments employing Kuwajima's reaction conditions revealed that the coupling reaction of the diphenylsilyl enol ether dimer **2a** and 4-*tert*-butylbromobenzene gave a 40% yield of arylated product. This result is in contrast to Kuwajima's findings, as he had reported that internal silyl enol ethers are unreactive under these conditions. Our results suggested that **2** is more reactive than the corresponding TMS enol ether derivatives. Further optimization of the reaction protocol by varying the phosphine ligand and the fluoride source led to a procedure that allowed for the coupling between **2a** and 4-*tert*-butylbromobenzene in THF at room temperature using $Pd(OAc)_2$/**5** in the presence of CsF in 93% yield (Table 1, entry 2). Ligand **5**, which has previously been

Table 1. Arylation of Diphenylsilyl Enol Ether



entry	ArBr	product	yield[b]	de
1[c]		**4a**	91%	93%
2		**4b**	93%	93%
3		**4c**	84%	94%
4		**4d**	74%	91%
5		**4e**	70%	95%
6[d]		**4f**	68%	88% (95%)[e]

[a] Reaction conditions: 1.0 equiv of monomeric diphenylsilyl enol ether (0.5 equiv **2a**), 1.1 equiv of CsF, 1.5 equiv of ArBr, 5 mol % $Pd(OAc)_2$, 10 mol % **5** in THF (4 mL/mmol **2a**). [b] Isolated yield (average of two experiments) of product with >95% purity as determined by GC and ^{1}H NMR. [c] Major diastereomer was determined to be trans[11] and the relative stereochemistry of all other products was assigned by analogy. [d] Performed with 2.0 equiv of ArBr. [e] Obtained after equilibration with K_2CO_3 in MeOH.

used for the direct α-arylation of ketones,[1c] was found to be most effective for the arylation of diphenylsilyl enol ethers. While the use of NaF, KF, TBAF on SiO_2, TBAT (1.0 M in THF), ZnF_2, and $TiCl_4$ gave poor results, CsF afforded good

(4) For Pd-catalyzed coupling reactions of silyl enol ethers, see: (a) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831. (b) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181. For Pd-catalyzed coupling reactions of silyl ketene acetals, see: (c) Galarini, R.; Musco, A.; Pontellini, R. *J. Mol. Catal.* **1992**, *72*, L11. (d) Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807. (e) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *123*, 11176.

(5) (a) Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, *6*, 939. (b) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *J. Chem. Soc., Chem. Commun.* **1983**, *7*, 344. (c) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242.

(6) (a) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. For other important Cu-catalyzed conjugate reductions using silanes as the hydride source, see: (b) Appella, D. H.; Moritani, Y.; Shintani, Y.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (c) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (d) Lipshutz, B. H.; Keithe, J. M.; Papa, P.; Vivian, R. W.; *Tetrahedron Lett.* **1998**, *39*, 4627. (e) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789. (f) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. (g) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273.

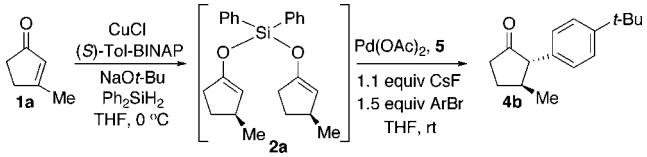
(7) (a) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129. For other examples where the silyl enol ether intermediates were used in C−C bond formations such as Aldol reaction, see: (b) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keithe, J. M. *Tetrahedron* **2000**, *56*, 2779.

