ACS Catalysis

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Microwave-Assisted Palladium(II)-Catalyzed Synthesis of Aryl Ketones from Aryl Sulfinates and Direct ESI-MS Studies Thereof

Malte Behrends,[†] Jonas Sävmarker,[†] Per J. R. Sjöberg,[‡] and Mats Larhed[†,*]

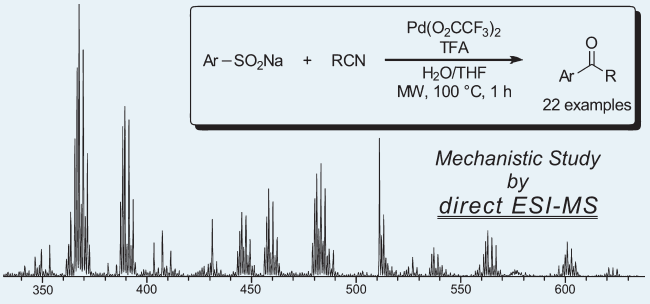
[†]Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden

[‡]Department of Physical and Analytical Chemistry, Uppsala University, BMC, Box-599, SE-751 23, Uppsala, Sweden

Supporting Information

ABSTRACT: A fast palladium(II)-catalyzed and microwave-promoted procedure using 6-methyl-2,2′-bipyridyl as ligand to synthesize aryl ketones from aryl sulfinates and nitriles is described. More importantly, the first detailed investigation of the reaction mechanism using direct ESI-MS studies is reported.

KEYWORDS: palladium, catalysis, desulfination, aryl sulfinates, aryl ketones, nitriles, ESI-MS, microwave



The ketone moiety is a common functional group that is found in a wide range of organic molecules; for example, in natural products and pharmaceuticals. There are numerous methods of producing ketones, and one class of reactions proceeds through the insertion of an arylpalladium species into a polar multiple bond, such as a nitrile. This methodology was first reported in the 1970s,[1] but it did not receive much attention until Larock's group reported the first catalytic palladium methodology.[2−4] Initially, the arylpalladium complexes were generated from an aryl halide by Pd(0) catalysis, but further development led to Pd(II)-catalyzed C−H activations and arylboronic acid addition protocols.[5−8]

In an attempt to develop a mild and less expensive method, we identified benzoic acids as useful aryl-palladium precursors for ketone synthesis,[9] but with the drawback of requiring an activating ortho substituent to react.[10] DFT calculations in our group indicated that aryl sulfinic acids and their salts would not require ortho substituents to generate the arylpalladium complex, which could further react with a nitrile (Scheme 1). Furthermore, sulfinic acids have been employed in Heck-type coupling reactions in the past,[1,11−13] but they have only seldomly been used as an arene source for desulfinative coupling reactions.[14−16] Although the sulfinic acid/sulfinate functionality is not that common, it is easily accessible by reduction of the corresponding aryl sulfonyl chloride.[17,18]

We recently presented our first results of this study at a conference,[19] and while preparing this manuscript, reports have been published describing similar desulfinative ketone synthesis.[20,21] This prompted us to present our own related results using 6-methyl-2,2′-bipyridyl as the ligand of choice. We report herein: (1) a microwave-promoted method for aryl ketone formation from aryl sulfinates using the nitrile in excess;[19] (2) the use of microwave heating to reduce reaction time to 1 h, as compared with 6−20 h under conventional heating;[20,21] and (3) the first mechanistic study of this reaction using direct ESI-MS analysis of ongoing reactions.

On the basis of the previous decarboxylative protocol,[10] a test reaction with 8% $Pd(O_2CCF_3)_2$ and 12% 6-methyl-2,2′-bipyridyl as the catalytic system with sodium *p*-tolylsulfinate (**1a**) as the arylpalladium precursor was performed in a 1:2 mixture of H_2O/MeCN (**2a**, 40-fold excess of the nitrile). This reaction was heated overnight at 100 °C and furnished 10% isolated yield of the desired methyl ketone, **3a**.

