Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Z. Tan, G. Wang, G. Huang, J. Wu, D. Wang, X. Chen, Q. Gui and H. Li, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB01726J.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

Journal Name

View Article Online
DOI: 10.1039/C7OB01726J

COMMUNICATION

Synthesis of 4-benzylpyridines via Pd-catalyzed CH_3-arylation of 4-picoline

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

DOI: 10.1039/x0xx00000x

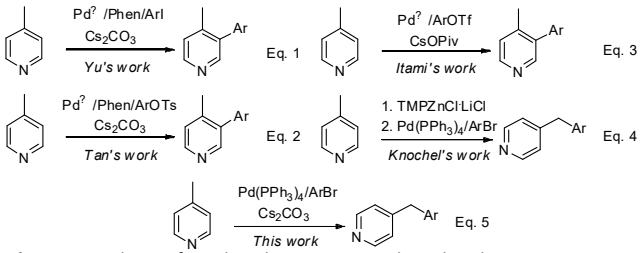
www.rsc.org/

Jing Wu,[a,b] Dadian Wang, [a] Xiang Chen,[a] Qingwen Gui,[a] Hua Li[b] Ze Tan,*[a] Genping Huang*[b] and Guangwei Wang*[b]

A highly efficient synthesis of 4-benzylpyridines was developed via Pd-catalyzed C(sp^3)-H arylation between 4-picoline and aryl halides. It was found that best yields were achieved with simple $Pd(PPh_3)_4$ catalyst and Cs_2CO_3 as base. Compared with known methods, our reaction does not require the use of strong organometallic reagent as the base.

Pyridine is one of the most important heteroaromatics in organic chemistry and it is widely present in many natural products and pharmaceutical compounds.[1] As such the synthesis of pyridine derivatives has always been the center of attention of organic chemists.[2] Recently arylation of pyridine via transition metal catalyzed C-H functionalization[3] has been an area of intensive research since it avoids the use of prefunctionalized pyridine compounds such as pyridine halides or pyridine organometallic compounds. However, it is well known that activation of the C-H bonds of pyridine ring is not easy because the pyridine ring is an electron poor aromatic ring. Moreover, pyridine ring can bind to the transition metal center to form inactive metal complex. Consequently, C-H activation of pyridine ring is far underdeveloped compared to other arenes. It was not until 2011 that Yu reported C3-arylation of the parent pyridine for the first time, in which they used aryl bromides and iodides as the arylating reagents (Scheme1, Eq. 1).[4] In 2013, our research group successfully replaced the aryl bromides and iodides with aryl tosylates as the coupling partners, thus allowing the use of phenol derivative as the source of aryl group (Scheme1, Eq. 2).[5] Itami recently reported that by using $Pd(OAc)_2$ as the catalyst and CsOPiv as the base, they were able to successfully couple pyridine with aryl triflate as well (Scheme1, Eq. 3).[6]

During our investigation in 2013, we noted that when we tried to couple 4-picoline with naphthol derived tosylates, what we obtained was not the C3-naphthyl substituted pyridines, instead, the arylation took place on the methyl group, thus generating the corresponding diaryl methane derivatives. A close examination of the literature revealed that even though Pd-catalyzed CH_3-arylations of nitro-substituted toluenes,[7a] 2-methyl pyridines, 2-methyl azines[7b-d] and 2-methyl azine N-oxides[7e,f] as well as other methyl substituted heteroaromatics[7g,h] are well known, report on the Pd-catalyzed arylation of 4-picoline derivatives is scarce. As far as we know, only one protocol has been developed by Knochel and co-workers in 2011 and they reported that CH_3-arylation of 4-picoline can be realized via Pd-catalyzed cross coupling of aryl halides with an organozinc compound generated by the reaction of 4-picoline with kinetically highly active LiCl-solubilized TMP base (TMP = 2,2,6,6-tetramethylpiperidyl) TMPZnCl·LiCl (Scheme1, Eq. 4).[8] It should be noted that in Itami's reaction,[6] C3-aryaltion was also observed with naphthyl triflates. In order to understand how the diaryl methane product was formed in our reaction and also in continuation on our effort on transition metal catalyzed C-H activations,[9] we undertook a detailed study on the coupling of 4-picoline with various aryl halides. Herein we present that by simply changing the catalyst system, we can successfully synthesize a variety of 4-benzylpyridines via Pd-catalyzed coupling of 4-picoline with arylbromides (Scheme1, Eq. 5).



