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A One-Pot Isomerization−Arylation of 2,3-Epoxycyclohexanone under Controlled Microwave Heating

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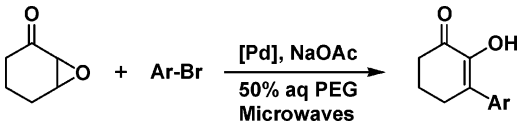

A fast one-pot method has been developed for the direct preparation of 3-aryl-1,2-cyclohexanediones from 2,3-epoxycyclohexanone via a microwave-assisted tandem epoxy ketone isomerization−Heck arylation reaction. The preparative microwave-assisted reactions were performed preferentially in 50% aqueous poly(ethylene glycol) utilizing sodium acetate as the base. Within 5−30 min of directed microwave heating, employing less than 0.05 mol % of palladium acetate and no phosphine ligand, up to 72% yield of C3-arylated diketones was isolated in an overall environmentally benign process. On the basis of the chemical reactivity of proposed intermediates, a reaction pathway is proposed where the acetate base promotes the rearrangement of the 2,3-epoxycyclohexanone into the active mono-enol form of 1,2-cyclohexanedione. An alternative classically heated procedure for isomerization−C3-arylation of 2,3-epoxycyclohexanone in DMF is also reported.

Introduction

The 1,2-cyclohexanedione moiety is known to primarily exist in the mono-enol form and constitutes a valuable and rigid hydrogen bond accepting/donating core structure for medicinal chemistry applications.[1−3] Because of structural similarities, this cyclic diketone functionality might also be regarded as a bioisostere of a weak carboxylic acid.[4] Furthermore, 1,2-cyclohexanedione derivatives are valuable starting materials in heterocyclic chemistry since several ring structures may be formed through double nucleophilic addition followed by dehydration.[5−8] C3-arylated 1,2-cyclohexanediones have also emerged as precursors to corresponding 3-arylcatechols via a smooth aromatization process.[9]

We have previously disclosed that 3-aryl-1,2-cyclohexanediones (**3**) can be synthesized directly from aryl bromides (**2**) and 1,2-cyclohexanedione (**4**) employing Pd(0) catalysis under Heck coupling conditions.[3,10] However, attempted vinylic substitution of the mono-enol form of 1,3-cyclohexanedione to produce the corresponding C2-arylated 1,3-diketone under mild basic conditions provided no product.[3,11] During initial testing, we suspected that the strong tendency for complexation between 1,3-cyclohexanedione and transition metal ions might inhibit the catalytic process by over-ligation of essential palladium species.[12] This led us to study the possibilities for successive in situ generation of 1,3-cyclohexanedione from 2,3-epoxycyclohexanone (**1**) utilizing Noyori's well-recognized Pd(0)-catalyzed epoxy ketone isomerization method,[13,14] followed by a subsequent Heck arylation[15−18] of the released 1,3-cyclohexanedione. Under these condi-

(1) Alterman, M.; Andersson, H. O.; Garg, N.; Ahlsen, G.; Loevgren, S.; Classon, B.; Danielson, U. H.; Kvarnstroem, I.; Vrang, L.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 3835−3844.
(2) Markgren, P.-O.; Schaal, W.; Haemaelaeinen, M.; Karlen, A.; Hallberg, A.; Samuelsson, B.; Danielson, U. H. *J. Med. Chem.* **2002**, *45*, 5430−5439.
(3) Garg, N.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 4158−4162.
(4) The pK_a value of 1,2-cyclohexanedione has been determined to 9.9 by a potentiometric method, see ref 3.
(5) Porter, A. E. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: New York, 1984; Vol. 3, pp 157−197.
(6) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873−4876.
(7) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453−1456.
(8) Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W. *Tetrahedron Lett.* **2003**, *44*, 1123−1127.
(9) Feigenbaum, A.; Pete, J. P.; Poquet-Dhimane, A. *Tetrahedron Lett.* **1988**, *29*, 73−74.
(10) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433−1445.
(11) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.
(12) Hall, B. J.; Brodbelt, J. S. *J. Am. Soc. Mass Spectrom.* **1999**, *10*, 402−413.
(13) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2095−2096.
(14) Suzuki, M.; Watanabe, A.; Noyori, R. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 230−236.

