The homocoupling of arylsulfonylhydrazides by palladium-catalysed desulfonation in air

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A simple and efficient preparation of biaryl derivatives from arylsulfonyl hydrazides has been developed using $Pd(OAc)_2$ as the catalyst in a mixed solvent of DMA and THF and without the use of any ligand and base.

Keywords: homocoupling,arylsulfonylhydrazide, desulfonation

Biaryl skeletons are found in many natural products, pharmaceuticals and ligands for catalysis.[1–4] Symmetrical biaryls are synthesised by homocoupling reactions, which include reductive coupling of aryl halides (known as the Ullmann reaction) and oxidative coupling of arylmetal compounds. The Ullmann reaction[5–10] was the first efficient process for the synthesis of symmetrical biaryls, but harsh conditions were required. Recently, extensive studies on the homocoupling reactions of arylboronic acids[11–19], potassium aryltrifluoroborates[20–22] aryl Grignard reagents[23,24] and arenediazonium salts[25–28] have been used because of their ready availability and stability.

The development of new electrophilic partners for these reactions has led to cross-coupling chemistry. Decarboxylative homocoupling using benzoic acids as substrates have been developed to afford corresponding symmetrical bi-aryl structures.[29,30] However, a strong electron-withdrawing group such as the nitro-substituent is essential for the reaction and harsh conditions are required.

More recent developments involve the use of arenesulfonates, which are readily available, inexpensive, and highly versatile. Last year, You and coworkers[31] reported the first example of the homocoupling of sodium benzenesulfinate. The transformation required the addition of 2.0 equiv. oxidant and a phase transfer catalyst (tetra-*n*-butylammonium bromide) to give a yield of 81% at 110 °C under nitrogen. Luo *et al.*[32] reported a green heterogeneous catalysed homocoupling under oxygen in water. Tian[33] reported that arylsulfonyl hydrazides were new coupling partners in Heck-type reaction. Subsequently, You[34] and Li[35] independently reported similar results concerning the direct arylation of heteroarenes with arylsulfonyl hydrazides. Here, we describe another application of arylsulfonyl hydrazides in homocoupling reaction to afford biaryls using a more convenient palladium catalysed homocoupling by desulfonation without oxidants and additives.

Results and discussion

We initiated our investigation on the model reaction of phenylsulfonyl hydrazide to optimise the critical reaction parameters. Homocoupling took place in the presence of $Pd(OAc)_2$ (3 mol%) and $Cu(OAc)_2$ (1 equiv.) in DMSO under air (Table 1, entry 1). Then we investigated the effect of solvents which had an obvious influence on the reaction obviously. The carefully optimised results are shown in Table 1. The yield obtained in other polar aprotic solvents such as DMF, DMA and NMP were also in the range 34–55% (Table 1, entries 2–4).

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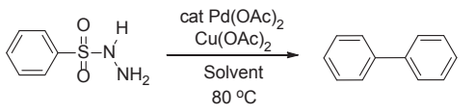
Table 1 Solvent selection of Pd-catalysed homocoupling



Entry	Solvent	Yield/%[b]	Entry	Solvent	Yield/%[b]
1	DMSO	46	11	DMA/toluene(1:1)	65
2	DMF	49	12	DMA/THF(1:1)	77
3	DMA	55	13	DMA/THF(9:1)	83
4	NMP	34	14	DMA/THF(4:1)	89
5	toluene	26	15	DMA/THF(3:1)	80
6	CH_3CN	38	16	DMA/THF(2:1)	77
7	1,4-dioxane	36	17	DMA/THF(1:2)	79
8	THF	40	18	DMA/THF(1:3)	73
9	DMA/dioxane (1:1)	71	19	DMA/THF(1:4)	66
10	DMA/CH_3CN(1:1)	70	20	DMA/THF(1:9)	57

[a]Reaction conditions: phenylsulfonyl hydrazides (0.5 mmol), $Pd(OAc)_2$ (3 mol%), $Cu(OAc)_2$ (0.5 mmol), solvent (1.0 mL) at 80 °C for 3 hours unless otherwise indicated.

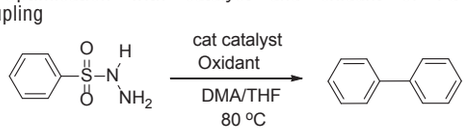
[b]Isolated cross-coupling yield, the v/v ratio of solvents was shown in parentheses.

