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Palladium-catalyzed C-3 desulfitative arylation of indolizines with sodium arylsulfinates and arylsulfonyl hydrazides†

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Derivatized indolizines were efficiently prepared by direct C-3 arylation of indolizines using sodium arylsulfinates and arylsulfonyl hydrazides. Pd-catalyzed desulfitative C-3 arylation with sodium arylsulfinates was achieved with the assistance of peroxides, and the catalytic efficiency was promoted by N-containing ligands. Arylsulfonyl hydrazides were also successfully applied in Pd-catalyzed desulfitative C-3 arylation with indolizines, and the side homocoupling reactions can be restrained in the component solvent under milder conditions. Various derivatives were synthesized in good yields by both methods, offering expedient protocols for the synthesis of C-3 functionalized indolizine molecules.

Introduction

Indolizine has a delocalized 10π-electron aromatic structure,[1] and is of theoretical and practical interest in a wide variety of natural products with useful biocidal activities.[2] The indolizine framework occupies a special place in heterocyclic systems due to the presence of this structurally challenging nitrogen heterocyclic moiety in a number of bioactive natural products[3] (Fig. 1) with antimicrobial (**1a–1d**), uterotrophic (**1e**, for estrogen binding affinity), anticancer (**1f–1h**), antidiabetic (**1i**), anti-inflammatory (**1j** and **1k**), antihistaminic, anti-acetylcholinic (**1l–1n**), antitubercular (**1o**) and antioxidant (**1p** and **1q**, for lipoxygenase) activities. Most of the work on indolizine derivatives has been concerned with the search for organic materials[4] and potential candidates for pharmaceutical research,[5] such as phosphatase inhibitors (**1r**), phosphodiesterase inhibitors (**1s**), PDE5A inhibitors (**1t**), L-type calcium channel blockers (**1u**) and leukotriene synthesis inhibitors (**1v**).[6]

The medicinal and biological relevance of the indolizine derivatives has created a need for the development of efficient synthetic strategies for obtaining such derivatives.[7] Traditionally, substituted indolizines can be obtained by the reaction of pyridinium ylides with ethylenic compounds to form dihydroindolizines which readily oxidize to the aromatic system. The enormous advances in metal-catalyzed direct arylation with C–H functionalization involved have envolved into the most powerful synthetic tools for generation of biaryl compounds.[8] Consequently, many synthetic methodologies for functionalized indolizine have been reported.[9] More effort has been paid to decorate the indolizine core and derivatized with interesting method, such as olefination,[10] alkynylation,[11] benzylation,[12] sulfenylation[13] and dimerization.[14]

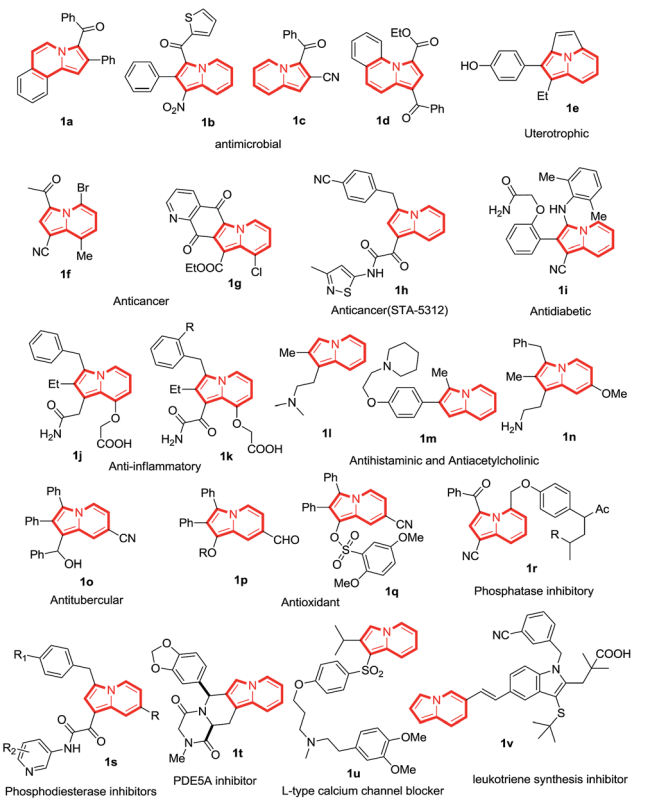

Fig. 1 Indolizine framework in bioactive natural products.