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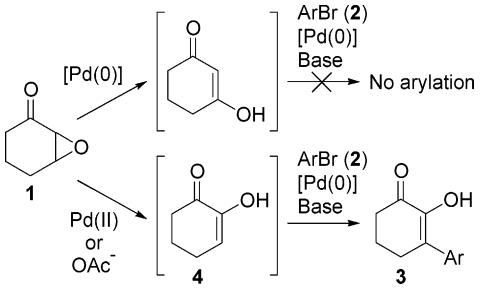
SCHEME 1



tions, the potentially chelating 1,3-diketone would be present only in small amounts during the course of the reaction, avoiding efficient trapping and deactivation of catalytic metal. To our surprise, starting from **1** and with an excess of bromobenzene (**2a**), only the isomeric 3-phenyl-1,2-cyclohexanedione (**3a**) was formed under the employed Heck conditions (Scheme 1). This finding encouraged us to investigate the synthetic value and the reaction route of this novel transformation.

Results

The isomerization−C3-arylation protocol initially employed for the **1** to **3** interconversion was similar to the earlier reported protocol for the Heck arylation[3] of 1,2-diketone **4**: 5.0 mol % of $Pd(OAc)_2$, 12.0 mol % of PPh_3 (triphenylphosphine), 1.0 equiv of **1**, 4.0 equiv of **2**, and 4.0 equiv of DIEA (diisopropylethylamine) in aqueous DMF. When applying these palladium(0) conditions with nonhindered electron-rich or neutral aryl bromides and classical oil bath heating at 100 °C for 17−41 h in sealed vessels, the resulting product mixture comprised predominantly C3-arylated **3** (Table 1, classical conditions). In fact, the DMF-based classical protocol enabled isolation of **3a**,**d**−**g**, in useful (45−72%) yields, although *p*-anisyl bromide (**2c**) delivered no arylated product whatsoever. Reacting electron-deficient aryl bromides led only to low (**3k**) or no yields and an extensive formation of dehalogenated arenes and biaryl side products. In this preparative attempt, as well as in the previously reported direct arylation of **4**, sterically hindered **2l**,**m** provided only very low yields (entries 12 and 13). Important from a mechanistic point of view, small amounts of intermediate **4** could be detected by GC-MS in most isomerization−arylation entries during the reaction progress. Overall, the yields of isolated **3** were comparable with the results previously obtained starting with pure **4**.[3] Attempts to substitute the aryl bromides for iodides or triflates under classical reaction conditions were unsuccessful. In the case of aryl triflates, no significant conversions took place, and with aryl iodides, a rapid conversion into biaryl structures immediately consumed the arylating agent.

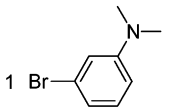
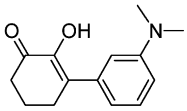
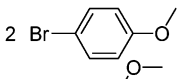
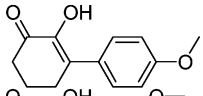
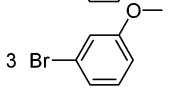
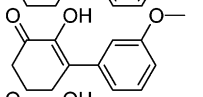
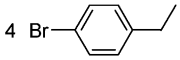
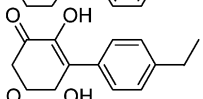
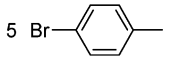
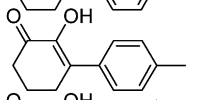
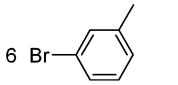
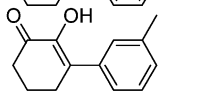
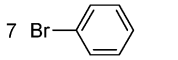
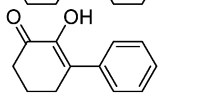
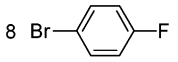
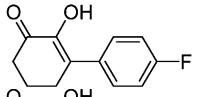
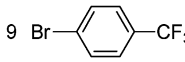
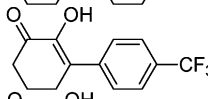
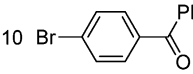
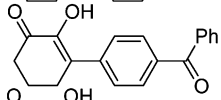
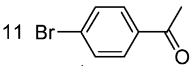
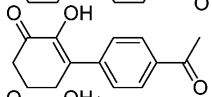
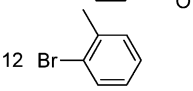
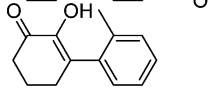
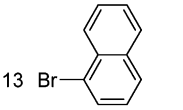
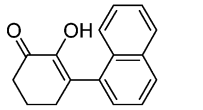
Since rapid single-mode microwave heating[19,20] to high temperatures is known to decomplex trapped palladium,[21] we decided to investigate this heating method under otherwise identical PPh_3-stabilized aqueous DMF conditions. Disappointingly, all attempts to carry out the isomerization−arylation reaction with **2f** at 150−180 °C with otherwise classical conditions resulted in low yields and problematic purification of **3a** due to aryl scrambling (p-Tol-Pd(PPh_3)$_2$X → Ph-Pd[P(p-Tol)Ph_2](PPh_3)X)[22−25] and accommodating problematic purifications.

