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An Alternative Approach to *para*-C−H Arylation of Phenol: Palladium-Catalyzed Tandem γ-Arylation/Aromatization of 2-Cyclohexen-1-one Derivatives

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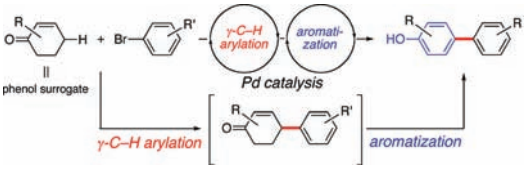
ABSTRACT



An efficient approach to prepare *para*-aryl phenols has been developed by using a Pd-catalyzed tandem γ-arylation/aromatization of 2-cyclohexen-1-one derivatives with aryl bromides. This approach provides various *p*-aryl phenols from the phenol surrogates, 2-cyclohexen-1-one derivatives, in a single reaction step on the basis of C−H arylation.

Biaryl compounds have attracted considerable synthetic interest[1] owing to their importance in various fields; they are ubiquitous in natural products, pharmaceuticals, and functional materials as structural motifs, as well as in metal catalysis as ligands.[2] Strategies for the efficient and selective construction of biaryls have been extensively explored.[3,4] The significant progress in metal-catalyzed cross-coupling reactions has greatly contributed to the development of these strategies. The coupling between an arylmetal and an aryl halide or pseudohalide is a representative method for synthesizing biaryls.[1] In recent years, highly efficient and atom-economical cross-coupling approaches to biaryls based on C−H arylation of arenes have been developed.[4] The newer transformations do not require complex prior preparation of arylmetals and/or aryl halides or pseudohalides as a coupling partner; hence, these transformations provide rapid and environmentally benign access to biaryls while reducing the consumption of chemical resources. Although the C−H arylations of arenes are highly efficient and ideal routes to biaryls, their scope is still limited.[4,5] In particular, the regiochemistry of these arylations remains a major concern. The C−H functionalizations of arenes generally proceed at the *ortho*-position

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(2) (a) Baudoin, O.; Gueritte, F. *Stud. Nat. Prod. Chem., Part J* **2003**, *29*, 355–417. (b) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (d) Demus, D., Goodby, J. W., Gray, G. W., Spiess, H.-W., Vill, V., Eds. *Handbook of Liquid Crystals*; Wiley-VCH: Weinheim, 1998. (e) Kraft, A.; Grimsdale, A. C.; Holmes, A. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 402–428. (f) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427.

(3) For selected examples of innovative synthetic approaches to biaryls, see: (a) Achburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2007**, *129*, 9109–9116. (b) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470–10471. (c) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951–3954.

(4) For reviews on C−H arylation of arenes, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (c) Ackermann, L.; Vicene, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826.

(5) The C−H arylation of electron-deficient heterocycles is still a limited reaction. See: Seiple, L. B.; Rodrigues, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196 and references therein.

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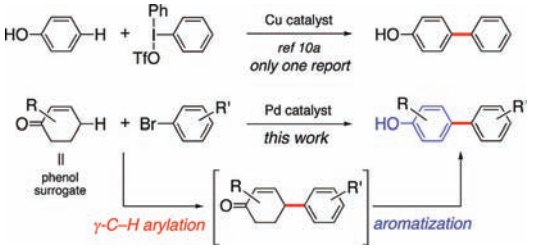
of a directing group on the arene, and other regioselectivities are quite rare.[4,6–8] Recently, a few pioneering studies have been reported on the *meta*-[9] and *para*-[10] selective C–H arylations of arenes. However, there is scope for further development with regard to the efficient construction of biaryls in the desired linkages.

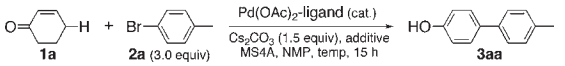
To effect such development, we envisaged an alternative approach to C–H arylation of arenes by modifying the conventional stepwise strategy of biaryl construction. The stepwise approach to biaryls—introduction of an aryl unit to a precursor of arene and subsequent arene formation of the arylated precursor—is a reliable method for constructing diverse biaryls; however, in this approach, the efficiency is compromised.[3] An alternative approach to C–H arylation of arenes could be the tandem stepwise approach in a single reaction step with the regioselective introduction of an aryl unit by C–H arylation; this approach could directly provide biaryls in the desired linkage from an arene surrogate on the basis of C–H arylation. Herein, we report on such an approach, namely, Pd-catalyzed tandem γ-arylation/aromatization of 2-cyclohexen-1-one derivatives with aryl bromides (Scheme 1).[11] This transformation provides *p*-arylated phenols from the phenol surrogates, 2-cyclohexen-1-one derivatives, in a single reaction step while introducing an aryl unit at the *p*-position by C–H arylation. That is, an alternative approach to *p*-C–H arylation of phenol, which is a rare reaction (Scheme 1),[12] has been developed.

