Heck Arylation of 1,2-Cyclohexanedione and 2-Ethoxy-2-cyclohexenone

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Introduction

The intermolecular Heck reaction is of the utmost importance in organic synthesis.[1] The reaction allows regioselective arylation at the terminal β-position of both electron-deficient olefins such as α,β unsaturated carbonyl compounds and of electron-rich enol ethers. The β-arylation of enol ethers, which relies on chelate control,[2] delivers aryl acetaldehydes after hydrolysis and β-arylation of the enol ether methyl α-methoxyacrylate, and subsequent hydrolysis provides aryl substituted α-keto acid derivatives.[3]

In a medicinal chemistry oriented research project[4] access to direct methods for the attachment of cyclic corestructures with combined hydrogen bond accepting and donating properties[5] were needed. In particular, a convenient synthetic route to 3-aryl-1,2-cyclohexanediones[6,7] **3** from aryl halides was desired. On the basis that the enol form of 1,2-cyclohexanedione (**1**) encompasses an α,β-unsaturated system,[8] we were prompted to commence a study of the Heck arylation of **1**.[1]

We herein report that C3-arylation of ketol **1** can be accomplished under traditional Heck arylation conditions in the presence of water. This reaction constitutes, to our knowledge, the first example of an arylation of an enol proposed to proceed by a Heck reaction mechanism.[1] Arylation of 2-ethoxy-2-cyclohexenone (**4**) and subsequent cleavage of the alkoxy group provides an alternative procedure to obtain **3**.

Results

Reactions of **1** (1 equiv) and aryl bromides **2a**−**h** (4 equiv) with a catalytic amount palladium acetate as precatalyst and triphenyl phosphine as ligand deliver **3a**−**h** in moderate yields (eq 1 and Table 1). The reactions were conducted with diisopropylethylamine as base in aqueous DMF[9] (DMF/water 85/15) at 100 °C. No diarylation product was observed. With smaller amounts of aryl bromide or water, considerably lower yields were observed. Aromatic bromides carrying electron-withdrawing groups, with the exception of **2g**, failed to produce arylated cyclohexane-1,2-diones. Furthermore, with aryl iodides as coupling partners a fast formation of biaryls predominated and no product from arylation of **1** was detected.[10,11]

Palladium-catalyzed arylation of enol ether **4** with electron-rich **2a**−**c,f** occurred smoothly (eq 2 and Table 2). Interestingly, even the electron-poor aryl bromides (**2i**−**m**) were useful as arylating agents with **4**, provided the more hindered tri-*o*-tolylphosphine was employed as supporting ligand (Table 2).[10,12] High isolated yields of the C3-arylated enol ethers **5a**−**c,f**,**i**−**m** were obtained with complete regioselectivity. Further deethylation of **5f,m** to afford **3** could also be efficiently achieved (eq 3).[13]

Since the sharp temperature profiles associated with microwave in-situ heating might help to minimize the

(1) For reviews on the Heck reaction see: (a) Heck, R. F. *Org React.* **1982**, *27*, 345. (b) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford 1991; Vol. 4, p 833. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (e) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Chemistry*; John Wiley & Sons: Chichester, 1995; p 125. (f) Soderberg, B. C. *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Volume Ed., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford 1995; Vol. 12, p 259. (g) Jeffery, T. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc: Greenwich 1996; Vol. 5, p 153. (h) Bräse, S.; de Meijere, A. *Metal-catalyzed Cross-Coupling Reactions;* Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weinheim, 1997; p 99.

(2) (a) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. (b) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Acta Chem. Scand.* **1993**, *47*, 212. (c) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603. (d) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285. (e) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858.

(3) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1987**, *28*, 3039.

(4) Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885.

(5) For carboxylic acid group isosteres see: (a) Korolkovas, A. *Essentials of Medicinal Chemistry;* John Wiley & Sons: Chichester 1988; p 81. (b) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action;* Academic Press: San Diego 1992; p 20.

