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A manganese/copper bimetallic catalyst for C–N coupling reactions under mild conditions in water

Yong-Chua Teo *, Fui-Fong Yong, Gina Shiyun Lim

Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616, Singapore

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ABSTRACT

An efficient and convenient bimetallic MnF_2/CuI catalyst in combination with *trans*-1,2-diaminocyclohexane has been developed for the cross-coupling of nitrogen heterocycles with aryl halides in water at moderate temperature. A variety of nitrogen nucleophiles including pyrazole, 7-azaindole, indazole, indole, pyrrole and imidazole afforded the corresponding products in moderate to good yields (up to 94%) under the described arylation conditions.

The transition metal catalyzed formation of carbon–carbon and carbon-heteroatom bonds has emerged as a versatile and powerful tool in chemical synthesis.[1] In particular, the N-arylation of nitrogen nucleophiles with aryl halides has acquired importance due to the versatility of the products, which are prevalent in compounds of biological, pharmaceutical and materials interest.[2] Among the various strategies developed to date, copper-catalyzed Ullmann condensations have proven to be a convenient method for the assembly of N-arylated compounds.[3] The synthetic scope of this reaction, however, is greatly limited by its harsh conditions such as elevated temperature (>140 °C), long reaction time, and stoichiometric amounts of copper reagents.[4] In the past decade, improvements on the Ullmann-type C–N cross-coupling have been mostly concerned with the development of catalytic systems that utilized new mono- or bidentate chelators to increase the reaction rates and lower substantially the reaction temperatures.[5–10] In spite of the significant progress made in the aforementioned transformation, most of these methodologies remain restricted to a certain degree due to the unavailability, air or moisture sensitivity and high expense resulting from the preparation of the ligands.

The application of bimetallic catalysis for the Ullmann condensation has been relatively unexplored. Taillefer et al. first reported an efficient $Fe(acac)_3$/CuO co-catalytic system for the arylation of nitrogen heterocycles with aryl halides.[11] Fu and co-workers reported a $FeCl_3$/CuO bimetallic catalyst that promoted the arylation of aliphatic/aryl amines and phenols in the presence of *rac*-BINOL as the ligand[12] while Liu demonstrated a Fe_2O_3/$Cu(acac)_2$ system for the arylations of aliphatic/aryl amines under microwave irradiation in DMSO/water.[13] The use of an iron co-catalyst and high temperature or microwave technology was critical for the success of these protocols.

Recently, the development of new strategies for cross-coupling reactions in water has stimulated interest among the synthetic community since they avoid environmental issues arising from the use of organic solvents.[14] However, these methods often entail the additional challenges of water tolerance for the catalyst/ligand system[15] and mostly require high reaction temperatures. Therefore, the exploration of a cross-coupling protocol that proceeds at low temperature in aqueous media is important.

Previously, we reported a protocol for the cross-coupling of azoles with aryl iodides using an $MnCl_2{\cdot}4H_2O$/*trans*-1,2-diaminocyclohexane catalytic system.[16] However, the use of aryl iodides and high reaction temperatures was necessary to achieve good yields of the products. Based on this precedent and as part of our continuing endeavors to develop environmentally friendly protocols that operate efficiently under mild conditions, herein we report the manganese/copper co-catalyzed C–N cross-coupling reactions between nitrogen heterocycles and aryl/heteroaryl halides in water. This novel system constitutes a rare example of efficient bimetallic catalysis and the first involving both manganese and copper reagents that operate in water at low temperature.