Scheme 1. *para*-C–H Arylation of Phenol and the Alternative Approach

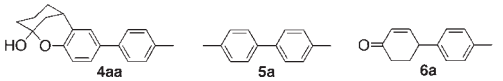


Pd-catalyzed γ-arylation of α,β-unsaturated ketones[13] and Pd-catalyzed dehydrogenation of 2-cyclohexen-1-one derivatives[14] and related compounds[15] to afford corresponding arenes have been previously reported. On the basis of these transformations, we investigated the Pd-catalyzed tandem γ-arylation/aromatization of 2-cyclohexen-1-one derivatives (Scheme 1). By partially employing the conditions used for γ-arylation of α,β-unsaturated ketones,[13] 2-cyclohexen-1-one (**1**, 1.0 mmol) was treated with 4-bromotoluene (**2a**, 2.0 mmol) in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and Cs_2CO_3 (1.15 mmol) with molecular sieves 4A (MS4A, 100 mg) in *N*,*N*-dimethylformamide (DMF, 5 mL) at 80 °C for 15 h; consequently, the desired 4-(*p*-tolyl)-phenol (**3aa**) was obtained in 33% yields. Side products **4aa** (0.28 mmol)[16] and 4,4′-bistoluene (**5a**, 0.55 mmol) were also obtained (Table 1, entry 1). Interestingly, the γ-arylation product, 4-(*p*-tolyl)-2-cyclohexen-1-one (**6aa**), was not isolated under the above-mentioned conditions. The desired product was directly obtained during the reaction. We speculated that both the γ-arylation[13] and subsequent aromatization of 2-cyclohexen-1-one[14] proceeded sequentially to produce biaryl **3aa** in a single reaction step. The additional self-Michael condensation of 2-cyclohexen-1-one appears to have proceeded for **4aa** during the reaction.

Table 1. Optimization of Reaction Conditions



entry	$Pd(OAc)_2$ (mol %)	ligand (mol %)	additive	temp (°C)	yield[a,b] (%)
1	5	PPh_3 (10)	-	80	33(28)[c,d]
2	10	PPh_3 (20)	-	80	53(7)[c]
3	20	PPh_3 (40)	-	80	48(12)[c]
4	10	PPh_3 (20)	-	80	56
5	20	PPh_3 (40)	-	80	57
6	10	$P^tBu_3 \cdot HBF_4$ (20)	-	80	ND
7	10	CyJohnPhos (20)	-	80	ND
8	10	dppe (10)	-	80	<19
9	10	dppf (10)	-	80	43
10	20	PPh_3 (40)	TBAB	80	16(20)
11	5	PPh_3 (10)	TBAB	rt	ND[e]
12	10	PPh_3 (20)	-	90	48
13	**20**	**PPh_3 (40)**	-	**90**	**64**
14	**20**	**PPh_3 (40)**	-	**70**	**66(5)**
15	**20**	**PPh_3 (40)**	-	**60**	**64(7)**



[a] Isolated yields. [b] Figures in parentheses are yields of side product **4aa**. [c] DMF was used as solvent instead of NMP. [d] The reaction was performed with 1.15 equiv of Cs_2CO_3 and 2.0 equiv of **2a** for 12 h. [e] Maier's conditions; 2.5 equiv of Cs_2CO_3 were utilized in the presence of 1.0 equiv of TBAB for 5 days. TBAB: tetrabutyl ammonium bromide. ND: Not detected. NMP: *N*-methylpyrrolidinone. DMF: *N*,*N*-dimethylformamide.

(6) For reviews on metal-catalyzed C–H functionalization of arenes, see: (a) Colby, D. A; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. See also ref 4.

(7) Some *meta*- or *para* C–H functionalizations of arenes have been developed. However, most of the reactions display unclear regioselectivity and provide some regioisomers. See: (a) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868–12869. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (c) Boebel, T. A.; Hartwig, J. F. *Organometallics* **2008**, *27*, 6013–6019. (c) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074.

