

Synthesis of Polysubstituted Olefins by Pd-Catalyzed Cross-Coupling Reaction of Tosylhydrazones and Aryl Nonaflates

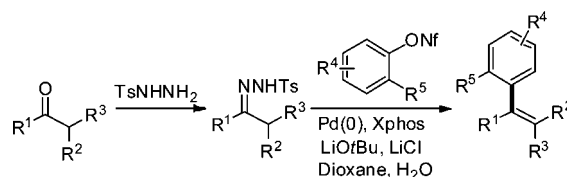
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ABSTRACT

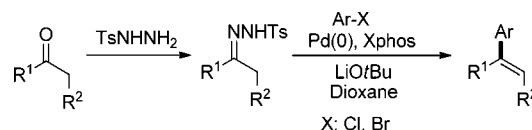


Aryl nonaflates are employed as electrophiles in the Pd-catalyzed cross-coupling with tosylhydrazones affording di-, tri-, and tetrasubstituted olefins. Fine tuning of the reaction conditions are required to accomplish the coupling successfully, including the addition of LiCl and the presence of small amounts of water. Under the optimized conditions, the reactions proceed with high yield and also high stereoselectivity depending on the nature of the coupling partners.

Pd-catalyzed cross-coupling reactions are currently the most reliable methods for the creation of $C_{sp^2}-C_{sp^2}$ bonds.¹ Well established methods are based on the combination of an organic halide or sulfonate with an organometallic reagent. At present, the judicious election of cross-coupling sequences allows the preparation of nearly all types of substituted alkenes.² Nevertheless, the incorporation of different types of coupling partners is highly desirable, as it enables the introduction of new classes of fragments through cross-couplings reactions.

In this context, we have recently uncovered a new Pd-catalyzed cross-coupling reaction that employs tosylhydrazones as nucleophilic coupling partners (Scheme 1).³ From

Scheme 1. Pd-Catalyzed Cross-Coupling Reactions Employing Carbonyls Mediated by Tosylhydrazone



our point of view, this reaction features some interesting properties; among them: (1) the reaction proceeds without the participation of a stoichiometric organometallic reagent; (2) since tosylhydrazones are readily prepared from carbonyl compounds, it represents a very simple way to transform carbonyls into reagents for cross-coupling reactions. Indeed, since our preliminary contribution, we and others have shown that the Pd-catalyzed reactions with tosylhydrazones are excellent routes for the preparation of polysubstituted olefins by reactions with aryl^{3b-d} and benzyl halides.⁴

To expand the scope of this reaction to a wider variety of substrates, we decided to study the employment of sulfonates as electrophilic components in the cross-coupling reaction.

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(2) For a recent review, see: Negishi, E.-i.; Wang, G.; Rao, H.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 3151.

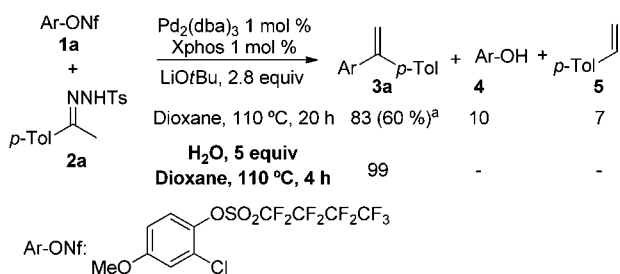
(3) (a) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587. (b) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2008**, *14*, 4792. (c) Barluenga, J.; Escribano, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2009**, *15*, 3291. (d) Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6856.

