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COMMUNICATION

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Desulfinative and denitrogenative palladium-catalyzed cross-coupling of arylsulfonyl hydrazides with aryl diazonium salts

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Palladium-catalyzed cross-coupling of arylsulfonyl hydrazides with aryl diazonium salts to provide biaryl products under relatively mild conditions is established. This reaction proceeded smoothly with tetrabutylammonium iodide and gave the corresponding products with C—C bonds formed using $PdCl_2$/bis (dicyclohexylphosphino) methane catalyst under air. This method also allowed easy access to significant functional biaryls for potential applications in medicinal and organic chemistry.

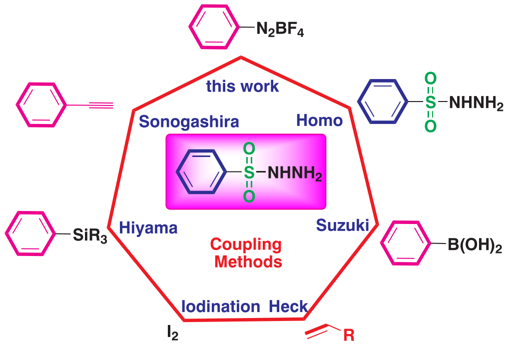
KEYWORDS
aryl diazonium salts, arylsulfonyl hydrazides, Pd-catalyzed cross-coupling

1 | INTRODUCTION

Aryl–aryl scaffolds are highly important structural motifs frequently found in natural products, pharmaceuticals and functional materials.[1–3] Transition metal-catalyzed C—C bond forming reactions represent powerful synthetic methods in organic synthesis,[4–8] which have been broadly applied in medicinal chemistry, organometallic chemistry and materials science.[9–11] Catalysis using palladium as the transition metal is certainly one of the most modern and powerful strategies for C—C bond formation, and the development of new palladium-catalyzed systems has aroused vigorous interest. Despite huge interest, palladium-catalyzed couplings involving very hindered structures and/or aryl chlorides as electrophiles are frequently beyond reach. Aryl iodides and, to a lesser extent, aryl bromides are not ideal electrophiles for developing sustainable chemistry, and thus the search for highly reactive electrophiles as substitutes has been a major concern.

Recently, C—C bond formation via C—N bond cleavage has attracted considerable attention, and versatile activated C—N bond-containing partners, such as diazonium salts, have been explored in cross-coupling reactions under transition metal catalysis. Aryl diazonium salts are certainly one of the most reactive aryl halide surrogates and have found many applications in palladium-catalyzed cross-coupling reactions during the last thirty years.[12–14] Aryl diazonium salts are easily accessed and isolated as crystalline compounds by diazotization of the corresponding aniline. To some extent, the use of diazonium salts follows many principles of green chemistry as it features cost, energy and waste benefits.[15–20]

Commercial arylsulfonyl halides,[5,21–24] sulfinates[25–28] and hydrazines[29–33] are recognized as new aryl sources that recently have been universally utilized in desulfinative arylation reactions.[34–36] Notably, owing to the features of good stability, versatile transformation models, compatibility with water and being free of unpleasant odor, arylsulfonyl hydrazines are regarded



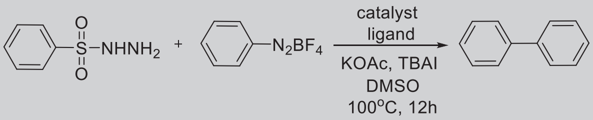
SCHEME 1 Palladium-catalyzed denitrogenative and desulfinative cross-coupling of arylsulfonyl hydrazides

as particularly favorable aryl precursors in desulfination reactions by C—S bond cleavage. Palladium-catalyzed denitrogenative and desulfinative cross-couplings of arylsulfonyl hydrazides have been studied (Scheme 1). Tian and co-workers first employed arylsulfonyl hydrazides as aryl sources in Heck-type coupling reactions via desulfination processes.[37] Zhao and co-workers[38] reported homocoupling of arylsulfonyl hydrazides and Deng and co-workers[39] reported desulfinative iodination with iodine. It is noted that the groups of Zhou[40] and Dou[41] have independently employed arylsulfonyl hydrazides as aryl sources in Hiyama and Suzuki coupling reactions by desulfination. Dong and co-workers reported palladium-catalyzed desulfinative Sonogashira coupling of arylsulfonyl hydrazides with terminal alkynes.[42] However, the new-type palladium-catalyzed denitrogenative and desulfinative cross-coupling of arylsulfonyl hydrazides with aryl diazonium salts is still rarely reported. Herein we report the first example of desulfinative coupling of aryl diazonium salts with arylsulfonyl hydrazides with good to excellent efficiency.