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Previous studies also applied bromoarenes[15] and chloroarenes[16] as arylation reagents to indolizines, arylation with relatively unreactive organo species, such as arylboronic species[17] and aryltrifluoroborate salts,[18] has also been reported. Owe to the important application of 3-aryl-indolizine[19] (such as full-color tenability of emission wavelength of the indolizine core C3-Indo-Fluor[20]), more effort for the synthesis of C-3 arylation indolizine derivatives should be paid.

Along with the development of new electrophilic partners for C–C bond formation, arenesulfonates and their analogues have been regarded as good substrate, which are easily availability, inexpensiveness, and high versatility. In our continuing interest in the discovery of new arylating reagents based on desulfitative coupling,[21] we are very interested at arylsulfinic acids and arylsulfonyl hydrazides. Arylsulfinic salts are stable and easy to handle reagents, which show great potential as aryl sources for the synthesis of various aromatic compounds. The density functional theory (DFT) calculation showed that C–SO_2R bond dissociation enthalpies (BDEs) are much lower than corresponding C–CO_2R BDEs, which proved arylsulfinic acids are more reactive substrates than arylcarboxylic acids.[22] Arylsulfinic acids have been widely used these years for Heck,[23] Hiyama,[21b] Suzuki cross-coupling reactions,[21c] C–H bond activation[24] and addition with triple bond[25] in recent years.[26]

Arylsulfonyl hydrazides are readily accessible solids and compatible with moisture, which can be prepared in one step from readily available arylsulfonyl chlorides and hydrazine hydrates. Arylsulfonyl hydrazides have been widely employed as sulfone[27] or thioether[28] sources to construct organic sulfur compounds through the cleavage of N–S and/or S–O bond. Recently, arylsulfonyl hydrazides have been employed as novel aryl sources by means of their C–S bonds, which would undergo the loss of N_2 and SO_2 gas *in situ*. In the presence of palladium catalysts and carbonyl compounds, arylsulfonyl hydrazides can readily convert into very active diazo compounds which are found to be very important cross-coupling partners. Arylsulfonyl hydrazides have been used as aryl sources *via* desulfitation–denitrogenation for Heck-type reaction[29] Hiyama,[30] Suzuki[31] and direct C–H bond arylations.[32] We have reported a novel protocol to construct C-3 indolizines using arylsulfonyl chloride as aryl sources[33] (Fig. 2). Despite this success, limitations of arylsulfonyl chloride have been noted such as moisture sensitivity and long reaction time. Thus it is necessary to explore air-stable, readily available, and inexpensive alternatives. Herein, we disclose practical and convenient procedures to synthesize various derivatized indolizines with arylsulfinic salts and arylsulfonyl hydrazides (Fig. 3).

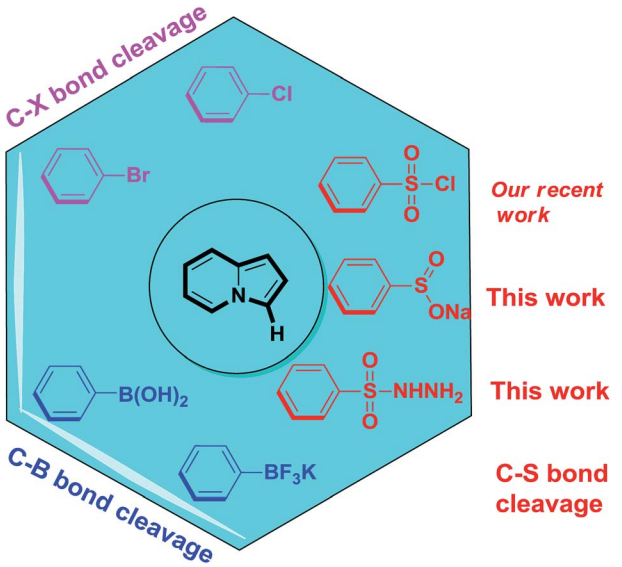


Fig. 2 Different bond cleavage types of indolizines' C-3 arylation.