A number of protocols for the utilization of aryl bromides in Heck couplings have recently been identified by using ligand-free reaction cocktails and only trace or homeopathic amounts of palladium.[26−30] From a preparative standpoint a phosphine-free catalyst is highly beneficial since aryl scrambling is avoided and triarylphosphines are difficult to remove.[31] Among available solvent alternatives, poly(ethylene glycol) (PEG) is known to promote Heck vinylation of various aryl bromides under phosphine-free conditions.[32] PEG has also been recognized as a particularly green solvent[33] and has been suggested to act as a phase transfer catalyst in Heck reactions with inorganic bases.[34] To invent a high-speed microwave promoted protocol for arylation of **1** allowing a low catalytic loading, aqueous poly(ethylene glycol) (PEG 200) was in initial experiments found to be a promising reaction medium.

We selected the rearrangement−arylation of **1** with **2a** using only 0.05 mol % of $Pd(OAc)_2$ and 20 min of microwave heating at 150 °C as an appropriate PEG model reaction for preparative optimization (Table 2). All reactions were performed in 1.0 mmol scale utilizing septum-sealed and microwave-transparent Pyrex vials. The highest yields of product **3a** resulted when 50% aqueous PEG 200 (entries 4 and 9−11) was used. It should also be noted that use of pure water or pure PEG afforded inefficient reactions. An additional advantage with aqueous PEG 200 concerned the convenient purification method. A rapid filtration of the cool reaction mixture through a short silica plug removed unreacted **2a** along with dehalogenated and homocoupled biaryl compounds, permitting pure **3a** to be separately eluated. The reaction showed good productivity with catalyst loadings as low as 0.05 mol %, although yields dropped

(15) De Meijere, A.; Meyer, F. E. *Angew. Chem.*, *Int. Ed. Engl.* **1994**, *33*, 2379−2411.
(16) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.
(17) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449−7476.
(18) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1133−1178.
(19) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.
(20) Kappe, C. O. *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 6250−6284.
(21) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727.
(22) Andersson, C. M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529−3536.
(23) Herrmann, W. A.; Brossmer, C.; Oefele, K.; Beller, M.; Fischer, H. *J. Organomet. Chem.* **1995**, *491*, C1−C4.
(24) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576−8581.
(25) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441−12453.
(26) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449−8452.
(27) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 7528−7531.
(28) de Vries, A. H. M.; Mulders, J.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285−3288.
(29) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559−1563.
(30) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2005**, *70*, 1786−1790.
(31) Lipshutz, B. H.; Frieman, B.; Birkedal, H. *Org. Lett.* **2004**, *6*, 2305−2308.
(32) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Reddy, N. R. *Org. Lett.* **2002**, *4*, 4399−4401.
(33) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195−218.
(34) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *C. R. Acad. Sci., Ser. II: Chem.* **1998**, *1*, 777−780.