(6) Relatively few examples are documented for the preparation of 3-aryl-1, 2-cyclohexanediones. Oxidations: (a) Goldblum, A.; Mechoulam, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1889. (b) Kawada, K.; Gross, R. S.; Watt, D. S. *Synth. Commun.* **1989**, *19*, 777. (c) Horiuchi, C. A.; Kiyomiya, H.; Takahashi, M.; Suzuki, Y. *Synthesis* **1989**, 785. Photolysis: (d) Feigenbaum, A.; Pete, J.-P.; Scholler, D. *J. Org. Chem.* **1984**, *49*, 2355. (e) Feigenbaum, A.; Pete, J.-P.; Scholler, D. *J. Org. Chem.* **1986**, *51*, 4424. Conjugate addition: (f) Tomboulian, P.; Bloomquist, C. A. A. *J. Org. Chem.* **1959**, *24*, 1239. (g) Charonnat, J. A.; Mitchell, A. L.; Keogh, B. P. *Tetrahedron Lett.* **1990**, *31*, 315.

(7) 1,2-Diketones have found widespread use in the syntheses of different heterocyclic compounds. For some examples, see the following. (a) Bredereck, H.; Gompper, R.; von Schuh, H. G.; Theilig, G. *Angew. Chem.* **1959**, *71*, 753. (b) Porter, A. E. A. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford 1984; Vol. 3, p 157. (c) Christl, M.; Kraft, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1369. (d) Gupta, A. K.; Fu, X.; Snyder, J. P.; Cook, J. M. *Tetrahedron* **1991**, *47*, 3665. (e) Kiselyov, A. S. *Tetrahedron Lett.* **1995**, *36*, 493.

(8) (a) Schwarzenbach, G.; Wittwer, C. *Helv. Chim. Acta* **1947**, *30*, 663. (b) Hesse, G.; Krehbiel, G. *Ann.* **1955**, *593*, 35.

(9) For examples of Heck reactions proceeding in water or in water/organic solvent mixtures, see: (a) Bumagin, N. A.; More, P. G.; Beletskaya I. P. *J. Organomet. Chem.* **1989**, *371*, 397. (b) Zhang, H.-C.; Daves, G. D., Jr. *Organometallics* **1993**, *12*, 1499. (c) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051. (d) Kiji, J.; Okano, T.; Hasegawa, T. *J. Mol. Catal. A: Chem.* **1995**, *97*, 73. (e) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465. See also ref 20.

(10) Attempts to use iodobenzene or 1-iodonaphthalene in the coupling reactions with 1,2-cyclohexanedione (**1**) and 2-ethoxy-2-cyclohexenone (**4**) were unsuccessful. In all reactions, with or without phosphine ligands (triphenylphosphine or tri-*o*-tolylphosphine), the formation of biaryls strongly dominated. We believe that the slow arylation of **1** and **4** may be attributed to difficulties in the migratory insertion and a fast concomitant biaryl generation with aryl iodides as arylating agents.

(11) It has been suggested that the reactivity and stoichiometry of the oxidative addition products of aryl iodides and bromides are substantially different. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

(12) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357 and references cited there.

(13) Garg, N.; Gogoll, A.; Westerlund, C.; Sundell, S.; Karlén, A.; Hallberg, A. *Tetrahedron* **1996**, *52*, 15209.

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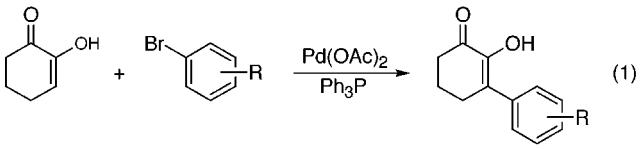
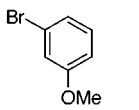
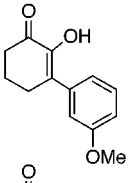
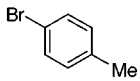
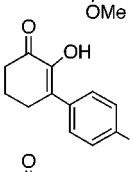
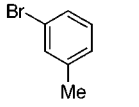
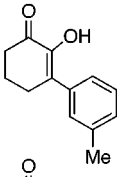
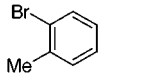
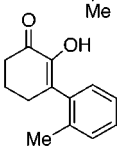
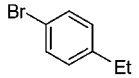
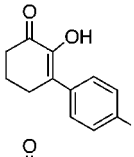
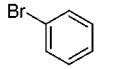
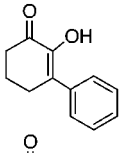
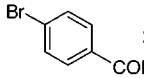
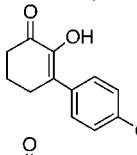
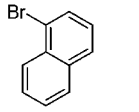
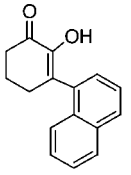
Table 1. Palladium-Catalyzed Arylation of 1,2-Cyclohexanedione (1) with Aryl Bromides[a]