Scheme 1 Synthesis of pyridine derivatives via Pd-catalyzed C-H activation.

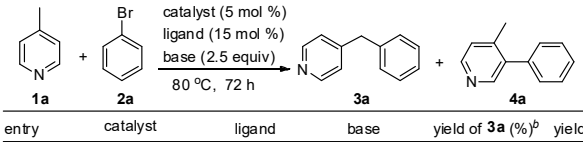
When we repeated the work of Yu's with 4-picoline and bromobenzene, we found that there is a small amount of pyridine benzyl arylation product **3a** formed in the crude product mixture (Table 1, entry 1). Surprisingly, when the catalyst ligand system was changed from $Pd(OAc)_2$/Phen to $Pd(PPh_3)_4$, with the reaction

[a] *State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China. E-mail: ztanze@gmail.com.*
[b] *Department of Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Tianjin University, Tianjin 300072, P. R. China. E-mail: gphuang@tju.edu.cn wanggw@tju.edu.cn*

Electronic Supplementary Information (ESI) available: Experimental details and spectra of all products. See DOI: 10.1039/x0xx00000x

temperature being 140 °C, the yield of product **3a** was increased to 30% while no C3-pyridine substitution product **4a** was obtained (Table 1, entry 2). Subsequently when we ran the reaction at 100 °C for 48 hours, the yield of **3a** was increased to 74% (Table 1, entry 3). Finally a yield as high as 86% could be achieved when the reaction temperature was further cooled down to 80 °C and the reaction time was extended to 72 hours (Table 1, entry 4). If the reaction was carried out at 80 °C with Yu's catalyst system, only biphenyl was formed in 42% yield. While the use of KOH and NaOH in place of Cs_2CO_3 gave **3a** in 67% and 55% yield, respectively, the use of other bases such as K_2CO_3, LiOH, NaH, DBU and DABCO failed completely (Table 1, entries 5-11). In addition, adding DMF, DMSO, DMI, NMP, toluene, THF or dioxane into the reaction mixture as solvent or cosolvent did not benefit the reaction either (not shown in Table 1; Considerably lower yields were obtained). Moreover, replacing PPh_3 with ligands such as dppf, BINAP, DPEPhos, Peppsi,[10] o-$(tol)_3P$ or tricyclohexylphosphine all led to disappointing results (Table 1, entries 12-17). Among the various ligands screened, only xantphos and dppp gave the desired product in yields around 70% (Table 1, entries 18 and 19). Tests also showed that no reaction took place in the absence of Pd-catalyst, showing the catalyst is essential for the reaction to proceed. Based on these results, we decided to set reacting 4-picoline (3 mL) with phenylbromide (0.5 mmol) in the presence of 5 mol % of $Pd(PPh_3)_4$ at 80 °C for 72 h as our standard conditions.

Table 1. Screening of the reaction conditions[a]

