Organic &
Biomolecular Chemistry

PAPER

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 7136

MIDA as a simple and highly efficient ligand for palladium-catalyzed Hiyama cross-coupling of aryl halides†

Mengping Guo,*[a,b] Liang Qi,[a,b] Qiaochu Zhang,[a,b] Zhiyong Zhu,[a] Wei Li[a] and Xiaogang Li[a,b]

Received 22nd May 2014,
Accepted 24th July 2014

DOI: 10.1039/c4ob01056f

www.rsc.org/obc

N-Methyliminodiacetic acid (MIDA) as a simple, air stable and water-soluble ligand has been used in the palladium-catalyzed Hiyama cross-coupling reaction of trimethoxyphenylsilane with aryl halides. The yield of the corresponding Hiyama coupling products is high up to around 90% in water and isopropanol under an ambient atmosphere in the presence of KOH and NaF.

Introduction

The synthesis of carbon–carbon bonds by transition metal catalyzed cross-coupling has developed into one of the most useful and important classes of reactions in modern synthetic organic chemistry over the past 40 years.[1] Among these cross-coupling reactions, the palladium-catalyzed Hiyama reaction of organosilane with aryl halides has attracted much attention in organic synthesis.[2] In the last two decades many efforts have been made to develop more active catalysts for the Hiyama coupling reaction.[3–8] In catalytic systems, a very important role was played by the appropriate selection of the catalyst which should show high activity, selectivity and stability under the reaction conditions.[9] Soluble palladium compounds containing phosphorus ligands have been widely used in C–C cross-coupling reactions because of their facile synthesis and structural versatility.[10,11] Although most of the phosphorus catalysts have exhibited excellent activity, the increasing environmental concerns[12–15] oblige us to develop environmental benign catalysts for the organic transformation.

Since the successful isolation of the first stable carbene by Arguengo in 1991, N-heterocyclic carbenes (NHCs) have been extensively studied in the field of organometallics as ligands comparable to the conventional phosphine ligands.[16–19] Some highly active palladium systems with carbene ligands for the Hiyama reaction have been developed.[20–22] However, NHCs always have bulky structures, and few studies on simple structures and electron-rich N-ligands have been conducted. Maybe, these simple ligands could make the reaction occur smoothly. It is necessary to try, assuming that *N*-methyliminodiacetic acid (MIDA) is a good candidate. It is a simple, air stable, low cost and highly active ligand. To the best of our knowledge, MIDA has not been used as a ligand in the transition-metal-catalyzed Hiyama cross-coupling reaction. It not only can be dissolved in water but also can be obtained easily and cheaply. Meanwhile, this ligand is stable in air, moisture and heat treatment, and it can be used to activate the Hiyama cross-coupling reaction in aqueous media under an ambient atmosphere. Moreover, such a catalyst shows potential applications in industry.

Results and discussion

Optimization of reaction conditions

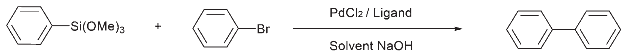
Initially the cross-coupling reaction of phenyltrimethoxysilane with bromobenzene was carried out in the system of 3 ml ethanol, 3 ml H_2O and 3 mmol NaOH without any protective atmosphere. After stirring for 4 h in an 80 °C oil bath, a yield of 41% biphenyl was obtained. The yields were different in various solvents. So the cross-coupling reaction of phenyltrimethoxysilane with bromobenzene was chosen as a model reaction to optimize the reaction conditions. The results are summarized in Table 1. Subsequently a series of alcohols were altered to examine the different activities in the base NaOH. Methanol, *n*-propanol, 1-butanol and PEG400 (Table 1, entries 1, 3, 5 and 6) provided general results of the cross-coupling reaction. Isopropanol showed higher activity than other alcohols with a good yield (Table 1, entry 4). Then some other common organic solvents were tested to choose the best one. Unfortunately THF, acetone, acetonitrile and 1,4-dioxane (Table 1, entries 8–11) all expressed poor vitality except DMSO (Table 1, entry 7). It is clear that isopropanol was the best solvent in the