TABLE 1. Rearrangement–Arylation of Expoxyketone 1 under Classical or Microwave Conditions

Entry	ArBr		Equiv of **2**	Conditions[a]	Temp (°C)	Heating Time[b]	Product		Isolated Yield (%)[c]
1		**2b**	4	Microwave	180	30 min		**3b**	71
2		**2c**	4 4	Classical Microwave	100 180	41 h 20 min		**3c**	0 58[d]
3		**2d**	4 2	Classical Microwave	100 150	41 h 20 min		**3d**	45 64
4		**2e**	4 1.5	Classical Microwave	100 150	17 h 20 min		**3e**	61 66
5		**2f**	4 1.5	Classical Microwave	100 150	17 h 20 min		**3f**	57 63
6		**2g**	4 1.5	Classical Microwave	100 150	17 h 20 min		**3g**	72 72
7		**2a**	4 1.5	Classical Microwave	100 150	17 h 20 min		**3a**	64 72
8		**2h**	4	Microwave	150	20 min		**3h**	60
9		**2i**	4	Microwave	150	20 min		**3i**	33
10		**2j**	4 4	Microwave Microwave	130 130	5 min 5 min		**3j**	10 19[e]
11		**2k**	4 4	Classical Microwave	100 130	17 h 5 min		**3k**	40 17
12		**2l**	4 10	Classical Microwave	100 180	17 h 10 min		**3l**	14 63
13		**2m**	4 10	Classical Microwave	100 180	17 h 10 min		**3m**	24 50

[a] Classical conditions: 1.0 mmol of **1**, 0.05 mmol of $Pd(OAc)_2$, 0.12 mmol of PPh_3, 4 mmol of **2**, 4 mmol of DIEA, 0.75 mL of water, and 4.25 mL of DMF in sealed vessels. Microwave conditions: 1.0 mmol of **1**, 20 μL of 25 mM $Pd(OAc)_2$ in MeCN (0.05 mol-% Pd), 1.5–10 mmol of **2**, 4 mmol of NaOAc, 3 mL of 50% aqueous PEG in sealed vessels. [b] Irradiation time for microwave heated reactions. The different ramp times were: rt → 130 °C = 40 s; rt → 150 °C and rt → 180 °C (75% H_2O) = 50 s; rt → 180 °C (50% H_2O) = 60 s. [c] 95% purity by GC-MS and ^1H NMR. [d] 75% aqueous PEG used as solvent. [e] Water:PEG:*t*-BuOH 2:1:1 used as solvent.

considerably upon further reduction in palladium concentration (Table 2, entry 8). All attempts to further accelerate the protocol by elevating the temperature above 150 °C reduced yields. Sodium acetate was found to be a highly suitable base, while DIEA afforded essentially no **3a** and the isolated compound was mixed with reduced 3-phenyl-2-cyclohexenone and small amounts of 3-phenyl-cyclohexanone.[35] The poor results with DIEA were unexpected when compared to the successful examples with aqueous DMF at 100 °C and classical oil bath heating (Table 1). A similar reduction obstacle in Heck arylations of α,β-unsaturated ketones was previously solved by addition of acetate anions to the reaction mixture.[36] The concomitant use of NaOAc and DIEA as a combined base pair under PEG-microwave conditions prevented the formation of saturated side products although the yield suffered to a moderate 25% (Table 2, entry 13). The addition of PPh_3 to the developed protocol afforded a less efficient reaction (entry 14), and was also experienced with use of classical conductive oil bath

(35) A set of different bases was screened. In short, under microwave conditions NaOAc was much superior also to K_2CO_3, $KHCO_3$, K_3PO_4, Na_2HPO_4, NaH_2PO_4, Et_3N, and triethanolamine. For α-arylation with strong bases, see: Culkin D, A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.

(36) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813–828.

TABLE 2. Rearrangement−Arylation of 1 with 2a under Various Microwave Conditions[a]

entry	$Pd(OAc)_2$ (mol %)	base	solvent	isolated yield (%)[b]
1	0.05	NaOAc	PEG	17
2	0.05	NaOAc	15% aq PEG	67
3	0.05	NaOAc	25% aq PEG	66
4	0.05	NaOAc	50% aq PEG	72
5	0.05	NaOAc	75% aq PEG	46
6	0.05	NaOAc	90% aq PEG	22
7	0.05	NaOAc	Water	8
8	0.02	NaOAc	50% aq PEG	23[c]
9	0.10	NaOAc	50% aq PEG	67
10	0.20	NaOAc	50% aq PEG	70
11	0.5	NaOAc	50% aq PEG	80
12	0.05	DIEA	50% aq PEG	<3[c,d]
13	0.05	NaOAc DIEA	50% aq PEG	25
14	0.05	NaOAc	50% aq PEG	33[e]
15	0.05	NaOAc	50% aq PEG	52[c,f]