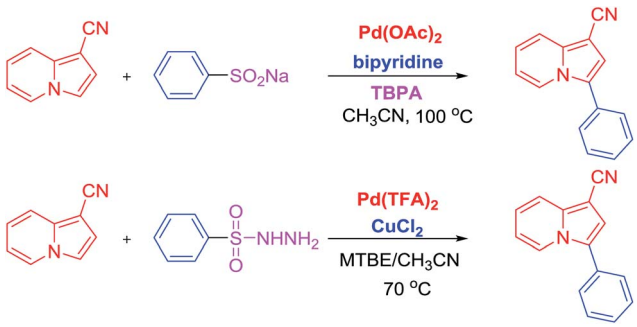


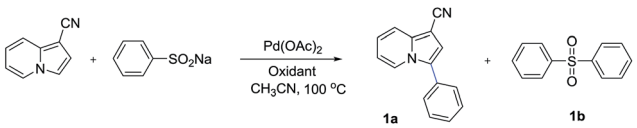
Fig. 3 Research outline for direct C-3 arylation of indolizines using sodium arylsulfinates and arylsulfonyl hydrazides.

Results and discussion

Optimization of C-3 desulfitative arylation with sodium arylsulfinates

The reaction of indolizine-1-carbonitrile with sodium benzenesulfinate was chosen as a model system for optimization studies (Table 1). Initially, the reaction was carried out in CH_3CN at 100 °C for 6 h in the presence of palladium acetate (3 mol%) as a catalyst and $Cu(OAc)_2$ (2 equiv.) as an oxidant only gave tiny amounts of the desired arylation product, but instead formed a large amount of unwanted sulfonyldibenzene by-product (Table 1, entry 1).[34] Although the addition of other Cu-salts and Ag-salts as oxidants to the reaction system also failed to occur desulfitative C-3 arylation (Table 1, entries 2–10), the presence of Ag-salts was observed to diminish the homo-coupling sulfonyldibenzene (Table 1, entries 7–10). When simultaneously adding benzoyl peroxide (BPO) as oxidants, we were pleased to find that ethyl 3-phenylindolizine-1-carboxylate was obtained in 56% yield without the detection of sulfonyldibenzene by-product (Table 1, entry 11). Other peroxides, such as di-*t*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), and *tert*-butyl peroxypivalate (TBPV) were significantly more effective, whereas di-*tert* amyl peroxide (DTAP) and *tert*-amyl hydroperoxide (TAHP) gave comparable results (Table 1, entries 12–16). *tert*-Butyl cumyl peroxide (TBCP) and dicumyl peroxide (DCP) were ineffective for the generation of **1a** (Table 1, entries 17 and 18). However, no **1a** was detected when the model reaction was performed with *tert*-butyl hydroperoxide (TBHP) (Table 1, entry 19). Among the oxidants tested, *tert*-butyl

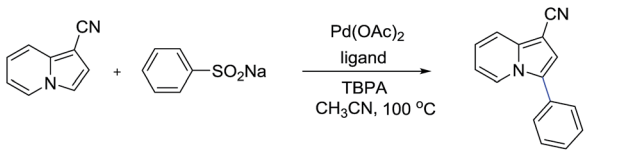
Table 1 Oxidant selection for Pd-catalyzed C-3 arylation of indolizines with sodium arylsulfinates[a,b]



Entry	Oxidant	Yield (%) of **1a**	Yield (%) of **1b**	Entry	Oxidant	Yield (%) of **1a**
1	$Cu(OAc)_2$	8	74	11	BPO	56
2	$CuCl_2$	10	65	12	DTBP	75
3	$CuBr_2$	5	60	13	TBPB	77
4	$Cu(OTf)_2$	14	71	14	TBPV	72
5	$Cu(TFA)_2$	18	61	15	DTAP	70
6	CuI	—	—	16	TAHP	68
7	AgOAc	29	23	17	TBCP	52
8	Ag_2CO_3	26	27	18	DCP	57
9	AgOTf	39	40	19	TBHP	—
10	$AgNO_3$	33	27	20	TBPA	81

[a] Reaction conditions: sodium benzenesulfinate (0.6 mmol), indolizine-1-carbonitrile (0.5 mmol), $Pd(OAc)_2$ (3 mol%), oxidant (0.5 mmol), CH_3CN (1.0 ml) at 100 °C for 6 hours under air unless otherwise indicated. [b] Isolated C-3 arylation yield.

