

Dalton Transactions

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



Dalton Transactions

COMMUNICATION

Selective Amination of Aryl Chlorides Catalysed by Ni(PMe₃)₄

Shumiao Zhang, Xiaoyan Li, Hongjian Sun*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/dalton

C,N-coupling reactions of aryl chlorides and aryl amines catalyzed by a nickel catalyst are reported. 17 new amines are synthesized in yields of 57-99%. The 2,6-dichloro substituted imines can be selectively aminated. Both mono- and di-aminated products are obtained. Different substrates and amines are tested to look into the influence of electronic effects and steric hindrance to the reaction. An inexpensive and convenient base, NaOH, is used. It is an efficient way to gain access to new amines and imines.

C,N-coupling reactions are important in building amines. The Palladium catalyzed Buchwald-Hartwig reaction and the Copper catalyzed Ullman amination reaction are known as the most significant C-N formation pathways.¹⁻³ A lot of examples for Pd or Cu catalyzed aryl halogen amination have been reported, applying to small molecules, total synthesis of natural products⁴ and organic electroactive materials⁵. The Ullman type reactions usually need excess copper with bromides or iodides as substrates.⁶

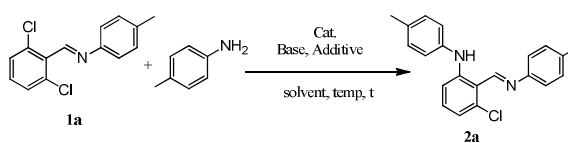
Nickel catalysts have arisen with great interest in the amination of aryl halides. Buchwald demonstrated the first nickel-catalyzed amination of aryl chlorides,⁷ and developed a highly active dppe-ligated Ni precatalyst for C,N-cross-coupling reactions.⁸ Hartwig reported Ni complexes containing a bisphosphine ligand with a side-bound benzonitrile ligand that catalyzed the coupling of aryl electrophiles with primary amines or ammonia.⁹ Ni(II)-(σ-aryl) complexes were employed as catalysts by Yang in the amination of aryl chlorides¹⁰ and the reaction can also transpire using Ni(PCy₃)₂Cl₂ with the help of iPrMgCl.¹¹ Nickel complexes containing NHC ligands¹² or other suitable ligands^{13,14} could also catalyze the C,N-coupling reactions.

In previous work, nickel catalysts were reported, but the catalyst scope is still narrow compared to the palladium or copper catalysts. As an inexpensive and readily available metal, nickel has a lot of advantages in catalytic reactions. The selectivity of C-Cl amination in polychloro substances has proven to be poor. It is important to

find a way to functionalize C-Cl bonds specifically in molecules.

We report here the Ni(PMe₃)₄-catalyzed selective amination of aryl chlorides using NaOH as a base. As shown in Table 1, several nickel complexes were used as catalysts in the model reaction and only Ni(PMe₃)₄ showed activity. It is possible to activate one C-Cl bond selectively in a di-chlorinated system by controlling the amount of amine added. The loading of the catalyst was initially intended to be at least 5 mol% for complete conversion of the substrate in 24h. Then bases were tested. Surprisingly, NaOH behaved better than other bases, giving a 95% yield. NaOH is inexpensive and convenient compared to the typical bases used in C,N-coupling, such as KO^tBu or Cs₂CO₃. The reaction temperature was set at 80 °C because the time saved by raising temperature from 80 °C to 100 °C was small. As NaOH cannot completely dissolve in organic solvents, phase transfer catalyst TBAB (tetra-*n*-butylammonium bromide), or TEBAC (benzyltriethylammonium chloride) or TBAI (tetrabutylammonium iodide), was taken into consideration to improve the reaction conditions. When the phase transfer catalyst was added in 5 mol% of the substrate, TBAB led to the best conversion. It not only doubled the reaction efficiency, but also lowered the catalyst loading to 4 mol%. The model reaction was also tried in different solvents. Reaction in DMSO led to no yield. CH₃CN and DMF resulted in uncontrollable impurities. Therefore, the best reaction condition for this catalytic system is 4 mol% of Ni(PMe₃)₄ as catalyst, NaOH as base and 5 mol% of TBAB in toluene for 12h (entry 13, table 1).

