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p-Toluenesulfonohydrazide as Highly Efficient Initiator for Direct C−H Arylation of Unactivated Arenes

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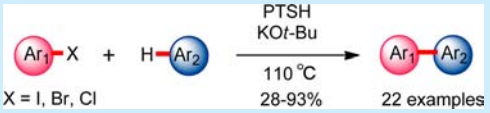
Supporting Information

ABSTRACT: *p*-Toluenesulfonohydrazide (PTSH) was shown to promote the highly efficient direct arylation of unactivated arenes with aryl iodides, bromides, or chlorides in the presence of potassium *tert*-butoxide without the assistance of any transition metals. The reaction proceeds through base-promoted homolytic aromatic substitution (BHAS) involving aryl radicals and arylradical anions as intermediates.



Biaryl scaffolds are available in a large number of natural products, bioactive molecules, agrochemicals, functional materials, and pharmaceuticals.[1] Over the past decades, various strategies have been developed to prepare biaryls among which the transition-metal-catalyzed cross-coupling reactions between organohalides and organometallic reagents are predominant in modern organic synthesis.[2] However, these methods suffer from some inevitable drawbacks such as employment of sensitive organometallic reagents and expensive metal catalysts. On the other hand, the disposal of toxic and stoichiometric side products is also unavoidable in these methods.[3] Recently, many transition metals have been reported as efficient catalysts for the direct arylation of unactivated aromatic C−H bonds.[4] But purification of the products which may be contaminated by transition metal impurities still remains a big issue.

The development of economic, efficient, and noncontaminant methodologies is always of great importance; thus, studies on transition-metal-free coupling reactions are of great significance. A review article by Shi classified the typical transition-metal-free coupling reactions and summarized their recent advances from different aspects.[5] Among diverse transition-metal-free coupling reactions, a direct arylation of arenes involving base promoted homolytic radical aromatic substitution (BHAS),[6] namely addition of aryl radicals to benzene derivatives followed by elimination of a hydrogen radical, has captured great attention. Many researchers devote themselves to this conceptually different reaction and have made breakthroughs in this area.[7] A series of ligands, including 1,10-phenanthroline,[7b] DMEDA,[7c] and their derivatives,[7d] have been found to be capable of promoting a biaryl construction process via BHAS. Although these ligands avoid the use of transition metals and enable the reaction to achieve acceptable yields, the limited substrate range and the requirement for high reaction temperatures impede their wide use in the field of chemical synthesis.[8] Most recently, Curren and Studer's elegant work revealed that phenylhydrazine can efficiently initiate the BHAS of unactivated arenes.[9] The reaction can take place under relatively mild conditions at low initiator loading. But it still shares with some drawbacks such as the limited substrate range. Consequently, the development of versatile and simple reagents that lead to improvements in the efficiency and generality of transition-metal-free cross-coupling reactions is the aim of studies in this area.

Herein, we report our latest development in the *p*-toluenesulfonohydrazide(PTSH)-initiated cross-coupling reaction between aryl halides and unactivated arenes through the BHAS mechanism at relatively low initiator loading. Compared with phenylhydrazine, PTSH can more efficiently initiate this coupling reaction under the same conditions (see Supporting Information (SI)) and the substrate scope of the reaction initiated by PTSH is broader than that of phenylhydrazine.

In this study, the reaction between iodobenzene (**1a**) and benzene (**2a**) was chosen as a model reaction for the optimization of reaction conditions (Table 1). The initial experiments were carried out to screen the potential initiators (Table 1, entries 1−4). The results showed that, with the aid of KO*t*-Bu in benzene at 110 °C, all hydrazides tested can efficiently initiate the cross-coupling reaction, and PTSH turned out to be optimal with the highest yield (97%, Table 1, entry 3). Notably, this cross-coupling reaction did not occur when initiators were absent, demonstrating the importance of hydrazides in this process (Table 1, entry 5). Other different bases including KOH, K_2CO_3, NaOMe, and LiO*t*-Bu were then tested but the outcomes were not fruitful. Bases weaker than KO*t*-Bu were found to be much less effective, giving little or no coupling product in these cases (Table 1, entries 6−9). The initiators were also tested in the reactions without KO*t*-Bu. Neither PTSH nor its sylvite[10] could initiate the reaction in the absence of KO*t*-Bu (Table 1, entries 10−11). Reducing the amount of KO*t*-Bu also caused a decreased yield of **3a** (85%, Table 1, entry 13). These results revealed that the structure of the K-alcoholate does indeed have an effect on the reaction outcome. The reaction could also take place at a lower temperature (80 °C) despite the reduced yield (64%, Table1, entry 12). Several solvents such as