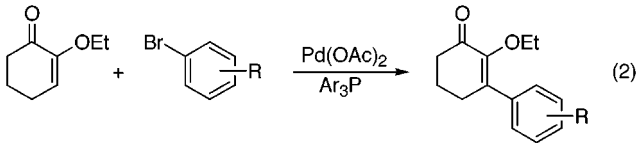
1 **2a-h** **3a-h**

aryl bromide	time (h)	isolated yield of **3a-h**[a]
 **2a**	16	 **3a** 38%
 **2b**	16	 **3b** 53%
 **2c**	16	 **3c** 66%
 **2d**	16	 **3d** 19%
 **2e**	16	 **3e** 66%
 **2f**	16	 **3f** 60%
 **2g**	48	 **3g** 26%
 **2h**	48	 **3h** 29%

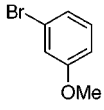
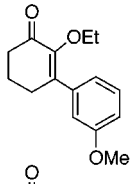
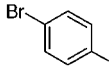
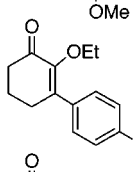
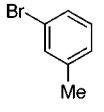
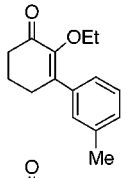
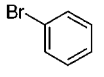
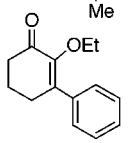
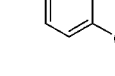
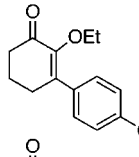
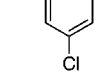
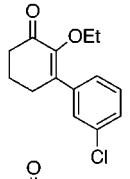
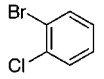
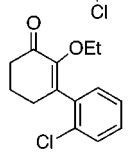
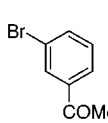
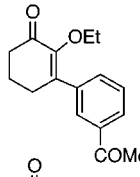
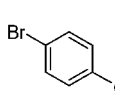
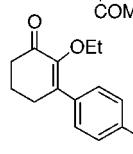
[a] The 1,2-cyclohexanedione (**1**) (1.0 equiv, 1.0 mmol), aryl bromide (4.0 equiv), $Pd(OAc)_2$ (0.05 equiv), Ph_3P (0.12 equiv), and *i*-Pr_2NEt (4.0 equiv) were heated at 100 °C under nitrogen in aqueous DMF. >95% Purity by GC-MS.

heat-induced decomposition of labile starting compound **1**,[14,15] we decided to assess this heating technique[16] under otherwise identical Heck reaction conditions (except for reaction scale). Upon continuous microwave treatment, the transformations were complete within 10 min[17] rather than several hours. But the yields of **3c** and **3f** were only slightly improved (Table 3). As was the case with the thermal version of the reaction, electron-poor

Table 2. Palladium-Catalyzed Arylation of 2-Ethoxy-2-cyclohexenone (4) with Aryl Bromides[a]

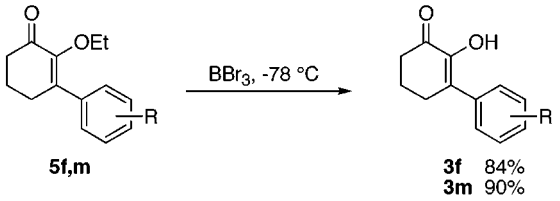


4 **2a-c,f,i-m** **5a-c,f,i-m**

aryl bromide	time (h)	isolated yield of **5a-c,f,i-m**[a]
 **2a**	48	 **5a** 65%[b]
 **2b**	48	 **5b** 76%[b]
 **2c**	16	 **5c** 83%[b]
 **2f**	16	 **5f** 86%[b,c]
 **2i**	48	 **5i** 72%[d]
 **2j**	48	 **5j** 68%[d]
 **2k**	96	 **5k** 32%[d]
 **2l**	16	 **5l** 66%[d]
 **2m**	60	 **5m** 76%[c,d]

[a] The 2-ethoxy-2-cyclohexenone (**4**) (1.0 equiv, 0.20 mmol), aryl bromide (4.0 equiv), $Pd(OAc)_2$ (0.05 equiv), Ar_3P (0.12 equiv), and *i*-Pr_2NEt (4.0 equiv) were heated at 100 °C under nitrogen in aqueous DMF. >95% Purity by GC-MS. [b] The phosphine ligand was Ph_3P. [c] The reaction was performed on a 2.0 mmol scale. [d] The phosphine ligand was $(o\text{-tol})_3P$.