[a] Septum-sealed vessel loaded with the following: 1.0 mmol of **1**, $Pd(OAc)_2$ in 20 μL of MeCN, 1.5 mmol of **2a**, 4 mmol of base, 3 mL of reaction medium. Heating at 150 °C for 20 min under N_2. [b] >95% purity by GC-MS. [c] <95% conversion of **1** and **4** by GC-MS. [d] Isolated **3a** below purity standards. [e] 0.10 mol % of PPh_3 added. [f] Oil bath heating employed.

heating (entry 15).[21] In conclusion, the conditions in entry 4 (Table 2) utilizing 0.05 mol % of $Pd(OAc)_2$ and 50% aq PEG were selected as our standard microwave protocol because of the high catalytic efficiency (turn-over frequency = 4320 h^{-1}), despite the fact that an increased concentration of $Pd(OAc)_2$ afforded slightly higher yields (entry 11).

We next decided to probe the substrate scope of the selected low catalyst protocol (microwave conditions, Table 1). Fine-tuning of the microwave heating protocol resulted in higher yields in the tandem isomerization−arylation reaction of **1** as compared with the classical protocol. This was true in all cases except entry 11. It should also be noted that an excess of **2** and a higher reaction temperature were required with more sluggish ortho-substituted substrates (Table 1, entries 12 and 13). Use of electron-rich **2b** resulted in improved yields and a general reduction in reaction time while the electron-deficient arylating agents generally produced lower yields (entries 8−11). In a number of reactions, intermediate **4** was again clearly identified before continued heating converted the diketone into product **3**. To our great dissatisfaction, all other investigated 2,3-epoxyketones were not found to react accordingly,[37] thereby limiting the generality of the presented isomerization−arylation method.

The most abundant byproducts included the corresponding dehalogenated arenes and symmetrical biaryls of **2**. The major reason for the somewhat moderate isolated yields was, however, connected to thermal degradation of **1** and/or **4**, plus oxidation/aromatization of **3** to form 3-hydroxybiaryls.[38] Electronically neutral and electron-rich **2a**,**d**−**g** tended to also promote a second arylation to produce the 3,6-diarylated products in minor amounts at temperatures above 150 °C. The formation of diarylated products was enhanced not only by high temperature, but also by high water concentration and a large excess of **2**.[39] Importantly, the microwave reactions presented in Table 1 afforded less than 1% of diarylated compound. Since α-arylation also took place when **1** was replaced by cyclohexanone or acetophenone at 180 °C furnishing 7% and 13% yields of each monoarylated product, this reaction must be assumed to be general for standard mono-ketones with weakly basic NaOAc.[35]

By using the microwave protocol, aryl iodides could be utilized as arylating agents; however, there was a pronounced difference in the reaction outcome compared with more productive aryl bromides. Despite the use of identical conditions with 1.0 equiv of **1**, 0.05 mol % of $Pd(OAc)_2$, 4 equiv of aryl iodide, and 4 equiv of NaOAc in 50% aqueous PEG 200 at 150 °C for 20 min, the highest isolated yields acquired were in the synthesis of **3a** and **3f** (29% and 31%, respectively). Incomplete conversions and homocoupling plagued the reactions. This result was not expected since aryl iodides undergo oxidative addition faster than the corresponding bromides, although it has been suggested that the reactivity and stoichiometry of the oxidative addition products of aryl bromides and aryl iodides are substantially different.[15−18,40] To further investigate this finding, a competitive reaction following the general microwave procedure (150 °C, 20 min) was accomplished, using 4 equiv each of *m*-tolyl bromide (**2g**) and phenyl iodide. GC-MS and ^1H NMR analysis showed an incomplete conversion of **1** and that phenyl-substituted **3a** (19%) was the only product, suggesting an efficient trapping of available Pd(0) by the phenyl iodide followed by an inefficient insertion of the generated Ph−Pd−I complex into the enol double bond of intermediate **4**. Utilization of aryl triflates with the microwave protocol afforded low conversion and no arylation, favoring competing phenol formation by oxidation of **4**. Aryl chlorides delivered no product **3** under these conditions.