The availability of structurally diverse sulfonates is much wider than that of halides, as sulfonates are readily prepared from phenols. During the development of our work, Alami reported the Pd-catalyzed reaction between tosylhydrazones and aryl triflates,⁵ in the context of their studies of isocombrastatins,⁶ a new type of anticancer agents. However, the coupling reaction with aryl triflates is restricted to the preparation of 1,1-diarylethylenes, employing tosylhydrazones derived from acetophenones, and therefore, its scope is very limited. For this reason, we decided to continue with our study to expand the coupling reaction to more challenging substrates. In this paper we report our progress in this reaction, which has led to the development of a wide scope cross-coupling between tosylhydrazones and aryl nonaflates, which allows high yielding syntheses of di-, tri-, and tetrasubstituted arylalkenes.

From the beginning of our study, we chose aryl nonaflates for various reasons: nonaflates exhibit similar reactivity as triflates as electrophiles in Pd-catalyzed cross-couplings but are more economically and easily prepared⁷ as well as more user-friendly than triflates.⁸ Moreover, nonaflates are more robust than triflates toward alkoxides and, therefore, provide better results in Pd-catalyzed cross-couplings that require the employment of these types of bases.⁹

As a model reaction we selected the coupling of hydrazone **2a**, derived from 4-methylacetophenone, and nonaflate **1a**, a quite demanding electrophilic component that will require addressing steric (*ortho* substitution) and chemoselectivity (ONf vs Cl) issues (Scheme 2).

Scheme 2. Pd-Catalyzed Cross-Coupling between the Tosylhydrazone **2a** and Nonaflate **1a**



The first experiment, employing the standard reaction conditions previously developed for aryl halides, furnished the cross-coupling product in a promising 60% yield after 20 h at 110 °C. Analysis of the GC/MS trace showed significant amounts of phenol **4**, which comes from the

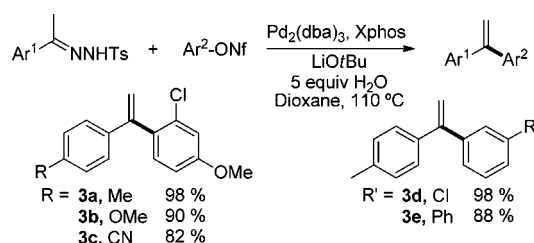
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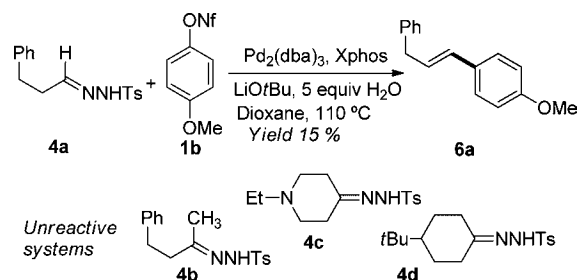
hydrolysis of the nonaflate, and olefin **5**, the Bamford–Stevens degradation product of the tosylhydrazone. Based on our experience in other coupling reactions with tosylhydrazones, we tested the addition of small amounts of water to the reaction mixture.^{3d} Indeed, when the reaction was conducted in the presence of 5 equiv of water, complete conversion was achieved after 4 h, leading to diarylethylene **3a** in quantitative yield.¹⁰ Noteworthy, the reaction proceeds with total regioselectivity, giving rise exclusively to the coupling product of the nonaflate **3a**, with no traces of the alkene that would come from coupling at the chloride position. These reaction conditions were applied to other nonaflates and tosylhydrazones derived from acetophenones (Scheme 3) leading to the diarylethylenes **3** in very high yields.

Scheme 3. Synthesis of 1,1-Diarylethylenes by Pd-Catalyzed Cross-Coupling between the Tosylhydrazones and Nonaflates



However, the reaction of nonaflate **1b** with hydrazone **4a**, derived from 3-phenylpropanal, under the same reaction conditions, turned out to be very sluggish, and the coupling product **6a** was obtained in very low yield. Moreover, the couplings with other hydrazones derived from alkyl ketones such as **4b**, **4c**, and **4d** did not occur at all, leading mainly to the alkenes derived from the Bamford–Stevens degradation (Scheme 4).