Table 2 Catalyst selection for Pd-catalyzed C-3 arylation of indolizines with sodium arylsulfinates[a]



Entry	Catalyst	Ligand	Yield[b] (%)
1	$Pd(OAc)_2$	—	81
2	$Pd(OAc)_2$	PPh_3	38
3	$Pd(OAc)_2$	BINAP	41
4	$Pd(OAc)_2$	DBN	84
5	$Pd(OAc)_2$	DBU	88
6	$Pd(OAc)_2$	1,10-Phenanthroline	90
7	$Pd(OAc)_2$	2,2′-Bipyridine	93
8	$Pd(OAc)_2$	TMEDA	84
9	$Pd(OAc)_2$	DMAP	72
10	PdI_2	2,2′-Bipyridine	85
11	$PdCl_2$	2,2′-Bipyridine	88
12	$Pd(CH_3CN)_2Cl_2$	2,2′-Bipyridine	79
13	$Pd(PPh_3)_4$	2,2′-Bipyridine	71
14	$Pd_2(dba)_3$	2,2′-Bipyridine	76
15	$PdCl_2$(dppf)	2,2′-Bipyridine	63
16	$PdCl_2(PPh_3)_3$	2,2′-Bipyridine	69
17	—	2,2′-Bipyridine	—

[a] Reaction conditions: sodium benzenesulfinate (0.6 mmol), indolizine-1-carbonitrile (0.5 mmol), catalyst (3 mol%), ligand (0.05 mmol), oxidant (0.5 mmol),CH_3CN (1.0 ml) at 100 °C for 6 hours under air unless otherwise indicated. [b] Isolated C-3 arylation yield.

peroxyacetate (TBPA) was preferentially chosen as the oxidant with the highest yield (Table 1, entry 20).

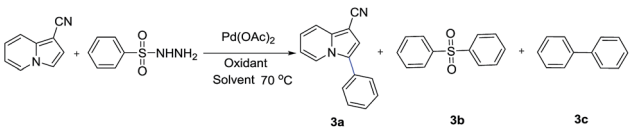
Then we attempted to append the ligands to enhance the reaction activity. However, decreased yields of products were obtained with the introduction of phosphine ligands (Table 2, entries 2 and 3). To our delight, N-contained ligands were crucial for the transformation. Among the N-ligand examined, such as DBN (1,5-diazabicyclo[4.3.0]non-5-ene), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), 1,10-phenanthroline, 2,2′-bipyridine, TMEDA (*N*,*N*,*N*′,*N*′-tetramethyl-ethane-1,2-diamine) and DMAP (4-dimethylaminopyridine), 2,2′-bipyridine was shown the best (Table 2, entries 4–9). During the screening of palladium catalysts, such as PdI_2, $PdCl_2$, $PdCl_2(CH_3CN)_2$, provided the products in 85%, 88%, 79% yield, respectively (Table 2, entries 10–12). Transformations with Pd(0) catalysts obtained moderate yields (Table 2, entries 13 and 14), and the formation of arylation product was about 63–69% using P-contained palladium catalyst (Table 2, entries 15 and 16). No product was formed in the absence of Pd (Table 2, entry 17).

Optimization of C-3 desulfitative arylation with arylsulfonyl hydrazides

We initiated our investigation of phenylsulfonyl hydrazide and indolizine-1-carbonitrile to optimize the reaction parameters. To our delight, the occurred in the presence of $Pd(OAc)_2$ (2 mol%) and $Cu(OAc)_2$ (1 mmol) in NMP (1-methyl-2-pyrrolidone) under 100 °C, and 23% of the desired products was detected (Table 3, entry 1). However, 22% yield of sulfonyldibenzene and 7% yield of biphenyl has also been detected by GC-MS. The side-reaction would consume the phenylsulfonyl hydrazide and restrict the C-3 arylation. The effects of catalysts, oxidants, solvents and reaction temperature were investigated. As shown in Table 3, we found the Cu salts were crucial for this transformation. Among the oxidant examined, such as AgOAc, BPO, DDQ and Oxone, no products were detected (Table 3, entries 2–5). We have reported that Cu(II) salts mediated homocoupling with arylsulfonyl hydrazides to afford biarylsulfone under 100 °C, and this transformation could be obviously restrain under lower temperature.[35] Intriguingly, when the reaction was performed under 70 °C, it gave 64% yield of desired arylation products, whereas gave less than 10% of the by-product (sulfonyldibenzene and biphenyl) (Table 3, entry 6). Other Cu(II) salts such as $Cu(OTf)_2$, $CuBr_2$ and $Cu(NO_3)_2$ have shown comparable activities to the transformation (Table 3, entries 7–9). On the contrary, one-valence copper such as CuBr did not coped with this reaction (Table 3, entry 10). Indeed, the yield increased to 80% when $CuCl_2$ was employed as the oxidant without the detection of desulfitative homocoupling by-products (Table 3, entry 11).

