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$MnCl_2 \cdot 4H_2O$-catalyzed Potential Protocol for the Synthesis of Aryl/Vinyl Sulfides

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$MnCl_2 \cdot 4H_2O$ is described as an efficient catalytic system for the cross coupling of aryl/vinyl halides with thiols using KOH as base and DMSO as solvent. By using this new catalytic system various aryl/vinyl sulfides were synthesized in moderate to good yields. Retention of stereochemistry is observed in the case of vinyl sulfides.

Organosulfur compounds are valuable motifs and find many applications in organic chemistry.[1] Among these, aryl/vinyl sulfides are important and attract much interest due to their biological/therapeutical[2] activity. We can find aryl sulfide moieties in many drugs which are being used in the treatment of various diseases like diabetes, Alzheimer's, Parkinson's,[3] cancer,[4] and HIV.[1b] In synthetic organic chemistry vinyl sulfides have widespread utility as enolate ion equivalents,[5] Michael acceptors[6] and key intermediates in the preparation of oxetanes.[7] In view of their significance, many methods have been developed for the synthesis of aryl/vinyl sulfides.[8,9] Among the existing methodologies in practical organic synthesis, cross coupling of aryl/vinyl halides with thiols is the most commonly used strategy for the synthesis of aryl/vinyl sulfides. Recently Xu et al. synthesized aryl sulfides by using CuI as catalyst and KF/Al_2O_3 as base.[8n]

Though the existing strategies are efficient in their own way, there are some drawbacks such as the use of moisture-sensitive catalysts/reagents which cause major problems in purification of the products and separation of the metal catalyst. In view of this, developing a simple, novel, and practicable catalytic system for the cross coupling of aryl/vinyl halides with thiols is desirable. We have undertaken studies to arrive at the present catalytic system, which can be more useful and affordable, for the synthesis of aryl/vinyl sulfides.

Literature survey indicates increased use of Mn as a catalyst in many coupling reactions[10] as it is economically affordable, easily available, and environmentally benign compared to other transition metals. Over the past, Pd,[8c,11] Ni,[8s,12] Cu,[9f,13] Fe,[14] In,[8m] and La[15] catalysts were explored for C–S cross-coupling reactions. However, there have been no reports on manganese-catalyzed C–S cross-coupling reactions so far. To the best of our knowledge we report herein for the first time C–S cross-coupling reaction mediated by $MnCl_2 \cdot 4H_2O$, in continuation of our work toward new catalytic systems[15] for organic transformations. The present approach will be a promising protocol as it avoids the use of co-metals and additives as well as complicated work-up procedures.

Iodobenzene and benzenethiol were reacted as model substrates in the study toward the development of $MnCl_2 \cdot 4H_2O$-catalyzed cross-coupling reactions. Initially, the ligand screening was taken up (Figure 1) and among different ligands L5 gave desired product in 35% yield after 24 h in the presence of K_3PO_4 and DMF. L1 and L2 did not influence the reaction whereas the rest of the ligands had little impact. Encouraged by this result, the efficiency of different bases such as K_2CO_3, Cs_2CO_3, and KOH in the presence of various solvents like toluene, water, DMSO, and DMF (Table 1), was evaluated.

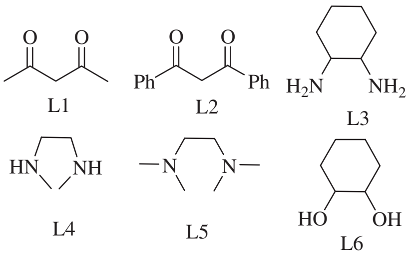
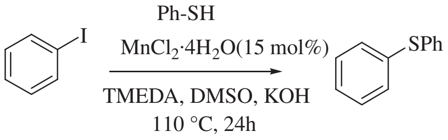


Figure 1. Screening of ligands for optimized conditions.

Table 1. Screening study of bases and solvents[a]

Entry	Base	Solvent	Yield[b]/%
1	K_3PO_4	PhMe	0
2	K_3PO_4	DMF	35
3	K_3PO_4	DMSO	42
4	K_2CO_3	PhMe	0
5	K_2CO_3	DMF	trace
6	K_2CO_3	DMSO	57
7	Cs_2CO_3	PhMe	0
8	Cs_2CO_3	DMF	trace
9	Cs_2CO_3	DMSO	63
10	KOH	PhMe	trace
11	KOH	DMF	58
12	KOH	DMSO	32[c]
13	KOH	DMSO	82
14	KOH	Water	0
15	none	DMSO	0

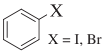
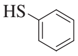
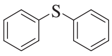
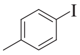
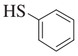
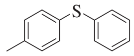
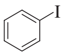
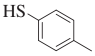
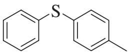
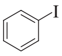
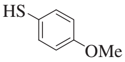
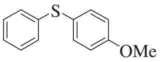
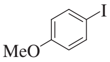
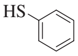
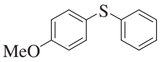
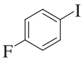
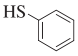
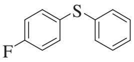
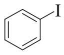
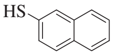
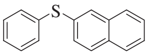
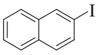
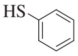
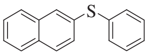
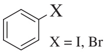
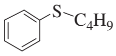
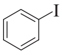
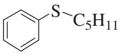
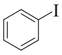
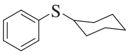
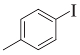
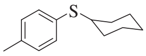
[a]Reaction conditions: iodobenzene (1.2 mmol), benzenethiol (1.0 mmol), $MnCl_2 \cdot 4H_2O$ (15 mol %), base (1.5 equiv), solvent (2.0 mL), 110 °C, 24 h. [b]Isolated yield. [c]At 70 °C.



