Manganese-catalyzed cross-coupling reactions of nitrogen nucleophiles with aryl halides in water[†]

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A facile and convenient strategy for the assembly of N-arylated heterocycles has been demonstrated using a $MnCl_2.4H_2O/trans-1,2$ -diaminocyclohexane catalyst and K_3PO_4 as the base in water.

Transition metal-catalyzed cross coupling reactions of nitrogen nucleophiles with aryl halides has emerged as a powerful synthetic strategy that finds widespread applications in the synthesis of pharmaceuticals, natural products and conducting materials.1 Typically, the classical methods for generating C-N bonds have been fuelled by either the copper-mediated² Ullmann reaction or the palladium-catayzed³ Buchwald–Hartwig amination reaction. In the past decade, the use of iron salts as alternatives to perform transition metal-mediated coupling reactions has also shown to be a promising strategy for sustainable development.⁴ Taillefer et al. described an efficient Fe/Cu cooperative system that catalyzed the assembly of N-arylated heterocycles,⁵ while Correa and Bolm reported the first ligand-assisted direct Fe-catalyzed N-arylation of nitrogen nucleophiles with aryl halides.⁶ Although significant progress has been made in the aforementioned transformations, there still remains a need to develop new, economical, and environmentally-friendly protocols that utilize cheap and sustainable metal catalysis. Previously, our group have developed efficient protocols for C-N cross-coupling reactions in water using either the Fe or Co catalytic systems.⁷ Encouraged by these precedents and our interest in manganese catalysis, we envisaged the application of manganese salts as cheap and sustainable alternative catalysts for this reaction.

The use of manganese salts for cross-coupling reactions is attractive from both economical and environmental points of view as they are readily available, cheap and more environmentally benign in comparison to other transition metals. However, examples of manganese-mediated coupling reactions are limited. Most of the manganese-catalyzed cross-coupling reactions reported thus far required the use of organometallic reagents or reactive halides such as activated aryl halides or chloroenyes.⁸ Rueping and Ieawsuwan developed the cross-coupling reaction of heterocyclic chlorides with aryl Grignard reagents using Mn(II) catalysts.⁹ Yuan and Bian developed the

manganese-catalyzed homocoupling reaction of halides in the presence of magnesium.¹⁰ Recently, Cahiez *et al.*. reported efficient cross-coupling reactions between aryl Grignard reagents and alkenyl halides,¹¹ and the homocoupling of Grignard reagents with atmospheric oxygen as oxidant.¹¹ Zhou and Xue also reported an oxidative homocoupling of Grignard chlorides in the presence of a re-oxidant.¹² Hererin, we report the first solely manganese-catalyzed *N*-arylation of nitrogen nucleophiles catalyzed by a combination of MnCl₂·4H₂O¹³ and *trans*-1,2-diaminocyclohexane in water. It is worth noting that the reaction only proceeded efficiently when water was used as the reaction medium. This has implications not only in terms of green chemistry, but also in the mechanistic aspects of the reaction.

In our initial study, the reaction between iodobenzene (1) and pyrazole (2) was chosen. Using the optimized conditions from previous protocols,⁷ the reaction was carried out using a combination of MnCl₂·4H₂O, N,N'-dimethylenediamine (L1) and $K_3PO_4 H_2O$ in water, affording the product in a moderate yield (Table 1, entry 1). This promising result prompted us to evaluate the merits of the assisting ligands for the arylation process. To our delight, the reaction carried out using trans-1,2-diaminocyclohexane (L3) as the assisting ligand gave the N-arylated product with an excellent yield of 78% (Table 1, entry 3). The necessity of the manganese salt and the ligand was confirmed when the absence of either one of these reagents resulted in no products being formed (Table 1, entries 7 and 8). Next, we probed the solvent effect using a series of organic solvents. Interestingly, we found that the reaction proceeded efficiently only when water was used as the sole reaction medium. Low yields were obtained when DMF, toluene or THF were employed as the solvent (Table 1, entries 9-11), and no products were detected in the case of DMSO or CH₃CN as the reaction medium (Table 1, entries 12 and 13). These organic solvents were used directly without undergoing rigorous drying processes. Further experiments revealed that the nature of the bases had a pronounced impact on the process. The choice of K₃PO₄·H₂O as the base was critical for this coupling reaction, as Cs₂CO₃ and K₂CO₃ were evaluated and shown to be ineffective. Finally, we proceed to screen the efficiency of other manganese salts for the *N*-arylation reaction. It is worth noting that good to excellent yields ranging from 65-78% were obtained for the majority of the manganese salts screened, including Mn(acac)₂, Mn(ClO₄). H₂O, MnF₂, Mn(OAc)₂ and MnO₂ (Table 1, entries 14-18). As such, this protocol has the added advantage of versatility in terms of the selection of the manganese salts for the reaction. With these findings, MnCl₂·4H₂O was the manganese salt of choice for the cross-coupling reactions, since it is the least