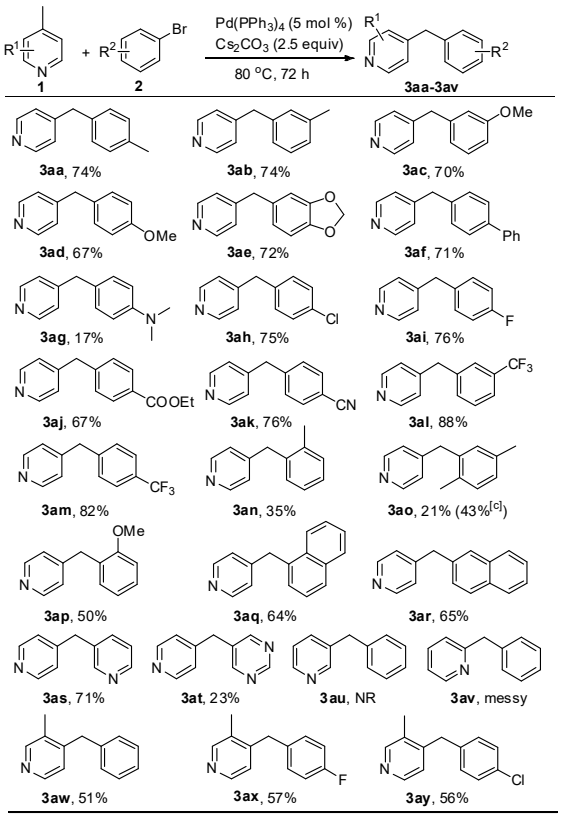


entry	catalyst	ligand	base	yield of **3a** (%)[b]	yield of 4a[e]
1[c]	$Pd(OAc)_2$	Phen	Cs_2CO_3	trace	53
2[c]	$Pd(PPh_3)_4$	-	Cs_2CO_3	30	ND
3[d]	$Pd(PPh_3)_4$	-	Cs_2CO_3	74	ND
4	$Pd(PPh_3)_4$	-	Cs_2CO_3	86	ND
5	$Pd(PPh_3)_4$	-	KOH	67	ND
6	$Pd(PPh_3)_4$	-	NaOH	55	ND
7	$Pd(PPh_3)_4$	-	K_2CO_3	0	ND
8	$Pd(PPh_3)_4$	-	LiOH	0	ND
9	$Pd(PPh_3)_4$	-	NaH	0	ND
10	$Pd(PPh_3)_4$	-	DBU	0	ND
11	$Pd(PPh_3)_4$	-	DABCO	0	ND
12	$dppfPdCl_2$	-	Cs_2CO_3	0	ND
13	$Pd(OAc)_2$	BINAP	Cs_2CO_3	50	ND
14	$Pd(OAc)_2$	DPEPhos	Cs_2CO_3	46	ND
15	Peppsi	-	Cs_2CO_3	35	ND
16	$(o\text{-}Tol_3P)_2PdCl_2$	-	Cs_2CO_3	15	ND
17	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	23	ND
18	$Pd(OAc)_2$	xantphos	Cs_2CO_3	70	ND
19	$(DPPP)_2PdCl_2$	-	Cs_2CO_3	72	ND

[a] Reaction conditions: **1a** (3.0 mL), **2a** (0.5 mmol), catalyst (0.025 mmol), ligand (0.075 mmol) and base (1.25 mmol), under N_2, 80 °C, 72 h. [b] Isolated yields of **3a**. [c] Reaction was conducted at 140 °C, 48 h. [d] Reaction was conducted at 100 °C, 48 h. [e] Yields determined by GC.

With the optimized conditions in hand, we next set out to explore the substrate scope of aryl bromides and the results were summarized in Table 2. As shown in Table 2, a variety of aryl bromides were compatible with this transformation. Phenyl bromides with electron withdrawing groups such as CF_3, F, Cl, CN, CO_2Et etc. on the phenyl ring reacted smoothly to give the desired products in good to excellent yields (67%-88%). As for the aryl bromides with electron-rich substituents, substrates bearing methyl and methoxy group reacted normally to give the corresponding benzylpyridine derivatives in yields ranging from 67-72%. On the other hand, substrate **2g** bearing a strong electron-donating group such as N,N-dimethyl group only afforded the desired product **3ag** in 17% after 72 h. We surmise this is because the oxidative insertion of the Pd-catalyst into the carbon-bromine bond in substrate **2g** is difficult due to the higher electron density on the phenyl ring. From the table, we can see that substrates bearing a substituent on the *ortho* position tend to generate the desired products in lower yields (35-50%), showing that the reaction is slightly sensitive towards steric hindrance (Table 2, entries, **3an**-**3ap**). Besides phenyl bromides, naphthyl bromides can also participate in the coupling well, providing the corresponding products **3aq** and **3ar** in 64% and 65% yield, respectively.

Table 2. Pd-catalyzed arylation of 4-picoline with bromobenzenes[a,b]

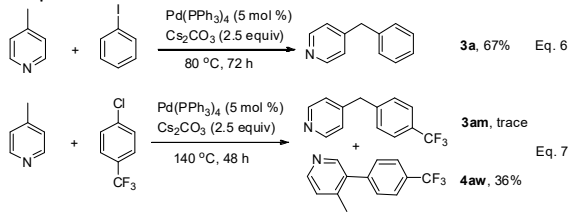


[a] Reaction conditions: **1a** (3.0 mL), **2** (0.5 mmol), $Pd(PPh_3)_4$ (5 moL %), and Cs_2CO_3 (1.25 mmol) at 80 °C for 72 h. [b] Isolated yields. [c] Reaction was conducted at 100 °C, 72 h.