Scheme 4. Unsuccessful Reactions under the Standard Conditions



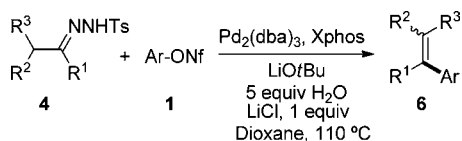
Cross-coupling and Heck reactions with aryl and alkenyl sulfonates are accelerated in the presence of added halide

(7) Aryl nonaflates are prepared with perfluoro-1-butanefluoride (see Supporting Information for details) that is available at half the price (\$/mmol) of anhydride triflate (Aldrich Chem. Co.).

(8) For a recent review on the advantages of the use of nonaflates in Pd-catalyzed cross-couplings, see: Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747.

salts.¹¹ For this reason, we studied the effect of the addition of ionic salts to the reaction mixture. Indeed, it was found that the addition of LiCl led to a spectacular increase in the yield. After some experimentation it was found that the coupling reactions could be achieved successfully by the addition of 1 equiv of LiCl and 5 equiv of H₂O.¹² These reaction conditions were then applied to a set of tosylhydrazones and sulfonates (Scheme 5, Table 1).

Scheme 5. Synthesis of Substituted Olefins by Pd-Catalyzed Reactions with Tosylhydrazones



The coupling proceeded with nearly quantitative yield for hydrazone **4a** derived from an aldehyde, giving rise exclusively to the *E*-alkenes (entries 1–4). Nevertheless,

in these cases it was necessary to employ a 1:2 nonaflate/hydrazone molar ratio to avoid the formation of trisubstituted olefins that occur by Heck reaction of the initially formed alkene **6** with the nonaflate.¹³ The coupling reactions with hydrazones derived from cyclic and acyclic alkyl ketones also took place with very high yields (entries 5–13). It is worth noting that these reactions do not proceed at all in the absence of LiCl.

With regard to the structure of the nonaflate, the reaction tolerates *ortho* substitution and also the presence of a chlorine substituent that may enable further derivatization through cross-coupling reactions.

The coupling reaction with nonaflates retains the characteristics reported for the reactions with aryl halides. For instance, the reactions with the hydrazone derived from 2-methoxycyclohexanone give exclusively the allyl ethers with total regioselectivity (entries 10–13), as previously reported for the couplings with aryl bromides.^{3d}

Moreover, the stereochemistry in the formation of the trisubstituted alkenes is noteworthy. The reactions with hydrazones derived from dialkyl ketones such as 3-pentanone afford exclusively the *E*-alkene (entry 5).

Table 1. Substituted Olefins **6** Prepared According to Scheme 5^a

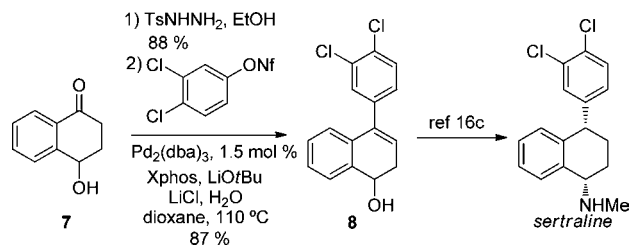
entry	compound 6	Pd(mol %)	<i>t</i> (h) ^c	yield (%) ^d	entry	compound 6	Pd(mol %)	<i>t</i> (h) ^c	yield (%) ^d
1 ^b		1	15	99	14 ^e		3	1	87
2 ^b		1	7	96	15		1	1	90
3 ^b		1	12	93	16 ^f		1	15	92
4 ^b		1	6	98	17 ^f		3	3	95
5		3	4	92	18 ^f		3	6	94
6		5	4	89	19 ^g		1	14	75
7		3	6	58	20 ^g		3	5	70
8		2	14	90	21 ^c		3	4	92
9		1	24	89	22		3	2	98
10		2	14	94					
11		3	14	95					
12		3	6	76					
13		3	12	83					