2 | RESULTS AND DISCUSSION

Initial experiments were carried out using phenylsulfonyl hydrazide and phenyl diazonium salt as model substrates, and we screened various catalysts and ligands (Table 1). Pd (II)–phosphine ligand systems were first examined on the basis of several recent reports.[43,44] However, the $PdCl_2$/P $(OPh)_3$-catalyzed reaction using tetrabutylammonium iodide (TBAI) as the additive and KOAc as the base in dimethylsulfoxide (DMSO) at 100°C gave only a trace amount of cross-coupling product (Table 1, entry 1). The screening of monodentate phosphine-based ligands, such as PCy_3, TFP (trifurylphosphine) and Xphos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), gave

TABLE 1 Desulfinative coupling of phenylsulfonyl hydrazides with phenyl diazonium salt with various catalysts and ligands[a]



Entry	Ligand	Yield (%)[b]	Entry	Catalyst	Yield (%)[c]
1	P $(OPh)_3$	<5	13	Pd $(PPh_3)_4$	8
2	PCy_3	28	14	Pd $(dba)_2$	12
3	TFP	33	15	Pd_3 $(dba)_2$	15
4	Xphos	47	16	Pd $(OAc)_2$	76
5	Dppe	70	17	Pd $(TFA)_2$	69
6	Dppp	81	18	Pd $(OTf)_2$	62
7	Xantphos	77	19	Pd $(CH_3CN)_2Cl_2$	79
8	DPEphos	83	20	Pd $(PhCN)_2Cl_2$	73
9	Dcype	89	21	Pd $(dppf)Cl_2$	86
10	Dcypm	93	22	Pd $(dppe)Cl_2$	82
11	Dcypp	90	23	Pd $(dppp)Cl_2$	87
12	Dcypm	91[b]	24	$PdCl_2$	88 [e]

[a] Reaction conditions: phenylsulfonyl hydrazide (1.0 mmol), phenyl diazonium salt (1.1 mmol), TBAI (1.5 mmol), KOAc (2.0 mmol), DMSO (2 ml), 100 °C, 12 h. Isolated yields.

[b] $PdCl_2$ (5 mol%), ligand (10 mol%).

[c] Catalyst (5 mol%), Dcypm (10 mol%).

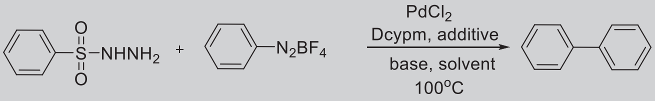
[d] $PdCl_2$ (5 mol%), Dcypm (20 mol%).

[e] $PdCl_2$ (10 mol%), Dcypm (10 mol%).