yields of product while minimizing the amount of desilylated byproduct. Employing THF as the solvent was also crucial; the use of toluene led to a slower reaction rate even at elevated temperatures. Although the potential competitive transfer of the silicon-bound phenyl group[8,9] during transmetalation could diminish the amount of the desired coupling product, the biaryl product was observed only at higher temperatures. A range of substrates, including electron-neutral (Table 1, entries 1−2), electron-rich (entries 3−4), and electron-poor (entry 5) aryl bromides along with ortho-substituted aryl bromides (entry 6), were found to be compatible under these conditions. The mild reaction conditions also tolerated the presence of functional groups such as an ester (entry 5) in the aryl bromide. It is noteworthy that the arylation reaction is highly regioselective. Formation of regioisomers or diarylated products could not be detected by GC analysis. The arylated products were produced generally with a high diastereomeric ratio (>95:5), with the trans isomer being favored.[11] The one exception was entry 6 where a diastereomeric ratio of 92:8 was observed. This ratio was improved to 97.5:2.5 after equilibration with K_2CO_3 in MeOH.

One-Pot Sequential Cu-Catalyzed Conjugate Reduction and Pd-Catalyzed Silyl Enol Ether Arylation. Purification of silyl enol ethers can be troublesome, and therefore the development of a one-pot protocol was investigated. After performing the asymmetric conjugate reduction following the previously described procedure,[6a] we carried out the arylation in the same reaction vessel after the addition of $Pd(OAc)_2$, ligand **5**, CsF, aryl bromide, and THF. Two important factors for the success of this one-pot protocol were determined to be (1) the use of lower quantities of catalyst in the reduction step and (2) the choice of solvent for each step.

Our initial attempt to effect a one-pot reaction, using equimolar amounts of CuCl/(*S*)-Tol-BINAP (5 mol %) and $Pd(OAc)_2$ (5 mol %), gave only a trace amount of the desired coupling product **4b** (Table 2). We felt that this disappointing

Table 2. Effect of the Relative Quantities of Catalysts

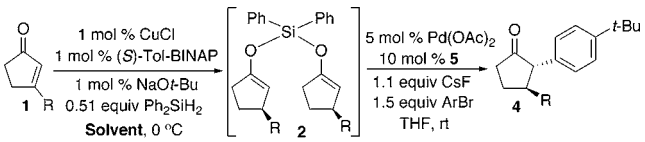


CuCl:(*S*)-Tol-BINAP	$Pd(OAc)_2$:**5**	yield (GC) of **4b**
5 mol %:5 mol %	5 mol %:10 mol %	trace
3 mol %:3 mol %	5 mol %:10 mol %	32%
1 mol %:1 mol %	5 mol %:10 mol %	74%

result was due to the presence of (*S*)-Tol-BINAP. While screening phosphine ligands for the arylation of silyl enol ethers, we found bisphosphine ligands such as Tol-BINAP to be ineffective, and using them afforded low yields of the arylated product. We believed that the Tol-BINAP in the reaction mixture binds to Pd with a higher affinity than does **5**, resulting in a low yield of arylated product. To support this hypothesis, we examined the effect of changing the ratio of the catalysts for the two steps of the reaction sequence. We found that the yield of **4b** increased as the quantity of the CuCl/Tol-BINAP catalyst was reduced relative to that of the Pd catalyst. It was determined that the use of 1 mol % CuCl/(*S*)-Tol-BINAP in the reduction step and 5 mol % $Pd(OAc)_2$/10 mol % **5** in the arylation step was optimal.

The choice of solvent affected both the enantioselectivity of the reduction and the yield of the arylation step (Table 3). Since THF was proven to be effective for the arylation

Table 3. Solvent Effect



	solvent					
	THF		toluene[b,c]		THF/*n*-pentane[b,c]	
R	ee[d]	yield	ee[d]	yield	ee[d]	yield
CH_3	72%	74%	96%		97%	72%
$(CH_2)_2Ph$	76%	80%	95%		95%	75%

[a] After reduction, the solvent was removed in vacuo and the second set of reagents were added followed by THF. [b] About 2/3 of solvent was removed in vacuo. [c] T = 78 °C. [d] Ee of **2** (3-substituted cyclopentanone)[14].

