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A Novel Palladium-Catalyzed Arylation–Dehydroaromatization Reaction: Synthesis of 7-Aryltetralones

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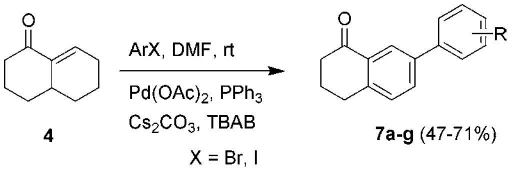
ABSTRACT



A new one-pot room-temperature palladium-catalyzed synthesis of 7-aryltetralones was discovered. This tandem process includes a palladium-catalyzed γ-selective arylation of the enone 4 followed by a dehydrogenation-aromatization of the initial cross-coupling product.

The palladium-catalyzed α-arylation of ketones and ester derivatives has greatly expanded the repertoire of useful methods in organic chemistry.[1,2] Key parameters for this transformation include the use of sterically hindered and electron-rich phosphine ligands and a suitable solvent. Important recent discoveries in this regard were made by the Buchwald[3] and Hartwig groups.[4] The arylation can be run with the carbonyl compound directly in the presence of a base. Alternatively, preformed enolates such as trialkylsilyl enol ethers can be arylated in the presence of ZnF_2 or $Zn(OtBu)_2$ as addititives.[4] Thus, the potential applications seem countless.

In the context of the synthesis of functionalized decalin derivatives, we became interested in the arylation of enone systems of type **A** (Figure 1). Besides possible regioisomers, for each pathway stereoisomers (*cis*/*trans*) might form.

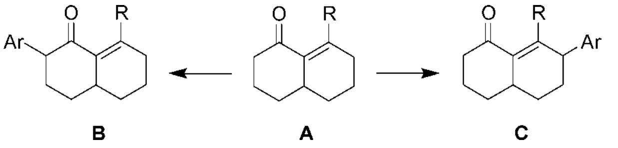


Figure 1. Issues of regio- and stereochemistry in the potential palladium-catalyzed arylation of 3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalenone derivatives **A**.

The parent substrate, enone **4**, was prepared essentially according to the literature by the copper-catalyzed 1,4-addition of 2-(3-bromopropyl)-1,3-dioxolane[5] (**2**) followed by acid-induced deprotection−cyclization of the ketoacetal **3** (Scheme 1).[6,7]

Initially, we examined the regioselective formation of the two possible triisopropylsilyl dienol ethers. Although the selective formation of the unwanted isomer **6** is possible under various conditions, the best ratio in favor of the dienol derivative **5** was 68:32. The enone **4** was also subjected to modified Kharasch conditions [(a) MeMgBr, $FeCl_3$; (b) TMSCl, Et_3N, HMPA, 23 °C, 2 h] resulting in the exclusive formation of the trimethylsilyl dienol ether corresponding

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(1) For a review, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245.

(2) For a review about coupling reactions of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem.* **2002**, *114*, 4350−4386; *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

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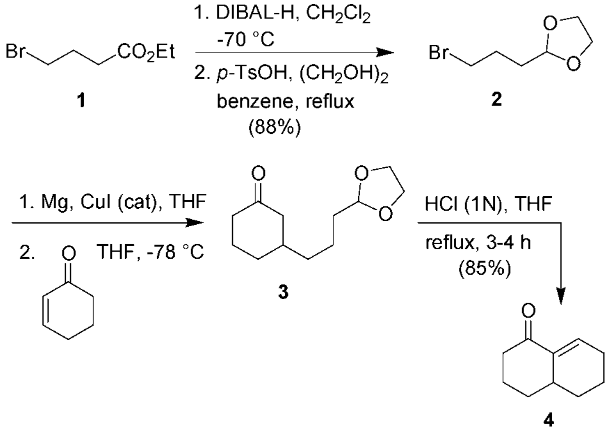
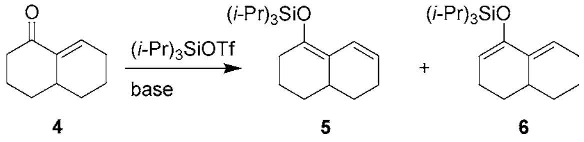
Scheme 1. Synthesis of Enone **4**



to **6**. These conditions are known to produce the thermodynamic dienol ether from a cyclic enone.[8] However, the trimethylsilyl derivative was not obtained very pure and proved to be somewhat unstable. Although the mixture of the two dienol ethers **5** and **6** could not be separated by chromatography, their structures could be assigned by comparison of the chemical shifts of the vinylic protons with corresponding signals of similar compounds.[9] Thus, the vinylic protons of **6** appear at $\delta = 4.92$ and 5.96 ppm, whereas the two vinylic protons of **5** resonate at $\delta = 5.53$ and 6.50 ppm. The latter is a doublet ($J = 9.8$ Hz), which clearly supports the assignment.