modest yields (Table 1, entries 2–4). We then screened a combination of $PdCl_2$ and some common and bidentate phosphine ligands including Dppe, Dppp, Xantphos (4,5-bis (diphenylphosphino)-9,9-dimethylxanthene), DPEphos (bis[2-(diphenylphosphino)phenyl] ether), Dcype (1,2-bis (dicyclohexylphosphino)ethane), Dcypm (bis (dicyclohexylphosphino)methane) and Dcypp (1,3-bis (dicyclohexylphosphino)propane) (Table 1, entries 5–11). Among them a 1:2 $PdCl_2$-to-Dcypm combination gave the best result. A higher Dcypm loading resulted in a decrease of the yield (Table 1, entry 12). Application of Pd $(PPh_3)_4$, Pd $(dba)_2$ and Pd_3 $(dba)_2$ as catalysts yielded traces of desired product (Table 1, entries 13–15). It was observed that most of the Pd (II) catalysts could successfully promote the reaction (Table 1, entries 16–24). Therefore, Pd $(OAc)_2$, Pd $(TFA)_2$ and Pd $(OTf)_2$ in combination with Dcypm were applied with less effect affording biphenyl in yields varying between 62 and 76% (Table 1, entries 16–18). We also tried to use the palladium source with nitrogen ligands using Dcypm as diphosphine ligand. However, these combinations behaved with lower catalytic activity than the $PdCl_2$–Dcypm system (Table 1, entries 19 and 20). The introduction of various palladium complexes with phosphine ligands (Pd $(dppf)Cl_2$, Pd $(dppe)Cl_2$ and Pd $(dppp)Cl_2$) did not increase the yields (Table 1, entries 21–23). Among the Pd (II) catalysts tested, $PdCl_2$ was the most effective affording the addition product in 93% yield. Marked improvement was observed when the $PdCl_2$ loading was increased to 10 mol%, achieving an 88% yield (Table 1, entry 24). Not surprisingly, the reaction did not produce biphenyl in the absence of the Pd (II) catalyst or ligand.

Next we examined the effect of additive, base and solvent on the reaction with $PdCl_2$ catalyst at 100°C using Dcypm as ligand. The additives NaI, KI and NH_4I instead of TBAI were not suitable (Table 2, entries 1–4).

TABLE 2 Desulfinative coupling of phenylsulfonyl hydrazides with phenyl diazonium salt with various additives, bases and solvents[a]



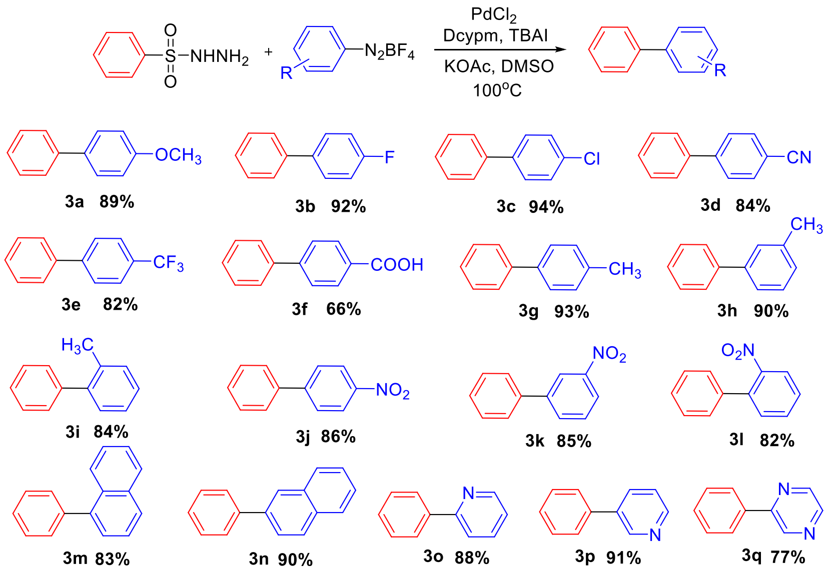
Entry	Additive	Base	Solvent	Yield (%)[b]
1	NH_4I	KOAc	DMSO	42
2	NaI	KOAc	DMSO	55
3	KI	KOAc	DMSO	71
4	TBAI	KOAc	DMSO	93
5	TBAI	K_2CO_3	DMSO	81
6	TBAI	Na_2CO_3	DMSO	76
7	TBAI	NaOAc	DMSO	86
8	TBAI	KOH	DMSO	17
9	TBAI	Cs_2CO_3	DMSO	13
10	TBAI	CsF	DMSO	7
11	TBAI	DABCO	DMSO	<5
12	TBAI	DBU	DMSO	<5
13	TBAI	KOAc	DMF	90
14	TBAI	KOAc	DMA	85
15	TBAI	KOAc	Toluene	62
16	TBAI	KOAc	Xylene	56
17	TBAI	KOAc	DME	73
18	TBAI	KOAc	1,4-Dioxane	60
19	TBAI	KOAc	*t*-BuOH	—
20	TBAI	KOAc	DCE	—

[a] Reaction conditions: phenylsulfonyl hydrazide (1.0 mmol), phenyl diazonium salt (1.1 mmol), $PdCl_2$ (5 mol%), Dcypm (10 mol%), additive (1.5 mmol), base (2.0 mmol), solvent (2 ml), 100 °C, 12 h.