(14) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665.
(15) 1,2-Cyclohexanedione is known to be thermally unstable. Fluka Catalogue, *Chemica, BioChemika, Analytika*, Norge/Sverige, 1997/98, p 439.



(3)

arylating derivatives afforded no coupling products. Two microwave-assisted reactions with olefin **4** were also conducted (Table 3). After a reaction time of 10−12 min, arylation with **2c** and **2f** provided **5c** and **5f** in 57% and 70% isolated yields, respectively.[17]

Discussion

We believe that the reaction of **1** with aryl bromides proceeds via formation of an aryl palladium π-complex and subsequent insertion of the enol double bond as depicted in Scheme 1.[18] The arylated ketols **3** are thereafter liberated by direct PdH elimination (path A)[19] or alternatively, a palladium enolate is created and eventually a syn-β-elimination provides free **3** (path B).[20] It is possible that the hydrogen bonding proton of the enol,[21] prior to π-complex formation, is replaced by a palladium atom which coordinates to the carbonyl oxygen atom and forms a stable palladium 1,2-diketonate complex.[22,23] We cannot exclude that such an olefinic palladium diketonate complex constitutes the reactive olefinic substrate that is attacked by the arylpalladium species and undergoes migratory insertion.[24] The ability of the carbonyl oxygen to undergo hydrogen bonding or coordinate to palladium seems important since neither cyclohexanone[25] nor 1,3-cyclohexanedione[23] were found to undergo arylation under our reaction conditions.

The limited yields of **3a**−**h** (Table 1), we believe, are mainly attributed to a concomitant decomposition of the ketol **1**. A control experiment where **1** was subjected to the Heck reaction conditions, but without the aryl bromide, demonstrated that **1** was slowly decomposed into unidentified compounds.[15] Apparently, the utilization of the microwave flash heating technique to promote formation of **3** in favor of decomposition was only moderately successful (Table 3).

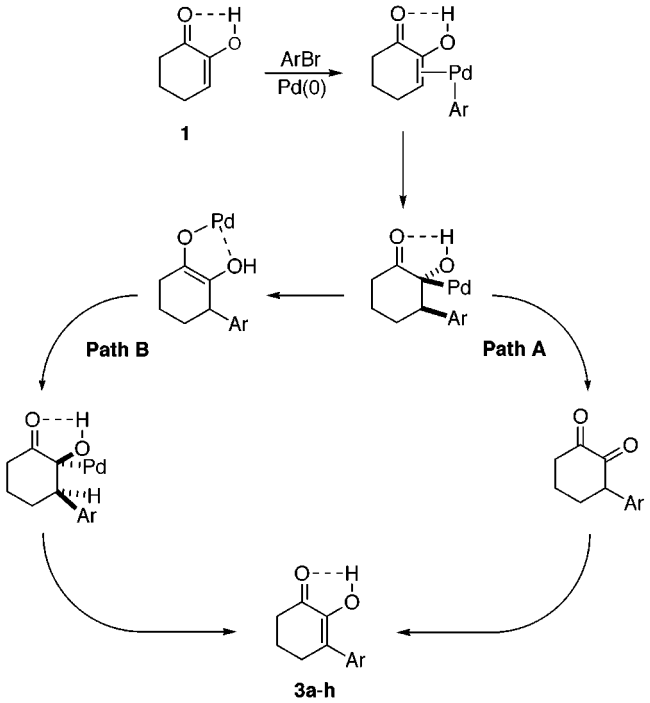
Intermolecular palladium-catalyzed direct substitution of halides in oxidative addition complexes for soft carbon

Table 3. Palladium-Catalyzed Arylation of 1 or 4 with Aryl Bromides under Microwave Heating[a]

diketone or enol ether	aryl bromide	time (min)	power (W)	isolated yield, %, of **3** or **5**[a]
1	**2c**	10	40	**3c** 69
1	**2f**	10	50	**3f** 66
4	**2c**	12	40	**5c** 57
4	**2f**	10	50	**5f** 70

[a] A mixture of the diketone **1** or enol ether **4** (1.0 equiv, 0.20 mmol), aryl bromide (4.0 equiv), $Pd(OAc)_2$ (0.05 equiv), Ph_3P (0.12 equiv), *i*-Pr_2NEt (4.0 equiv), and aqueous DMF were continuously irradiated for 10−12 min under nitrogen in a sealed Pyrex tube. >95% Purity by GC-MS.

