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Copper-promoted site-selective carbonylation of sp^3 and sp^2 C–H bonds with nitromethane†

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Copper-promoted direct carbonylation of unactivated sp^3 C–H and aromatic sp^2 C–H bonds of amides was developed using nitromethane as a novel carbonyl source. The sp^3 C–H functionalization showed high site-selectivity by favoring the C–H bonds of α-methyl groups. The sp^2 C–H carbonylation featured high regioselectivity and good functional group compatibility. Kinetic isotope effect studies indicated that the sp^3 C–H bond breaking step is reversible, whereas the sp^2 C–H bond cleavage is an irreversible but not the rate-determining step. Control experiments showed that a nitromethyl intermediate should be involved in the present reaction.

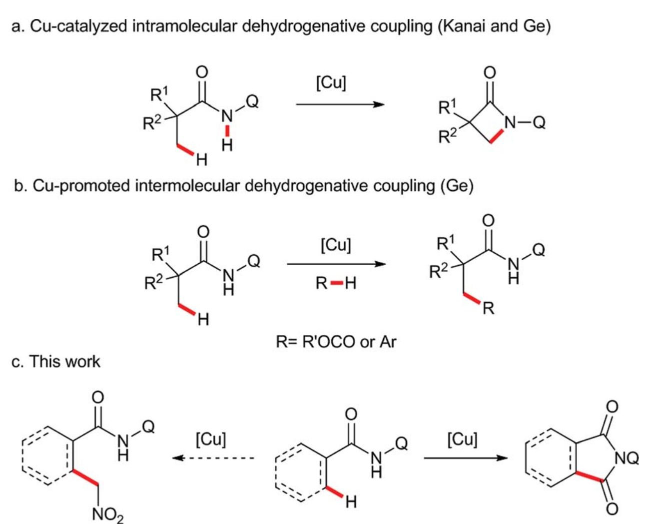
Introduction

Transition metal-catalyzed direct C–H functionalization is one of the most convenient and efficient tools for selective C–C bond formation, and significant advances have been accomplished in this field during the past few years.[1] Among the methods in this category, directing-group-assisted cross dehydrogenative coupling has attracted considerable attention due to its high regioselectivity and efficiency.[2] In 2007, Miura and co-workers reported the first example of ligand-assisted regioselective copper-promoted cross dehydrogenative coupling of sp^2 C–H bonds of 2-phenyl-pyridines and benzoxazoles.[3] Following this pioneering study, a variety of nucleophiles and substrates were proven to be effective in this process.[4] In these transformations, employing noble metals, such as palladium, rhodium, ruthenium or iridium, can be avoided, and therefore the reactions are more economical and synthetically useful than their counterparts. Recently, the copper-promoted direct functionalization of unactivated sp^3 C–H bonds has also been achieved using bidentate directing groups. The intramolecular sp^3 C–H amidation was developed by Kanai,[5] You,[6] and us[7] independently (Scheme 1a). Subsequently, the copper-promoted cross dehydrogenative acyloxylation[8] and arylation[9] of unactivated sp^3 C–H bonds were realized in our laboratory (Scheme 1b). However, the ligand directed copper-promoted dehydrogenative coupling of two sp^3 C–H bonds remains a challenge.

Based on the abovementioned studies, we envisaged that the site-selective dehydrogenative coupling of an unactivated sp^3 C–H bond and another reactive sp^3 C–H bond species, such as nitromethane,[10] alkylnitriles,[11] or carbonyl compounds,[12] could be performed by copper catalysis with bidentate directing group assistance. Therefore, we carried out the reaction of a series of aliphatic amides bearing the 8-aminoquinoline directing group with nitromethane in the presence of copper catalysts. To our surprise, an unexpected carbonylated compound was obtained instead of the dehydrogenative coupling product (Scheme 1c).[13] Herein, we report this unprecedented β-carbonylation of amides with nitromethane as the carbonyl source *via* the copper-promoted C–H bond activation and a subsequent Nef type reaction.[14]

Results and discussion

Our investigation commenced with 2-ethyl-2-methylpentanamide bearing a bidentate 8-aminoquinoline directing group (**1a**) as the



Scheme 1 Copper-promoted dehydrogenative coupling of sp^3 C–H bonds.