[b] Isolated yields.

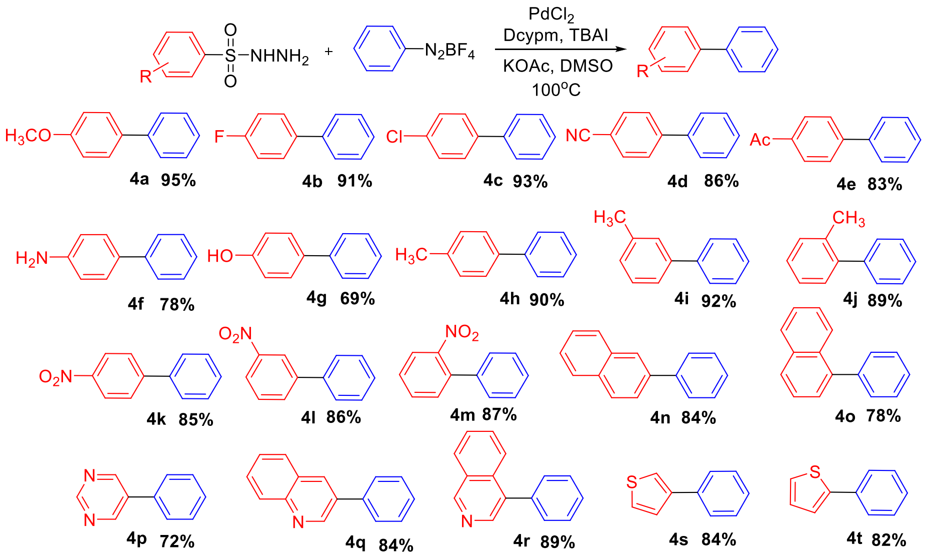
Subsequently, the influence of base was studied (Table 2, entries 5–12). Potassium acetate proved superior, though potassium carbonate, sodium carbonate and sodium acetate afforded low yields of the coupled adducts (Table 2, entries 5–7). Reactions with potassium hydroxide, cesium carbonate and cesium fluoride afforded only trace amounts of products (Table 2, entries 8–10). Two alternative bases, DABCO and DBU, were demonstrated to be not effective for this transformation (Table 2, entries 11 and 12). Various solvents were screened by further optimization, and the results revealed that aprotic solvent is a better choice for the reaction (Table 2, entries 13–19). Both DMF and DMA were as effective as DMSO as solvent (Table 2, entries 13 and 14). The use of other solvents such as toluene, xylene, DME and/or 1,4-dioxane resulted in yields of biphenyl of 56–73% (Table 2, entries 15–18). Unfortunately, the desired products were not obtained in *t*-BuOH and DCE (Table 2, entries 19 and

TABLE 3 Cross-coupling of phenylsulfonyl hydrazides with various aryl diazonium salts[a]



[a]Reaction conditions: phenylsulfonyl hydrazide (1.0 mmol), aryl diazonium salt (1.1 mmol), PdCl$_2$ (5 mol%), Dcypm (10 mol%), TBAI (1.5 mmol), KOAc (2.0 mmol), DMSO (2 ml), 100 °C, 12 h. Products are shown with isolated yields.