Table 1. Regioselectivity in the Formation of the Silyl Dienol Ethers **5** and **6**

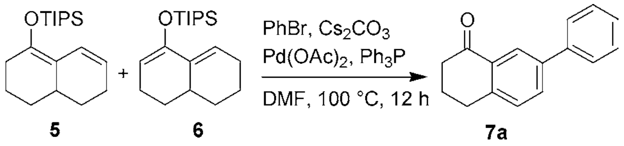


entry	conditions	ratio **5**: **6**[a]	yield of **5** + **6** (%)
1	2,6-lutidine, CH_2Cl_2, −20 °C, 1 h	0:100	95
2	2,6-diisopropyl-*N*,*N*-dimethylaniline, CH_2Cl_2, −20 °C, 24 h	0:100	96
3	Cy_2NEt, CH_2Cl_2, −78 °C, 2 h	30:70	89
4	$KN(SiMe_3)_2$, THF/DMF (1:1), −78 °C, 24 h	50:50	82
5	*i*-Pr_2EtN, CH_2Cl_2, −20 °C, 24 h	58:42	95
6	*i*-Pr_2EtN, CH_2Cl_2, −78 °C, 24 h	68:32	98

[a] The ratio **5**/**6** was determined by ^{1}H NMR spectroscopy.

We then asked ourselves whether the regiochemistry of the dienol ethers would be transformed to the corresponding arylated derivatives in a Buchwald−Hartwig arylation. Thus, dienol **6** ether was subjected to a palladium-catalyzed arylation reaction with bromobenzene in the presence of $Pd(OAc)_2$, Ph_3P, and Cs_2CO_3 as additive (Scheme 2).

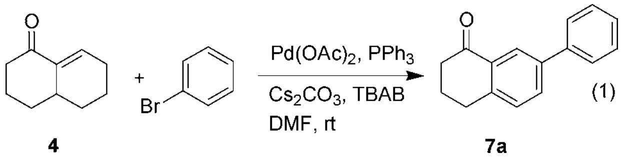
Scheme 2. Arylation of Silyl Dienol Ether **6** and a Mixture of **5** and **6**



5 : 6	yield of **7a** [%]
0 : 100	42
68 : 32	45

Suprisingly, the only product that we could isolate was the 7-phenyltetralone **7a**. There were no Heck-type products[10,11] and no α-arylated products detectable in the reaction mixture. If the reaction was run on a mixture of **5** and **6** (**5**:**6** = 68:32), the same compound **7a** was isolated as the only product.

Since it was described earlier that α,β-unsaturated ketones could be directly arylated in the γ-position with bromoarenes and $Pd(OAc)_2/PPh_3$ in DMF/Cs_2CO_3 at 60−120 °C,[12] we applied these conditions directly to enone **4**. Treatment of enone **4** with bromobenzene under these conditions afforded as well the unexpected biaryl derivative **7a** in 32−45% yield (eq 1). The normal γ-arylation product could not be detected by LC-MS after reaction workup.



(1)

Next, we tried to optimize this reaction by varying additives, solvent, and phosphine ligands. As described in the literature, certain tetraalkylammonium salts can positively affect palladium-catalyzed Heck-type reactions.[13] It was found that addition of 1 equiv of tetrabutylammonium bromide (TBAB) to the reaction mixture dramatically increased the yield of the reaction, resulting in 71% yield of 7-phenyltetralone (Table 2, entry 3). In addition, heating of the mixture was not necessary. These optimization studies were followed by LC-MS using 10 mol % of biphenyl as an internal standard. Regarding the solvent, DMF gave the best yield (entry 3), followed by NMP (70%, entry 6). Among various ligands that were tried, triphenylphosphine was found

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(10) For the Heck reaction of dienol ethers, see: Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett.* **2003**, *5*, 3815−3817.

(11) For a recent review about the Heck reaction, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

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Table 2. Effect of Trialkylammonium Salts, Solvents, and Phosphine Ligands on the Reaction of Enone **4** with Bromobenzene

entry	key variables	yield of **7a** [%][d]
1[a]	no PTC, 120 °C	45
2[a]	Bu_4NBr, 60 °C	20
3[a]	Bu_4NBr, 23 °C	71
4[a]	Bu_4NOAc, 23 °C	7
5[a]	Bu_4NClO_4, 23 °C	48
6[b]	NMP	70
7[b]	dimethylacetamide	67
8[c]	$t\mathrm{Bu}_3\mathrm{P}$	tr
9[c]	$(o\text{-tolyl})_3\mathrm{P}$	27
10[c]	$(\mathrm{furyl})_3\mathrm{P}$	0
11[c]	dppf	10

[a] Reaction conditions: DMF, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), additive (1 equiv). [b] Reaction conditions: solvent, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), TBAB (1 equiv), 3 d, 23 °C. [c] Reaction conditions: DMF, $Pd(OAc)_2$ (5 mol %), phosphine (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), TBAB (1 equiv), 3 d, 23 °C. [d] Isolated yields.