(8) We have developed uniquely regioselective or regiocontrolled C–H functionalizations of arenes. See: (a) Imahori, T.; Kondo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 8082–8083. (b) Imahori, T.; Suzawa, K.; Kondo, Y. *Heterocycles* **2008**, *76*, 1057–1060. (c) Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450–2451.

(9) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597.

(10) Recently, *para*-selective C–H arylations of arenes have been reported. See: (a) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458–462. (b) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867.

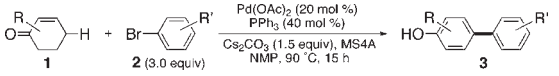
(11) A related biaryl construction, which provides 4-aryltetralones, has been developed. See: Varseev, G. N.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3881–3884.

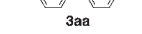
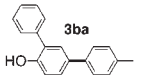
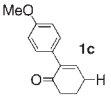
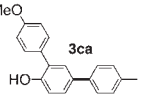
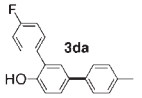
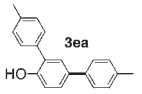
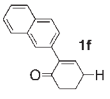
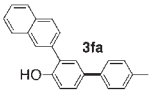
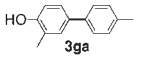
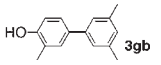
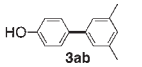
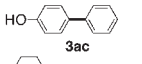
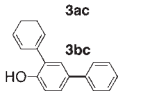
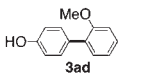
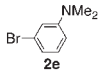
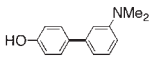
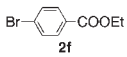
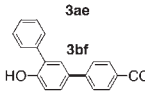
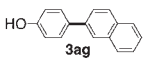
(12) Only one example of the selective *para*-C–H arylation of phenol has been reported in ref 10a (Scheme 1).

Next, the conditions were varied to optimize the reaction efficiency (Table 1).[17] Treating the substrate with 10 mol % $Pd(OAc)_2$ and 20 mol % PPh_3 provided **3aa** in 53% yield (entry 2). An evaluation of various solvents indicated that *N*-methylpyrrolidone (NMP) was also suitable for the tandem reaction. When the reaction was performed in NMP at 80 °C, slightly better results were obtained. With 20 mol % $Pd(OAc)_2$, the yield of **3aa** increased up to 57% (entry 5). Other combinations of the Pd catalyst and phosphine ligand did not provide good yields (entries 6–9); $Pd(OAc)_2$ and PPh_3 gave the best results.[17] Additionally, we investigated the effect of additives. Tetrabutyl ammonium bromide (TBAB) was found to be the critical additive in the related tandem γ-arylation and aromatization reaction developed by Maier.[11] However, the addition of TBAB did not improve our results (entries 10,11). Other additives also gave poor results.[17] The reaction temperature also affected the results (entries 4,5, 12–15). The best result was obtained when 20 mol % $Pd(OAc)_2$ and 40 mol % PPh_3 were used at 70 °C in NMP, producing **3aa** in 66% yield (entry 14).

We selected the reaction conditions listed as entry 13 in Table 1 (90 °C in NMP, 20 mol % $Pd(OAc)_2$, and 40 mol % PPh_3) to investigate the scope of our new approach to biaryls (Table 2).[18] The reaction of 2-aryl-2-cyclohexen-1-ones (**1b**–**1f**)[19] with **2a** proceeded in moderate to good yields to afford various terphenyls[20] (45%–73%, entries 2–6,11,14). Various aryl groups such as phenyl (**1b**), 4-methoxyphenyl (**1c**), 4-fluorophenyl (**1d**), *para*-tolyl (**1e**), and 2-naphthyl (**1f**) were found to be compatible. The substituents on the aryl groups affected the results. An electron-donating methoxy group reduced the yield slightly (45%, entry 3).[21] The reaction was also compatible with an alkyl group on the 2-cyclohexene-1-one nucleus. The reaction of 6-methyl-2-cyclohexen-1-one (**1g**)[22] with **2a** afforded 2-methyl-4-(*para*-tolyl)phenol (**3ga**) in 47% yield (entry 7). When 5-bromo-*meta*-xylene (**2b**) was used as an aryl bromide, the corresponding biaryl was obtained in 60% yield (entry 8). Next, the scope of aryl bromides as a coupling partner was investigated (entries 8–15).