---

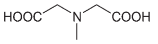
[a] *Institute of Coordination Catalysis, College of Chemistry and Bio-engineering, Yichun University, Yichun 336000, PR China. E-mail: guomengping65@163.com*
[b] *Engineering Center of Jiangxi University for Lithium Energy, Yichun University, Yichun 336000, PR China*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob01056f

Table 1 Effect of the solvent on the Hiyama reaction of phenyltrimethoxysilane with bromobenzene



Ligand:



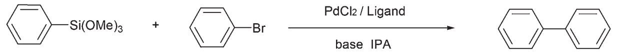
Entry	Solvent–H_2O (v : v = 1 : 1)	Yield (%)
1	Methanol	44
2	Ethanol	41
3	PEG400	52
4	IPA	75
5	*N*-Propanol	46
6	1-Butanol	54
7	DMSO	64
8	THF	48
9	1,4-Dioxane	21
10	Acetone	24
11	Acetonitrile	29
12	IPA–H_2O (6 : 0)	Trace
13	IPA–H_2O (5 : 1)	Trace
14	IPA–H_2O (4 : 2)	52
15	IPA–H_2O (2 : 4)	48
16	IPA–H_2O (1 : 5)	31
17	IPA–H_2O (0 : 6)	Trace

Reaction conditions: phenyltrimethoxysilane 1.2 mmol, bromobenzene 1 mmol, NaOH 3 mmol, $PdCl_2$ 0.02 mmol, ligand (MIDA) 0.02 mmol, solvent 3 ml, H_2O 3 ml, 80 °C, stirred for 4 h. *In situ* reaction. Isolated yield.

system, but the reaction could not occur smoothly due to the lack of adequate water (Table 1, entries 12–17).

As we know, the base in the Hiyama reaction was a significant element especially NaOH and KOH, which were the common bases in the Hiyama cross-coupling reaction. So some common inorganic bases and some organic bases were used in the reaction. The results are summarized in Table 2. Both NaOH and KOH (Table 2, entries 1 and 2) provided better yields than other bases, but KOH was a little better than NaOH. According to the results, strong bases show higher activities than weak ones. Although KOH was the best base in the cross-coupling reaction, the yield of the product was not ideal. Fluorion is a critical additive in the reaction of organosilicon. Silicane need to be activated by fluorion because of its low reaction activity. Generally fluorion is from TBAF, TASF, NaF, KF and so on, but TBAF and TASF cost much higher than inorganic salts. So we try to add NaF to provide fluorion to promote the cross-coupling reaction. The results are summarized in Table 3. It is clear that the yield of the cross-coupling reaction was better while both 3 mmol KOH and 3 mmol NaF were added (Table 3, entry 3). If only NaF was added as a base, the yield was not ideal even after increasing the amount of NaF (Table 2, entry 5, Table 3, entry 5). What is more, in order to confirm that MIDA serves as a ligand in the reaction, a reaction was carried out in the optimized system (Table 4, entry 15). It is obvious that the palladium-catalyzed ligand-free Hiyama reaction could not occur smoothly. So MIDA serves as a ligand in this reaction.

Table 2 Effect of the base on the Hiyama reaction of phenyltrimethoxysilane with bromobenzene



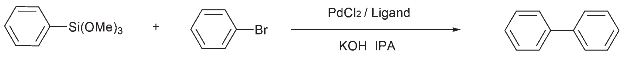
Entry	Base	Yield (%)
1	NaOH	72
2	KOH	81
3	Na_2CO_3	25
4	K_2CO_3	25
5	NaF	20
6	KH_2PO_4	Trace
7	$K_3PO_4 \cdot 3H_2O$	Trace
8	Na_3PO_4	Trace
9	DMF	Trace
10	DMA	27
11	Cs_2CO_3	30
12	Morpholine	Trace

Reaction conditions: phenyltrimethoxysilane 1.2 mmol, bromobenzene 1 mmol, base 3 mmol, $PdCl_2$ 0.02 mmol, Ligand (MIDA) 0.02 mmol, IPA 3 ml, H_2O 3 ml, 80 °C, stirred for 4 h. *In situ* reaction. Isolated yield.