Table 1. Optimization of reaction condition for C,N-coupling reaction^a



School of Chemistry and Chemical Engineering, Key Laboratory of Special Functional Aggregated Materials, Ministry of Education, Shandong University, Shanda Nanlu 27, 250199 Jinan, PR China
E-mail: hjsun@sdu.edu.cn

[†]Electronic Supplementary Information (ESI) available: ¹H-NMR, ¹³C-NMR, ¹⁹F-NMR and ESI-MS data for the new compounds. For ESI data see DOI: 10.1039/x0xx00000x

	Cat./mol	Base	Solvent	Additive/ mol	Yieldb/%
1	10%NiL ₄	NaOH	toluene	none	95
2	5%NiL ₄	NaOH	toluene	none	95
3	3%NiL ₄	NaOH	toluene	none	34
4	10%	NaOH	toluene	none	0
5	Ni(PPh ₃) ₂ Cl ₂	NaOH	toluene	none	0
6	5%NiL ₄	KOH	toluene	none	84
7	5%NiL ₄	Na ₂ CO ₃	toluene	none	-
8	5%NiL ₄	Et ₃ N	toluene	none	0
9	5%NiL	NaOMe	toluene	none	-
10	5%NiL ₄	KO ^t Bu	toluene	none	60
11	5%NiL ₄	NaOH	toluene	none	94 ^c
12	5%NiL ₄	NaOH	toluene	5%	95 ^d
				TBAB	
13	4%NiL ₄	NaOH	toluene	5%	95 ^d
				TBAB	
14	4%NiL ₄	NaOH	DMSO	5%	0 ^d
				TBAB	
15	4%NiL ₄	NaOH	CH ₃ CN	5%	Impu rities ^d
				TBAB	
16	4%NiL ₄	NaOH	DMF	5%	Impu rities ^d
				TBAB	
17	4%NiL ₄	NaOH	toluene	5%	72 ^d
				TBAI	
18	4%NiL ₄	NaOH	toluene	MgSO ₄	30
19	4%NiL ₄	NaOH	toluene	5%	65 ^d
				TEBAC	

^a Reaction conditions: aryl chloride (0.15 mmol), amine (0.15 mmol), NaOH (0.15 mmol), 80°C, 24h in toluene (2 mL)

^b Isolated yield by column chromatography using 50 : 1 petroleum ether : Et₃N.

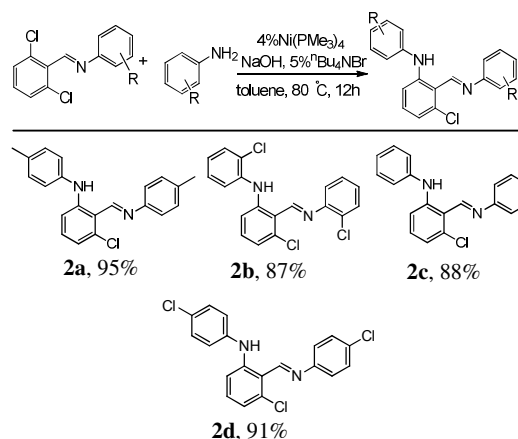
^c Reaction temperature 100°C, reaction time 21h.

^d Reaction time 12h.

^e L = PMe₃.

The substrates explored are shown in Schemes 1 - 3. The amination of different types of chlorinated Schiff bases with aryl amines was studied. Initially, amines that were the same as the ones in building the Schiff bases were tested (Scheme 1). One equivalent of the amine was added to obtain the mono-aminated product. It was reported that it was difficult to obtain the mono-(C,N)-coupling product from di- or tri- chlorinated compounds.¹⁴ In this catalytic system, all the yields are high when using aryl amines. Mono-aminated products were the only products by controlling the amount of amine added. The anchoring group, the imine group, is also of great importance in the selective amination. Alkyl amines are not fit for this reaction.