TABLE 4 Cross-coupling of various arylsulfonyl hydrazides with phenyl diazonium salts[a]

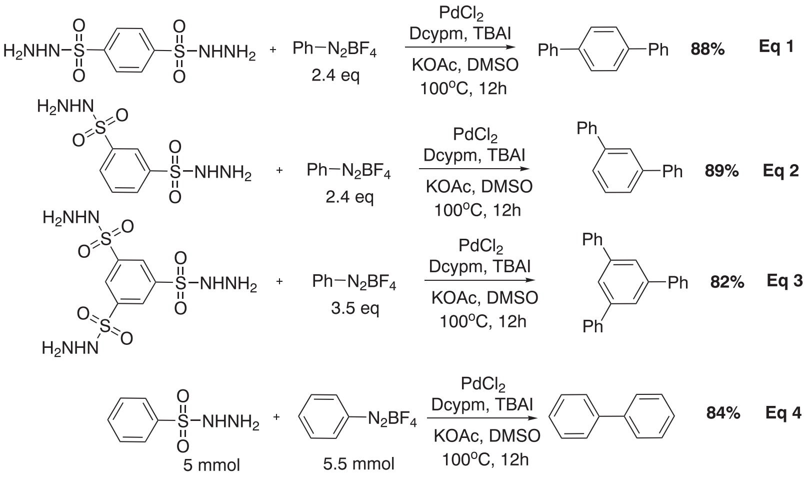


[a]Reaction conditions: arylsulfonyl hydrazide (1.0 mmol), phenyl diazonium salt (1.1 mmol), PdCl$_2$ (5 mol%), Dcypm (10 mol%), TBAI (1.5 mmol), KOAc (2.0 mmol), DMSO (2 ml), 100 °C, 12 h. Products are shown with isolated yields.

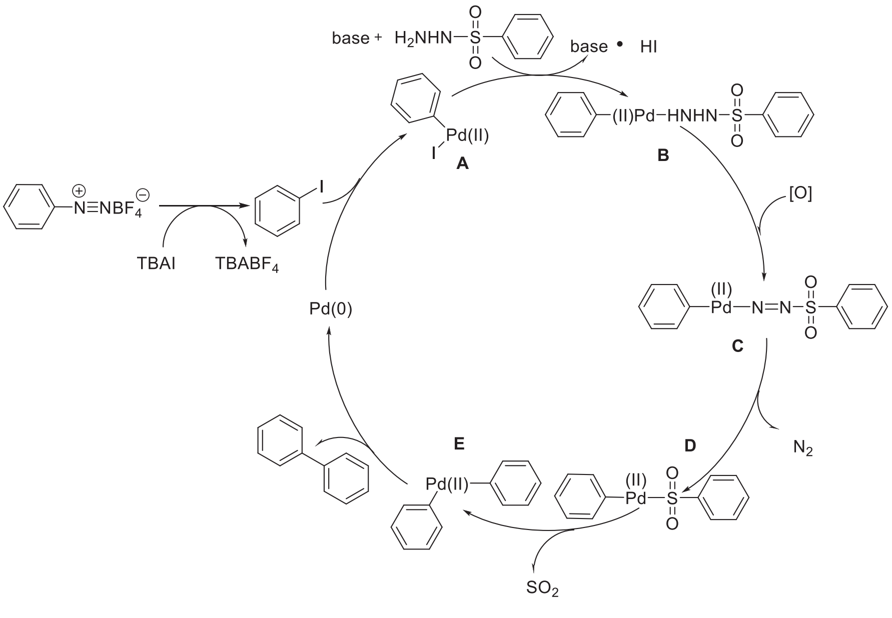
20). The reaction could not be further improved by lengthening the reaction time to 24 h. Moreover, the yield was slightly decreased when the reaction was performed at a lower or higher temperature. Controlled experiments were conducted without the addition of base or iodide; however, no desired products were observed.

Encouraged by these results, we applied the desulfinative protocol described above to a range of aryl diazonium salts and arylsulfonyl hydrazides (Table 3). The scope of aryl diazonium salts was initially explored in the presence of phenylsulfonyl hydrazide. Gratifyingly, introduction of methoxy, fluoro, chloro, cyano and trifluoromethyl groups into the phenyl ring of diazonium salts was well tolerated, and the coupling products were isolated in good to excellent yields (Table 3, 3**a**–3**e**). Notably, 4-(diazenyl) benzoic acid successfully underwent coupling to give **3f**, albeit in a low yield. Steric hindrance, often problematic in metal-catalyzed coupling reactions, does not pose a problem. The majority of the phenyl diazonium salts with *para*-substitutions gave good yields, while the *ortho*- and *meta*-substituted phenyl diazonium salts afforded a slightly lower yield (Table 3, 3**g**–3**l**). Naphthyl-substituted diazonium salts could also be employed in this reaction to afford the products **3 m** and **3n** in good yields. It is worth noting that this protocol is also applicable to heterocyclic aromatics such as pyridine and pyrazine (Table 3, 3**o**–3**q**).

