

Olefin Preparation via Palladium-Catalyzed Oxidative De-Azotative and De-Sulfitative Internal Cross-Coupling of Sulfonylhydrazones

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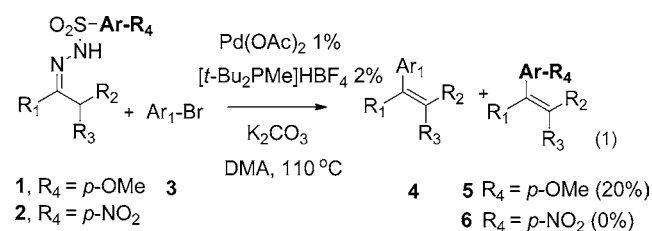
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S Supporting Information

ABSTRACT: A novel reactivity of sulfonylhydrazones under Pd catalysis is described, where SO₂ and N₂ are formally extruded to afford the product of an apparent internal coupling reaction. The reaction is effective with both carbocyclic and heterocyclic aromatic precursors.



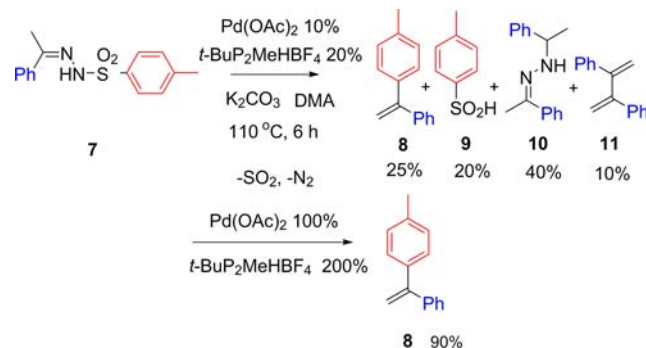
The synthesis of highly substituted olefins from activated ketone derivatives such as enol perfluoro-sulfonates and boronic acids or sulfonyl hydrazones and aryl halides has been used extensively in synthesis. During the preparation of an active pharmaceutical ingredient, we reported an interesting side reaction which was observed during our attempts to couple sulfonylhydrazones with aryl bromides bearing α -amino groups.¹ We reported that the reaction of **1** with the aryl bromide **3** (Ar₁ = *o*-anilino derivative) produced the expected Barluenga product² **4**, albeit under modified reaction conditions (eq 1).



However, in the presence of an electron-rich sulfonylhydrazone (such as **1**) significant amounts of the “internal” cross-coupled product **5** were formed as well. The formation of the latter could be suppressed, in order to meet our synthetic needs, by employing electron-deficient substrates of the general structure **2**. In that case none of the “internal” product **6** was observed and **4** was obtained in high yield.

We found the formation of **5** intriguing and considered the possibility of using this side reaction synthetically. We envisioned using it as a more general and atom-economical way to prepare olefins from ketones and various aryl or heteroarylsulfonylhydrazones.³ If we could force the two organic moieties to couple intramolecularly, extruding SO₂ and N₂, we may have an alternative to the more traditional, stepwise, ketone activation by enol derivative formation followed by transition-metal-catalyzed coupling with organometallic compounds. In other words, instead of separately preparing the

Scheme 1. Reaction of Sulfonylhydrazone **7** under Pd Catalysis



nucleophilic and electrophilic coupling partners, they would both be contained in the same molecule (Scheme 1).⁴

