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Palladium-Catalyzed Desulfitative Cross-Coupling Reaction of Sodium Sulfinates with Benzyl Chlorides

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ABSTRACT

A palladium-catalyzed approach for the synthesis of diarylmethanes from sodium sulfinates and benzyl chlorides is described. Various aromatic sodium sulfinates were used as aryl sources via extrusion of SO₂ and gave the diarylmethanes in moderate to good yields.

Diarylmethanes are versatile intermediates in the synthesis of pharmaceuticals and biologically active compounds, and they are also employed as subunits in the design of supramolecular structures. Consequently, development of efficient methods for construction of diarylmethanes has stimulated considerable interest. Traditionally, diarylmethanes are synthesized via Friedel—Crafts benzylation of benzylic electrophiles in the presence of Lewis acid. However, this approach is mainly suitable for electron-rich arenes and often suffers from low regioselectivity. The reduction of diaryl ketones could provide an alternative approach for preparation of diarylmethanes. Recently,

promising transition-metal-catalyzed methods for diaryl-methane synthesis have been the Suzuki-Miyaura-type coupling of benzylic electrophiles with arylboronic acids. ^{7,8} Metal-catalyzed C-H bond activation and subsequent C-C bond-forming reaction can provide an efficient synthesis with a reduced number of synthetic operations. ⁹

the transition-metal-catalyzed cross-coupling reactions of benzylic halides with arylmetals (or benzylmetals with aryl

halides)^{5,6} have been proven to be very powerful for con-

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Various methods have been developed using direct benzylation of heteroarenes and directing-group containing arenes under transition-metal catalysis. The Goossen group and others developed various methods for decarboxylative coupling reactions using inexpensive and readily available aromatic carboxylic acids as substrates. The decarboxylative cross-coupling reactions with aryl halides have proved to be very effective and powerful for biaryl synthesis. However, this strategy requires *ortho*-functionalized benzoic substrates and is not suitable for cross-coupling reactions with benzyl halides due to the easy formation of very stable benzyl benzoate derivatives. Meanwhile, we and others developed various palladium-catalyzed desulfitative Heck-type reactions, addition reactions, homocoupling reactions, and cross-coupling

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reactions with C–H bonds¹⁶ using sodium sulfinates as substrates. Unlike the decarboxylative coupling reactions, no electron-withdrawing or donating group *ortho* to the sulfinic acids group is necessary. We also found that the reaction of benzylic halides with sodium sulfinates generates stilbene derivatives in the absence of transition metals. The formation of benzyl sulfone intermediate plays an important role in this transformation.¹⁷ In continuing with our interest in using aryl sodium sulfinates as aryl sources, herein we describe a palladium-catalyzed desulfitative cross-coupling reactions of sodium sulfinates with benzyl chlorides, affording diarylmethanes in moderate to good yields.¹⁸

Table 1. Optimization of the Reaction Conditions^a

entry	catalyst	ligand	base	solvent	yield ^b (%)
1	$Pd(OAc)_2$	PPh_3	Na_2CO_3	dioxane	45
2	$PdCl_2$	PPh_3	Na_2CO_3	dioxane	40
3	$PdBr_2$	PPh_3	Na_2CO_3	dioxane	24
4	$Pd(OH)_2$	PPh_3	Na_2CO_3	dioxane	trace
5	$Pd(acac)_2$	PPh_3	Na_2CO_3	dioxane	25
6	$Pd(COD)Cl_2 \\$	PPh_3	Na_2CO_3	dioxane	44
7	$Pd(TFA)_2$	PPh_3	Na_2CO_3	dioxane	20
8	$Pd(OAc)_2$	dppe	Na_2CO_3	dioxane	50
9	$Pd(OAc)_2$	DPEphos	Na_2CO_3	dioxane	21
10	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	Na_2CO_3	dioxane	58
11	$Pd(OAc)_2$	$o-Tol_3P$	Na_2CO_3	dioxane	trace
12	$Pd(OAc)_2$	$m ext{-}\mathrm{Tol}_3\mathrm{P}$	Na_2CO_3	dioxane	57
13	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	$NaHCO_3$	dioxane	60
14	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	t-BuOK	dioxane	62
15	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	$\mathrm{CH_{3}ONa}$	dioxane	65
16	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	$\mathrm{CH_{3}ONa}$	anisole	66
17	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	$\mathrm{CH_{3}ONa}$	toluene	64
18	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	$\mathrm{CH_{3}ONa}$	DMSO	trace
19	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	$\mathrm{CH_{3}ONa}$	cyclohexane	72
20^c	$Pd(OAc)_2$	$p ext{-} ext{Tol}_3 ext{P}$	$\mathrm{CH_{3}ONa}$	cyclohexane	88

 a Conditions: 1a (0.2 mmol), 2a (0.2 mmol), catalyst (5 mol %), ligand (10 mol %), base (0.3 mmol), solvent (0.6 mL), 120 °C, 4 h under air unless otherwise noted. b GC yield. c 160 °C.