In our initial study, iodobenzene (**1**) and pyrazole (**2**) were chosen as model substrates. A preliminary reaction was carried out using a combination of $MnCl_2$, *trans*-1,2-diaminocyclohexane and K_3PO_4 at 60 °C in water. However, no conversion of iodobenzene

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* Corresponding author. Tel.: +65 6790 3846; fax: +65 6896 9414.
E-mail address: yongchua.teo@nie.edu.sg (Y.-C. Teo).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
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into product **3a** was observed, even after prolonged stirring (Table 1, entry 1). A control reaction carried out using CuI, but in the absence of the Mn additive only gave the product in a poor yield of 9% (entry 2). To our delight, the coupling of pyrazole with iodobenzene gave a moderate yield of 51% in the presence of catalytic amounts of both $MnCl_2$ and CuI (entry 3). This co-catalyzed N-arylation result prompted us to further evaluate the efficiency of other metal salts and bases for the N-arylation process (entries 4–10). Optimized conditions were achieved using MnF_2 (30 mol %), CuI (10 mol %), *trans*-1,2-diaminocyclohexane (20 mol %) and KOH (2 equiv) in water at 60 °C for 24 h which afforded the arylated product in a good yield of 88% (entry 10). A control experiment carried out in the absence of Mn additive using KOH as the base gave a poor yield of 24% (entry 11). This indicates the necessity for the Mn salt together with the copper salt as a bimetallic catalyst for this reaction. Attempts to lower the reaction temperature (40 °C) or decrease the Mn catalyst loading (10 mol %) led to traces or lower yields of the product (entries 12 and 13). Interestingly, we also found that the reaction proceeded efficiently in water only; lower yields of 50% and 54% were obtained when either DMF or toluene was employed as the solvent. This method is attractive for several reasons: (i) it employs a sustainable and environmentally-friendly catalytic system that is a combination of MnF_2/CuI which are inexpensive and readily available; (ii) it avoids the time consuming and uneconomical transformations associated with the synthesis of specially designed ligands; (iii) it offers experimental simplicity and mild conditions which exclude the need for an inert atmosphere and anhydrous solvent; (iv) it uses water as the reaction medium which is abundant, cheap and environmentally benign.

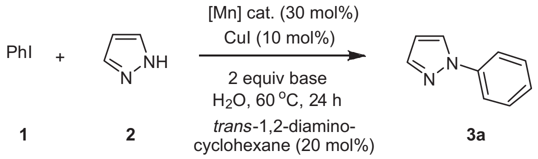
With the optimized conditions in hand, we next investigated the scope of the process with respect to aryl halides. The coupling reactions of pyrazole as the model heterocycle with differently substituted aryl halides were carried out. In general, the corresponding N-arylation products were obtained in moderate to good yields. The steric effect was significant as *ortho*-substituents hampered the reaction and led to traces or lower yields of the products (Table 2, entries 2–4). The protocol was tolerant of both electron-donating and electron-withdrawing groups as good yields were obtained regardless of the electronic nature of the substituent. No significant electronic effects were observed for both *meta*-and *para*-substituted aryl iodides (entries 5–13). Although aryl iodides are interesting substrates, we extended the protocol to aryl bromides as the electrophilic counterpart as these are of much greater interest for industrial applications. In most cases, good yields were obtained when the reactions were carried out at 100 °C (entries 14–21).

In a second set of experiments, the scope of the process was tested with a series of nitrogen heterocycles and aryl iodides. The arylated azoles were obtained in moderate to good yields from the cross-couplings of 7-azaindole and indazole (Table 3, entries 1–6). Lower yields were observed for indole, imidazole and pyrrole under the standard conditions, but elevating the reaction temperature to 100 °C led to an improvement in yields (entries 7–15). Moreover, the arylation of a representative substituted pyrazole, 3-methylpyrazole also gave the corresponding *N*-phenyl derivatives in good yields (entries 16–18).

Finally, we were successful in extending the system to include heteroaryl iodides as coupling partners, which are important pharmaceutical intermediates. Our catalytic system promoted efficiently the cross-coupling reactions between 7-azaindole and indole with 3-iodopyridine and 3-iodothiophene and pyrazole with 2-iodopyridine and 3-iodothiophene (Table 4, entries 1–6).