Scheme 1



(16) (a) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (b) Mingos, D. M. P.; Whittaker, A. G. *Chemistry Under Extreme or Non-Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; John Wiley & Sons: New York, and Spektrum Akademischer Verlag: Heidelberg, 1997; p 479. (c) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233. (d) Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, 373. For microwave-assisted Pd-catalyzed coupling reactions see: (e) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219. (f) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582. (g) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583. (h) Díaz-Ortiz, A.; Prieto, P.; Vázquez. *Synlett* **1997**, 269. (i) Li, J.; Mau, A. W.-H.; Strauss, C. R. *J. Chem. Soc., Chem. Commun.* **1997**, 1275. (j) Wali, A.; Muthukumaru Pillai, S.; Satish, S. *React. Kinet. Catal. Lett.* **1997**, *60*, 189.

(17) The substantially shorter reaction times obtained under microwave heating is probably arising from rapid heating to high temperatures under pressurized conditions, rather than a result of a specific microwave effect. (a) Hájek, M. *Collect. Czech. Chem. Commun.* **1997**, *62*, 347. (b) Larhed, M., Ph.D. Thesis, Uppsala University, Oct. 1997. See also ref 14.

(18) Nonprotected enamines were recently reported to undergo intramolecular Heck reactions. Chen, C.-Y.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676.

(19) A β-elimination over carbon and oxygen from a α-hydroxy σ-complex, to give a carbonyl group and a palladium hydride, has been proposed in the catalytic cycle of the Wacker process. Bäckvall, J. E., Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

(20) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715.

(21) The electrostatic repulsion between the coplanar carbonyl dipoles has been suggested to be more important for the enolization of **1** than the stabilization of the enol form by hydrogen bonding. Hammond, G. S. *Steric effects in Organic Chemistry;* Newman, M. S., Ed.; John Wiley and Sons: New York 1956; p 450.

(22) For examples of isolated five-membered Pd(II) 1,2-diketonate complexes see: (a) Morita, H.; Sakurai, H.; Shimomura, S.; Kawaguchi, S. *Transition Met. Chem.* **1977**, *2*, 210. (b) Morita, H.; Shimomura, S.; Kawaguchi, S. *Bull. Chem. Soc., Jpn.* **1979**, *52*, 1838. (c) Greaves, S. J.; Griffith, W. P. *Polyhedron* **1988**, *7*, 1973. (d) Griffith, W. P.; Mostafa, S. I. *Polyhedron* **1992**, *11*, 2997.

(23) The pK_a value for 1,2-cyclohexanedione was determined to be 9.9 by the potentiometric method. This pK_a value was in good agreement with the literature value (10.3). 1,3-cyclohexanedione is a stronger acid ($pK_a = 5.3$). *Beil.* **7**, *E III*, 3209.

(24) To investigate if the reaction mixture was depleted of palladium catalyst, experiments were performed with higher concentration of precatalyst (10% $Pd(OAc)_2$ and 24% Ph_3P). No increase in the yields were detected. Furthermore, addition of $ZnCl_2$, $MgCl_2$, $MgBr_2$, and $NiCl_2$ did not improve the yields.

(25) We were aware of only one report on palladium-catalyzed intermolecular α-arylation of simple ketones while performing the synthetic work. (a) Hou, D.; Mas, J. L. U.S. Patent, 4992591, 1991. *Chem. Abstr.* **1991**, *115*, 28927z. After the completion of our laboratory work, four reports conducted under similar palladium-catalyzed conditions appeared in the literature. (b) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 6, 1740. (c) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (e) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. In the general methods for direct α-arylation (a, c, d, and e) the use of a strong base is obligatory.

nucleophiles, such as malonate or β-keto esters, is not facile. The presence of a cyano group[26] combined with strong bases, e.g. *t*-BuOK or NaH, is reported to be essential for successful reactions (Takahashi arylation).[27,28] Therefore, it seems less likely that **3** is derived from a direct halide displacement by an enolate anion.[25,29] Moreover, no arylated products were traced in reactions where NaH had been employed as base.