Common organic solvents were examined but without improvement in yield (Table 1, entries 5–8). We then considered the use of mixed solvents. We chose DMA which was best in the first solvent screen, to mix with other solvents. The mixture displayed a sharp increase in the yield of the reaction (65–71%) (Table 1, entries 9–11). It proceeded smoothly in a solvent comprising DMA and THF (volume ratio is 1:1) with a yield of 77% (Table 1, entry 12). Finally, we varied the composition of DMA and THF in the range of 9:1 to 1:9 (Table 1, entries 13–20). In general, an increase of DMA favoured the formation of biphenyl and the volume ratio of 4:1 was the best (Table 1, entry 14).

The optimisation of the catalysts and oxidants in the reaction then followed. The screening of palladium catalysts, such as $PdCl_2$, PdI_2, $PdCl_2(CH_3CN)_2$, provided biphenyl in 79%, 80%, 77% yield, respectively (Table 2, entries 1–3). Decreased yields were obtained with the introduction of phosphine ligands (Table 2, entries 4 and 5). Pd(0) catalysts gave moderate yields (Table 2, entries 6 and 7). No product was formed in the absence of Pd (Table 2, entry 8). The formation of biphenyl was up to 89% using $Pd(OAc)_2$ as catalyst (Table 2, entry 9). Oxidants were crucial for this transformation. Among the oxidants examined [$Cu(OAc)_2$, AgOAc, BPO, DDQ, Oxone and TBHP], $Cu(OAc)_2$ was the best (Table 2, entries 9–14). Under O_2, the yield of biphenyl decreased to 61%, while under N_2, no product was formed (Table 2, entries 15 and 16).

With the optimised reaction conditions in hand, we investigated the effect of electronic and structural variations

Table 2 Optimisation with catalyst and oxidant of Pd-catalysed homocoupling

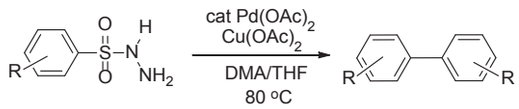


Entry	Catalyst	Oxidant	Yield/%[b]
1	$PdCl_2$	$Cu(OAc)_2$	79
2	PdI_2	$Cu(OAc)_2$	80
3	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	77
4	$PdCl_2$(dppf)	$Cu(OAc)_2$	46
5	$PdCl_2(PPh_3)_3$	$Cu(OAc)_2$	53
6	$Pd(PPh_3)_4$	$Cu(OAc)_2$	72
7	$Pd_2(dba)_3$	$Cu(OAc)_2$	76
8	–	$Cu(OAc)_2$	–
9	$Pd(OAc)_2$	$Cu(OAc)_2$	89
10	$Pd(OAc)_2$	AgOAc	82
11	$Pd(OAc)_2$	BPO	78
12	$Pd(OAc)_2$	DDQ	69
13	$Pd(OAc)_2$	Oxone	83
14	$Pd(OAc)_2$	TBHP	68
15	$Pd(OAc)_2$	O_2	61
16	$Pd(OAc)_2$	N_2	–

[a]Reaction conditions: phenylsulfonyl hydrazides (0.5 mmol), catalyst (3 mol%), oxidant (0.5 mmol), solvent (1.0 mL, the v/v ratio of solvents was 1:1) at 80 °C for 3 hours unless otherwise indicated.
[b]Isolated cross-coupling yield.

in the phenylsulfonyl hydrazides. The scope of the reaction is presented in Table 3. As expected, a series of functional groups on the phenyl ring of phenylsulfonyl hydrazides, such as bromo, chloro, fluoro, iodo and cyano were compatible with this procedure, and the products were isolated in moderate to good yields (Table 3, entries 1–5). Halogens were tolerant of the palladium catalysed homocoupling of the arylsulfonyl hydrazides (Table 3, entries 1–4), suggesting that arylsulfonyl hydrazides may have higher coupling reactivities than the related aromatic halides. This revealed the excellent chemoselectivity of this method. Notably, many heteroatom functional groups, such as OCH_3, SCH_3 and $N(CH_3)_2$ all coped