step, we began by examining the use of THF for the conjugate reduction step. The use of THF in both steps afforded a high yield (74%) of the desired arylated product. However, a significant decrease in the enantioselectivity of the reduction (∼70% ee) was seen. Reinvestigation into the appropriate solvent system for the asymmetric conjugate reduction revealed that the use of nonpolar solvents such as toluene and *n*-pentane[12] was necessary to maintain high enantioselectivity. Initially, toluene, which we have previously used,[6a]

(8) (a) Mowery, M. E.; Deshong, P. *J. Org. Chem.* **1999**, *64*, 1684. (b) Mowery, M. E.; Deshong, P. *Org. Lett.* **1999**, *1*, 2137. (c) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; Deshong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. (d) Correia, R.; Deshong, P. *J. Org. Chem.* **2001**, *66*, 7159. (e) Riggleman, S.; Deshong, P. *J. Org. Chem.* **2003**, *68*, 8106. (f) McElroy, W. T.; Deshong, P. *Org. Lett.* **2003**, *5*, 4779. (g) Seganish, W. M.; Deshong, P. *J. Org. Chem.* **2004**, *69*, 1137.

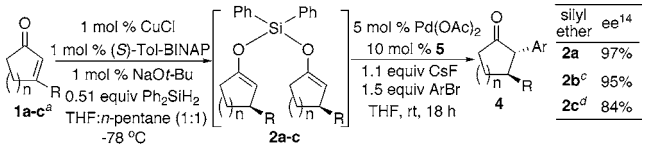
(9) (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835, and references therein. (b) Kellemeyn, J. M.; Denmark, S. E. *Org. Lett.* **2003**, *5*, 3483. (c) Ober, M. H.; Denmark, S. E. *Org. Lett.* **2003**, *5*, 1357. (d) Tymonko, S. A.; Denmark, S. E. *J. Org. Chem.* **2003**, *68*, 9151.

(10) For examples where fluorinated silanes are used in Pd-catalyzed coupling reactions, see: (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268. (b) Hatanaka, Y.; Goda, K.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994**, *50*, 8301. (c) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075. (d) Matsuhashi, H.; Asai, S.; Hirabayashi, K.; Hatanaka, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 437.

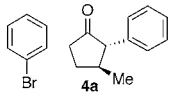
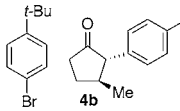
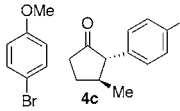
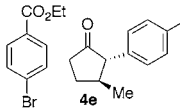
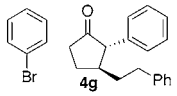
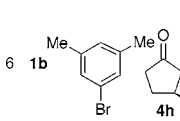
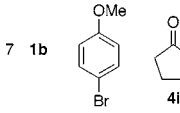
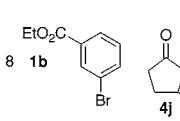
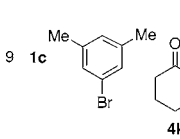
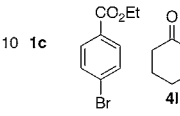
(11) ^{1}H NMR spectrum of *trans*-2-phenyl-3-methylcyclopentanone was consistent with that previously reported: Baldwin, J. E.; Bonacorsi, S., Jr. *J. Am. Chem. Soc.* **1993**, *153*, 10621.

(12) *n*-Pentane could be used in place of toluene in the conjugate reduction of lactones. Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253.