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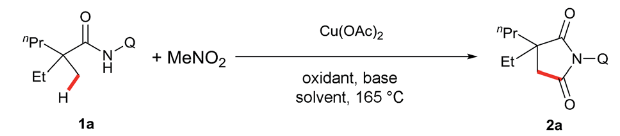
Table 1 Optimization of the sp^3 C–H carbonylation[a]

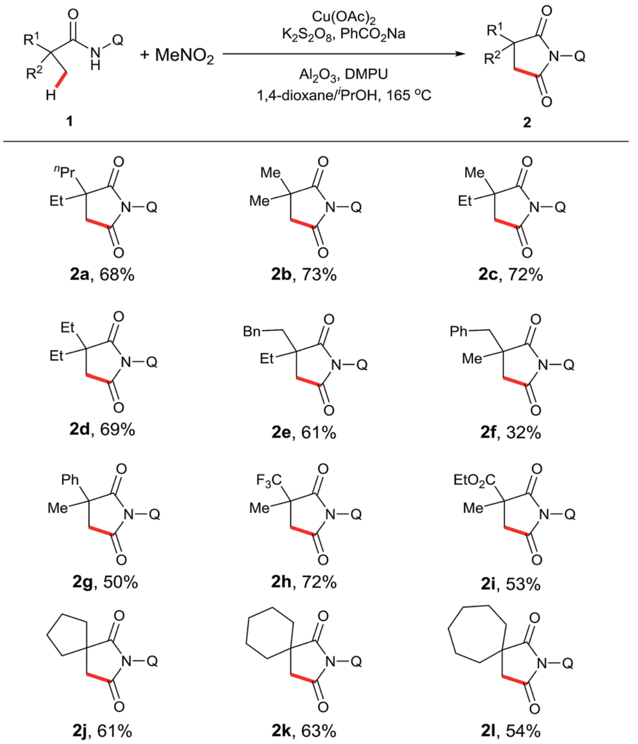


Entry	Oxidant	Base	Solvent	Yield[b] (%)
1		K_2HPO_4	$MeNO_2$	0
2		K_2HPO_4	1,4-Dioxane	8
3		K_2HPO_4	MeCN	Trace
4		K_2HPO_4	^{t}BuOH	11
5		K_2HPO_4	^{t}AmOH	10
6		K_2HPO_4	^{i}PrOH	14
7	O_2	K_2HPO_4	^{i}PrOH	Trace
8	AgOAc	K_2HPO_4	^{i}PrOH	Trace
9	$(t\mathrm{BuO})_2$	K_2HPO_4	^{i}PrOH	18
10	$Na_2S_2O_8$	K_2HPO_4	^{i}PrOH	19
11	$K_2S_2O_8$	K_2HPO_4	^{i}PrOH	24
12	$K_2S_2O_8$	Na_2HPO_4	^{i}PrOH	26
13	$K_2S_2O_8$	NaOAc	^{i}PrOH	31
14	$K_2S_2O_8$	$PhCO_2Na$	^{i}PrOH	39
15	$K_2S_2O_8$	$PhCO_2Na$	^{i}PrOH/1,4-dioxane (0.45 : 0.55)	54
16[c]	$K_2S_2O_8$	$PhCO_2Na$	^{i}PrOH/1,4-dioxane (0.45 : 0.55)	65
17[c,d]	$K_2S_2O_8$	$PhCO_2Na$	^{i}PrOH/1,4-dioxane (0.45 : 0.55)	71(68)
18[c,d,e]	$K_2S_2O_8$	$PhCO_2Na$	^{i}PrOH/1,4-dioxane (0.45 : 0.55)	0
19[c,d,f]	$K_2S_2O_8$	$PhCO_2Na$	^{i}PrOH/1,4-dioxane (0.45 : 0.55)	0

[a] Reaction conditions: **1a** (0.3 mmol), $Cu(OAc)_2$ (1 eq.), oxidant (2 eq.), base (1 eq.), solvent (2 mL), 165 °C, 24 h. [b] Yields are based on **1a**, determined by ^{1}H NMR using dibromomethane as the internal standard. Isolated yield is in parenthesis. [c] Al_2O_3 (60 mg). [d] DMPU (2 eq.). [e] No $MeNO_2$. [f] No $Cu(OAc)_2$.

model substrate (Table 1). Succinimide **2a** was initially obtained in 8% yield in the presence of $Cu(OAc)_2$ and K_2HPO_4 at 165 °C under air (entry 2). Encouraged by this result, we examined different solvents and found that ^{i}PrOH was a superior candidate (entry 6). Further investigation revealed that addition of an external single electron transfer oxidant can improve the yield, and $K_2S_2O_8$ was proven to be the best pick (entries 9–11). Screening of bases showed that employing $PhCO_2Na$ as an additive, which was used in our previous report of intramolecular amidation, further increased the yield to 39% (entry 14). Mixed solvents were next surveyed, and a mixture of ^{i}PrOH and dioxane led to a better yield (entry 15). Interestingly, the addition of Al_2O_3 and DMPU[15] finally gave the best results for this dehydrogenative carbonylation reaction (entry 17). The control experiments showed that no desired product was observed in the absence of $MeNO_2$ or the copper catalyst (entries 18 and 19).