In summary, we have developed an original example of cooperative bimetallic catalysis based on Mn and Cu reagents in water. The N-arylation of various nitrogen heterocycles with differently substituted aryl iodides proceeded effectively in water at 60 °C in most instances. The low cost and readily available Mn and Cu salts, the operational simplicity, and mild reaction conditions render this transformation as an attractive alternative for the assembly of N-arylated products and should be applicable to custom synthesis

Table 1
Optimization studies on Mn/Cu catalytic systems for the N-arylation of pyrazole (**2**) in water[a]



Entry	[Mn] cat. (0.3 equiv)	Base	Yield[b] (%)
1	$MnCl_2$	K_3PO_4	0[c]
2	–	K_3PO_4	9[d]
3	$MnCl_2$	K_3PO_4	51
4	MnF_2	K_3PO_4	60
5	$Mn(OAc)_2$	K_3PO_4	41
6	$Mn(acac)_2$	K_3PO_4	17
7	$Mn(ClO_4)_2$	K_3PO_4	30
8	MnO_2	K_3PO_4	trace
9	MnF_2	Cs_2CO_3	17
10	MnF_2	KOH	88
11	–	KOH	24[d]
12	MnF_2	KOH	trace[e]
13	MnF_2	KOH	55[f]

[a] Reactions and conditions: pyrazole (1.47 mmol), iodobenzene (2.21 mmol), base (2.94 mmol), CuI (10 mol %), [Mn] source (30 mol %), *trans*-1,2-diaminocyclohexane (20 mol %), H_2O (0.75 mL), 60 °C, 24 h.

[b] Yield of isolated product.

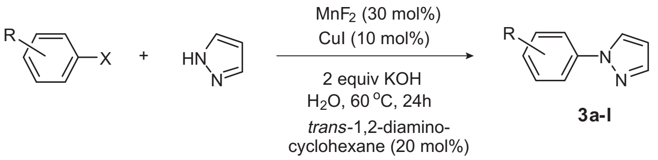
[c] Without Cu source.

[d] Without Mn source.

[e] Reaction stirred at 40 °C.

[f] Catalyst: MnF_2 (10 mol %) and CuI (10 mol %).

Table 2
Mn/Cu co-catalyzed N-arylation of pyrazole (**2**) with various substituted aryl halides in water[a]



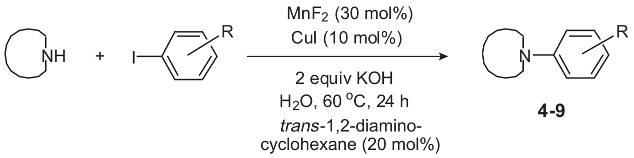
Entry	X	R	Product	Yield[b] (%)
1	I	H	**3a**	88
2	I	2-OMe	**3b**	30
3	I	2-Me	–	Trace
4	I	2-Cl	–	Trace
5	I	3-Me	**3c**	75
6	I	3-Cl	**3d**	77
7	I	$3-CF_3$	**3e**	80
8	I	$3-NO_2$	**3f**	70
9	I	4-OMe	**3g**	75
10	I	4-F	**3h**	62
11	I	4-Cl	**3i**	80
12	I	4-Br	**3j**	50
13	I	$4-CF_3$	**3k**	76
14	Br	H	**3a**	71[c]
15	Br	3-OMe	**3l**	70[c]
16	Br	3-Me	**3c**	84[c]
17	Br	3-Cl	**3d**	75[c]
18	Br	$3-CF_3$	**3e**	70[c]
19	Br	4-OMe	**3g**	65[c]
20	Br	4-F	**3h**	64[c]
21	Br	4-Cl	**3i**	70[c]