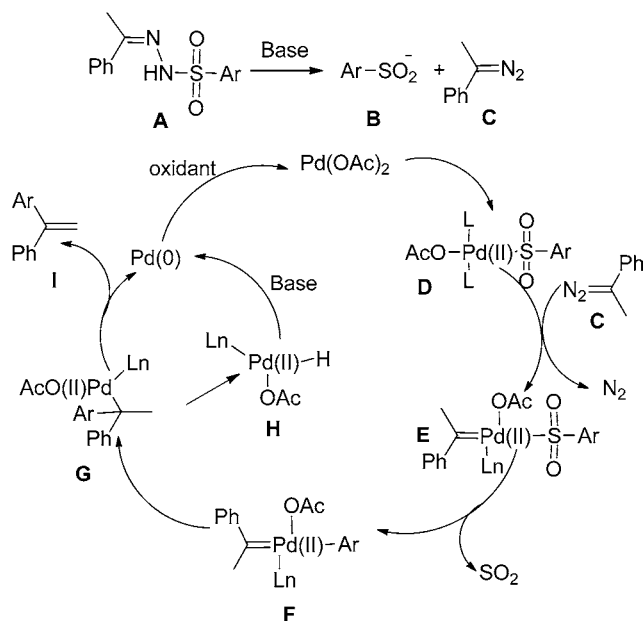
Our investigation started with the tosyl hydrazone of acetophenone (**7**, Scheme 1) which, when subjected to our optimized reaction conditions Pd(OAc)₂, [t-Bu₂PMe]HBF₄, K₂CO₃ in dimethylacetamide at 100 °C, afforded a 25% yield of the desired product **8**. In addition, the sulfonic acid **9** was observed, as expected (see companion paper), along with the intriguing product **10** and diene **11**. Our initial assumption was that **8** was formed by the combination of a vinyl Pd species (from the decomposition of the diazo intermediate **C**, Scheme 2) and sulfinate **B** (i.e., **9** in Scheme 1).⁵ However, when the reaction was performed with 1 equiv of catalyst, a 90% yield of **8** was isolated from the reaction mixture without a trace of **9–11**.

This interesting result prompted us to speculate that a Pd(II) species (Scheme 2) was responsible for the desired product **8**, while the impurities **9–11** were produced by side reactions of **C** that may or may not involve Pd.⁶ Interestingly, no cyclopropane

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Scheme 2. Mechanistic Possibilities for the Formation of I



or styrene by-products were observed in the reaction. As a working hypothesis then, we assumed that the aryl sulfinate B could displace one of the acetate groups at Pd(OAc)₂, to produce D, which would then insert the diazo intermediate C to form the Pd(II) species E followed by loss of SO₂ to give F. Aryl migration as in the accepted Barluenga mechanism (resulting in species G) would afford 8 and Pd(0), which, in a catalytic cycle but not in a stoichiometric reaction, needs to be reoxidized to Pd(II). It is the rate of this oxidation that, we believe, is the key to the success of this process, and therefore we decided to introduce a stoichiometric oxidant as well as investigate the other reaction parameters in order to optimize this reaction (Table 1). A number of practical oxidants⁷ were tested in the reaction, using our Pd(OAc)₂, *t*-Bu₂PMeHBF₄, K₂CO₃ conditions (Table 1, entries 1–5), and atmospheric oxygen appears to be the most effective, giving approximately 60% isolated yield of the desired 8, although the byproduct 10 was also produced in 25% yield. Other solvents (Table 1, entries 6–12) were significantly less effective than DMA affording even higher yields of 10. At this point it is not clear if this reactivity difference is due to the solubility of oxygen in these solvents or just the inherent reactivity of 7 in these solvents. Other metal precursors such as Pd₂dba₃, Pd(O₂CCF₃)₂, Pd(COD)Cl₂, Cl₂Pd(CH₃CN)₂ in combination with *t*-Bu₂PMeHBF₄ gave similar results as the Pd(OAc)₂ precursor, and Pd–N-heterocyclic carbene complexes were not useful catalysts. Non-carbonate bases such as *t*-BuOLi, *t*-BuONa, or *t*-BuOK, in combination with or without *t*-Bu₂PMeHBF₄, gave no 8 with the majority of the reaction products (>60%) being a combination of 10 and 11.