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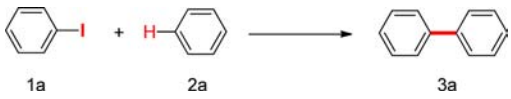
Table 1. Optimization of Arylation Reaction Conditions[a]



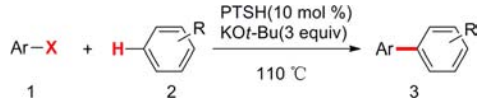
entry	initiator	base (equiv)	solvent	t (°C)	yield (%)[b]
1	2-PyCONHNH$_2$	KO*t*-Bu (3 equiv)	benzene	110	86
2	3-PyCONHNH$_2$	KO*t*-Bu (3 equiv)	benzene	110	82
3	**PTSH**	**KO*t*-Bu (3 equiv)**	**benzene**	**110**	**97**
4	TsNHNHTs	KO*t*-Bu (3 equiv)	benzene	110	79
5	–	KO*t*-Bu (3 equiv)	benzene	110	0
6	PTSH	KOH (3 equiv)	benzene	110	0
7	PTSH	K_2CO_3 (3 equiv)	benzene	110	0
8	PTSH	LiO*t*-Bu (3 equiv)	benzene	110	0
9	PTSH	NaOMe (3 equiv)	benzene	110	12
10	PTSH	–	benzene	110	0
11	PTSH sylvite	–	benzene	110	0
12	PTSH	KO*t*-Bu (3 equiv)	benzene	80	64
13	PTSH	KO*t*-Bu (2 equiv)	benzene	110	85
14[c]	PTSH	KO*t*-Bu (3 equiv)	CCl_4	110	0
15[c]	PTSH	KO*t*-Bu (3 equiv)	DMSO	110	0
16[c]	PTSH	KO*t*-Bu (3 equiv)	DMF	110	0
17[c]	PTSH	KO*t*-Bu (3 equiv)	CH_3CN	110	0

[a]Reaction conditions: **1a** (1.0 mmol), benzene (5.0 mL), initiator (10 mol %), and base in a sealed Schelenk tube, heated, 24 h, N_2. [b]Yields were determined by ^{1}H NMR. [c]**1a** (1.0 mmol), benzene (20 mmol), PTSH (10 mol %), KO*t*-Bu (3.0 mmol), and solvent (5.0 mL) in a sealed Schelenk tube, 110 °C, 24 h, N_2.

CCl_4, DMSO, DMF, and CH_3CN were applied to this reaction to replace benzene. Disappointingly, the reaction did not work in any of these menstruums (Table 1, entries 14−17).

With optimized conditions in hand, we examined the substrate scope of this hydrazide initiated direct arylation by reacting structurally and electronically diverse aryl halide with benzene (Table 2). Simple iodobenzene and other iodides containing both electron-donating and -withdrawing groups can be efficiently coupled with benzene to generate corresponding biphenyl derivatives in good yields (Table 2, entries 1−7). Heteroaryl iodides also reacted smoothly with benzene (Table 2, entries 8−10). The reaction system was further applied to aryl bromides. To our delight, it went well with the aryl bromides to provide moderate to good yields with a prolonged reaction time (Table 2, entries 11−14). Our reaction system can also be applied to chlorobenzenes. *p*-Cyanochlorobenzene furnished a satisfying yield (Table 2, entry 17), which agreed with the report that introduction of a conjugating or electron-withdrawing group enhanced the reactivity of aryl halides.[7d] Simple chlorobenzene and chlorobenzenes with an electron-donating group were described as nonreactive in the recent reports.[7] However, in our reaction system, coupling reactions using simple chlorobenzene and *p*-methoxylchlorobenzene as substrates could also take place