We began our study by examining the reaction of benzyl chloride (1a) with *p*-toluenesulfinic acid sodium salt (2a) in dioxane by using Pd(OAc)₂/PPh₃ as catalyst and Na₂CO₃ as base. When benzyl chloride reacted with an equal amount of 2a under air, the desired product was obtained in 45% yield as detected by GC–MS and ¹H NMR methods (Table 1, entry 1). Then various palladium salts were investigated for this reaction under similar reaction

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conditions. Similar yields were observed when PdCl₂ and Pd(COD)Cl₂ were used as the catalysts (entries 2 and 6). Other palladium salts such as PdBr₂, Pd(OH)₂, Pd(acac)₂, and Pd(TFA)₂ were less effective (entries 3–5 and 7). With Pd(OAc)₂ as the catalyst, the effect of ligand on the reaction yield was investigated by screening various phosphine ligands. Among them, p-Tol₃P (tri-p-toluenephosphine) showed the best reactivity, and the desired product was obtained in 58% yield (entry 10), whereas the use of o-Tol₃P completely inhibited the reaction (entry 11). Base also affected the reaction yields slightly. The use of CH₃ONa can further improve the reaction yield to 65% (entry 15). The choice of solvents was crucial for this reaction. The reaction in DMSO did not give any desired product (entry 18). Other solvents such as anisole, toluene, and cyclohexane were proved to be also good reaction media (entries 16, 17 and 19). When the reaction temperature increased to 160 °C, the reaction yield was improved to 88% using cyclohexane as solvent (entry 20).

Table 2. Reaction of 2a with Various Benzyl Chlorides^a

$R_{1} = \begin{array}{c} \text{II} & \text{SO}_{2} \text{Na} & \frac{\text{Pd}(\text{OAc})_{2}}{p - \text{Tol}_{3} P} \\ \hline & \text{cyclohexane} \end{array} R_{1} = \begin{array}{c} \text{Re} \\ \hline \\ \text{Cyclohexane} \end{array}$									
1 2a			160 °C, 4 h		3				
entry	benzyl chloride		product		yield (%) ^b				
1	CI	1a		3a	80				
2	CI	1b		3b	72				
3	CI	1c		3с	72				
4	CI	1d		3d	70				
5		l 1h		3e	50				
6	F	1e	F	3f	63				
7	CI	1f	cı	3g	66				
8	O_2N	Cl 1g	O_2N	3h	51				

 a Conditions: 1 (0.2 mmol), 2a (0.2 mmol), Pd(OAc)₂ (5 mol %), p-Tol₃P (10 mol %), CH₃ONa (0.3 mmol), cyclohexane (0.6 mL), 160 °C, 4 h under air. b Isolated yield.

With the optimized reaction conditions established, the scope of the reaction with respect to p-toluenesulfinic acid sodium salt (2a) and various benzyl chlorides (1) was investigated (Table 2). The reactions with benzyl chlorides bearing electron-donating groups (entries 2-5) and electron-withdrawing substituents (entries 6-8) at the aromatic ring

proceeded smoothly to give the desired products in moderate to good yields. The position of the substituents did not affect the reaction yields, and o-, m-, and p-methylbenzyl chlorides all gave the desired products in good yields (entries 2—4). However, the use of 4-methoxybenzyl chloride and 4-nitrobenzyl chloride both decreased the reaction yields significantly. Notably, replacement of benzyl chloride with benzyl bromide dramatically decreased the reaction yield under similar reaction conditions partly due to the much higher reactivity of benzyl bromide.

Table 3. Reaction of **1d** with Various Sodium Sulfinates (2)^a

 a Conditions: **1d** (0.2 mmol), **2** (0.2 mmol), Pd(OAc)₂ (5 mol %), p-Tol₃P (10 mol %), CH₃ONa (0.3 mmol), cyclohexane (0.6 mL), 160 °C, 4 h under air. b Isolated yield.

Under the optimized reaction conditions, the substituent effect on the reaction yield was investigated and the results are presented in Table 3. In general, alkyl substituents on the para position of sulfinic acid group did not affect the reaction yield significantly (entries 2–4). However, a methoxy substituent profoundly decreased the reaction yield, and the corresponding product 3m was obtained in 52% yield (entry 5). Halogen substituents such as fluoro, chloro, and trifluoromethyl were tolerated under the

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Scheme 1. Control Experiments

optimal reaction conditions, and the desired products were obtained in moderate to good yields (entries 6–8). An electron-withdrawing group such as nitro on the aromatic ring of sulfinic acid dramatically decreased the reaction yield, and only a trace amount of product was obseved when (4-nitrophenyl)sulfinic acid sodium salt (2j) reacted with 1d (entry 9). In all cases, cross-coupled diarylmethanes were the major products as determined by ¹H NMR method. ¹⁹

To get more information about the reaction mechanism, several control experiments were set up under the standard conditions. When the reaction of **1a** with **2a** was set up at 60 °C under air, 1-(benzylsulfonyl)-4-methylbenzene (**4a**) was obtained in 83% yield, and no corresponding ester (**5a**) was observed (scheme 1). Treatment of **4a** under the standard reaction conditions did not afford the final product **3a**. This means the product was not generated from **4a** or **5a** via extrusion of SO₂. Based on these observations, a tentative mechanism to rationalize the transformation is illustrated in Scheme 2. Oxidative addition of Pd(0) species with **1a** generates an intermediate Bn-Pd(II)-Cl (A). The replacement of chloride with arylsulfinic acid sodium salt forms an intermediate **B**, which can be further converted

Scheme 2. Proposed Mechanism

into intermediate C via extrusion of SO_2 . A reductive elimination of C affords the final product and regenerates Pd(0) species, thus closing the catalytic cycle.

In conclusion, we have demonstrated a palladium-catalyzed approach for the synthesis of diarylmethanes via desulfitative benzylation of aromatic sulfinic acid sodium salts with benzyl chlorides. The reaction showed good selectivity and tolerated various functional groups. This method provides an alternative route for the synthesis of diarylmethanes from benzyl chlorides. The scope, mechanism, and synthetic applications of this reaction are being explored in our laboratory.

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Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.