Then, the scope of arylsulfonyl hydrazides was explored in the reaction with phenyl diazonium salts. It is noteworthy that either an electron-donating or an electron-withdrawing group such as methoxy, fluoro, chloro, cyano and acetyl was introduced into the diaryls without any problem by employing phenylsulfonyl hydrazides bearing such a group on the aromatic ring at *para* position (Table 4, 4**a**–4**e**). In general, the expected product yields were higher with arylsulfonyl hydrazides bearing electron-donating substituents, whereas the use of arylsulfonyl hydrazides containing electron-withdrawing



SCHEME 2 Polyarylation of phenylsulfonyl hydrazides using the method presented



SCHEME 3 Possible mechanism for cross-coupling

substituents led to the products in modest isolated yields. It is important to note that unprotected hydroxyl groups or amino groups in the arylsulfonyl hydrazides did not hinder the reaction and no O- or N-arylating product was detected in these cases (Table 4, 4**f** and 4**g**). Steric hindrance in the arylsulfonyl hydrazides was not a problem. Reaction of *meta*- or *ortho*-substituted phenylsulfonyl hydrazides delivered the biaryls in high yields (Table 4, 4**h**–4**m**). Naphthylsulfonyl hydrazides selectively transferred the aryl moiety, furnishing products **4n** and **4o**. This method can be extended to heteroarylsulfonyl hydrazides to synthesize arylheteroaryls **4p–4 t**, which are of particular interest for the development of new drugs.

We next examined the reactivity of di- or tri-arylation of phenylsulfonyl hydrazides to afford terphenyls (Scheme 2). The reaction of arylsulfonyl hydrazides with various amounts of phenyl diazonium salt furnished the *p*-terphenyl, *m*-terphenyl and 3-phenyl-*m*-terphenyl in good to excellent yields (Scheme 2, equations (1)–(3)). Under the same conditions, a 5 mmol scale of phenylsulfonyl hydrazide and phenyl diazonium salt could be completely transformed to afford a yield of 84% of the desired product (Scheme 2, equation (4)).

Based on our experimental results and literature evidence, a plausible reaction mechanism is proposed, a shown in Scheme 3. After initial formation of iodobenzene by *in situ* Sandmeyer-type iodination reaction of phenyl diazonium salt with TBAI, the combination of $PdCl_2$ and Dcypm generates the active [Pd(0)] catalyst which undergoes oxidative addition into the Ph—I bond to form phenylpalladium (II) complex **A**. Afterwards, the Pd (II) species **B** is generated from intermediate **A** and phenylsulfonyl hydrazide by deprotonation with base. Organometallic complex **B** generates (arylsulfonyl) diazene Pd (II) species **C** via oxidative dehydrogenation under oxygen atmosphere, and the subsequent entropically favorable denitrogenation of intermediate **C** converts to (arylsulfonyl) arylpalladium (II) complex **D**. Intermediate **D** is generated from diaryl Pd (II) complex **E** via desulfination. Finally, reductive elimination forms the desired biphenyl and regenerates [Pd(0)] to complete the catalytic cycle.

3 | CONCLUSIONS

We have verified that arylsulfonyl hydrazides and aryl diazonium salts can be used as versatile coupling participants in $PdCl_2$/Dcypm-catalyzed cross-coupling reactions. Various arylsulfonyl hydrazides and aryl diazonium salts were smoothly converted under the standard conditions to form the corresponding biaryl products in good to excellent yields. Advantages of this reaction include good functional group tolerance, high reactivity, relatively mild conditions and easy access to the coupling partners. Terphenyls were effectively transformed in the reaction with phenyl diazonium salt, and the reaction could be scalable with good efficiency.

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