Table 4. One-Pot Reaction



silyl ether	ee[14]
2a	97%
2b[c]	95%
2c[d]	84%

entry	enone	ArBr	product	yield[e] de
1	**1a**		**4a**	72% 93%[f]
2	**1a**		**4b**	75% 93%
3	**1a**		**4c**	71% 94%
4	**1a**		**4e**	54% 95%
5	**1b**		**4g**	75% 96%
6	**1b**		**4h**	58% 98%
7	**1b**		**4i**	55% 98%
8	**1b**		**4j**	44% 97%
9	**1c**		**4k**	52% 94%
10	**1c**		**4l**	42% 92%

[a] **1a** (n = 1, R = Me), **1b** (n = 1, R = $(CH_2)_2$Ph), **1c** (n = 2, R = Me). [b] Reaction conditions: 1.0 equiv of enone **1**, 1 mol % CuCl, 1 mol % (*S*)-Tol-BINAP, 1 mol % NaO*t*-Bu, 0.51 equiv of Ph_2SiH_2 in THF/*n*-pentane (1:1, 2 mL per mmol of enone **1**) at −78 °C. After reduction, about 2/3 of the solvent was removed in vacuo and 1.1 equiv of CsF, 1.5 equiv of ArBr, 5 mol % $Pd(OAc)_2$, and 10 mol % ligand **5** were added followed by THF (2 mL per mmol of enone). [c] Reduction was carried out at 0 °C. [d] (*S*)-BIPHEMP was used in place of (*S*)-Tol-BINAP. [e] Yields are the average of two isolated yields of >95% purity as determined by GC and ^{1}H NMR. [f] Major diastereomer was determined to be trans.

was employed and removed in vacuo after the reduction was completed. This left a gel-like crude material to which THF and the remaining reaction components were added. However, the coupling with aryl bromides performed in this way afforded product in poor yield. We subsequently found that the use of a *n*-pentane/THF solvent (1:1) system afforded the production of the silyl enol ether with high enantioselectivity (95−97% ee). Additionally, *n*-pentane, in contrast to toluene, was easily removed from the reaction mixture, leaving the intermediate silyl enol ethers in THF.[13] These underwent coupling with aryl bromides, providing comparable yields to the reactions in which THF was used for both steps.

These optimized one-pot reaction conditions were applied to the reaction of a variety of β-substituted cyclopentenones (Table 4). Both methyl and phenethyl-substituted cyclopentenones were reduced in high ee (97 and 95%, respectively), and the resulting in situ-generated diphenylsilyl enol ethers were coupled with various aryl bromides regioselectively in good to moderate yields. This protocol could also be applied to cyclohexenone substrates. Reduction of 3-methyl cyclohexenone and the subsequent arylation of the corresponding diphenylsilyl enol ether afforded the α-arylated cyclohexanone in moderate yields (Table 4, entries 9−10). In all cases, a high level of diastereoselectivity (>90% de) was observed.

In conclusion, we have developed a protocol for the Pd-catalyzed coupling of silyl enol ethers with aryl bromides. Enantiomerically enriched β-substituted diphenylsilyl enol ethers **2**, which were prepared from Cu-catalyzed asymmetric conjugate reduction, were coupled with various aryl bromides using Pd/**5** in the presence of CsF. This new method provides a simple means to access α-arylated cycloalkanones with two new tertiary stereogenic centers in excellent enantio- and diastereoselectivity that are difficult to prepare via other methods.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) After the asymmetric reduction was carried out in THF/*n*-pentane (1:1), about 2/3 of the solvent was removed under vacuum and **2** in the remaining THF was subsequently used in arylation by adding $Pd(OAc)_2$, **5**, ArBr, and additional THF. See Supporting Information for details. Later, it was found that the slow addition of the cyclopentenone (5−6 h/mmol of enone) to the suspension of CuCl, NaO*t*-Bu, and Ph_2SiH_2 in THF also gave comparably high ee. However, the protocol using a THF/*n*-pentane cosolvent system is preferred due to its experimental convenience.

(14) Ee of each product was determined by analyzing the ee of unarylated 3-substituted cyclopentanone by HPLC or the diastereomeric ketals of unarylated 3-substituted cyclopentanone by NMR, and the absolute stereochemistry at the C3 position of the product was assigned in accord with a previous report.[8a] See Supporting Information for details.