The formation of the arylated enol ethers **5** can be explained with an analogous reaction sequence as in Scheme 1. In this coupling, the C3-functionalized product **5** is probably liberated after isomerization via a palladium-enolate followed by syn-β-elimination.[20] Notably, the reaction conditions for arylation of both **1** and **4** are identical (except for the choice of ligand with the electron-deficient aryl bromides).

In conclusion, we propose that the palladium-catalyzed reaction of 1,2-cyclohexanedione with aryl bromides in aqueous DMF proceeds via Heck arylation of the enol form of the dione. The simple procedure, good functional group tolerance, and availability of the starting materials render the palladium-catalyzed arylation of 1,2-cyclohexanedione and 2-ethoxy-2-cyclohexenone valuable complements to other existing methods[6] for the preparation of 3-aryl-1,2-cyclohexanediones.

Experimental Section

General Methods. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded (in δ scale) at 400 MHz. ^{13}C NMR spectra were recorded at 100.4 MHz using ^{1}H-decoupled modes. Chemical shifts were indirectly referenced to TMS by the solvent signal ($CHCl_3$: 7.26 and $CDCl_3$: 77.0). Signal assignments were made from homonuclear and heteronuclear correlated spectra. Low resolution MS spectra (EI^+) were measured at an ionization potential of 70 eV. The mass detector was interfaced with a gas chromatograph equipped with a HP-1 (25 m × 0.20 mm) capillary column. High-resolution MS analyses (EI^+, mean value of three determinations) were performed by Mr E. Nilsson, Instrumentstationen, Kemicentrum, Lund, Sweden. Infrared spectra were recorded on a FTIR spectrophotometer. All palladium-catalyzed reactions were carried out in heavy-walled Pyrex tubes, sealed with a screw cap fitted with a Teflon gasket. The microwave treatment was performed with a MicroWell 10 single-mode cavity[30] from Labwell AB, SE-753 19 Uppsala, Sweden. The Pyrex tubes used in the microwave experiments (8 mL, l = 150 mm) were sealed with a silicon septum. It is not recommended to repeat these reactions in a multimode domestic microwave oven producing nonuniform irradiation.[16b] **Caution! It is important to note that when carrying out microwave-heated reactions in closed vessels it is possible to generate quite large pressures, and therefore it is imperative that an appropriate septum is utilized as a pressure relief device.** The pK_a of **1** was determined by an alkalimetric titration (KOH) with a computerized instrument.[31] TLC was carried out using precoated silica gel plates ($60F_{254}$ 80.2 mm, Merck) in 15−30% diethyl ether in isohexane, and the spots were detected with UV light. Column chromatography was carried out using silica gel (Merck G60) and gradient elution using diethyl ether and isohexane. The elemental analyses were performed by MikroKemi AB, Uppsala, Sweden.

Materials. 1,2-Cyclohexanedione (**1**) was obtained from Sigma, and palladium(II) acetate was purchased from Merck-Schuchardt. 2-Ethoxy-2-cyclohexenone (**4**) was prepared as described in this section but is also sold by Aldrich. Triphenylphosphine (Merck) was recrystallized from 95% ethanol, and diisopropylethylamine (Fluka) was stored over potassium hydroxide. All other reagents obtained from commercial sources were used without further purification. Products **3b**,[6d] **3f**,[6c,d,f] and **5f**[6e] have been synthesized and characterized by other authors.

General Procedure for the Preparation of 2-Hydroxy-3-aryl-2-cyclohexenones (3a−h). A mixture of **1** (1.0 mmol, 112 mg), aryl bromide (4.0 mmol), diisopropylethylamine (4.0 mmol, 515 mg), $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), Ph_3P (0.12 mmol, 31.5 mg), and water (0.75 mL) in DMF (4.25 mL) was degassed under a nitrogen flow for 5 min. The reaction mixture was stirred and heated at 100 °C for an appropriate time (see Table 1). The reaction mixture was allowed to cool and was poured into a saturated aqueous ammonium chloride solution. The aqueous layer was extracted with diethyl ether, and the combined organic phases were washed with saturated aqueous ammonium chloride, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified on a silica gel column to give pure **3a−h.**

The experiments with NaH as base were conducted as described above (but in absence of water).