Discussion

We propose that the general reaction pathway depicted in the lower part of Scheme 1 for the one-pot **1** to **3** transformation takes place in both DMF (classical conditions) and PEG (microwave conditions). After the essential formation of enol **4**, a subsequent Heck C3-arylation takes place, exploiting a Pd(0) catalytic system generated by reduction of $Pd(OAc)_2$.[18] To further understand the complete reaction route, we decided to next investigate the intriguing rearrangement process under both reaction conditions.

Classical Conditions. When control reactions were carried out with metal block heating at 100 °C for 17 h in 15% aqueous DMF excluding both **2** and $Pd(OAc)_2$, **1** was only partly converted to **4** even though PPh_3 (0.12

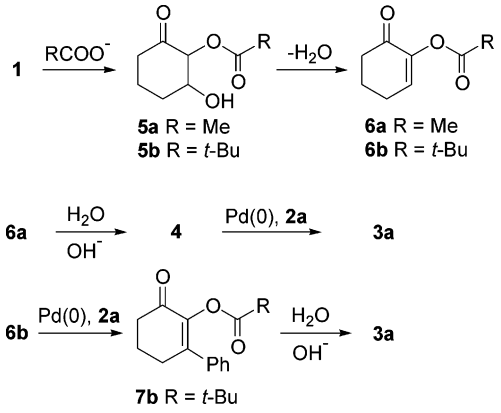
(37) The following compounds have been tested: 2,3-epoxy-4,4-dimethylcyclohexenone, 2,3-epoxycyclopentanone, chalconoxide, and benzalacetoneoxide.

(38) Typically, several byproducts assigned to be aliphatic ketones according to observed ^{13}C NMR peaks could be released with ether from the flash silica column after elution of **3** (corresponding to 10−40% of utilized **1**).

(39) To determine the structure of the byproduct, the Heck reaction was performed, using an excess of **2a** with 3 h of microwave heating at 180 °C. Not more than 12% of the 3,6-diarylated product could be isolated.

(40) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135.

SCHEME 2



equiv) and/or DIEA (4 equiv) was present. Furthermore, use of either 5 mol % of $Pd(OAc)_2$ or 5 mol % of $PdCl_2$ in the reaction mixture resulted in epoxide conversion to mainly **4** and partially to phenol. No traces of 1,3-cyclohexanedione were found in any of the above-mentioned cases, but interestingly, by exclusion of base and by replacing $Pd(OAc)_2$ with the Pd(0) catalyst $Pd(PPh_3)_4$, 1,3-cyclohexanedione was cleanly formed.[13] In short, we hold Pd(II) to be the most active reagent responsible for the **1** to **4** rearrangement under classical conditions.[41]

Microwave Conditions. After exclusion of **2** and $Pd(OAc)_2$ from otherwise unmodified 50% aqueous PEG reaction mixtures (Table 1), attempted test reactions with microwave heating at 150 °C for 20 min resulted in clean conversion of **1** into **4**. Replacement of NaOAc with the stronger base DIEA resulted neither in the consumption of **1** nor in the formation of **4**. Thus, there were reasons to believe that the acetate played a different role in the isomerization than simply by acting as a Brönstedt base. By replacing $Pd(OAc)_2$ with the Pd(0) complex $Pd(PPh_3)_4$, 1,3-cyclohexanedione could be cleanly formed when no acetate base was added. The information obtained above strongly indicated that isomerization in the path leading to **4** was much faster in the studied Heck-type environment than in the competing Pd(0)-catalyzed rearrangement to the 1,3-diketone product. Moreover, acetate ions appeared crucial for generation of the 1,2-diketone.[38]

To understand the mechanism of isomerization of **1** to **4**, attempts were made to detect key intermediates formed in the PEG-NaOAc reaction medium at room temperature or upon gentle heating (up to 80 °C). Formation of **4** readily took place in all cases, although none of the expected intermediates could be detected. To create a more sluggish model system and to enhance the possibility to gain further information, we decided to employ the sterically bulky pivaloate functionality as an acetate substitute. For unambiguous identification, the suggested intermediates **5b**, **6a**, and **6b** were first synthesized and purified.

