



Manganese-catalyzed cross-coupling reactions of aliphatic amines with aryl halides

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ABSTRACT

An efficient and convenient protocol has been developed for the N-arylation of aliphatic amines with differently substituted aryl halides using a $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ /L-proline catalyst and NaOt-Bu as the base in DMSO.

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The aliphatic amination of aryl halides is an important and frequently employed reaction for the synthesis of organic compounds containing the N-aryl moiety, which are present in many bioactive pharmaceuticals and conducting materials.¹

The most widely employed methods for such carbon–nitrogen bond-forming processes have been realized using copper,² palladium³ and nickel⁴ metal salts, and high yields can be attained in most instances. In the past decade, promising strategies involving the use of iron salts have also emerged as alternatives to perform transition metal-mediated C–N cross-coupling reactions. Bolm and Correa reported a ligand-assisted direct FeCl_3 /DMEDA-catalytic system for the arylation of various nitrogen nucleophiles⁵ and sulfoximines,⁶ while Guo et al. described an efficient Fe_2O_3 /L-proline-catalyzed N-arylation of various amines.⁷ Although significant progress has been made on the aforementioned transformation, there still remains a need to develop new catalytic systems that are cheap and environmentally safe.

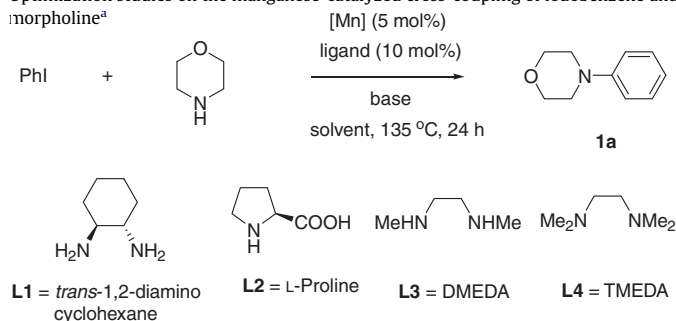
Recently, our group developed an efficient protocol for the cross-coupling reaction of azoles with substituted aryl iodides in water using a combination of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ and *trans*-1,2-diamino-cyclohexane as the catalytic system.⁸ Encouraged by these precedents and to expand our interest in manganese catalysis, we envisaged the application of manganese salts for the N-arylation of aliphatic amines. Herein, we report $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ /L-proline as an inexpensive and readily available catalyst system using NaOt-Bu as the base to prepare N-arylated aliphatic amines.

In our initial study, the reaction between iodobenzene and morpholine was chosen as a model system for optimizing the reaction conditions. The reaction carried out using a combination of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, *trans*-1,2-diaminocyclohexane and NaOt-Bu in DMSO gave the product in a moderate yield of 37% (Table 1, entry 1). This prompted us to evaluate further the merits of various ligands for

the reaction. The best assisting ligand was found to be L-proline in combination with $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, which gave the product in a

Table 1

Optimization studies on the manganese-catalyzed cross-coupling of iodobenzene and morpholine^a



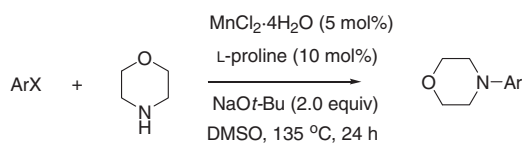
Entry	[Mn] source	Ligand	Base	Solvent	Yield ^b (%)
1	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L1	NaOt-Bu	DMSO	37
2	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L2	NaOt-Bu	DMSO	72
3	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L3	NaOt-Bu	DMSO	55
4	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L4	NaOt-Bu	DMSO	67
5	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L2	Cs_2CO_3	DMSO	Trace
6	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L2	K_2CO_3	DMSO	Trace
7	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L2	KOt-Bu	DMSO	22
8	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L2	K_3PO_4	DMSO	Trace
9	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L2	NaOt-Bu	DMF	Trace
10	$\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$	L2	NaOt-Bu	Toluene	0
11	$\text{Mn}(\text{ClO}_4) \cdot \text{H}_2\text{O}$	L2	NaOt-Bu	DMSO	60
12	$\text{Mn}(\text{acac})_2$	L2	NaOt-Bu	DMSO	58
13	MnF_2	L2	NaOt-Bu	DMSO	67
14	$\text{Mn}(\text{OAc})_2$	L2	NaOt-Bu	DMSO	60
15	—	L2	NaOt-Bu	DMSO	50

^a The reaction was carried out with morpholine (1.47 mmol), iodobenzene (2.94 mmol), base (2.94 mmol), [Mn] source (5 mol%), ligand (10 mol%), solvent (0.75 mL) at 135 °C for 24 h.

^b Isolated yield after column chromatography.