Table 2. Direct Arylation of Arenes with Aryl Halides[a]



entry	Ar−X	arene, **2**	product, **3**	yield (%)[b]
1	Ph−I, **1a**	benzene, **2a**	**3a**	90
2	*p*-MeC$_6$H$_4$−I, **1b**	**2a**	**3b**	83
3	*m*-MeC$_6$H$_4$−I, **1c**	**2a**	**3c**	76
4	*o*-MeC$_6$H$_4$−I, **1d**	**2a**	**3d**	78
5	*p*-MeOC$_6$H$_4$−I, **1e**	**2a**	**3e**	91
6	*p*-CNC$_6$H$_4$−I, **1f**	**2a**	**3f**	87
7	*p*-PhC$_6$H$_4$−I, **1g**	**2a**	**3g**	93
8	2-pyridyl−I, **1h**	**2a**	**3h**	79
9	3- pyridyl−I, **1i**	**2a**	**3i**	65
10	3-thienyl−I, **1j**	**2a**	**3j**	71
11[c]	*p*-MeOC$_6$H$_4$−Br, **1k**	**2a**	**3e**	86
12[c]	*p*-MeC$_6$H$_4$−Br, **1l**	**2a**	**3c**	78
13[c]	*p*-CNC$_6$H$_4$−Br, **1m**	**2a**	**3f**	80
14[c]	2-pyridyl−Br, **1n**	**2a**	**3h**	77
15[c]	*p*-MeOC$_6$H$_4$−Cl, **1o**	**2a**	**3e**	35
16[c]	Ph−Cl, **1p**	**2a**	**3a**	28
17[c]	*p*-CNC$_6$H$_4$−Cl, **1q**	**2a**	**3f**	71
18[d]	*p*-MeOC$_6$H$_4$−I, **1e**	toluene, **2b**	**3k**	56[e]
19[d]	*p*-MeC$_6$H$_4$−I, **1b**	anisole, **2c**	**3l**	62[f]
20[d]	*p*-MeOC$_6$H$_4$−I, **1e**	pyridine, **2d**	**3m**	85[g]
21[d]	*p*-MeOC$_6$H$_4$−I, **1e**	pyrazine, **2e**	**3n**	90
22[d]	*p*-MeOC$_6$H$_4$−I, **1e**	naphthalene, **2f**	**3o**	75[h]

[a]Reaction conditions: **1** (1.0 mmol), benzene (5.0 mL), PTSH (10 mol %), and KO*t*-Bu (3.0 equiv) in a sealed Schelenk tube, 110 °C, 24 h, N_2. [b]Isolated yield based on **1**. [c]Reaction time: 48 h. [d]**1** (1.0 mmol), arene (120 mmol), and KO*t*-Bu (3.0 equiv) in a sealed Schelenk tube 135 °C, 24 h, N_2. [e]Ratio of $o/m/p$ = 3.6:1.5:1.0. [f]Ratio of $o/m/p$ = 3.8:1.4:1.0. [g]Ratio of $o/m/p$ = 3.2:1.8:1.0. [h]Ratio of α/β = 1.0:3.0.

to a certain extent although relatively low yields were observed (Table 2, entries 15−16).

Further exploration of the substrate scope and regioselectivities were carried out by reacting aryl iodides **1b** and **1e** with different arenes (Table 2, entries 18−22). Regioisomeric mixtures favoring the ortho products were obtained under the optimized conditions. Notably, the deficiency of electron density improved the coupling efficiency. For example, pyrazine furnished the corresponding product in high yield (90%, Table 2, entry 21). With increased electron density in the arenes, lower efficacy was observed (Table 2, entries 18−19). These facts highlight the importance of the C−H bond acidity in the arylation reactions and suggest the PTSH initiated direct arylation of aromatic C−H bonds to proceed by BHAS with aryl radicals.[7c,g]

To understand the mechanism of this reaction, several experiments were conducted. When radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,1-diphenylethylene were added, the reactions were completely shut off and no desired product could be obtained (Table 3, entries 2−3). These results contrast well with the 97% yield obtained without the use of radical scavengers (Table 3, entry 1). All these data indicated that the transformation proceeded via radical intermediates. Furthermore, a kinetic isotope experiment was performed (see SI) and the observed low K_H/K_D value implies that the cleavage of the aromatic C−H bond is not the rate-determining step in the arylation reaction (Scheme 1).