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Table 1	Optimization	studies	for t	he man	ganese-catalyzed	cross
coupling	of iodobenzene	e (1) and	l pyra	zole (2)	in water ^a	

	PhI + NH -	[Mn] (10 mol %) Ligand (20 mol%) K ₃ PO _{4.} H ₂ O Divent, 130°C, 24 h	N N 3a	
	MeHN NHMe L1	Me ₂ N NMe ₂	H_2N NH_2	
	COOH H L4			~
Entry	[Mn] source	Ligand	Solvent	Yield $(\%)^b$
1	MnCl2·4H2O	L1	H ₂ O	31
2	MnCl ₂ ·4H ₂ O	L2	H ₂ O	Trace
3	MnCl ₂ ·4H ₂ O	L3	H ₂ O	78
4	MnCl ₂ ·4H ₂ O	L4	H ₂ O	0
5	MnCl ₂ ·4H ₂ O	L5	H_2O	0
6	MnCl ₂ ·4H ₂ O	L6	H_2O	0
7	MnCl ₂ ·4H ₂ O	_	H_2O	0
8		L6	H_2O	0
9	MnCl ₂ ·4H ₂ O	L3	DMF	21
10	MnCl ₂ ·4H ₂ O	L3	Toluene	8
11	MnCl ₂ ·4H ₂ O	L3	THF	5
12	MnCl ₂ ·4H ₂ O	L3	DMSO	0
13	MnCl ₂ ·4H ₂ O	L3	CH ₃ CN	0
14	$Mn(acac)_2$	L3	H_2O	78
15	Mn(ClO ₄) ₂ ·H ₂ O	L3	H_2O	75
16	MnF_2	L3	H_2O	72
17	$Mn(OAc)_2$	L3	H_2O	71
18	MnO ₂	L3	H ₂ O	65

^a Unless otherwise noted, the reaction was carried out with 1H-pyrazole (1.47 mmol), iodobenzene (2.21 mmol), K₃PO₄·H₂O (2.94 mmol), Mn source (10 mol%) and ligand (20 mol%) in water (0.75 mL) at 130 °C for 24 h. ^b Isolated yield after column chromatography.

expensive. In summary, the optimal conditions for the N-arylation of pyrazole were achieved using a combination of MnCl₂·4H₂O (10 mol%), trans-1,2-diaminocyclohexane (L3) (20 mol%) and K₃PO₄·H₂O (2 equiv.), stirred in water at 130 °C for 24 h.

In order to rule out the possibility that the catalysis was assisted by traces of Cu salts¹⁴ or other contaminants that might be present in the Mn salts, we had carried out the reaction of pyrazole and iodobenzene using high purity 99.99% MnCl₂·4H₂O (Sigma) under the optimized conditions. This reaction afforded the product **3a** in a good isolated yield of 64%. As such, we can conclude that metal contaminants, if present, do not play any significant role in this Mn-catalyzed cross-coupling reaction.

Having optimized the reaction conditions for the manganese catalyzed arylation process, a study was initiated to explore the generality of various aryl halides with pyrazole. The results are shown in Table 2.

In general, good to excellent yields were obtained for sterically unhindered aryl halides. Ortho-substituted aryl halides gave poor yields regardless of the electronic nature of the substituent (Table 2, entries 2 and 3). Also, this protocol was limited only to aryl iodides, since the employment of bromobenzene and 4-bromoanisole as electrophilic partners gave only trace amounts of the products. The reactivity of the

Table 2 N-a	arylation	of pyrazole	2 with	aryl	halides	catalyzed	by
MnCl ₂ ·4H ₂ O	/L3 in wa	iter ^a					

	ArX + (N)NH	$\frac{\text{MnCl}_2 \cdot 4\text{H}_2\text{O}(10 \text{ mol }\%)}{\text{L3}(20 \text{ mol}\%)}$ $\xrightarrow{\text{K}_3\text{PO}_4\text{H}_2\text{O}}$ $\text{H}_2\text{O}, 130^{\circ}\text{C}, 24 \text{ h}$	N-Ar 3a-i	
Entry	ArX	Product		Yield (%)
1		N.N.	3a	78
2	OMe	N.N MeO	3b	16
3		N, N CI	3c	10
4	Me	Me N'N	3d	75
5		N-N-CI	3e	80
6	F ₃ C	N, N, CF ₃	3f	74
7	MeO	N-N-OMe	3g	67
8	F	N.N.F	3h	73
9	CI-	N-N-CI	3i	86
10	Br	N Br	3j	75
11	F ₃ C-	N CF3	3k	70