2-Hydroxy-3-(3-methylphenyl)-2-cyclohexenone (3c). Yellow semisolid, 134 mg (66%). ^{1}H NMR ($CDCl_3$): 7.53 (s, 1H, Ar), 7.52 (d, J = 7.8 Hz, 1H, Ar), 7.29 (t, J = 7.8 Hz, 1H, Ar), 7.14 (d, J = 7.3 Hz, 1H, Ar), 6.71 (s, 1H, OH), 2.79 (t, J = 5.9 Hz, 2H, H-4), 2.63 (t, J = 6.6 Hz, 2H, H-6), 2.38 (s, 3H, Me), 2.15−2.09 (m, 2H, H-5). ^{13}C NMR ($CDCl_3$): 195.5, 143.4, 137.7, 137.0, 129.1, 128.7, 128.4, 128.1, 125.3, 35.8, 28.9, 22.6, 21.6. IR (CH_2Cl_2): 3417, 1665, 1626, 1374 cm^{-1}. MS *m*/*z* (% relative intensity): 202 (M^+, 100), 187 (71), 174 (23), 159 (13), 115 (22), 91 (17). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.2; H, 6.9. Found: C, 77.7; H, 7.1. HRMS calcd 202.0994. Found 202.0994.

Preparation of 2-Ethoxy-2-cyclohexenone (4). 1,2-Cyclohexanedione (40 mmol, 4.48 g), *p*-toluenesulfonic acid monohydrate (1.05 mmol, 200 mg), and 20 mL of 99.5% ethanol were dissolved in 120 mL of dry benzene in a 250-mL flask equipped with a Dean−Stark trap.[32] The reaction mixture was heated to boiling, and the azeotrope (benzene, ethanol and water) was removed for 16 h. The residual solution was washed with 10% aqueous sodium hydroxide which had been saturated with sodium chloride and water and was thereafter concentrated at reduced pressure. Column chromatography of the crude liquid yielded 2.36 g (42%) pure product.

General Procedure for the Preparation of 2-Ethoxy-3-aryl-2-cyclohexenones (5a−c,f,i−m). A mixture of **4** (0.20 mmol, 28.0 mg), aryl bromide (0.80 mmol), diisopropylethylamine (0.80 mmol, 103 mg), $Pd(OAc)_2$ (0.010 mmol, 2.24 mg), phosphine ligand (0.024 mmol, see Table 2), and water (0.15 mL) in DMF (0.85 mL) was degassed under a nitrogen flow for 5 min. The reaction mixture was stirred and heated at 100 °C for an appropriate time (see Table 2). The reaction mixture was allowed to cool and was poured into cold water. The aqueous layer was extracted with diethyl ether, and the combined organic phases were washed with water, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified on a silica gel column to give pure **5a−c,f,i−m.**

(26) See ref 1e, p 244.

(27) (a) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932. (b) Uno, M.; Seto, K.; Masuda, M.; Ueda, W.; Takahashi, S. *Tetrahedron Lett.* **1985**, *26*, 1553. (c) Sakamoto, T.; Katoh, E.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1664. (d) Sakamoto, T.; Kondo, Y.; Suginome, T.; Ohba, S.; Yamanaka, H. *Synthesis* **1992**, 552.

(28) Intermolecular arylations of soft carbon nucleophiles lacking cyano groups have been reported with aryl lead(IV) compounds, (a) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729, or with a copper(I) catalyst. (b) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606.

(29) For examples of Pd-catalyzed intramolecular arylations of enolate anions (from β-diketones or monoketones) see: (a) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4151. (b) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454. (c) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11. (d) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577. (e) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581.

(30) Stone-Elander, S. A.; Elander, N.; Thorell, J.-O.; Solås, G.; Svennebrink, J. *J. Label. Cmpds. Radiopharm.* **1994**, *10*, 949.

(31) The operation of this type of instrument for the determination of pK_a and log *P* has been described in detail. Avdeef, A. *Lipophilicity in Drug Action and Toxicology*; Pliska, V., Testa, B., van de Waterbeemd, H., Eds.; VCH: Weinheim, 1996; p 109.

(32) Gannon, W. F.; House, H. O. *Org. Synth.* **1960**, *40*, 41.