Table 2. Pd-Catalyzed Tandem γ-Arylation/Aromatization of 2-Cyclohexen-1-one Derivatives



Entry	1	2	Product (3)	Yield (%)[a]
1	 **1a**	 **2a**	 **3aa**	66[b]
2	 **1b**	**2a**	 **3ba**	73
3	 **1c**	**2a**	 **3ca**	45[c,d]
4	 **1d**	**2a**	 **3da**	63
5	 **1e**	**2a**	 **3ea**	59
6	 **1f**	**2a**	 **3fa**	64
7	 **1g**	**2a**	 **3ga**	47
8	**1g**	 **2b**	 **3gb**	60
9	**1a**	**2b**	 **3ab**	64
10	**1a**	 **2c**	 **3ac**	60
11	**1b**	**2c**	 **3bc**	59
12	**1a**	 **2d**	 **3ad**	61[e]
13	**1a**	 **2e**	 **3ae**	52
14	**1b**	 **2f**	 **3bf**	60
15	**1a**	 **2g**	 **3ag**	52[e]

[a] Isolated yield. [b] The reaction was performed at 70 °C. [c] NMR yield using internal standard ($ClCH_2CH_2Cl$). [d] The reaction was performed at 80 °C. [e] DMF was utilized as solvent.

(13) (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203–6206. (b) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177–180.

(14) (a) Wilds, A. L.; Djerassi, C. *J. Am. Chem. Soc.* **1946**, *68*, 1715–1719. (b) Horning, E. C; Horning, M. G. *J. Am. Chem. Soc.* **1947**, *69*, 1359–1361. (c) Wilds, A. L.; Werth, R. G. *J. Org. Chem.* **1952**, *17*, 1154–1161. Quite recently, a Pd(II)-catalyzed aromatization of 2-cyclohexen-1-one under mild reaction conditions has been reported. See: (d) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209–213.

(15) Pd(II)-catalyzed aromatization of 2-cyclohexan-1-one-based enamine has been reported. See: (a) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88–110. (b) Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186–191.

(16) The structure of **4aa** was determined by comparing analytical data with that of an analog. For the analogous compound, see: Cacchi, S.; Misiti, D.; Palmieri, G. *J. Org. Chem.* **1982**, *47*, 2995–2999.

(17) Selected examples are listed in Table 1. A detailed optimization of reaction conditions is described in the Supporting Information.

(18) We tentatively carried out the reaction at higher temperature (90 °C). When uncontrollable side reactions occurred, the reactions were investigated at lower temperature.

(19) 2-Aryl-2-cyclohexen-1-one were synthesized as reported. See: Felpin, F.-X. *J. Org. Chem.* **2005**, *70*, 8575–8578.

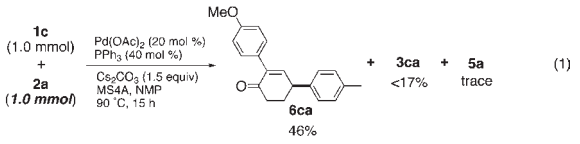
(20) For utilities of terphenyls, see: Miguez, J. M. A.; Adrio, L. A.; Sousa-Pedrares, A.; Vila, J. M.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 7771–7774 and references therein.

(21) An inseparable side product was produced in the reaction. Thus, the yield of the desired product **3ca** was estimated from ^1H NMR of the mixture using an internal standard (1,2-dichloroethane). See Table 2. The authentic sample of **3ca** was obtained by purification with HPLC (InertSustain C18, H_2O/CH_3CN = 35/65).

(22) 6-Methyl-2-cyclohexen-1-one was synthesized using a reported method. See: Marques, F. A.; Lenz, C. A.; Simonelli, F.; Maia, B. H. L. N. S.; Vellasco, A. P.; Eberlin, M. N. *J. Nat. Prod.* **2004**, *67*, 1939–1941.

The use of various aryl bromides, 5-bromo-*meta*-xylene (**2b**), bromobenzene (**2c**), 2-bromoanisole (**2d**), 3-bromo-*N,N*-dimethylaniline (**2e**), ethyl 4-bromobenzoate (**2f**), and 2-bromonaphthalene (**2g**), afforded the desired products in moderate to good yields (52%−64%).[23] The position of the substituents on the aryl bromides did not seem to hinder the reactions. In spite of its steric bulk, 2-bromoanisole had good reactivity (61%, entry 12). *m*-Substituted aryl bromides also provided good results (entries 13,15). Various 2-cyclohexene-1-one derivatives and aryl bromides provided acceptable results.