The following optimization is about solvents applied in this reaction. The effects of solvents were investigated and the by-products sulfonyldibenzene have also been detected (Table 3, entries 12–16). Among solvents explored, DMSO, DMF and DMA afforded the desired arylation products with 82%, 77% and 71% yields (Table 3, entries 12–14). The reaction did not occur at all when carried out in toluene or xylene (Table 3, entries 15 and 16). Furthermore, the side reaction did not occur at all when carried out in CH_3CN, indicating that it may be a better choice

Table 3 Oxidant and solvent selection for Pd-catalyzed C-3 arylation of indolizines with sodium arylsulfinates[a,b]



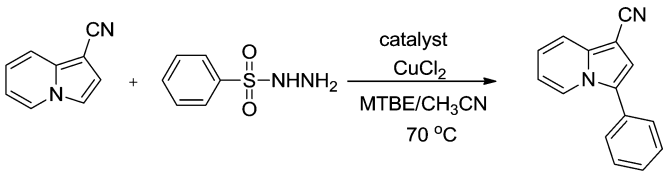
Entry	Oxidant	Solvent	Yield (%) of **3a**	Yield (%) of **3b**	Yield (%) of **3c**
1[c]	$Cu(OAc)_2$	NMP	23	22	7
2	AgOAc	NMP	—	—	—
3	BPO	NMP	—	—	—
4	DDQ	NMP	—	—	—
5	Oxone	NMP	—	—	—
6	$Cu(OAc)_2$	NMP	64	5	4
7	$CuBr_2$	NMP	76	4	—
8	$Cu(OTf)_2$	NMP	73	5	10
9	$Cu(NO_3)_2$	NMP	70	8	—
10	CuBr	NMP	—	—	—
11	$CuCl_2$	NMP	80	4	—
12	$CuCl_2$	DMSO	82	21	—
13	$CuCl_2$	DMF	77	29	—
14	$CuCl_2$	DMA	71	38	—
15	$CuCl_2$	Toluene	—	—	—
16	$CuCl_2$	Xylene	—	—	—
17	$CuCl_2$	CH_3CN	70	—	—
18	$CuCl_2$	THF	82	4	—
19	$CuCl_2$	1,4-Dioxane	85	6	—
20	$CuCl_2$	MTBE	88	2	—
21	$CuCl_2$	DME/CH_3CN	86	—	—

[a] Reaction conditions: indolizine-1-carbonitrile (0.5 mmol), phenylsulfonyl hydrazides (0.6 mmol), $Pd(OAc)_2$ (3 mol%), oxidant (1 mmol), solvent (1.0 ml, the v/v ratio of solvents was 1 : 1) at 70 °C for 6 hours unless otherwise indicated. [b] GC-MS yield using hexane as internal standard. [c] The reaction was performed under 100 °C.

for this reaction (Table 3, entry 17). Although THF and 1,4-dioxane afforded the same or a higher yield of the desired product, the competing homo-coupling product, sulfonyldibenzene, was the minor product in these cases(Table 3, entries 18 and 19). Intriguingly, when MTBE (methyl *tert*-butyl ether) was used as the solvent, it gave a 88% yield of desulfitative C-3 arylation product, whereas gave less than 5% of the by-product (Table 3, entry 20). Subsequently, we further considered the application of component solvent. It proceeded smoothly in solvent comprised of DME and CH_3CN (volume ratio 1 : 1) with a yield of 86% (Table 3, entry 21). To our delight, the application of MTBE and CH_3CN could obviously reduce the formation of by-products. The isolation yield was up to 80% (Table 4, entry 1).