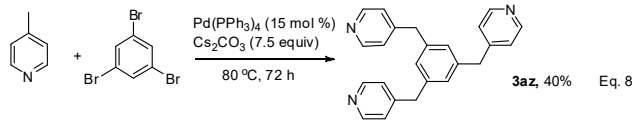
We were also able to couple 3-bromopyridine with 4-picoline to synthesize bipyridine compound **3as** in 71% yield. On the other hand, the coupling of 3-bromopyrimidine with 4-picoline only provided the desired product **3at** in 23% yield. It should be mentioned attempts to couple 3-picoline with phenylbromide under our standard conditions led to complete failure whereas the coupling with 2-picoline gave rather messy result (Table 2, entries **3au** and **3av**). Even though attempts to couple 4-ethylpyridine or lepidine with phenyl bromide under our standard condition only gave the desired coupling products in trace amount (not shown in

Table 2), we were glad to see that 3,4-dimethylpyridine is a viable substrate for our reaction. We successfully coupled 3,4-dimethylpyridine with phenyl bromide, 4-fluorophenylbromide and 4-chlorophenyl bromide and the corresponding products **3aw**, **3ax**, **3ay** were obtained in yields above 50%. It should be noted that in all cases we tested, formation of C3-arylation product was not observed.

Besides aryl bromides, we also investigated the reactions of 4-picoline with iodo- and chlorobenzene derivatives (Eq. 6 and 7). The coupling of iodobenzene with 4-picoline proceeded satisfactorily to give **3a** in 67 % yield whereas no reaction took place when p-chlorobenzotrifluoride was subjected to our standard reaction conditions. When the reaction temperature was raised to 140 °C for 48 h, much to our surprise, the main product was the C3-arylation product **4aw** whereas the desired product **3am** was only isolated in trace amount (Eq. 7). This result suggests that C(sp^2)-H activation process may become the major reaction pathway at higher temperature.



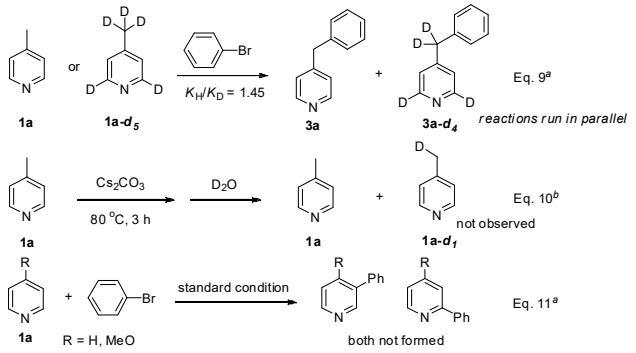
In order to demonstrate the synthetic potential of our strategy, our method was successfully applied to the synthesis of **3az**, a metal-driven self-assembly pyridine ligand.[11] The reported synthesis of **3az** not only requires the use of strong base LDA in conjunction with $ZnCl_2$ but also the yield is only 31%.[11] With our method, **3az** could be constructed in 40% yield with much simpler experimental operations (Eq. 8).



[a] Reaction conditons: 4-picoline (3.0 mL), 1,3,5-tribromobenzene (0.5 mmol), $Pd(PPh_3)_4$ (0.075 mmol), Cs_2CO_3 (3.75 mmol), at 80 °C for 72 h.