An initial ligand screen gave a similar result for dmphen (2,9-dimethyl-1,10-phenanthroline, **4e**). Other ligands such as 2,2′-bipyridyl (**4a**), 6,6′dimethyl-2,2′-bipyridyl (**4c**) and dppp (bis(diphenyl-phosphin)propane, **4f**) afforded product formation in only small amounts. Homocoupling, providing 4,4′-dimethylbiphenyl as a byproduct, was detected in the reactions using DMSO (**4g**) and 6,6′dimethyl-2,2′-bipyridyl (**4c**) and in the ligand-free reaction.

An increase in the yield of **3a** was observed when the reaction was followed by hydrolysis with 2 M HCl. Therefore, the effect of trifluoroacetic acid (TFA) on the reaction was studied. The addition of stoichiometric amounts (1−5 equiv) led to a slight increase in yield, but the addition of 10 equiv of TFA afforded more than 80% yield (GC) of the desired product. Additional hydrolysis did not improve the outcome, which indicated that the one-step in situ hydrolysis by the excess of TFA was sufficient.

The influence of temperature was explored, and 100 °C was found to be the most effective. Fine-tuning of the catalytic conditions identified 8 mol % of $Pd(O_2CCF_3)_2$ and 12 mol % of ligand **4b** as the most effective combination. Even though

Received: August 18, 2011
Revised: September 16, 2011
Published: September 20, 2011

Scheme 1. General Reaction

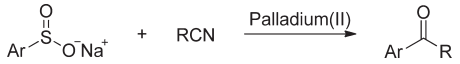
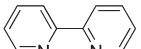
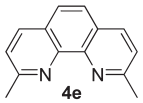
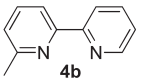
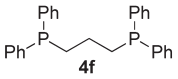
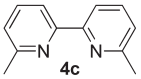
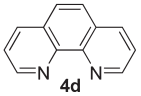


Table 1. Ligand Screen

Ligand	Yield[a]	Ligand	Yield[a]
 **4a**	39%	 **4e**	8%
 **4b**	87%	 **4f**	n.d.
 **4c**	8%	DMSO[b] **4g**	10%
 **4d**	31%	no ligand	traces

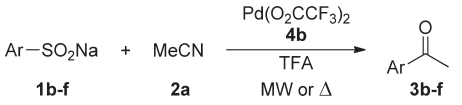
[a] Isolated yield, >95% purity. Reaction conditions: A 0.5−2 mL process vial was charged with *p*-MePhSO$_2$Na (0.5 mmol), Pd(O$_2$CCF$_3$)$_2$ (0.04 mmol), ligand (0.06 mmol), H$_2$O/THF 1/1 (1.4 mL), MeCN (2.5 mmol), and CF$_3$CO$_2$H (5 mmol). The sealed vial was heated in a microwave reactor at 100 °C for 1 h. [b] 100 μL of DMSO were added.

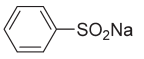
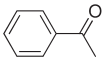
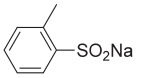
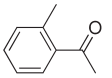
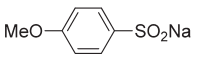
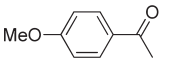
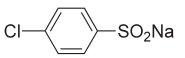
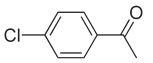
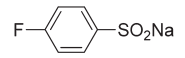
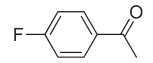
MeCN (**2a**) is an inexpensive and easy to handle solvent, we decided to switch to a cosolvent system, using the nitrile in only small excess. This was carried out to further broaden the scope of the reaction, enabling the use of solid nitriles. When the excess of **2a** was decreased from 40 to 10 and even to 5 equiv, no significant decrease in yield was observed. Only when the ratio of **2a** and sulfinate **1a** was lowered further did the yield drop to less than 40%. Various ratios of water/dioxane and water/THF were investigated as solvent systems, the latter leading to better results with higher yields and no byproduct formation.

With these improved reaction conditions, we performed a second ligand screen under microwave (MW) heating conditions (Table 1), employing five bidentate nitrogen ligands (**4a**−**4e**) and one bidentate phosphine ligand (**4f**), DMSO (**4g**). A control experiment with no added ligand was also performed. Ligand **4f** led to no desired product, and the ligand-free reaction provided only trace amounts of aryl ketone **3a**. In accordance with our preliminary screen, **4g** was also found to be a poor ligand for the ketone formation. Among the bidentate nitrogen ligands, the dimethylated bipyridyl and phenanthroline compounds **4c** and **4e** were inferior to their nonmethylated equivalents **4a** and **4d**, which were employed in the recently reported methods.[20,21] The best result under our reaction conditions was achieved with 6-methyl-2,2′-bipyridyl (**4b**), which provided the product **3a** in 87% isolated yield.