In order to assess the effect of the ligand (Figure 1), using Pd(OAc)₂ and K₂CO₃, under an air atmosphere, we examined a variety of phosphines (Table 1, entries 13–20). To our surprise, there does not appear to be a dramatic effect of the ligand on product distribution, although there are some significant differences between alkyl and ferrocene-based phosphines (for example compare, in Table 1, entries 5 and 13 with entry 18).

A substantial increase in the yield of 8, and commensurate decrease in the undesired products, occurred when Bu₄N⁺I⁻ was added to the reaction mixture (Table 1, entries 21–25).

Table 1. Exploration of Oxidant, Solvent, and Ligand in the Reaction of 7 under Pd-Catalysis^a

entry	L	oxidant	solv/add.	8, % ^b	9, %	10, %	11, %
1	19	Cu(OAc) ₂	DMA	20	35	0	0
2	19	AgOAc	DMA	9	31	45	0
3	19	BQ	DMA	5	30	0	0
4	19	DCP	DMA	10	10	14	0
5	19	air	DMA	60	11	25	8
6	19	air	CH ₃ CN	22	8	59	0.5
7	19	air	DCE	46	7	5	3
8	19	air	<i>i</i> -BuOH	20	23	42	6
9	19	air	PhCl	19	0	15	0.5
10	19	air	MEK	23	10	58	2
11	19	air	toluene	48	0	45	1.5
12	19	air	dioxane	27	19	38	10
13	15	air	DMA	63	17	16	7
14	14	air	DMA	40	17	19	6
15	12	air	DMA	33	16	28	8
16	17	air	DMA	31	18	31	10
17	21	air	DMA	50	42	10	22
18	20	air	DMA	30	15	58	14
19	13	air	DMA	57	21	11	16
20	16	air	DMA	38	34	22	9
21	19	air ^c	DMA	83	0	12	6
			Bu ₄ N ⁺ I ⁻				
22	18	air	DMA	82	0	8	2
			Bu ₄ N ⁺ I ⁻				
23	19	air	DMA	73	8	18	7
			Bu ₄ N ⁺ Br ⁻				
24	18-O2	air	DMA	57	15	9	4
			Bu ₄ N ⁺ I ⁻				
25	–	air	DMA	46	1	22	16
			Bu ₄ N ⁺ I ⁻				

^aPd(OAc)₂ (S/C ratio = 10) was used as the metal precursor in the specified solvent (7–10 mL/g of 7). M/L ratio is 1:2 for the monodentate and 1:1 for the bidentate ligands. ^bHPLC area %. ^cControl experiments under Ar atmosphere and degassed solvents showed only 10% conversion with 10 mol % of catalyst.

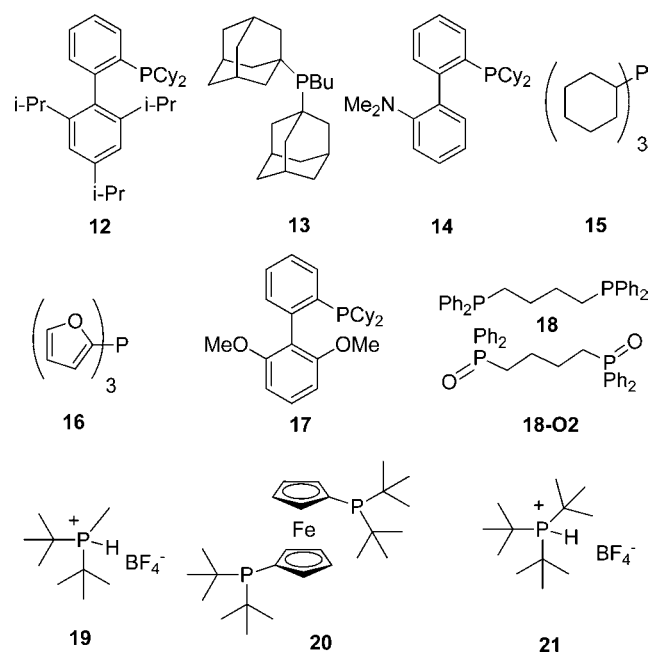


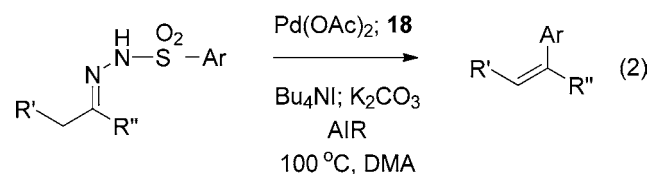
Figure 1. Ligands explored in Table 1.