Although the detailed mechanism of the proposed tandem γ-arylation/aromatization reaction remains unclear at this stage of our investigations, some mechanistic insights have been obtained. The reaction of **1c** with *1.0 equiv* of **2a** mainly provided the γ-arylation product **6ca** in 46% yield with only a small amount of **3ca** (< 17%, including impurity) and a trace amount of **5a** (eq 1), whereas the use of *3.0 equiv* of **2a** yielded **3ca** as the main product (45%, Table 2, entry 3). This result suggests that an excess amount of aryl bromide is necessary to promote aromatization. Generation of homocoupling side products of aryl bromides (**5a**) seems to be involved in the aromatization process. Moreover, the expected reaction intermediate (**6ca**) was detected, which supports the proposed sequence of γ-arylation/aromatization.



On the basis of these mechanistic insights and related reports,[13−15,24,25] a mechanism of the tandem γ-arylation/aromatization reaction is proposed, as shown in Figure 1. The γ-arylation of 2-cyclohexen-1-one (**1a**) initially proceeds *via* palladation at the γ-position with ArPdBr, which is generated from the oxidative addition of the aryl bromide (**2x**) to Pd(0), and subsequent reductive elimination of Pd(0).[13] Next, the aromatization of a 2-cyclohexen-1-one unit occurs.[14,15] On the basis of the result of tandem γ-arylation/aromatization of **1c** with *1.0 equiv* of **2a** (eq 1), we speculate that the aromatization could be a result of the palladium-catalyzed reductive coupling of aryl bromides.[24] Palladation of the generated 4-aryl-2-cyclohexen-1-one (**6ax**) at the 6- or 4-position with ArPdBr proceeds in the presence of a Cs base. Subsequent β-elimination of *anionic Pd(0)*, which is the key intermediate in Pd-catalyzed reductive homocoupling of aryl halides,[24] provides 4-aryl-cyclohexa-2,5-dienone or 4-aryl-cyclohexa-2,4-dienone.[14,15,25] After straight tautomerization, 4-aryl-phenol (**3ax**) is obtained. Reentry of Pd(0) into the next catalytic cycle could be accomplished *via* the reductive homocoupling reaction of aryl bromides. Oxidative addition of another aryl bromide (**2x**) to the anionic Pd(0) followed by reductive elimination regenerates Pd(0), providing the homocoupling side product **5x**.[24] An alternative plausible mechanism is the generation of a Pd(IV) species after the palladation at the 6- or 4-position of 4-aryl-2-cyclohexen-1-one with another aryl bromide followed by β-elimination of ArPd(II)Ar to produce the corresponding dienone.[24b]

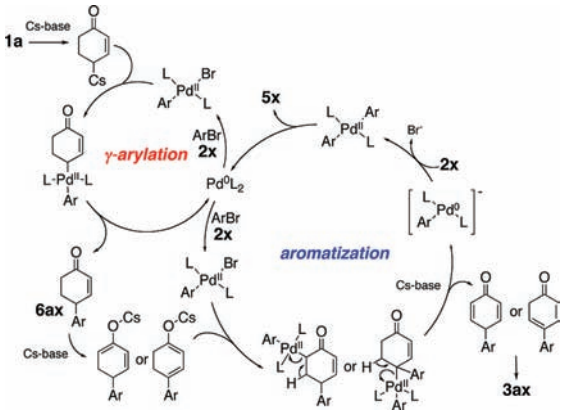


Figure 1. Proposed mechanism of the tandem γ-arylation/aromatization of 2-cyclohexen-1-one derivatives.

In summary, we have developed a Pd-catalyzed tandem γ-arylation/aromatization of 2-cyclohexen-1-one derivatives with aryl bromides, which is an alternative approach to the *p*-C−H arylation of phenol with a phenol surrogate. In this approach, widely accessible 2-cyclohexen-1-one derivatives[14d,19,22] function as the phenol surrogate. Although this transformation gives moderate to good yields, a wide range of *p*-aryl phenols could be efficiently synthesized in a single reaction step on the basis of C−H arylation. Further optimization and expansion of the scope of this reaction as well as mechanistic studies are currently underway.

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

The authors declare no competing financial interest.

(23) When **2d** or **2g** was utilized as an aryl bromide, the reaction in DMF provided better results.

(24) (a) Jutand, A.; Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261–274. (b) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205–1208. (c) Kurobashi, M.; Waki, Y.; Tanaka, H. *J. Org. Chem.* **2003**, *68*, 3938–3942. See also ref 15a.

(25) For palladium-catalyzed dehydrogenation of ketones to produce α,β unsaturated ketones, see: (a) Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779–3790. (b) Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569.