Under gentle warming of **1** with sodium pivaloate in aqueous PEG, *trans*-**5b** could quickly be detected in solution by GC-MS (Scheme 2). After a considerable amount of *trans*-**5b** had built up, the epimer *cis*-**5b** and the corresponding elimination product **6b** were formed.

A series of arylation experiments were later performed under microwave conditions at 150 °C with bromobenzene (**2a**) as the arylpalladium precursor, using both of the carboxylate bases and a number of preolefins as substrates (Table 3). Thus, replacement of NaOAc for sodium pivaloate in the preparative arylation of **1** with **2a** furnished a complex product mixture and low yield of **3a** (13%, entry 1). This result indicated that the pivaloate anion to some extent might act as an acetate surrogate, enabling ring-opening, enol generation, and final Heck arylation, although all examples proceeding through pivaloate intermediates occurred more sluggish and with extensive phenol formation compared to analogous acetate promoted reactions (Table 3). As expected, the direct arylation of cyclohexanedione **4** in entry 2 provided a cleaner process, allowing the isolation of **3a** in 54% yield. We believe that thermal decomposition of **4** explains the lower yield compared to the corresponding reaction with **1**.[3] Alcohol *trans*-**5b** is thought to act as the pivaloate analogue to reactive **5a** in the reaction cascade and its use afforded both C3-phenylated nonhydrolyzed **7b** and enol product **3a**, regardless of the choice of carboxylate salt (Table 3, entries 3 and 4). Rewardingly, arylation of pivaloate olefin **6b** under otherwise general PEG conditions gave an almost identical product outcome (45% **3a** and 22% **7b**) as observed with *trans*-**5b**. The acetate analogue **6a** provided product **3a** in 23% yield without any traces of a potential intermediate **7a** (entry 5). It is intresting to note the product difference between the arylation of acetate ester **6a** and the artificial pivaloate substrates *trans*-**5b** and **6b**. With **6a**, the absence of detected intermediate **7a** supports a rapid hydrolysis and a subsequent arylation of free **4**. In contrast, the more stable vinyl carboxylate **6b** must be recognized as a true Heck vinyl substrate (Scheme 2).

TABLE 3. Arylation of Structure 1, 4, 5b, 6a, and 6b with 2a under Various Microwave Conditions[a]

entry	substrate	equiv of **2a**	base	isolated yield (%)[b] **3a**	**7b**
1	**1**	4	NaOCO-*t*-Bu	13	0
2	**4**	1.5	NaOAc	54	
3	*trans*-**5b**[c]	4	NaOAc	45	25
4	*trans*-**5b**[c]	4	NaOCO-*t*-Bu	45	13
5	**6a**[c]	1.5	NaOAc	23	
6	**6b**[c]	4	NaOAc	45	22

[a] Septum-sealed vessel loaded with the following: 1.0 mmol of **1**, **4**, **5b**, **6a**, or **6b**, 0.05 mol % of $Pd(OAc)_2$, 1.5 or 4.0 mmol of **2a**, 4 mmol of base, and 3 mL of 50% aqueous PEG. Reactions were heated at 150 °C for 20 min. [b] >95% purity by GC-MS. [c] For synthesis of **5b**, **6a**, and **6b**, see the Supporting Information.

We interpret the results obtained accordingly: Under preparative microwave conditions with NaOAc, the assumed isomerization of **1** is suggested to be initiated by the nucleophilic addition of acetate to the α-carbonyl forming the short-lived cis/trans-adduct **5a**, followed by base-promoted elimination to 2-acetoxycyclohex-2-enone (**6a**, Scheme 2). Structure **6a** thereafter undergoes cleavage of the ester to produce intermediate **4**, followed by the Pd(0)-catalyzed Heck arylation step to produce product **3** (Scheme 2).[42]

(41) Base-mediated isomerization of α,β-epoxyketones has been described but is suggested to be of minor importance in this case, see: House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428−2433.