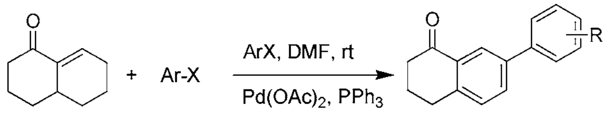
to be the best one (entry 3). In the absence of a phosphine ligand the reaction does not take place at all. Electron-donating and hindered phosphines (t-Bu_3P, entry 8; $furyl_3P$, entry 10) seemingly decrease the rate of the aromatization step. With these ligands, mixtures of bi- and triarylated products were detected by LC-MS.

Again, the reaction is highly γ-selective, and no α-arylated products were detected. Actually, the putative product of the normal γ-arylation was detected by LC-MS $\{[M]^+(\mathbf{7a}) + 4\}$ at the beginning of the reaction. Furthermore, in some cases intermediates with $\{[M]^+(\mathbf{7a}) + 2\}$ were detected. The rate of the dehydrogenation-aromatization is very high, and only the aromatic product was detected at the end of the reaction. With 1 equiv of bromobenzene, the reaction does give **7a** as well, but conversion and yield were lower.

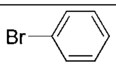
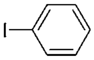
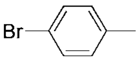
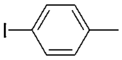
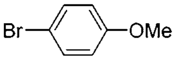
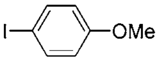
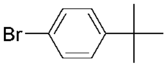
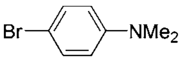
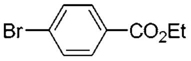
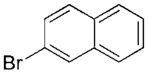
We assume that the reaction proceeds via γ-arylation of the dienolate anion, followed by a fast dehydrogenation/aromatization of the intermediate in a tandem process. Most likely the aromatization is initiated by insertion of a PdL_2 species into an activated C−H bond, followed by the elimination of PdL_2H_2. In essence, a reversal of classical hydrogenation steps must take place. Addition of some electron donors or hydrogen donors (HCO_2H, cyclohexadiene, CuBr) that could be sacrificed did not allow us to isolate nonaromatized intermediates. Addition of other reagents (styrene, methyl acrylate, benzoquinone) that might speed the aromatization step only decreased the yield of **7a**. In the absence of bromobenzene or in the presence of chlorobenzene only products of self-condensation of enone **4** were detected.

Using the optimized conditions we coupled a number of haloarenes with the enone **4**. As it turned out, the reaction has broad scope, at least for enone **4**, and both aryl bromides and iodides could be coupled in moderate to good yields (Table 3). The 7-aryltetralones show a characteristic peak in the ^{1}H NMR spectrum in the range between $\delta = 8.16-8.33$ ppm, which can be attributed to the isolated proton at C-8.

Table 3. Synthesis of 7-Aryltetralones **7a**−**g**



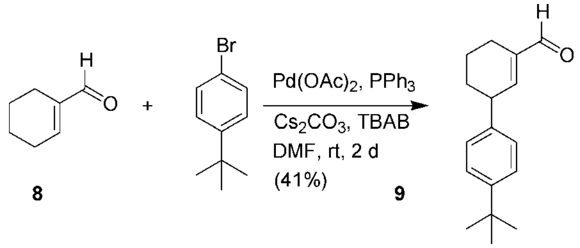
4 **7a-g** (47-71%)

entry[a]	Ar-X	product	isolated yield [%]
1		**7a**	71
2		**7a**	68
3		**7b**	51
4		**7b**	54
5		**7c**	62
6		**7c**	55
7		**7d**	59
8		**7e**	47
9		**7f**	48
10		**7g**	50

[a] Reaction conditions: DMF, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), TBAB (1 equiv), 23 °C.

7-Aryltetralones have been used, for example, in the synthesis of CCR5 antagonists as anti-HIV-1 agents.[14] These aryltetralones were prepared in a multistep sequence consisting of an intramolecular Friedel−Crafts cyclization of the corresponding phenylbutyric acids followed by palladium-catalyzed Suzuki coupling with arylboronic acids. As a whole only a few examples of 7-aryltetralones **7** are described in the literature.[15]

In a control experiment we applied the optimized conditions to the coupling of 1-cyclohexene-1-carbaldehyde and 1-bromo-4-*tert*-butylbenzene (eq 2). Somewhat surprisingly, we isolated not the expected biphenyl-3-carbaldehyde but rather the normal γ-arylation product (41% yield). Charac-



(2)

teristic for this compound is a signal at $\delta = 6.79$ ppm for the terminal enal H. The γ-H resonates at $\delta = 3.62$ ppm. Related compounds are prepared by multistep sequences.[16]

To summarize, we developed a new convenient synthesis of 7-aryltetralones by a novel room-temperature palladium-catalyzed arylation dehydroaromatization sequence. This strategy of applying the arylation/aromatization to a cyclic precursor containing one double bond and an electron-withdrawing group might be a valuable option for accessing certain biaryl compounds. Further studies that are underway in our laboratory should help to elucidate the structural requirements and the experimental ancillary conditions.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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