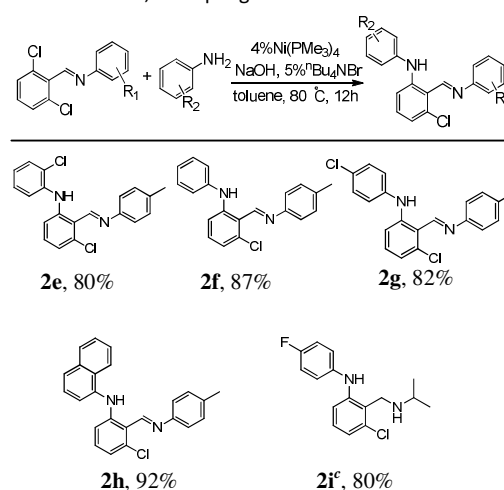
Scheme 1. Scope of C,N-coupling products using the same amine with the one in imines^{a,b}



^a Reaction conditions: aryl chloride (1.5 mmol), amine (1.5 mmol), NaOH (1.5 mmol), ⁿBu₄NBr (0.075 mmol), Ni(PMe₃)₄ (0.060mmol), toluene (4 mL), 80°C, 12h.

^b Isolated yield by column chromatography using 50:1 petroleum ether : Et₃N.

Scheme 2. C,N-coupling with diverse amines^{a,b}



^a Reaction conditions: aryl chloride (1.5 mmol), amine (1.5 mmol), NaOH (1.5 mmol), ⁿBu₄NBr (0.075 mmol), Ni(PMe₃)₄ (0.060mmol), toluene (4 mL), 80°C, 12h.

^b Isolated yield by column chromatography using 50:1 petroleum ether : Et₃N.

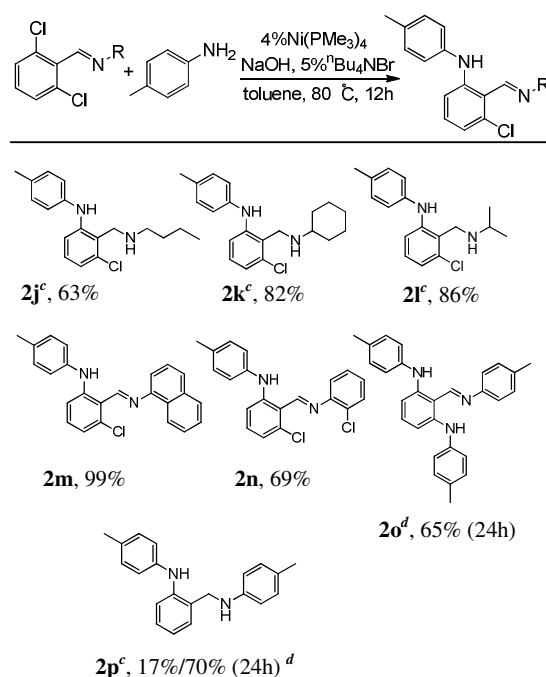
^c The imine product is reduced by NaBH₄ to obtain **2i**.

The reaction was carried out with different aryl amines (Scheme 2). It turned out that 1-naphthylamine had the highest yield (entry 2h). It was disclosed that the amines containing electron-withdrawing groups had lower activities.¹⁵ In our case

entries 2e and 2g reached a yield of 80% and 82%, respectively. Even for 4-fluoro amine (entry 2i) the yield is still 80%. To obtain 2i, the related Schiff base had to be reduced to the amine by NaBH₄. The reductive procedure was almost quantitative.

Scheme 3 shows the catalytic reactions of the Schiff bases containing diverse backbones with 4-methylaniline. Some products were reduced to provide the corresponding amines (entries 2j, 2k, 2l, 2p). It can be concluded from entries 2j and 2n that the steric hindrance effect (the butyl group) and electron-withdrawing group (the ortho-Cl group) of the backbone influenced the reaction negatively. Mono-chloro substituted imine reacted slowly (entry 2p), giving 17% product in 12h and 70% yield in 24h. The same situation occurred in the di-amination of two chlorine atoms of the substrate (entry 2o). The reason for the difference of the reaction rates between mono- and di-chlorinated substrates can be attributed to the electronic effect of the other chlorine atom on the aryl ring. The second chlorine atom makes the C-Cl activation easier. To improve the production yield, reaction time was doubled and the yield of di-amination product rose to 65%. Finally, hexachlorobenzene coupled with p-toluidine to give a moderate yield of product (Scheme 4). In the case of 2q, only one chlorine atom could be activated slowly, indicating the importance of the anchoring group. In Schiff bases, C=N is the anchoring group, directing the metal selectively and activating the *ortho*-(C-Cl) bond effectively.