At the outset, different transition metal catalysts, *viz.* $Pd(OAc)_2$, $Ni(OAc)_2$, $Co(OAc)_2$, $AuCl_3$, $RuCl_3$, $RhCl_3$ and $FeCl_2$, were screened using $CuCl_2$ as an oxidant in MTBE/CH_3CN to determine their catalytic efficacy (Table 4, entries 1–6). We were astonished to see that only the palladium salt could bring about the desired conversion (Table 4, entry 1), and therefore the studies were directed to look at the prospective of other palladium salts too. All the palladium(II) salts tried, *viz.* PdX_2, $PdCl_2(PPh_3)_3$, $Pd(dppf)Cl_2$, $Pd(PhCN)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$, and

Table 4 Catalyst selection on the reaction[a]



Entry	Catalyst	Yield (%)	Entry	Catalyst	Yield (%)
1	$Pd(OAc)_2$	80	11	$PdCl_2(PPh_3)_3$	73
2	$Ni(OAc)_2$	—	12	$Pd(dppf)Cl_2$	77
3	$Co(OAc)_2$	—	13	$Pd(PhCN)_2Cl_2$	81
4	$AuCl_3$	—	14	$Pd(CH_3CN)_2Cl_2$	79
5	$RuCl_3$	—	15	$Pd(OTs)_2$	89
6	$RhCl_3$	—	16	$Pd(TFA)_2$	92
7	$FeCl_2$	—	17	$Pd(PPh_3)_4$	—
8	$PdCl_2$	82	18	$Pd_2(dba)_3$	—
9	$PdBr_2$	84	19	$Pd(dba)_2$	—
10	PdI_2	77	20	—	—

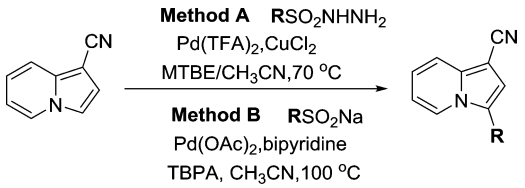
[a] Reaction conditions: indolizine-1-carbonitrile (0.5 mmol), phenylsulfonyl hydrazides (0.6 mmol), catalyst (3 mol%), $CuCl_2$ (1 mmol), MTBE/CH_3CN (1.0 ml, v/v = 1 : 1) at 70 °C for 6 hours unless otherwise indicated.

$Pd(OTs)_2$, invariably worked well (Table 4, entries 8–15), but the performance of $Pd(TFA)_2$ was maximum, providing the C3-aryl product **1a** in 92% yield at 70 °C (Table 4, entry 16). As evident, the yield of **1a** was not obtained at all when Pd(0) catalysts was used (Table 4, entries 17–19). The experiment under identical conditions without the aid of a palladium salt ended with no conversion (Table 4, entry 20).

Substrate scope of the C-3 desulfitative arylation of indolizines with sodium arylsulfinates and arylsulfonyl hydrazides

With the optimized reaction conditions in hand, we investigated the effect of electronic and structural variations of the arylsulfonyl hydrazides (column A) and sodium arylsulfinates (column B). The scope of both reaction-types are presented in Table 5, for the comparison of two coupling reagents. As expected, a series of electron-donating functional groups on the phenyl ring of phenylsulfonyl hydrazides, such as methoxy, methyl and *tert*-butyl were compatible under this procedure, and the products were isolated in good to excellent yields (Table 5, column A, entries 1–3). The halogen functional groups are tolerant to the palladium-catalyzed C-3 arylation of arylsulfonyl hydrazides (Table 5, column A, entries 4 and 5). Encouraged by these promising results, we further applied the optimized reaction conditions to examine the substrate scope of arylsulfonyl hydrazides having electron-withdrawing substituents. Gratifyingly, nitro and trifluoromethyl functionalities on the phenyl ring of sulfonyl hydrazides, also afforded the desired products in good yields (Table 5, column A, entries 6 and 7). These results implied that the electronic effect is not critical for this transformation. In comparison, different functionalities on the phenyl ring of sodium arylsulfinates, whether they were