^a Unless otherwise noted, the reaction was carried out with 1H-pyrazole (1.47 mmol), aryl halide (2.21 mmol), K₃PO₄·H₂O (2.94 mmol), MnCl₂·4H₂O (10 mol%) and L3 (20 mol%) in water (0.75 mL) at 130 °C for 24 h. ^b Isolated yield after column chromatography.

aryl iodine moiety was confirmed by the chemoselective results from arenes with mixed halides, whereby the coupling only takes place on the carbon atom with the iodo substituent in the presence of other halides (Table 2, entries 8-10). These results were similar to previous reports on catalytic systems based on Fe and Co.

Finally, the scope of the manganese-catalyzed crosscoupling reaction was tested with other nitrogen heterocycles, and cyclic and acyclic amide derivatives. As shown in Table 3, 7-azaindole and indazole were effective nucleophilic partners for the coupling reaction, which afforded the corresponding products with good to excellent yields (Table 3, entries 1-5). The N-arylation of a representative substituted pyrazole, 3-methylpyrazole, also gave the N-phenyl derivatives with good yields (Table 3, entries 6-8). Poor yields were observed

	NuH +	Mr ArX –	$K_{3}PO_{4}H_{2}O$ (20 mol %) $K_{3}PO_{4}H_{2}O$	Nu-Ar	
Entry	NuH	ArX	Product		Yield (%) ^b
1			N	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	87
2				Ha Me	91
3				40 ∕−CI	77
4	N N H		N.N.	5a	90
5)—cı 5b	82
6	Me N N H		Me	6a	78
7			Me	Me	75
8					72
9			N	7a	25
10				Me 7h	20

^{*a*} Unless otherwise noted, the reaction was carried out with nitrogen nucleophile (1.47 mmol), aryl halide (2.21 mmol), K_3PO_4 ·H₂O (2.94 mmol), MnCl₂·4H₂O (20 mol%) and L3 (40 mol%) in water (0.75 mL) at 130 °C for 48 h. ^{*b*} Isolated yield after column chromatography.

in the coupling of indole with aryl iodides (Table 3, entries 9 and 10). Currently, this catalytic system is not effective when heterocycles such as pyrrole, imidazole or triazole are employed in the process, as only trace amount of the products are observed. Moreover, reactions carried out using benzylamine, pyrrolidin-2-one, benzamide and aniline were also unsuccessful.

In summary, a convenient route to *N*-arylated products promoted by a ligand-assisted Mn catalysis in water has been developed. The low cost and readily available Mn salts, the mild reaction conditions, and the operational simplicity and practicality render this transformation an attractive alternative to various arylated *N*-heterocycles. Further investigation to broaden Mn catalysis as a sustainable strategy for other cross-coupling reactions is ongoing.