Scope and limitations of substrates

With the optimized conditions in hand, we further studied the generality of the cross-coupling reactions of aryl halides with aryltrimethoxysilane in the presence of 2 mol% $PdCl_2$ per ligand (MIDA) and 3 mmol of KOH at 80 °C in water and isopropanol (v : v = 1 : 1). The results are shown in Table 4. Various 4-substituted aryl bromides and aryl chlorides, bearing either electron-donating or electron-withdrawing groups, such as –OMe, $-CH_3$, $-CF_3$ and $-NO_2$, provided the corresponding products in moderate to good yields. Regardless of the reactants with electron-withdrawing groups or electron-donating groups, the additive NaF could promote the cross-coupling reactions. Besides, the aryl halides with electron-withdrawing groups commonly have a positive activity than electron-donating groups, even if aryl halides are substituted by chlorine (Table 4, entries 4 and 5). For example, 4-nitrobenzene chloride and 4-trifluoromethyl chlorobenzene, afforded

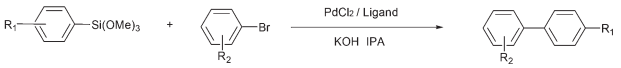
Table 3 Effect of F^- on the Hiyama reaction of aryltrimethoxysilane with bromobenzene

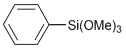
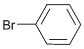
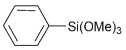
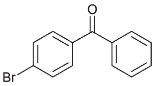
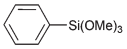
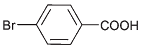
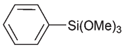
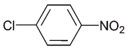
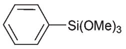
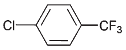
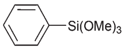
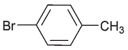
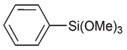
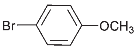
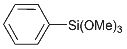
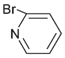
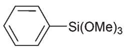
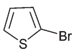
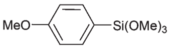
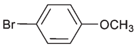
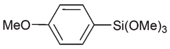
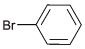
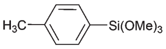
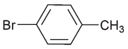
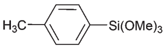
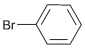
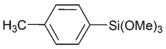
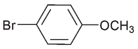
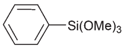
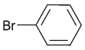


Entry	NaF	Yield (%)
1	1 mmol	88
2	3 mmol	92
3	5 mmol	65
4	Free	81
5[a]	5 mmol	25

Reaction conditions: phenyltrimethoxysilane 1.2 mmol, bromobenzene 1 mmol, KOH 3 mmol, $PdCl_2$ 0.02 mmol, ligand (MIDA) 0.02 mmol, IPA 3 ml, H_2O 3 ml, 80 °C, stirred for 4 h. [a] Without 3 mmol KOH. *In situ* reaction. Isolated yield.

Table 4 Hiyama coupling-reaction of aryl bromides with phenyl trimethoxysilane



No.	Entry	Aryl bromide	Yield[a] (%)	Yield[b] (%)
1			81	92
2			63	84
3			53	78
4			89	97
5			58	76
6[c]			42	65
7[d]			40	63
8			81	94
9			72	85
10[e]			64	77
11			80	93
12[f]			39	57
13			84	96
14[g]			51	62
15[h]			Trace	Trace

Reaction conditions: phenyltrimethoxysilane 1.2 mmol, bromobenzene 1 mmol, KOH 3 mmol, $PdCl_2$ 0.02 mmol, ligand (MIDA) 0.02 mmol, IPA 3 ml, H_2O 3 ml, 80 °C, stirred for 6 h. *In situ* reaction. Isolated yield. [a] Without NaF. [b] 3 mmol NaF was used. [c–g] 80 °C, stirred for 12 h. [h] Without the ligand.

excellent yields in the system in which NaF participated. Meanwhile 4-bromine toluene and 4-bromoanisole reacted with trimethoxyphenylsilane, trimethoxy(*p*-toly)silane or trimethoxy (4-methoxyphenyl)silane all provided moderate cross-coupling yields without the additive, despite delayed reaction time (Table 4, entries 6, 7, 12 and 14). Under the same conditions the yields of these cross-coupling products were improved while using NaF. Heterocyclic compounds,pyridine and thiophene (Table 4, entries 8 and 9), provided good yields when reacted with trimethoxyphenylsilane.