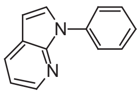
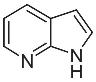
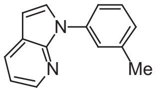
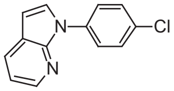
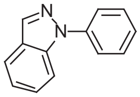
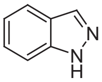
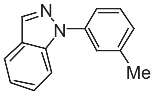
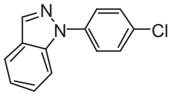
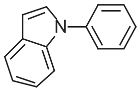
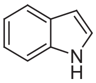
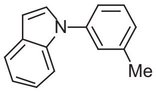
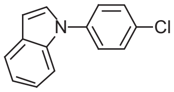
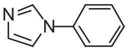
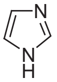
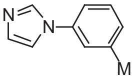
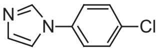
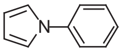
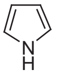
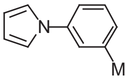
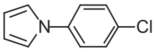
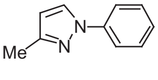
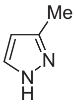
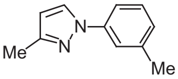
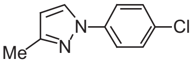
[a] Reactions and conditions: pyrazole (1.47 mmol), aryl halide (2.21 mmol), KOH (2.94 mmol), CuI (10 mol %), MnF_2 (30 mol %), *trans*-1,2-diaminocyclohexane (20 mol %), H_2O (0.75 mL), 60 °C, 24 h.

[b] Yield of isolated product.

[c] Reaction temperature: 100 °C.

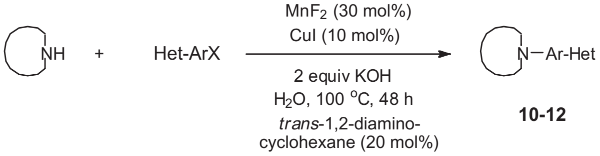
Table 3
Mn/Cu co-catalyzed N-arylation of azoles with various substituted aryl halides in water[a]

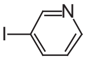
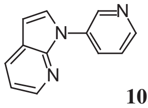
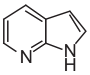
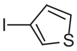
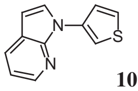
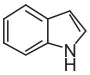
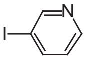
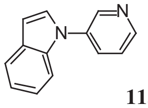
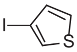
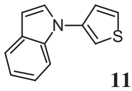
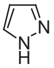
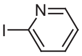
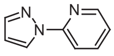
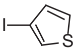
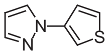


Entry	NuH	Product		Yield[b] (%)
1			**4a**	93
2			**4b**	85
3			**4c**	75
4			**5a**	84
5			**5b**	94
6			**5c**	91
7			**6a**	82[c]
8			**6b**	78[c]
9			**6c**	82[c]
10			**7a**	63[c]
11			**7b**	60[c]
12			**7c**	65[c]
13			**8a**	57[c]
14			**8b**	53[c]
15			**8c**	62[c]
16			**9a**	63
17			**9b**	81
18			**9c**	60

[a] Reactions and conditions: N-nucleophile (1.47 mmol), aryl iodide (2.21 mmol), KOH (2.94 mmol), CuI (10 mol %), MnF_2 (30 mol %), *trans*-1,2-diaminocyclohexane (20 mol %), H_2O (0.75 mL), 60 °C, 24 h.
[b] Yield of isolated product.
[c] Reaction temperature: 100 °C.

Table 4
Mn/Cu co-catalyzed N-arylation of azoles with various substituted heteroaryl halides in water[a]



Entry	NuH	Het-ArX	Product	Yield (%)[b]
1			 **10a**	94
2			 **10b**	92
3			 **11a**	78
4			 **11b**	70
5			 **12a**	94
6			 **12b**	57

[a] Reactions and conditions: N-nucleophile (1.47 mmol), heteroaryl iodide (2.21 mmol), KOH (2.94 mmol), CuI (10 mol %), MnF_2 (30 mol %), *trans*-1,2-diaminocyclohexane (20 mol %), H_2O, 100 °C, 24 h.
[b] Yield of isolated product.

and industrial processes. In addition, the use of water as the solvent greatly enhances the economical and environmental friendliness of this catalytic system. Further work to broaden the scope of this system to other cross-coupling reactions is in progress.

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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.2011.10.128.

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