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Table 2N-Arylation of morpholine with various aryl halides catalyzed by MnCl₂·4H₂O/l-proline^a

Entry	ArX	Product	Yield ^b (%)
1			1a 72
2			1b (m) 16
3			Trace ^c
4			1c (m) 1d (p) 60
<i>m:p</i> = 1.5:1			
5			1e (m) 43
6			1f (m) 45
7			1b (m) 1g (p) 70
<i>m:p</i> = 1:1			
8			1h (m) 1i (p) 56
<i>m:p</i> 1:1			
9			1e (m) 1j (p) 73
<i>m:p</i> = 1:2			
10			1k (p) 43
11			1a 70
12			1b (m) 1g (p) 75
<i>m:p</i> = 1:1			
13			1b (m) 1g (p) 60
<i>m:p</i> = 1:1			

^a The reaction was carried out with morpholine (1.47 mmol), aryl halide (2.94 mmol), NaOt-Bu (2.94 mmol), MnCl₂·4H₂O (5 mol %), l-proline (10 mol %), DMSO (0.75 mL) at 135 °C for 24 h.^b Isolated yield after column chromatography.^c Not isolated.

good yield of 72% in DMSO (Table 1, entry 2). Next, we screened various bases and preliminary results showed that NaOt-Bu was the base of choice for this coupling reaction. Coupling reactions using Cs₂CO₃, K₂CO₃, KOt-Bu and K₃PO₄ were shown to be less, or not effective (Table 1, entries 5–8). Next, we probed the solvent effect and found that DMSO was the only solvent that proved to be effective for this coupling. Reactions in DMF and toluene gave only traces, or none of the product, respectively (Table 1, entries 9 and 10). Finally, we evaluated the efficiency of a series of manganese salts for the arylation reaction. The products were obtained in moderate to good yields ranging from 58% to 67% when Mn(acac)₂, Mn(ClO₄)₂·H₂O, MnF₂ and Mn(OAc)₂ were used as the metal catalyst (Table 1, entries 11–14). Thus, the optimum conditions for the N-arylation of morpholine involved a combination of MnCl₂·4H₂O⁹ (5 mol %), l-proline (**L2**, 10 mol %) and NaOt-Bu (2 equiv), in DMSO at 135 °C for 24 h. Control experiments performed without the Mn source gave the product in moderate yield only (Table 1, entry 15).

Having determined the optimized conditions for the manganese-catalyzed arylation, a study was initiated to explore the generality of the reaction of a variety of substituted aryl halides with morpholine (Table 2). In general, *ortho*-substituted aryl halides gave poor yields regardless of the electronic nature of the substituent (Table 2, entries 2 and 3) while moderate to good yields were obtained for sterically unhindered aryl halides (Table 2, entries 4–10). It is noteworthy that aryl bromides were shown to be reactive and gave good yields under these catalytic conditions (Table 2, entries 11–13).

Interestingly, *cis*e substitution effects could be observed in the products shown in Table 2. The *ortho*-substituted aryl halides affor-

Table 3N-Arylation of amines with iodobenzene catalyzed by MnCl₂·4H₂O/l-proline^a

Entry	Amine	Product	Yield (%) ^b
1			2a 50
2			2b 45
3			2c 40
4			2d 49
5			2e 50
6			2f 80
7			2g 22

^a The reaction was carried out with amine (1.47 mmol), iodobenzene (2.94 mmol), NaOt-Bu (2.94 mmol), MnCl₂·4H₂O (5 mol %), l-proline (10 mol %), DMSO (0.75 mL) at 135 °C for 24 h.^b Isolated yield after column chromatography.

ded only *meta*-amination products due to steric reasons, while the *para*-substituted aryl halides gave a mixture of *meta*- and *para*-amination products perhaps via a benzyne intermediate. However, in the case of *meta*-substituted aryl halides, the observed *cine* substitution effects were less pronounced (Table 2, entries 5 and 6). This effect was also described in the report by Guo et al.⁷

Finally, the scope of the manganese-catalyzed cross-coupling reaction was investigated with respect to iodobenzene. As revealed by the data in Table 3, several amine substrates were arylated under these manganese catalytic conditions.

Both linear and branched alkyl primary amines afforded the expected products in moderate yields ranging from 45% to 50% (Table 3, entries 1–4). The arylation of a representative cyclic primary amine, cyclohexylamine, gave the arylated product in 50% yield (Table 3, entry 5) while pyrrolidine gave an excellent 80% yield of product (Table 3, entry 6). Although satisfactory results were obtained in the case of primary amines, a poor coupling yield was obtained with benzylamine (Table 3, entry 7).

In summary, a convenient and promising route to N-arylated aliphatic amines using a ligand-assisted manganese catalytic system has been developed. The use of a low cost and readily available Mn salt, the ligand L-proline, and the practical nature of the protocol render this transformation an attractive coupling strategy. Further investigation to broaden Mn catalysis as a sustainable method for other cross-coupling reactions is ongoing.

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Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.098.

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