(42) Treatment of **3a** under microwave Heck conditions with sodium pivaloate in place of NaOAc did not yield **7b**, ruling out the possibility that **7b** may be formed through transesterification.

Conclusion

In summary, arylation of 2,3-epoxycyclohexanone (**1**) under Heck reaction conditions produces C3-arylated 1,2-cyclohexanediones **3** in moderate to high yields. The epoxy ketone first undergoes $Pd(OAc)_2$- or NaOAc-induced rearrangement to provide the intermediate 1,2-cyclohexanedione (**4**), which subsequently reacts as the olefinic counterpart in a palladium(0)-catalyzed Heck arylation reaction, exchanging the enolic C3-hydrogen for an aryl group. With regard to the use of controlled microwave heating and aqueous PEG 200 as the reaction medium, this combination reduces reaction time from hours to minutes, expands the substrate scope of the reaction, and allows the use of only 0.05 mol % of $Pd(OAc)_2$ in the absence of normally essential phosphine ligands.

The complicated pathway for the transformation of **1** into products **3** should not be perceived as an obstacle from a preparative point of view. Instead, we would like to emphasize the great convenience of this one-pot, multistep protocol, enabling a unique and environmentally benign opportunity for transformation of the easily accessible 2,3-epoxycyclohexanone into various 3-aryl-1,2-cyclohexanedione derivatives.

Experimental Section

General Procedure for Rearrangement−Arylation of 1 with Classical Conditions (Table 1). The following chemicals were added to a thin-necked Pyrex tube: $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), PPh_3 (0.12 mmol, 31.5 mg), aryl bromide **2** (4 mmol), DIEA (4 mmol, 0.68 mL), DMF (4.25 mL), water (0.75 mL), and epoxyketone **1** (112 mg, 1 mmol). The mixture was flushed with N_2 and sealed with a screw-cap. The contents were thereafter magnetically stirred and heated on an oil bath at 100 °C for 17 h or until full conversion was achieved. The reaction was extracted with ether and dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The crude product was purified by column chromatography (ether/isohexane) to give the pure product **3**.

General Procedure for Rearrangement−Arylation of 1 with Microwave Conditions (Table 1). The following chemicals were added to a 5-mL process vial: NaOAc (4 mmol, 0.33 g), $Pd(OAc)_2$ (0.0005 mmol, 20 μL of 25 mM stock solution in acetonitrile), aryl halide **2** (according to Table 1), PEG 200 (1.5 mL), water (1.5 mL), and epoxyketone **1** (1 mmol, 112 mg). The mixture was flushed with N_2 and sealed with a septum. The contents were thereafter magnetically stirred and microwave heated at a specified temperature for an appropriate time (see Table 1). The reaction mixture was applied to a dry packed silica gel column and nonpolar matter was rinsed out by passing isohexane or 3% ether in isohexane (**3b**, **3c**, **3m**) through the column, using reduced pressure. Compound **3** was eluted from the column by passing 20−50% ether in isohexane through the column at reduced pressure.

3-(4-Fluorophenyl)-2-hydroxy-2-cyclohexenone (3h). White crystalline solid, 60% yield (124 mg, 0.60 mmol, >95% by GC-MS), mp 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 8.9 Hz, J_{FH} = 5.5 Hz, 2H), 6.99 (m, 2H), 6.77 (s, 1H), 2.67 (t, J = 6.1 Hz, 2H), 2.53 (t, J = 6.6 Hz, 2H), 2.02 (dt, J = 6.6, 6.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 162.6 (d, J_{FC} = 249.0 Hz), 143.7 (d, J_{FC} = 1.5 Hz), 133.4 (d, J_{FC} = 3.5 Hz), 130.5 (d, J_{FC} = 8.1 Hz), 127.0, 115.4, 36.0, 29.0, 22.8. IR (KBr) 3378, 1664 cm^{-1}. MS *m/z* (rel intensity 70 eV) 206 (M^+, 100), 178 (21), 109 (10). Anal. Calcd for $C_{12}H_{11}FO_2$: C, 69.89; H, 5.38. Found: C, 69.79; H, 5.32.

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

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