^a Reaction conditions: Nonaflate **1**, (0.5 mmol), hydrazone **4** (0.55 mmol, 1.1 equiv), LiCl (0.5 mmol), LiOtBu (2.8 equiv), H₂O (5 equiv), Pd₂dba₃ (1–5 mol %), Xphos (1–5 mol %), dioxane (1.5 mL). ^b A 2:1 molar ratio hydrazone **4**/nonaflate **1** was employed. ^c Reaction times are not optimized. ^d Isolated yields after column chromatography. ^e Obtained as a 1:1 mixture of isomers. ^f Stereochemistry determined by NOESY experiments. ^g Obtained as a single stereoisomer. The stereochemistry is proposed based on the previous examples.

Interestingly, the coupling reaction with a hydrazone derived from a propiophenone and nonaflate **1a**, which features a chlorine in the ortho position, afforded exclusively the *Z*-olefin **6p** (entry 16), while the reaction with meta substituted benzenonaflate provided a 1:1 mixture of the two expected *Z/E* isomers (entry 14). The effect of the ortho substituent is general for coupling reactions of ortho substituted nonaflates with hydrazones derived from aryl alkyl ketones (Table 1, entries 16–18). In all cases the stereoisomer was obtained that features the alkyl group and the *o*-substituted arene in a *cis* arrangement.¹⁴ Moreover, triaryl substituted alkenes could be prepared stereoselectively taking advantage of the ortho-directing effect (Table 1, entries 19–20). These are interesting results indeed, as they represent a new entry into stereochemically defined trisubstituted olefins, not easily available through other methods.¹⁵ A detailed justification of this ortho-directing effect based on DFT-molecular modeling studies is included in the Supporting Information. Finally, the employment of the hydrazone derived from an α -branched ketone led to the corresponding tetrasubstituted alkene,^{5b} also with very high yield (entry 22).

To illustrate the usefulness of the cross-coupling method we prepared the dihydronaphthalene derivative **8**, which is the direct precursor of the antidepressant sertraline, in one single step from the tosylhydrazone of 4-hydroxytetralone **7** (Scheme 6). Noteworthy, the coupling is completely chemoselective; no coupling reaction through a chloro-substituent is detected. Moreover, unlike in most of the

Scheme 6. Concise Formal Synthesis of Sertraline



syntheses of sertraline, protection of the hydroxy group is not required, and therefore this represents an advance when compared with previously reported procedures.¹⁶

In conclusion, we have developed proper conditions to carry out the Pd-catalyzed cross-coupling reaction between tosylhydrazones and aryl nonaflates. The process is very general with regard to both coupling partners, the hydrazone and the ketone, and occurs with very high yields in most of the cases. The stereoselectivity of reactions with *o*-substituted aryl nonaflates is worth noting. Taking into account the wide availability of nonaflates that are easily prepared from phenols, this reaction represents an important addition to the usefulness of Pd-catalyzed cross-coupling with tosylhydrazones.

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Supporting Information Available: Experimental details. Characterization data for olefins **3**, **6**, and **8** and nonaflates **1**. Justification of the ortho-directed stereoselectivity and computational studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) As suggested by one referee, we conducted the coupling reaction employing 2.8 equiv of LiOH as base, both in the presence or in the absence of *t*BuOH respectively. Both reactions proceeded with 100% conversion but led to a 88:12 mixture of **3a** and the phenol that comes from hydrolysis of the nonaflate followed by coupling at the chloride position (GC/MS).

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(12) The reaction in the presence of LiCl but without H₂O proceeds with a conversion below 50% after 20 h.

(13) The presence of a mixture of trisubstituted olefins was detected by GC/MS.

(14) The stereochemistry of the double bond was determined in all cases by NOESY experiments.

(15) For stereoselective Heck reaction, see: Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *Tetrahedron Lett.* **1999**, *40*, 2101.