The isolated yield of **8** increased to 83% with **19** as the ligand, while the cheaper and more stable ligand **18** gave an 82% yield with a <10% combined yield of **9–11**. Interestingly, Bu_4NBr does not perform as well as the iodide derivative (compare entries 21 and 23 in Table 1). Although the role of the Bu_4NI is not understood at this time, it does not appear to be merely stabilizing Pd nanoparticles, as has been shown elsewhere.⁸ The presence of a highly dative ligand affects the success of this reaction, since the absence of ligand or its substitution by the corresponding phosphine oxide reduced the efficiency of the reaction (Table 1, entries 24–25).

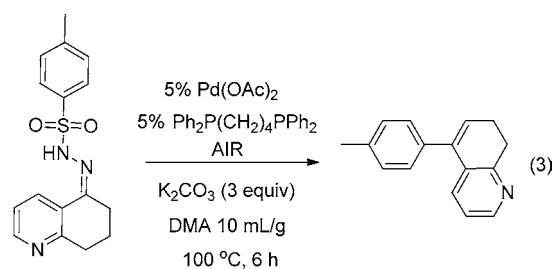
Table 2. Scope of the Reaction under Optimized Conditions (eq 2)

entry	hydrazone	product	pdt/ yield
1			22 / 78%
2			23 / 82%
3			24 / 85%
4			25 / 68%
5			26 / 71%
6			27 / 78%
7			28 / 70%
8			29 / 77%
9			30 / 80%
10			31 / 83%
11			32 / 16%
12			33 / 79%
13			34 / 89%

Using the optimized conditions for this reaction (eq 2), we investigated its scope (Table 2). In most cases substituents

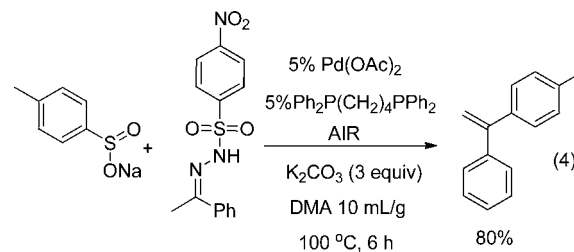


on the ketone moiety do not markedly affect the reaction, and fluoro, chloro, and cyano aromatics give a good yield of the desired product (Table 2, entries 1, 3, 4). On the other hand, the electronic nature of the sulfonylhydrazone is very important and electron-deficient hydrazones do not couple well intramolecularly (Table 2, entry 11). Heteroaromatics always present a unique challenge in many Pd-catalyzed reactions, and we were pleased to see that our reaction can be extended to heteroaromatic ketones (eq 3). A thorough assessment of this chemistry



and its application to more heteroaromatic ketones and heteroaryl sulfonylhydrazones is underway and will be reported shortly.

Finally, we have been able to take advantage of the fact that electron-deficient sulfonylhydrazones do not perform well in the intramolecular version of the reaction to develop an intermolecular version of this chemistry (eq 4). Indeed, when the



NO_2 -sulfonylhydrazone was reacted under our optimized reaction conditions in the presence of an external sulfinic acid derivative, a useful yield of the intermolecular coupling product was obtained.

This observation, which has mechanistic implications for the intramolecular reaction discussed above, is being studied further, and further applications will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01494.

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Notes

The authors declare no competing financial interest.

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