Notes and references

- (a) J. F. Hartwig, Nature, 2008, 455, 314; (b) S. L. Buchwald and L. Jiang, in Metal-catalyzed cross-coupling reactions, ed. A. De Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, vol. 2, p. 699; (c) I. P. Belatskaya and A. V. Cheprakov, Coord. Chem. Rev., 2004, 248, 2337; (d) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, Chem. Rev., 2007, 107, 5318; (e) J. P. Corbet and G. Mignani, Chem. Rev., 2006, 106, 2651; (f) S. V. Ley and A. W. Thomas, Angew. Chem., Int. Ed., 2003, 42, 5400.
- 2 (a) H. Zhang, Q. Cai and D. W. Ma, J. Org. Chem., 2005, 70, 5164;
 (b) F. Y. Kwong, A. Klapars and S. L. Buchwald, Org. Lett., 2002,
 4, 581; (c) T. D. Quach and R. A. Batey, Org. Lett., 2003, 5, 4397;
 (d) D. S. Jiang, H. Fu, Y. Y. Jiang and Y. F. Zhao, J. Org. Chem., 2007, 72, 672; (e) H. J. Cristau, P. P. Cellier, J. F. Spindler and M. Taillefer, Chem.-Eur. J., 2004, 10, 5607; (f) M. Taillefer,
 A. Ouali, B. Renard and J. F. Spindler, Chem.-Eur. J., 2006, 12, 5301; (g) R. Martín, C. H. Larsen, A. Cuenca and S. L. Buchwald, Org. Lett., 2007, 9, 3379.
- 3 (a) J. F. Hartwig, Angew. Chem., Int. Ed., 1998, 37, 2046;
 (b) J. Barluenga, F. Aznar and C. Valés, Angew. Chem., Int. Ed., 2004, 43, 343; (c) S. Wagaw and S. L. Buchwald, J. Org. Chem., 1996, 61, 7240; (d) S. L. Buchwald, C. Mauger, G. Mignani and U. Scholz, Adv. Synth. Catal., 2006, 348, 23; (e) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman and S. L. Buchwald, Angew. Chem., Int. Ed., 2006, 45, 6523; (f) Q. L. Shen and J. F. Hartwig, J. Am. Chem. Soc., 2007, 129, 7734; (g) D. S. Surry and S. L. Buchwald, Angew. Chem., Int. Ed., 2006, 47, 6338; (h) N. Marion and E. M. Nolan, Acc. Chem. Res., 2008, 41, 1440; (i) J. F. Hartwig, Acc. Chem. Res., 2008, 41, 1534; (j) E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, Angew. Chem., Int. Ed., 2007, 46, 2768; (k) A. R. Muci and S. L. Buchwald, Top. Curr. Chem., 2002, 219, 131 and ref. cited therein.
- 4 For general reviews, see: (a) C. Bolm, J. Legros, J. Le Paih and L. Zani, Chem. Rev., 2004, 104, 6217; (b) A. Fürstner and R. Martin, Chem. Lett., 2005, 34, 624; E. B. Bauer, Curr. Org. Chem., 2008, 12, 1341. For recent contributions on Fe-catalyzed C-N reaction, see: (c) A. Correa and C. Bolm, Adv. Synth. Catal., 2008, 350, 391; (d) A. Correa, M. Carril and C. Bolm, Chem.-Eur. J., 2008, 14, 10919; (e) D. Guo, H. Huang, J. Xu, H. Jiang and H. Liu, Org. Lett., 2008, 10, 4513.
- 5 M. Taillefer, N. Xia and A. Oualli, *Angew. Chem., Int. Ed.*, 2007, **46**, 934.
- 6 A. Correa and C. Bolm, Angew. Chem., Int. Ed., 2007, 46, 8862.
- 7 (a) Y.-C. Teo and G.-L. Chua, Chem.-Eur. J., 2009, 15, 3072;
 (b) Y.-C. Teo, Adv. Synth. Catal., 2009, 351, 720.
- 8 (a) G. Cahiez, D. Bernard and J. F. Normant, J. Organomet. Chem., 1976, 113, 99; (b) S.-K. Kang, J.-S. Kim, K. Fugami, K. Oshima and K. Utimoto, Chem. Lett., 1987, 16, 2203; (c) S.-K. Kang, J. S. Kim and S.-C. Choi, J. Org. Chem., 1997, 62, 4208; (d) M. Alami, P. Ramiandrasoa and G. Cahiez, Synlett, 1998, 325; (e) S.-K. Kang, W.-Y. Kim, Y.-T. Lee, S.-K. Ahn and J.-C. Kim, Tetrahedron Lett., 1998, 39, 2131; (f) G. Cahiez, F. Lepifre and P. Ramiandrasoa, Synthesis, 1999, 2138; (g) S.-K. Kang, T.-G. Baik, X. H. Jiao and Y.-T. Lee, Tetrahedron Lett., 1999, 40, 2383; (h) G. Cahiez, D. Luart and F. Lecomte, Org. Lett., 2004, 6, 4395; (i) H. Shinokubo and K. Oshima, Eur. J. Org. Chem., 2004, 2081.
- 9 M. Rueping and W. Ieawsuwan, Synlett, 2007, 247.
- 10 Y. Yuan and Y. Bian, Appl. Organomet. Chem., 2008, 22, 15.
- 11 (a) G. Cahiez, A. Moyeux, J. Buendia and C. Duplais, J. Am. Chem. Soc., 2007, **129**, 13788; (b) G. Cahiez, O. Gager and F. Lecomte, Org. Lett., 2008, **10**, 5255.
- 12 Z. Zhou and W. Xue, J. Organomet. Chem., 2009, 694, 599.
- 13 MnCl₂·4H₂O with \geq 99% purity purchased from Sigma Aldrich was used in all experiments reported here.
- 14 S. L. Buchwald and C. Bolm, Angew. Chem., Int. Ed., 2009, 48, 5586.