To evaluate the scope and limitations for this microwave protocol, we investigated a variety of different sulfinates with respect to their reactivity toward MeCN (Table 2). The unsubstituted phenyl sulfinate **1b** readily afforded the corresponding

Table 2. Scope of Sulfinates



Entry	Ar-SO$_2$Na	Product	Yield[a]
1	 **1b**	 **3b**	77%[b] 61%[c]
2	 **1c**	 **3c**	66%[b]
3	 **1d**	 **3d**	79%[b] 31%[a]
4	 **1e**	 **3e**	79%[b] 49%[a]
5	 **1f**	 **3f**	73%[b]

[a] Isolated yield, >95% purity. [b] Reaction conditions: A 0.5−2 mL process vial was charged with ArSO$_2$Na (0.5 mmol), Pd(O$_2$CCF$_3$)$_2$ (0.04 mmol), **4b** (0.06 mmol), H$_2$O/THF 1/1 (1.4 mL), MeCN (2.5 mmol), and CF$_3$CO$_2$H (5 mmol). The sealed vial was heated in a microwave reactor at 100 °C for 1 h. [c] Same as footnote b, but heated in a heating block at 100 °C for 16 h.

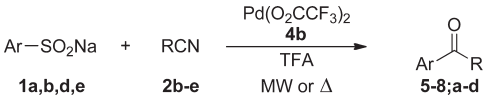
ketone **3b** in 77% yield (Table 2, entry 1). This reaction was also performed using a heating block and gave **3b** in a slightly lower yield of 61%. The *ortho*-methylphenyl sulfinate (**1c**) led to the desired ketone **3c** in a satisfying yield of 66% (entry 2). The electron-rich sulfinate **1d** furnished the product in a good yield of 79% (entry 3). The electron-deficient phenyl sulfinates **1e** and **1f** gave yields of 75% (**3e**) and 73% (**3f**), respectively, and are therefore comparable to the other starting materials. Performing the reaction under conventional heating with sulfinates **1d** and **1e** led to a significant decrease in yields (Table 2, entries 3 and 4). This difference might be due to the problem of correctly measuring the reaction temperature in a sealed vial, regardless of heating methodology.[22]

To further extend the scope of the ketone formation, a range of nitriles (propionitrile (**2b**), benzonitrile (**2c**), benzylcyanide (**2d**), and *p*-bromo benzonitrile (**2e**)) were reacted with a selection of sulfinates (Table 3, 1a, b, d, e). As depicted in Table 3, most reactions gave moderate to excellent yields, and the nitrile insertion was successfully performed with aliphatic (66−91%) as well as aromatic (51−84%) and benzylic nitriles (66−87%). Importantly, the use of only 3 equiv of *p*-bromo benzonitrile (**2e**) afforded good isolated yields (51−67%) of the benzophenone derivatives (Table 3, entries 4, 8, 12, 16). Moreover, no traces of products resulting from activation of the Ar−Cl/Br bond (dehalogenation, biaryl formation) in **1e** or **2e** were observed. The yields of the conventionally heated reactions were lower than of the microwave reactions.

In all cases, the corresponding amide, formed by hydrolysis of the organic nitrile, was observed as a byproduct in the crude mixture. We believe that this competing hydrolysis is responsible for the slightly lower yields when using only 3 equiv of nitrile.