Table 5 The reaction of indolizine-1-carbonitrile with various arylsulfonyl hydrazides and sodium arylsulfinates



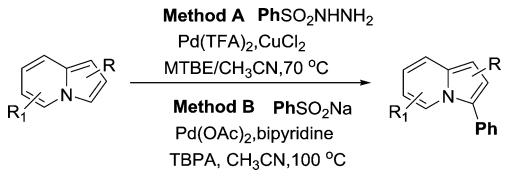
Entry	R	Yield[a] (%)	Yield[b] (%)
1	4-OCH_3–C_6H_5	94	90
2	4-CH_3–C_6H_5	91	92
3	4-*t*-Bu–C_6H_5	87	85
4	4-F–C_6H_5	90	82
5	4-Cl–C_6H_5	84	88
6	4-NO_2–C_6H_5	86	81
7	4-CF_3–C_6H_5	85	78
8	3-CH_3–C_6H_5	83	87
9	3-F–C_6H_5	91	91
10	3-Cl–C_6H_5	88	86
11	3-Br–C_6H_5	90	85
12	3-CF_3–C_6H_5	83	81
13	3-CHO–C_6H_5	76	77
14	2-CH_3–C_6H_5	81	88
15	2-Br–C_6H_5	77	84
16	2-$C_{10}H_7$	82	86
17	1-$C_{10}H_7$	71	77

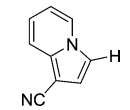
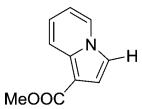
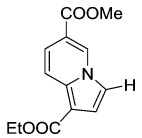
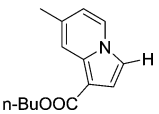
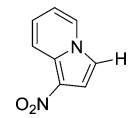
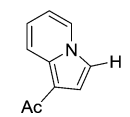
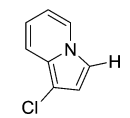
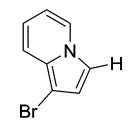
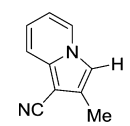
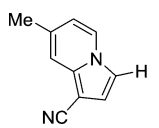
[a] Reaction conditions of method A: indolizine-1-carbonitrile (0.5 mmol), arylsulfonyl hydrazides (0.6 mmol), $Pd(TFA)_2$ (3 mol%), $CuCl_2$ (1 mmol), MTBE/CH_3CN (1.0 ml, v/v = 1 : 1) at 70 °C for 6 hours unless otherwise indicated. [b] Reaction conditions of method B: indolizines (0.5 mmol), sodium arylsulfinate (0.6 mmol), $Pd(OAc)_2$ (3 mol%), bipyridine (10 mol%), TBPA (0.6 mmol), CH_3CN (1.0 ml) at 100 °C for 6 hours unless otherwise indicated.

electron-withdrawing or electron-donating groups, are compatible (Table 5, column B, entries 1–7). Although electron-withdrawing substituted sodium arylsulfinates showed slightly decrease reactivity to electron-donating ones. The excellent reactivity and high selectivity with bromo and chloro functional groups, suggesting that both arylsulfonyl hydrazides and sodium arylsulfinates may have higher coupling reactivities than the related aromatic halides, which revealed excellent chemoselectivity of this method (Table 5, entries 5, 10 and 11). Functional groups, such as trifluoromethyl, fluoro, and aldehyde, which are useful in further synthetic transformations, were tolerated under the current conditions (Table 5, entries 9, 12 and 13). The *ortho*-substituted sodium arylsulfinates, such as *ortho*-methyl and *ortho*-bromo, can also afford a good product yield, thus showing steric hindrance has little effect on this reaction (Table 5, column A, entries 14 and 15). On the other side, the hindrance of the phenyl ring of arylsulfonyl hydrazides had slight effect on the efficiency (Table 5, column B, entries 14 and 15). It was interesting that polycyclic aromatic hydrocarbons (PAHs) substrates are still work under both two procedure (Table 5, entries 16 and 17).