Scheme 3. Different Schiff bases coupling with 4-methylaniline^{a,b}



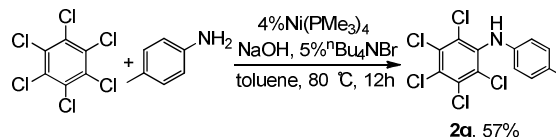
^a Reaction conditions: aryl chloride (1.5 mmol), amine (1.5 mmol), NaOH (1.5 mmol), ^tBu₄NBr (0.075 mmol), Ni(PMe₃)₄ (0.060 mmol), toluene (4 mL), 80 °C, 12h.

^b Isolated yield by column chromatography using 50:1 petroleum ether : Et₃N.

^c The imine product is reduced by NaBH₄.

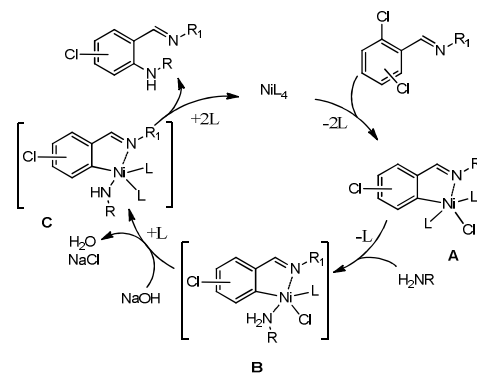
^d The reaction time is 24 h.

Scheme 4. Preparation of 2q



The mechanism of this catalytic cycle is considered to be a Ni(0)/Ni(II) procedure (Scheme 5). Previous work in our group showed that the oxidative addition of Ni(0) to the C-Cl bond in Schiff bases formed Ar-Ni(II)-Cl species.¹⁶ After the coordination of the anchoring group imine, the oxidative addition of the C-Cl bond at the Ni(0) center occurs to provide nickel(II) intermediate A. Ligand replacement of one trimethylphosphine ligand of A by one amine molecule gives rise to intermediate B. In the presence of NaOH, B transforms into intermediate C with the formation of NaCl and H₂O. The amines have to be both basic enough to coordinate to the nickel center and acidic enough to carry on deprotonation.¹⁵ The reductive elimination between the Ni-N and Ni-C bond of C delivers the final product, ortho-aminated imine, with the regeneration of catalyst Ni(PMe₃)₄.

Scheme 5. Proposed Mechanism of the C,N-coupling reactions



Conclusions

In conclusion, a C,N-coupling reaction of di-chlorinated Schiff bases with aryl amines catalyzed by Ni(PMe₃)₄ is described. The di-chlorinated substrates could be both mono-aminated and di-aminated selectively. Different amines and Schiff bases are tested, giving good yields. NaOH is used as a base instead of expensive and unstable bases. This catalytic system establishes an effective strategy to functionalize aryl C-Cl bonds effectively.

Acknowledgements

Support of this work by NSFC (No.21072113/21272138) is gratefully acknowledged.