Experimental

Aryl chlorides, aryl bromides and MIDA were purchased from Alfa Aesar. Trimethoxyphenylsilane, trimethoxy(*p*-toly)silane and trimethoxy (4-methoxyphenyl)silane were purchased from TCI. Other chemicals were obtained commercially and used without any prior purification. All products were isolated by thin layer chromatography on a silica gel using *n*-hexane and ethyl acetate unless otherwise noted. Compounds described in the literature were characterized by ^1H NMR and ^{13}C NMR spectra compared with reported data. ^1H NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard. All the Hiyama reactions were carried out under air. A mixture of aryl halide (1.0 mmol), aryltrimethoxysilane (1.2 mmol), base (3.0 mmol), $PdCl_2$ (0.02 mol%, 0.0036 g), ligand MIDA (0.02 mol%, 0.0029 g), H_2O (3.0 ml), and IPA (3.0 ml) were stirred at 80 °C for the indicated time. The reaction mixtures were extracted with ethyl acetate (3 × 10 ml). The solvent was concentrated under vacuum.

Conclusions

In conclusion, MIDA, a simple, easily obtained and air stable ligand could activate the aryl halides in the palladium-catalyzed Hiyama reaction in water and isopropanol. Simple ligands may have the same function with bulky electron-rich ones, when used in a suitable system.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (no. 21063015) and the Scientific Research Fund of Jiangxi Provincial Education Department (no. GJJ 12597) for their financial support.

Notes and references

1 F. S. Hannah, R. J. D. Warren Galloway and D. R. Spring, *Chem. Soc. Rev.*, 2012, **41**, 1845.

2 S. E. Denmark and C. S. Regens, *Acc. Chem. Res.*, 2008, **41**, 1486.

3 Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1988, **53**, 918.

4 J.-Y. Lee and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 5616.

5 D. A. Powell and G. C. Fu, *J. Am. Chem. Soc.*, 2004, **126**, 7788.

6 S. E. Denmark, *J. Am. Chem. Soc.*, 1999, **121**, 5821.

7 X. Dai, N. A. Strotman and G. C. Fu, *J. Am. Chem. Soc.*, 2008, **130**, 3302.

8 T. Yanase, Y. Monguchi and H. Sajiki, *RSC Adv.*, 2012, **2**, 590.

9 I. B1aszczyk and A. M. Trzeciak, *Tetrahedron*, 2010, **66**, 9502.

10 A. M. Trzeciak and J. J. Ziólkowski, *Coord. Chem. Rev.*, 2005, **249**, 2308.

11 A. M. Trzeciak and J. J. Ziólkowski, *Coord. Chem. Rev.*, 2007, **251**, 1281.

12 T. Matsumoto, M. Ueno, N. Wang and S. Kobayashi, *Chem. – Asian J.*, 2008, **3**, 196.

13 T. Mallat and A. Baiker, *Chem. Rev.*, 2004, **104**, 3037.

14 N. Jamwal, M. Gupta and S. Paul, *Green Chem.*, 2008, **10**, 999.

15 S. F. J. Hackett, R. M. Brydson, M. H. Gass, I. Harvey, A. D. Newman, K. Wilson and A. F. Lee, *Angew. Chem., Int. Ed.*, 2007, **46**, 8593.

16 A. J. Arduengo III, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361.

17 S. Díez-González, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612.

18 D. Pugh and A. A. Danopoulos, *Coord. Chem. Rev.*, 2007, **251**, 610.

19 P. L. Arnold and I. J. Casely, *Chem. Rev.*, 2009, **109**, 3599.

20 S. Roy and H. Plenio, *Adv. Synth. Catal.*, 2010, **352**, 1014.

21 X.-Y. Xu, B.-C. Xu, Y.-X. Li and S. H. Hong, *Organometallics*, 2010, **29**, 6343.

22 D. R. Snead, S. Inagaki, K. A. Abboud and S. H. Hong, *Organometallics*, 2010, **29**, 1729.