We next investigated the scope of the reaction with a series of indolizines and phenylsulfonyl hydrazides or sodium

Table 6 The reaction of various indolizines with phenylsulfonyl hydrazides and sodium phenylsulfinates



Entry	Indolizine	Yield[a] (%)	Yield[b] (%)
1		92	93
2		88	90
3		91	87
4		84	89
5		77	83
6		82	86
7		87	81
8		89	91
9		79	82
10		91	88

[a] Reaction conditions of method A: indolizines (0.5 mmol), phenylsulfonyl hydrazides (0.6 mmol), $Pd(TFA)_2$ (3 mol%), $CuCl_2$ (1 mmol), MTBE/CH_3CN (1.0 ml, v/v = 1 : 1) at 70 °C for 6 hours unless otherwise indicated. [b] Reaction conditions of method B: indolizines (0.5 mmol), sodium benzenesulfinate (0.6 mmol), $Pd(OAc)_2$ (3 mol%), bipyridine (10 mol%), TBPA (0.6 mmol), CH_3CN (1.0 ml) at 100 °C for 6 hours unless otherwise indicated.

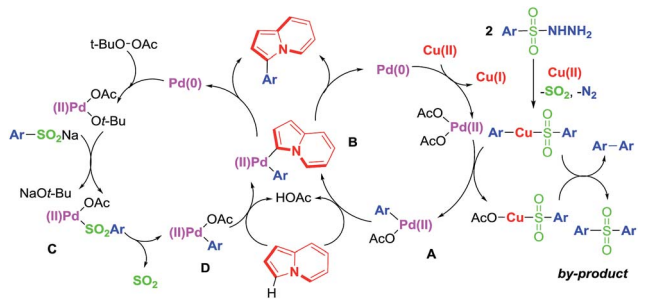


Fig. 4 Mechanism proposed.

phenylsulfinates. To further explore the application of this method, we tried many C-1 functional groups. Cyano and ester groups all demonstrated reactivity and the products were isolated in good yield, thus extending the potential applications of the method (Table 6, entries 1–4). Other substituents in C-1 have also been investigated, such as nitro, acetyl, chloro and bromo were successfully tolerance under reported conditions (Table 6, entries 5–8). Meanwhile, 2-methylindolizine-1-carbonitrile, bearing a sterically hindered group at its C2-positions, also underwent the reaction with phenylsulfonyl hydrazides or sodium phenylsulfinate smoothly, providing the corresponding products in slightly lower yields (79–82%) (Table 6, entry 9). C6-substituted methyl group also worked well and the desired product was produced in an excellent yield (Table 6, entry 10).

Mechanism

On the basis of the previous chemistry and the results of our study, a plausible Pd(0)/Pd(II) mechanism for the desulfitative arylation as shown in Fig. 4 was proposed. First, arylsulfonyl hydrazides was oxidized by Cu(II) to afford aryl(arylsulfonyl) copper, which could occurred ligand exchange with $Pd(OAc)_2$ to form arylpalladium intermediate A. The electrophilic palladation occurs at the preferential C3-position of indolizine to form intermediate B, following the removal of HOAc. The subsequent reductive elimination generates the arylation products, then the formed Pd(0) is oxidized to Pd(II) by Cu(II) to furnish the cycle. In addition, the reductive elimination of phenyl(phenylsulfonyl) copper might cause the formation of by-product such as sulfonyldibenzene and biphenyl. A plausible mechanism to rationalize the transformation with arylsulfinic acid sodium salt is also illustrated in Fig. 3. First, the Pd(II) catalyst reacts with the sulfinic acid to form an intermediate C, which is subsequently undergoes desulfination to generate the aryl-palladium complex D. This intermediate species displaced by indolizine to form intermediate B. A reductive elimination of C affords the desired product and the Pd(0) catalyst is reoxidized to Pd(II) by TBPA, thus closing the catalytic cycle.

Conclusions

In summary, we have developed the Pd-catalyzed desulfitative C-3 arylation with sodium arylsulfinates and arylsulfonyl hydrazides. These method have given straightforward access to valuable C-3 substituted indolizine derivatives. Desulfitative C-3 arylation with sodium arylsulfinates was achieved by the assistance of peroxide for the restrain of unwanted sulfonyldibenzene by-product, and the catalytic efficiency was promoted by N-contained ligand. Desulfitative C-3 arylation with arylsulfonyl hydrazides were also successful, and the side homocoupling reactions can be restrained in component solvent under milder conditions. Further substrate scope and mechanistic studies are ongoing in our laboratory.

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