Notes and references

- (a) M. A. Topchiy, A. F. Asachenko, M. S. Nechaev, *Eur. J. Org. Chem.* 2014, 3319. (b) G.-D. Roiban, G. Mehler, M. T. Reetz, *Eur. J. Org. Chem.* 2014, 2070. (c) S. M. Crawford, C. B. Lavery, M. Stradiotto, *Chem. Eur. J.* 2013, **19**, 16760. (d) S. M. Raders, J. N. Moore, J. K. Parks, A. D. Miller, T. M. Leibing, S. P. Kelley, R. D. Rogers, K. H. Shaughnessy, *J. Org. Chem.* 2013, **78**, 4649. (e) K. D. Collins, F. Glorius, *Nat. Chem.* 2013, **5**, 597. (f) T. Iwai, T. Harada, K. Hara, M. Sawamura, *Angew. Chem. Int. Ed.* 2013, **52**, 12322. (g) S. Guo, Y. Wang, C. Sun, J. Li, D. Zou, Y. Wu, Y. Wu, *Tetrahedron Letters* 2013, **54**, 3233. (h) R. K. Rao, I. Karthikeyan, G. Sekar, *Tetrahedron* 2012, **68**, 9090. (i) L. L. Hill, J. L. Crowell, S. L. Tutwiler, N. L. Massie, C. C. Hines, S. T. Griffin, R. D. Rogers, K. H. Shaughnessy, G. A. Grasa, J. C. Christopher, *J. Org. Chem.* 2010, **75**, 6477.
- (a) Y. Zhang, V. César, G. Storch, N. Lugan, *Angew. Chem. Int. Ed.* 2014, **53**, 6482. (b) B. Mu, J. Li, Y. Wu, *Appl. Organometal. Chem.* 2013, **27**, 537. (c) S. Meiries, G. L. Duc, A. Chartoire, A. Collado, K. Speck, K. S. A. Arachchige, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* 2013, **19**, 17358. (d) G. Le Duc, S. Meiries, S. P. Nolan, *Organometallics* 2013, **32**, 7547. (e) A. Chartoire, A. Boreux, A. R. Martin, S. P. Nolan, *RSC Adv.* 2013, **3**, 3840. (f) S. Meiries, K. Speck, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Organometallics* 2013, **32**, 330. (g) M. Hoyos, R. S. Sprick, C. Wang, M. L. Turner, O. Navarro, *Journal of Polymer Science Part A: Polymer Chemistry* 2012, **50**, 4155. (h) A. Chartoire, X. Frogneux, A. Boreux, A. M. Z. Slawin, S. P. Nolan, *Organometallics* 2012, **31**, 6947. (i) A. K. K. Lewis, S. Caddick, F. G. N. Cloke, N. C. Billingham, P. B. Hitchcock, J. Leonard, *J. Am. Chem. Soc.* 2003, **125**, 10066.
- (a) P. Wagner, M. Bollenbach, C. Doebelin, F. Bihel, J.-J. Bourguignon, C. Salomé, M. Schmitt, *Green Chem.* 2014, **16**, 4170. (b) C. Salomé, P. Wagner, M. Bollenbach, F. Bihel, J.-J. Bourguignon, M. Schmitt, *Tetrahedron* 2014, **70**, 3413. (c) S. Borjian, D. M. Tom, M. C. Baird, *Organometallics* 2014, **33**, 3928. (d) C. A. Wheaton, J.-P. J. Bow, M. Stradiotto, *Organometallics* 2013, **32**, 6148. (e) R. N. Prabhu, R. Ramesh, *Tetrahedron Letters* 2013, **54**, 1120. (f) R. J. Burton, M. L. Crowther, N. J. Fazakerley, S. M. Fillery, B. M. Hayter, J. G. Kettle, C. A. McMillan, P. Perkins, P. Robins, P. M. Smith, *Tetrahedron Letters* 2013, **54**, 6900. (g) P. G. Alsabeh, R. J. Lundgren, R. McDonald, C. C. Johansson Seechurn, T. J. Colacot, M. Stradiotto, *Chem. Eur. J.* 2013, **19**, 2131. (h) M. Beller, C. Breindl, T. H. Riermeier, A. Tillack, *J. Org. Chem.* 2001, **66**, 1403.
- (a) P. Tao, J. Liang, Y. Jia, *Eur. J. Org. Chem.* 2014, 5735. (b) J. Liang, W. Hu, P. Tao, Y. Jia, *J. Org. Chem.* 2013, **78**, 5810. (c) M. K. Ghorai, Y. J. Nanaji, *Org. Chem.* 2013, **78**, 3867. (d) A. Gangjee, O. A. Namjoshi, S. Raghavan, S. F. Queener, R. L. Kisliuk, V. J. Cody, *Med. Chem.* 2013, **56**, 4422. (e) R. Ding, J.-G. Fu, G.-Q. Xu, B.-F. Sun, G.-Q. Lin, *J. Org. Chem.* 2013, **79**, 240. (f) D. Waghay, J. Zhang, J. Jacobs, W. Nulens, N. Basarić, L. V. Meervelt, W. Dehaen, *J. Org. Chem.* 2012, **77**, 10176. (g) R. Ding, B.-F. Sun, G.-Q. Lin, *Org. Lett.* 2012, **14**, 4446.