dx.doi.org/10.1021/cs200428u |*ACS Catal.* 2011, 1, 1455–1459

Table 3. Variation of Nitriles



1a,b,d,e 2b-e 5-8;a-d

Entry	$ArSO_2Na$	R	Product	Yield[a]	Entry	$ArSO_2Na$	R	Product	Yield[a]
1	**1a**	Et **2b**	**5a**	91%[b] 83%[c]	9	**1d**	**2b**	MeO **7a**	66%[b] 64%[c]
2	**1a**	Ph **2c**	**5b**	84%[b] 74%[c]	10	**1d**	**2c**	MeO **7b**	74%[b] 65%[c]
3	**1a**	Bn **2d**	**5c**	87%[b]	11	**1d**	**2d**	MeO **7c**	77%[b] 56%[c]
4	**1a**	4-BrPh **2e**	**5d** Br	68%[d]	12	**1d**	**2e**	MeO **7d** Br	62%[d]
5	**1b**	**2b**	**6a**	89%[b]	13	**1e**	**2b**	Cl **8a**	73%[b] 73%[c]
6	**1b**	**2c**	**6b**	70%[b]	14	**1e**	**2c**	Cl **8b**	77%[b] 54%[c]
7	**1b**	**2d**	**6c**	76%[b] 22%[c]	15	**1e**	**2d**	Cl **8c**	66%[b] 58%[c]
8	**1b**	**2e**	**6d** Br	61%[d]	16	**1e**	**2e**	Cl **8d** Br	51%[d]

[a] Isolated yield, >95% purity. [b] Reaction conditions: A 0.5−2 mL process vial was charged with $ArSO_2Na$ (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol), **4b** (0.06 mmol), H_2O/THF 1/1 (1.4 mL), RCN (2.5 mmol), and CF_3CO_2H (5 mmol). The sealed vial was heated in a microwave reactor at 100 °C for 1 h. [c] Same as footnote b, but heated in a heating block at 100 °C for 16 h. [d] Same as footnote b, but RCN (1.5 mmol).

Compared with previous studies, in which only ortho-functionalized aromatic acids could be successfully employed in Pd^{II}-catalyzed decarboxylations,[9,10,23] the sulfinic acids/sulfinates examined in this study show no limitations in this regard. Furthermore, the presented methodology can be successfully performed on a larger scale, which was shown by the reaction between **1a** and **2a** (5 mmol scale), affording the product in an isolated yield of 62%.

An electrospray ionization mass spectrometry (ESI-MS)[24] study was performed to give insight into the reaction mechanism. ESI-MS is generally considered to be a soft MS ionization technique. It promotes only few fragmentation products and is therefore a useful tool for direct studies of catalytic intermediates, in this case, organometallic intermediates.[25−31]

For the ESI-MS study, the model reaction between sodium *p*-tolylsulfinate (**1a**) and MeCN (**2a**) (Table 1) with 6-methyl-2,2′-bipyridyl (**4b**) as the ligand was chosen for investigation. The reaction was heated in a microwave reactor at 100 °C. After 10 min, an aliquot was withdrawn from the reaction mixture and diluted with MeCN (1:9, v/v). The ESI-MS(+) spectrum of the ongoing reaction was immediately recorded by scanning the first quadrupole (Q1) of a triple-quadrupole instrument. Several groups of peaks with *m*/*z* signals characteristic for the isotopic pattern of singly charged monopalladium-complexes were detected. Comparatively, there were very few cationic complexes not containing palladium (Figure 1).

On the basis of the *m*/*z*-signals, MS/MS, and MS^3 as well as scanning for specific neutral loss, structures of the intermediates