Scheme 2 Synthesis of 1,3,5-tris(pyridin-4-ylmethyl)benzene.[a]

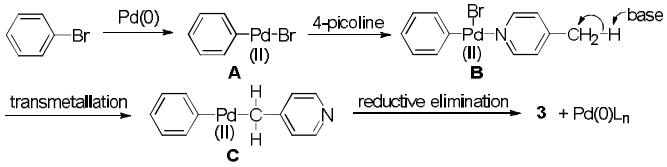
In order to gain some information on the mechanism of this new transformation, several control experiments were performed. Since the reaction may proceed through a C(sp^3)-H activation process similar to Yu's protocol,[4] we examined the kinetic isotope effect by studying the reaction rate of **1a** and its deuterated analogue **1a**-d_5. The kinetic isotopic effect (k_H/k_D) was 1.45 for parallel reactions of **1a** and **1a**-d_5[12] with phenyl bromide under the standard reaction conditions (Eq. 9). This rather small KIE suggested that the cleavage of the C(sp^3)-H bond was not involved in the rate determining step. Moreover, no deuterium was incorporated into the methyl group of **1a** after we treated **1a** with Cs_2CO_3 at 80 °C for 3 h and quenched the reaction with D_2O (Eq. 10). Additionally examination of recovered 4-picoline using a mixture of **1a** and **1a**-d_5 as starting material did not show H/D exchange (not shown in Scheme 3). All these results mean that direct deprotonation via Cs_2CO_3 may not be possible and the deprotonation step may be assisted by the Pd-catalyst via the formation of a pyridine-Pd complex (Unfortunately, attempts to identify a possible intermediate **B** using ^{31}P NMR failed; see mechanistic discussion below). This hypothesis is corroborated by the fact, with the optimized conditions, there are no desired products formed for pyridine derivatives such as 2,4-dimethylpyridine, 2-chloro-4-methylpyridine. We believe that the substituent on the 2-position makes the coordination of the Pd-catalyst to the nitrogen atom of the pyridine ring more difficult, thus shutting down the deprotonation step. When 4-methyl pyridine was replaced with either pyridine or 4-methoxypyridine, no 2- or 3-phenyl substituted pyridine was formed under our standard condition (Eq. 11). This means C2-H or C3-H activation was not active under our reaction condition. Thus the possibility of our reaction going through an initial C(sp^2)-H activation followed by subsequent C(sp^3)-H activation can be largely ruled out. Additionally, the reaction is also unlikely to involve the formation of a benzylic radical intermediate since the reaction proceeded normally when a stoichiometric amount of radical scavenger TEMPO was added to the reaction mixture.



[a] Reaction conditions: $Pd(PPh_3)_4$ (0.025 mmol), bromobenzene (0.5 mmol), Cs_2CO_3 (1.25 mmol), **1a** (15.4 mmol) or **1a**-d_5 (15.4 mmol), under 80 °C, 72 h. [b] Reaction conditions: **1a** (3.0 mL), Cs_2CO_3 (1.25 mmol), D_2O (10 mmol).

Scheme 3 Control experiments.

Based on the results above and known literature reports,[13] a tentative mechanism is proposed and shown below (Scheme 4). As usual, phenyl bromide undergoes oxidative addition with Pd(0) catalyst to generate intermediate **A** which subsequently complexes with a molecule of 4-picoline to form intermediate **B**. Next, base abtracts one hydrogen from the CH_3 group and the carboanion generated can undergo transmetallation with the Pd(II) center to form the diorgano palladium (II) species **C**. After reductive elimination, the final product **3** is produced and Pd(0) catalyst is regenerated and the catalytic cycle is completed.



Scheme 4 Possible reaction mechanism

In summary, we have successfully developed an efficient synthesis of 4-benzylpyridine derivatives via Pd-catalyzed C(sp^3)-H arylation of 4-picoline with aryl halides. Best yields were achieved with simple $Pd(PPh_3)_4$ catalyst and Cs_2CO_3 as base. Compared with

known methods, our reaction does not need to use strong organometallic reagent as the base and the reaction is very simple to run. We believed that coordination of 4-picoline to the organo-Pd intermediate generated in the reaction mixture is essential for the activation of the C(sp^3)-H bond. Efforts are underway to expand the reaction scope and the results will be reported in due course.