2-Ethoxy-3-(3-methylphenyl)-2-cyclohexenone (5c). Yellow oil, 38 mg (83%). ^{1}H NMR ($CDCl_3$): 7.34 (s, 1H, Ar), 7.33 (d, $J \approx 8$ Hz, 1H, Ar), 7.26 (t, $J = 7.5$ Hz, 1H, Ar), 7.14 (d, $J = 7.3$ Hz, 1H, Ar), 3.70 (q, $J = 6.8$ Hz, 2H, CH_2CH_3), 2.75 (t, $J = 5.9$ Hz, 2H, H-4), 2.56 (t, $J = 6.6$ Hz, 2H, H-6), 2.37 (s, 3H, Me), 2.08 (m, 2H, H-5), 1.10 (t, $J = 6.8$ Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): 196.1, 148.0, 144.4, 137.5, 129.2, 128.6, 128.0, 127.9, 125.1, 67.9, 38.7, 30.9, 22.6, 21.4, 15.4. IR (CH_2Cl_2): 2996, 2972, 1673, 1602, 1454 cm^{-1}. MS *m/z* (% relative intensity): 230 (M^+, 100), 215 (22), 201 (33), 187 (49), 171 (39), 131 (63), 115 (75), 91 (45). Anal. Calcd for $C_{15}H_{18}O_2 \cdot {}^1/_4\ H_2O$: C, 76.8; H, 7.9. Found: C, 76.9; H, 7.7. HRMS calcd 230.1307. Found 230.1306.

Cleavage of 5f and 5m To Provide 3f and 3m. To a solution of **5f** or **5m** (0.10 mmol) in dichloromethane (2.0 mL) was added boron tribromide (0.12 mmol, 0.12 mL 1.0 M solution in dichloromethane) dropwise during 5 min at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then kept in a refrigerator for 3 h at −12 °C. The reaction mixture was thereafter poured into cold saturated aqueous ammonium chloride and extracted with diethyl ether. The combined organic layer was washed with saturated aqueous ammonium chloride, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified on a silica gel column to give pure **3f** or **3m**.

Cleavage of compound **5f** gave 16 mg (84%) of pure isolated **3f** using the procedure described above.

2-Hydroxy-3-(4-(trifluoromethyl)phenyl)-2-cyclohexenone (3m). White solid, 23 mg (90%), mp = 109−111 °C. ^{1}H NMR ($CDCl_3$): 7.83 (d, $J = 8.3$ Hz, 2H, Ar), 7.64 (d, $J = 8.3$ Hz, 2H, Ar), 6.84 (s, 1H, OH), 2.80 (t, $J = 6.1$ Hz, 2H, H-4), 2.66 (t, $J = 6.8$ Hz, 2H, H-6), 2.15 (m, 2H, H-5). ^{13}C NMR ($CDCl_3$): 195.4, 144.1, 140.7, 129.7, 128.5, 125.9, 125.0, 35.7, 28.5, 22.5. IR (CH_2Cl_2): 3075, 1668, 1635, 1454 cm^{-1}. MS *m/z* (% relative intensity): 256 (M^+, 100), 228 (39), 187 (72), 159 (20), 151 (22). Anal. Calcd for $C_{13}H_{11}F_3O_2$: C, 60.9; H, 4.3. Found: C, 61.2; H, 4.5.

General Procedure for the Microwave-Assisted Preparation of 3c, 3f, 5c, and 5f. A mixture of **1** or **4** (0.20 mmol), aryl bromide (0.80 mmol), diisopropylethylamine (0.80 mmol, 103 mg), $Pd(OAc)_2$ (0.010 mmol, 2.24 mg), Ph_3P (0.024 mmol, 6.29 mg), and water (0.18 mL) in DMF (1.2 mL) was placed in a Pyrex tube and was degassed under a nitrogen flow for 5 min. The tube was sealed with a silicon septum, positioned in the MicroWell 10 microwave reactor, and the sample was irradiated with a suitable power for an appropriate time (see Table 3). The reaction mixture was allowed to cool for 5 min and was thereafter poured into cold saturated aqueous ammonium chloride. The aqueous layer was extracted with diethyl ether, and the combined organic phases were washed with saturated aqueous ammonium chloride, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The crude product was purified on a silica gel column as described earlier.

Acknowledgment. We thank the Swedish Natural Science Research Council for financial support. We also thank Dr. Nicholas Bonham for performing the pK_a determination and Dr. Adolf Gogoll for assistance in the NMR analyses.

Supporting Information Available: Characterization data for compounds **3a**,**b**, **3d**−**h**, **5a**,**b**, **5f**, and **5i**−**m** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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