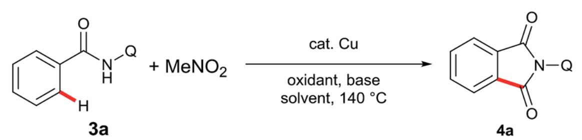
With the optimal conditions established, we examined the scope of aliphatic amide substrates (Scheme 2). Pivalamide proved to be an excellent substrate in this transformation, affording the carbonylation product in 73% yield (**2b**). Replacing the methyl group on the α-carbon with other alkyl groups, such as ethyl and propyl, gave the corresponding product in good yields (**2c** and **2d**). When the α-carbon was substituted with a benzyl group, the carbonylation occurred exclusively on the carbon center of the methyl group, presumably due to a steric effect (**2f**). α-Phenyl amide could participate in the



Scheme 2 Scope of sp^3 C–H carbonylation. Reaction conditions: **1** (0.3 mmol), $Cu(OAc)_2$ (0.3 mmol), $K_2S_2O_8$ (0.6 mmol), $PhCO_2Na$ (0.15 mmol), Al_2O_3 (60 mg), DMPU (0.6 mmol), $MeNO_2$ (1.0 mL), 1,4-dioxane (0.9 mL), ^{i}PrOH (1.1 mL), 165 °C, 24 h.

reaction to readily provide the desired product (**2g**). Furthermore, substrates containing trifluoromethyl (**2h**) or methoxycarbonyl groups (**2i**) on the α-carbon proved to be viable. It is worth noting that the starting material was recovered with

Table 2 Optimization of the sp^2 C–H carbonylation[a]



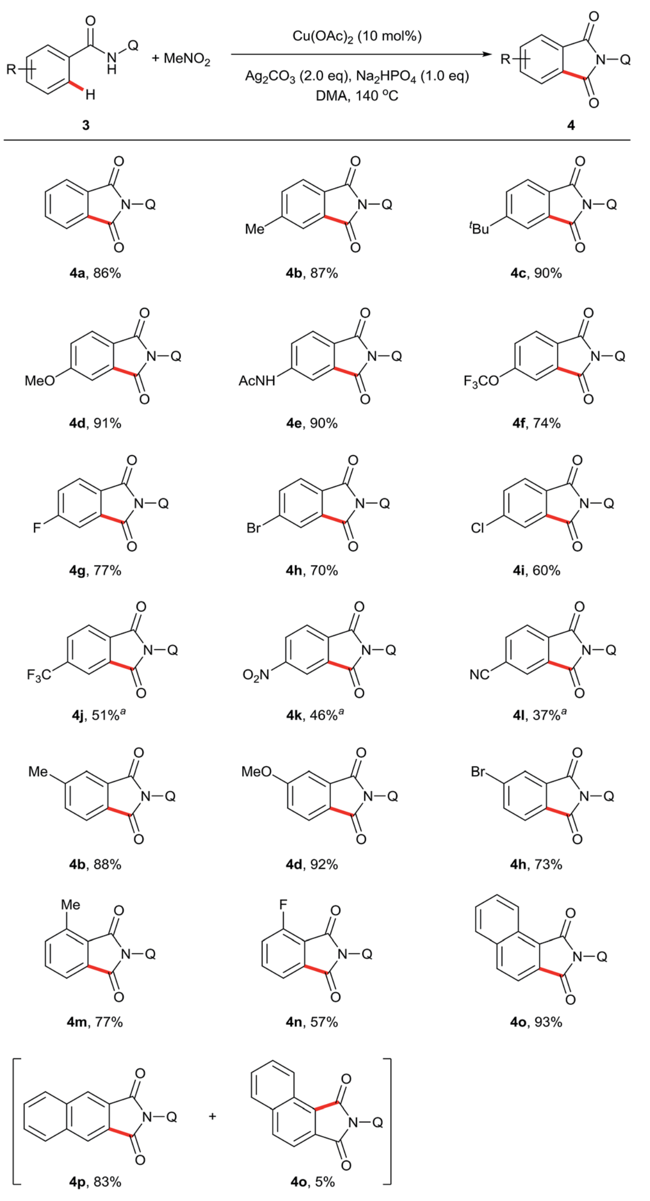
Entry	Cu source	Oxidant	Base	Solvent	Yield[b] (%)
1	$Cu(OAc)_2$	O_2		1,4-Dioxane	17
2	$Cu(OAc)_2$	MnO_2		1,4-Dioxane	28
3	$Cu(OAc)_2$	NMO		1,4-Dioxane	33
4	$Cu(OAc)_2$	Ag_2O		1,4-Dioxane	19
5	$Cu(OAc)_2$	Ag_2CO_3		1,4-Dioxane	45
6	$Cu(OAc)_2$	Ag_2CO_3		DMA	74
7	$Cu(OAc)_2$	Ag_2CO_3	$PhCO_2Na$	DMA	69
8	$Cu(OAc)_2$	Ag_2CO_3	Py	DMA	86
9	$Cu(OAc)_2$	Ag_2CO_3	Na_2HPO_4	DMA	90(86)
10	CuCl	Ag_2CO_3	Na_2HPO_4	DMA	76
11	—	Ag_2CO_3	Na_2HPO_4	DMA	0