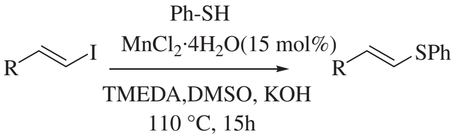
Scheme 1. Cross coupling of aryl halides with thiols.

DMSO proved to be the best among different solvents studied. KOH played a significant role in taking forward the reaction whereas the remaining bases were comparatively less effective. The combination of KOH/TMEDA and DMSO evolved out as promising, resulting in high yields (Scheme 1 and Table 1, Entry 13). In the absence of $MnCl_2 \cdot 4H_2O$ or KOH,

Table 2. Coupling of aryl halides with thiols[a]

Entry	Aryl iodide	Thiol	Product	Yield[b]/%
1				82 25 (Br)
2				74
3				75
4				72
5				71
6				77
7				76
8				75
9		C_4H_9SH		70 25 (Br)
10		$C_5H_{11}SH$		68
11				65
12				62

[a]Reaction conditions: aryl halides (1.2 mmol), thiol (1.0 mmol), $MnCl_2 \cdot 4H_2O$ (15 mol %), KOH (1.5 equiv), L5 (1 mol %), DMSO (2.0 mL) at 110 °C, 24 h. [b]Isolated yield.



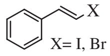
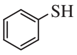
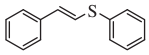
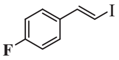
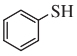
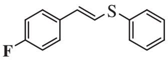
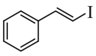
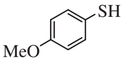
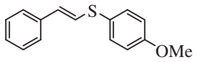
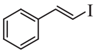
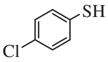
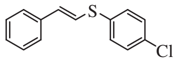
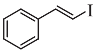
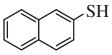
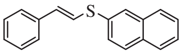
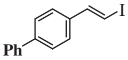
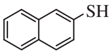
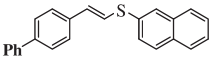
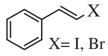
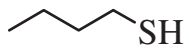
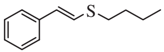
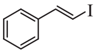
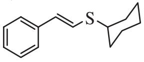
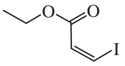
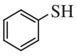
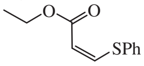
Scheme 2. Cross coupling of vinyl halides with thiols.

no reaction took place even at elevated temperatures and longer reaction times.

In general, all the reactions were clean, and the aryl sulfides were obtained in high yields under the optimized conditions.[16] The scope of the catalytic system was evaluated by carrying out the study of various aryl halides and benzenethiols. Electron-donating groups like methyl and methoxy on aryl halides or/and thiols slightly decreased the yields (Table 2). Aliphatic/cyclic thiols were proven less reactive when compared to aromatic thiols.

Encouraged by these results, we extended the $MnCl_2 \cdot 4H_2O$-catalyzed cross-coupling reaction to vinyl halides also (Scheme 2). It was observed that the reaction time was reduced to 15 h. The catalytic system worked well for both electron-rich and electron-poor vinyl iodides with various benzenethiols. There was no significant effect of substituents when present on vinyl halides. Coupling of vinyl halides with aliphatic/cyclic thiols also resulted in good yields under the optimized conditions. Aromatic thiols gave better yields compared to aliphatic thiols (Table 3).

Table 3. Coupling of vinyl halides with thiols[a]

Entry	Vinyl iodide	Thiol	Product	Yield[b]/%
1				76 25 (Br)
2				72
3				71
4				73
5				74
6				72
7				64 24 (Br)
8				60
9				0

[a]Reaction conditions: *trans*-β-iodostyrene (1.2 mmol), thiol (1.0 mmol), catalyst (15 mol %), KOH (1.5 equiv), L5 (1 mol %), DMSO (2.0 mL) at 110 °C, 15 h. [b]Isolated yield.

Aryl/vinyl bromides were also found to be effective for cross-coupling reaction with thiols under similar optimized conditions (Tables 2 and 3). However, lower yields were observed in the coupling reaction of aryl bromide or *trans*-β-bromo-styrenes and different thiols compared to aryl/vinyl iodides respectively. Furthermore, retention of stereochemistry is observed in the case of vinyl halides.

In conclusion, we have developed an active, moisture-stable, inexpensive, and nontoxic catalytic system for the synthesis of aryl/vinyl sulfides in good yields. The catalytic system consists of catalytic amount of $MnCl_2 \cdot 4H_2O$, KOH as base, and TMEDA as a ligand in DMSO solvent.

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