Table 3 Pd-catalysed homocoupling of various substrates



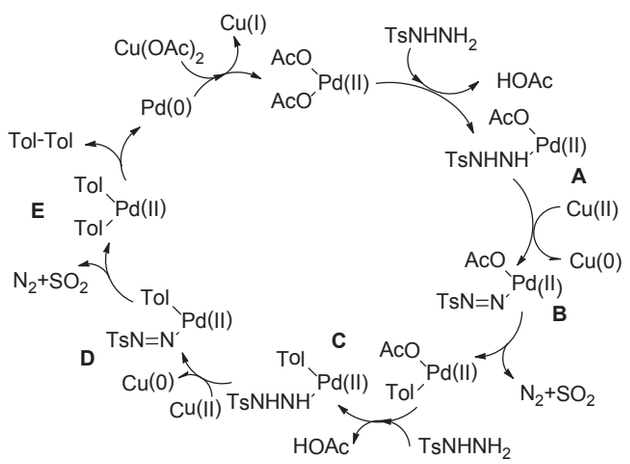
Entry	R	Yield/%[b]	M.p./°C	M.p./°C lit.
1	4-F	85	87–88	88–90 [36]
2	4-Cl	90	146–147	149–154 [36]
3	4-Br	88	164–165	168–170 [36]
4	4-I	84	201–203	205–206 [36]
5	4-CN	78	230–232	233–234 [37]
6	4-$N(CH_3)_2$	83	192–193	194–196 [36]
7	4-OCH_3	91	175–176	173–174 [36]
8	4-SCH_3	89	186–187	188–189 [36]
9	4-CH_3	92	119–120	122–124 [36]
10	3-CH_3	86	–	–
11	2-CH_3	79	–	–
12	2-Naphthyl	85	184–185	180–182 [36]
13	1-Naphthyl	78	143–145	142–144 [38]
14	2-benzofuran	69	196–197	198–200 [36]

[a]Reaction conditions: phenylsulfonyl hydrazides (0.5 mmol), $Pd(OAc)_2$ (3 mol%), $Cu(OAc)_2$ (0.5 mmol), solvent (1.0 mL, DMA/THF = 1:1) at 80 °C for 3 hours unless otherwise indicated.
[b]Isolated cross-coupling yield.

with these reaction conditions, which further expanded its good chemical selectivity (Table 3, entries 6–8). Steric hindrance on the phenyl ring of the arylsulfonyl hydrazides had a slight effect on the efficiency (Table 3, entries 9–11). It was interesting that polycyclic aromatic hydrocarbons (PAHs) substrates worked under the procedure (Table 3, entries 12 and 13). Importantly, the product with a heterocyclic ring was formed in moderate yield when 2-benzofuran was subjected to the procedure (Table 3, entry 14).

Mechanism

A plausible mechanism to rationalise this transformation is illustrated in Scheme 1. The release of SO_2 and N_2 may be the crucial driving force to the catalytic process. First, the Pd(II) acetate reacts with the 4-tolylsulfonyl hydrazide to form a $TsNHNH_2$-Pd(II)-OAc intermediate A, which is subsequently oxidised to intermediate B. Tolyl-Pd(II)-OAc was generated accompanied by the release of nitrogen and sulfur dioxide. This was then displaced by another 4-tolylsulfonyl hydrazide to form intermediate C. The oxidised intermediate species D undergoes a similar sequence to generate the di-tolyl-palladium complex E. A reductive elimination of E affords the desired product and the Pd(0) catalyst is reoxidised to Pd(II) by $Cu(OAc)_2$, thus completing the catalytic cycle.



Scheme 1 Possible mechanism.

Conclusion

In conclusion, we have described a new homocoupling reaction using arylsulfonyl hydrazides as the coupling partners under palladium catalysis. Importantly, this transformation is practical as it does not require the use of strong bases, expensive ligands nor rigorous exclusion of air. The transformation was promoted by mixed solvent and proceeds with the release of N_2 and SO_2. The detailed mechanism is being studied in our lab.

Experimental

All solvents were purified and dried according to standard methods prior to use. Proton NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III spectrometer. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. The multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), multiplet (m), and broad resonances (br). HRMS (EI) data were collected on a high resolution mass spectrometer AT95XP, Thermo Finnigan, USA. All materials were purchased from common commercial sources and used without additional purification.

Typical procedure

A mixture of the arylsulfonyl hydrazides (0.5 mmol), $Pd(OAc)_2$ (3 mol%) and $Cu(OAc)_2$ (0.5 mmol) was stirred in DMA/THF = 1:1 (1 mL) at 80 °C for 3 h. Afterwards, 1 mL water was added to the reaction solution which was then filtered through a filter paper. The solution was extracted by Et_2O (1 mL) three times. The organic phase was combined and evaporated under reduced pressure. The residue was purified on a SiO_2 column, and eluted with mixtures of petrol and ethyl acetate to afford the desired product.

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Electronic Supplementary Information

All products are known compounds, and the spectroscopic data for the products is given in the ESI available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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