dx.doi.org/10.1021/cs200428u |*ACS Catal.* 2011, 1, 1455–1459

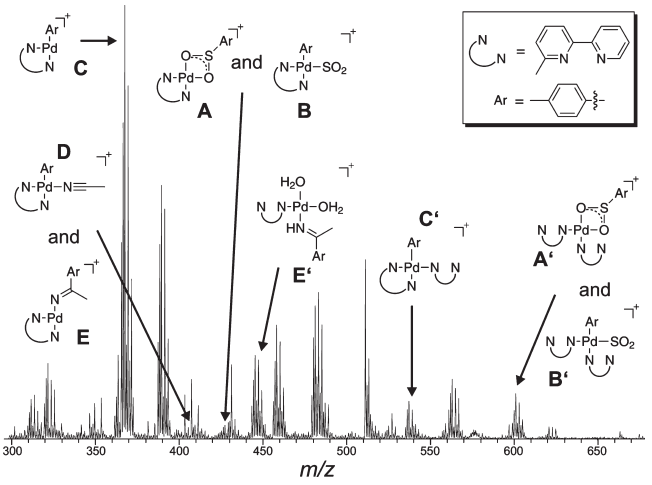
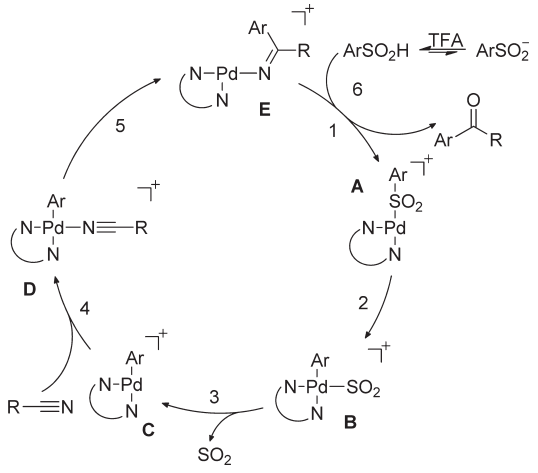


Figure 1. ESI-MS(+) spectrum for the reaction of **1a** and **2a**, with assigned Pd^{II} intermediates.

Scheme 2. Proposed Mechanism Based on the ESI-MS Study



were proposed.[32] The intermediates were assigned to different classes with letters **A**−**E**, on the basis of their plausible role in the reaction (Figure 1). Despite their identical masses, complex classes **A** and **B** were found independently during the ESI-MS study through different techniques (i.e., neutral loss of aryl sulfinate and SO_2, respectively).[33]

A corresponding negative ESI-MS(−) scan was performed, as well, but no anionic palladium complexes could be detected.

Scheme 2 presents the suggested catalytic cycle. One complex from each class (**A**−**E**) is given. The general mechanism is in agreement with previous proposals for similar reactions,[10,20,21] and SO_2 and ammonium hydroxide are the byproducts of the reaction. The following key steps are included in the catalytic pathway: (1) Coordination of the aryl sulfinate to Pd^{II} generating species **A**, which is (2) rearranged to complex **B** by insertion of the Pd^{II} center into the aryl-sulfur bond. Next, step (3) is the desulfination of the aryl sulfinate to give Ar−Pd σ complexes of class **C**, which are the most abundant organopalladium complexes in the ESI-MS(+) spectra. Coordination of the nitrile (4) provides the catalytic complex **D**, and subsequent 1,2-insertion of the nitrile (5) generates the ketimine intermediate **E**, which is likely to be the rate-determining step. Finally, (6) protonation of ketimine complex **E** affords the free ketimine, which under acidic conditions will be hydrolyzed to the ketone product, releasing an active Pd^{II} species. The ESI-MS study was repeated also with phenanthroline as the ligand and a second time under the above-mentioned conditions but with sodium phenylsulfinate. These experiments showed corresponding *m*/*z*-signals supporting the structures given in Figure 1 and Scheme 2.[33]

CONCLUSIONS

The herein presented new microwave promoted Pd^{II}-catalyzed method using the robust 6-methyl-2,2′-bipyridyl ligand allows for the fast synthesis of aryl ketones not only from functionalized but also from unsubstituted benzene sulfinates. With the aid of ESI-MS, MS/MS, and MS^3, all key intermediates were detected, suggesting that the reaction pathway involves desulfination of the sulfinate, generating an aryl-palladium species, followed by addition to the nitrile. Currently, our group is undertaking efforts to further expand the scope of this reaction. In addition, a more intense investigation of the reaction mechanism is underway by means of comprehensive DFT calculations.

ASSOCIATED CONTENT

Supporting Information. General experimental procedure paragraphs, compound characterization data, and copies of spectra and chromatograms. This information is available free of charge via the Internet at http://pubs.acs.org/.

AUTHOR INFORMATION

Corresponding Author

*Phone: +46-18-4714667. Fax: +46-18-4714474. E-mail: mats.larhed@orgfarm.uu.se.

ACKNOWLEDGMENT

We thank the Swedish Research Council and the Knut and Alice Wallenberg Foundation for financial support and Dr. Luke Odell for a critical review of this manuscript.

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(33) For detailed ESI-MS(+) and ESI-MS/MS(+) spectra, see the Supporting Information.