G. Wang would like to thank National Basic Research Program of China (2015CB856500) for financial support.

Notes and references

1 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, 4th ed.; Blackwell Publishing: Oxford, **2000**, 63-120.
2 (a) A. R. Katritzky, *Advances in Heterocyclic Chemistry*; Academic Press Pittsburgh, 2010; (b) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642-2713.
3 For some reviews on arylation via transition metal catalyzed C-H activations, see: (a) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792-9826; (b) B. Fabio and R. Renzo, *Tetrahedron* 2009, **65**, 10269-10310; (c) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.,* 2007, **107**, 174-238.
4 M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 19090-19093.
5 F. Dai, Q. Gui, J. Liu, Z. Yang, X. Chen, R. Guo and Z. Tan, *Chem. Commun*., 2013, **49**, 4634-4636.
6 J. Jiao, K. Murakami and K. Itami, *Chem. Lett*., 2016, **45**, 529-531.
7 (a)J. Inoh, T. Satoh, S. Pivsa-Art, M. Miura and M. Nomura, *Tetrahedron Lett*. 1998, **39**, 4673-4676; (b) P. M. Burton and J. A. Morris, *Org. Lett*. 2010, **12**, 5359-5361; (c) G. Song, Yan Su, X. G., K. Han and X. Li, *Org. Lett*. 2011, **13**, 1968-1971; (d) D. Zhao, M. Zhu, Y. Wang, Q. Shen and J. Li, *Org. Biomol. Chem*., 2013, **11**, 6246-6249; (e) L. Campeau, D. J. Schipper, and K. Fagnou, *J. Am. Chem. Soc*. 2008, **130**, 3266-3267; (f) D. J. Schipper, L. Campeau and K. Fagnou, *Tetrahedron*, 2009, **65**, 3155-3164; (g) J. J. Mousseau, A. Larive´e, and A. B. Charette, *Org. Lett*. 2008, **10**, 1641-1643; (h) B. S. Cho and Y. K. Chung, *Chem. Commun*., 2015, **51**, 14543-14546.
8 S. Duez, A. K. Steib, S. M. Manolikakes and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 7686-7690.
9 (a) J. Liu, S. Zhuang, Q. Gui, X. Chen, Z. Yang and Z. Tan, *Adv. Synth. Catal*., 2015, **357**, 732; (b) J. Liu, L. Yu, S. Zhuang, Q. Gui, X. Chen, W. Wang, Z. Tan, *Chem. Commun.*, 2015, **51**, 6418; (c) Q. Gui, X. Chen, L. Hu, D. Wang, J. Liu and Z. Tan, *Adv. Synth. Catal.*, 2016, **358**, 509; (d) X. Chen, Z. Tan, Q. Gui, L. Hu, J. Liu, J. Wu and G. Wang, *Chem. Eur. J.*, 2016, **22**, 6218; (e) L. Hu, X. Chen, Q. Gui, Z. Tan, and G. Zhu, *Chem. Commun.*, 2016, **52**, 6845; (f) L. Hu, Q. Gui, X. Chen, Z. Tan and G. Zhu, *Org. Biomol. Chem*., 2016, **14**, 11070; (g) L. Hu, Y. Yu and Z. Tan, *Chem. Commun.*, 2017, **53**, 4597.
10 J. L. Farmer, H. N. Hunter and M. G. Organ, *J. Am. Chem. Soc.*, 2012, **134**, 17470-17473.
11 For application of 1,3,5-tris(pyridin-4-ylmethyl)benzene, see: D. K. Chand, M. Fujita, K. Biradha, S. Sakamoto and K. Yamaguchi, *Dalton Trans*., 2003, **13**, 2750-2756.
12 For synthesis of **1a-*d*$_5$**, see: J. W. Pavlik, T. Vongnakorn and S. Tantayanon, *J. Heterocycle Chem.*, 2009, **46**, 213-216.
13 For selected examples, see: (a) D. García-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc*., 2006, **128**, 1066-1067; (b) S. I. Gorelsky, D. Lapointe and K. Fagnou, *J. Am. Chem. Soc*., 2008, **130**, 10848-10849; (c) K. D. B. Yamajala, M. Patil and S. Banerjee, *J. Org. Chem*., 2015, **80**, 3003-3011; (d) T. M. Figg, M. Wasa, J.-Q. Yu and D. G. Musaev, *J. Am. Chem. Soc*., 2013, **135**, 14206-14214; (e) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J. L. Peglion, E. Clot and O. Baudoin, *J. Am. Chem. Soc*., 2008, **130**, 15157-15166; (f) C. E. Kefalidis, O. Baudoin and E. Clot, *Dalton Trans*., 2010, **39**, 10528-10535.