- (a) C. Wetzel, A. Mishra, E. Mena-Osteritz, A. Liess, M. Stolte, F. Würthner, P. Bäuerle, *Org. Lett.* 2013, **16**, 362. (b) D. Waghay, A. Cloet, K. Van Hecke, S. F. Mertens, S. De Feyter, L. Van Meervelt, M. Van der Auweraer, W. Dehaen, *Chem. Eur. J.* 2013, **19**, 12077. (c) I. S. Perejeanu, T. J. Müller, *Org. Biomol. Chem.* 2013, **11**, 5127. (d) D. Sakamaki, A. Ito, K. Tanaka, K. Furukawa, T. Kato, M. Shiro, *Angew. Chem. Int. Ed.* 2012, **51**, 8281.
- (a) C. Xi, X. Yan, X. Yang, *Catal. Sci. Technol.* 2014, **4**, 4169. (b) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* 2009, **48**, 6954.
- J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* 1997, **119**, 6054.
- N. H. Park, G. Teverovskiy, S. L. Buchwald, *Org. Lett.* 2014, **16**, 220.
- (a) R. A. Green, J. F. Hartwig, *Angew. Chem. Int. Ed.* 2015, **54**, 3768. (b) S. Ge, R. A. Green, J. F. Hartwig, *J. Am. Chem. Soc.* 2014, **136**, 1617.
- C. Chen, L.-M. Yang, *J. Org. Chem.* 2007, **72**, 6324.
- X.-L. Li, W. Wu, X.-H. Fan, L.-M. Yang, *Org. Biomol. Chem.* 2014, **12**, 1232.
- (a) M. Nirmala, G. Prakash, R. Ramachandran, P. Viswanathamurthi, J. G. Malecki, W. Linert, *Journal of Molecular Catalysis A: Chemical* 2015, **397**, 56. (b) A. R. Martin, D. J. Nelson, S. Meiries, A. M. Slawin, S. P. Nolan, *Eur. J. Org. Chem.* 2014, 3127. (c) N. F. Fine Nathel, J. Kim, L. Hie, X. Jiang, N. K. Garg, *ACS Catal.* 2014, **4**, 3289. (d) A. R. Martin, Y. Makida, S. b. Meiries, A. M. Slawin, S. P. Nolan, *Organometallics* 2013, **32**, 6265. (e) K. Matsubara, S. Miyazaki, Y. Koga, Y. Nibu, T. Hashimura, T. Matsumoto, *Organometallics* 2008, **27**, 6020. (f) R. A. Kelly, N. M. Scott, S. Diez-González, E. D. Stevens, S. P. Nolan, *Organometallics* 2005, **24**, 3442. (g) R. Omar-Amrani, A. Thomas, E. Brenner, R. Schneider, Y. Fort, *Org. Lett.* 2003, **5**, 2311. (h) C. Desmarests, R. Schneider, Y. Fort, *J. Org. Chem.* 2002, **67**, 3029. (i) B. Gradel, E. Brenner, R. Schneider, Y. Fort, *Tetrahedron Letters* 2001, **42**, 5689.
- (a) G. Manolikakes, A. Gavryushin, P. J. Knochel, *Org. Chem.* 2008, **73**, 1429. (b) E. Brenner, Y. Fort, *Tetrahedron Letters* 1998, **39**, 5359.
- (a) C. Desmarests, R. Schneider, Y. Fort, *Tetrahedron Letters* 2001, **42**, 247. (b) C. Desmarests, R. Schneider, Y. Fort, *Tetrahedron* 2001, **57**, 7657.
- M. Pompeo, J. L. Farmer, R. D. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* 2014, **53**, 3223.
- (a) Q. Niu, X. Zhang, S. Zhang, X. Li, H. Sun, *Inorganica Chimica Acta* 2015, **426**, 165. (b) J. Li, X. Li, L. Wang, Q. Hu, H. Sun, *Dalton Trans.* 2014, **43**, 6660. (c) J. Li, X. Li, H. Sun, *Organometal. Chem.* 2013, **743**, 114. (d) J. Li, C. Wang, X. Li, H. Sun, *Dalton Trans.* 2012, **41**, 8715. (e) Y. Shi, M. Li, Q. Hu, X. Li, H. Sun, *Organometallics* 2009, **28**, 2206. (f) Y. Chen, H. Sun, U. Flörke, X. Li, *Organometallics* 2008, **27**, 270. (g) R. Cao, H. Sun, X. Li, *Organometallics* 2008, **27**, 1944.