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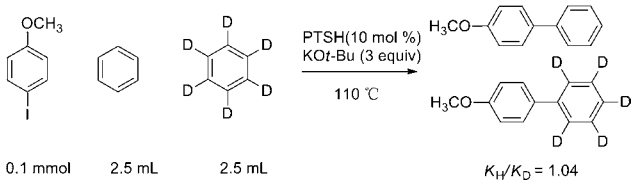
Table 3. Radical Trapping Experiments

entry	scavenger	yield (%)[a]
1	–	97
2	TEMPO (1.0 equiv)	0
3	1,1-diphenylethylene (1.0 equiv)	0

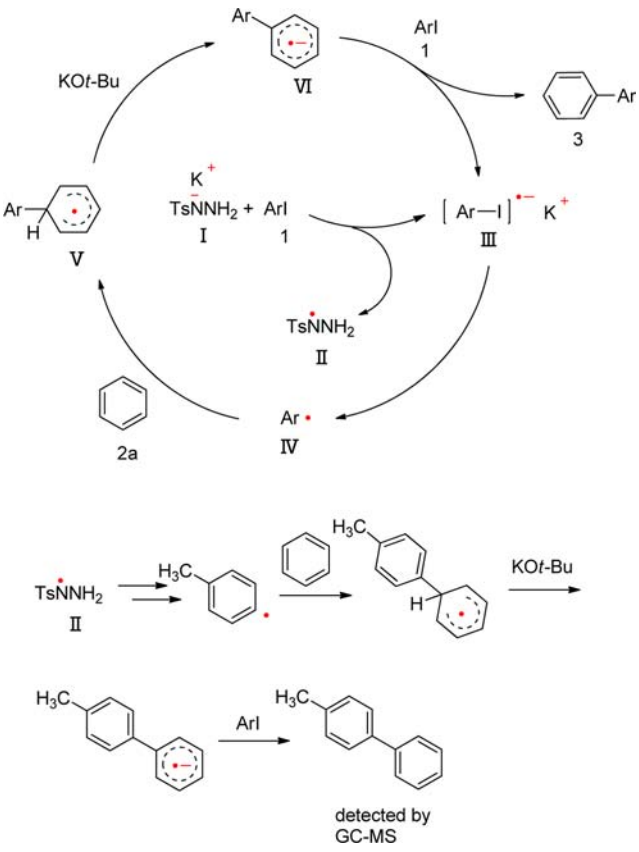
[a]Yields were determined by ^{1}H NMR.

Scheme 1. Kinetic Isotope Experiment



Based on the above data and related results reported by others,[6,7,11] a plausible mechanism is illustrated in Scheme 2.

Scheme 2. Proposed Mechanism



PTSH is first deprotonated by KO*t*-Bu to form **I**, which subsequently transfers an electron to iodobenzene, yielding the intermediate radical anion **III** and hydrazide radical **II**. Aromatic radical **IV** is then formed from **III**'s fragment, followed by addition to the arene to deliver radical **V**, which undergoes deprotonation to generate **VI**. Finally, an electron transfers from **VI** to an aryl halide to give the final product **3** and sustain the radical chain process. The radical **II** generated initially undergoes a fragmentation to deliver a 4-methylbenzene radical, which is involved in BHAS with arenes to generate the corresponding side products to be detected by GC-MS.

In summary, we have disclosed *p*-toluenesulfonohydrazide (PTSH) as a cheap and commercially available reagent enabling the efficient construction of biaryls by initiating direct C−H arylation of unactivated arenes in the presence of KO*t*-Bu. This hydrazide initiated biaryl synthesis concerns a chain BHAS mechanism and can be efficiently carried out with as low as a 10 mol % initiator loading. Compared to the existing methods, the reaction conditions are relatively mild and can be applied to iodic, bromic, and even chloric arenes. Further investigations to apply this new method to other reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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