[a] Reaction conditions: **3a** (0.3 mmol), $Cu(OAc)_2$ (10 mol%), oxidant (2 eq.), base (1 eq.), solvent (2 mL), 140 °C, 24 h. [b] Yields are based on **3a**, determined by ^{1}H NMR using dibromomethane as the internal standard. Isolated yield is in parenthesis.

N-(quinolin-8-yl)isobutyramide as the substrate under the standard conditions, indicating that a quaternary α-carbon is required for this reaction. In addition, the removability of the quinolyl moiety was previously demonstrated in our laboratory.[13e]

To further expand the scope of the substrates and broaden the synthetic utility of this reaction, we next investigated the carbonylation of sp^2 C–H bonds (Table 2). To our delight, the reaction could be realized with a catalytic amount of $Cu(OAc)_2$. The optimal results were acquired with 2 equivalents Ag_2CO_3 and 1 equivalent $PhCO_2Na$ in DMA at 140 °C (entry 8).

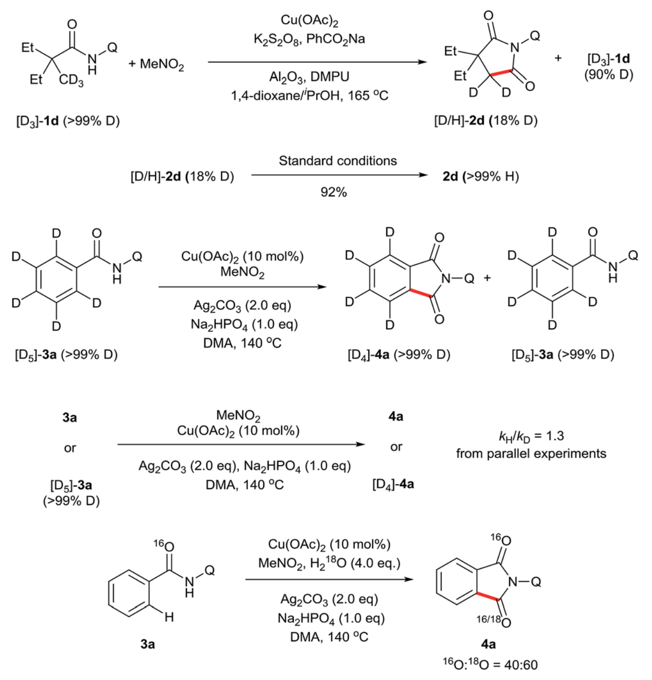
Next, we examined the compatibility of the reaction with aromatic amide derivatives, which are summarized in Scheme 3. As expected, a wide range of functional groups including halogens were well tolerated under the optimized conditions. Substrates with electron-donating groups on the phenyl ring gave the desired products in good to excellent yields (**4d**, **4e**, and **4f**). Conversely, substrates containing halogen atoms afforded the phthalimides with slightly reduced yields (**4g**, **4h**, **4i**, and **4n**). Electron-withdrawing group substituted aromatic amides also provided the corresponding carbonylation products in moderate yields (**4j**, **4k**, and **4l**). Furthermore, 1-naphthamide and 2-naphthamide derivatives reacted to produce good yields (**4o** and **4p**).



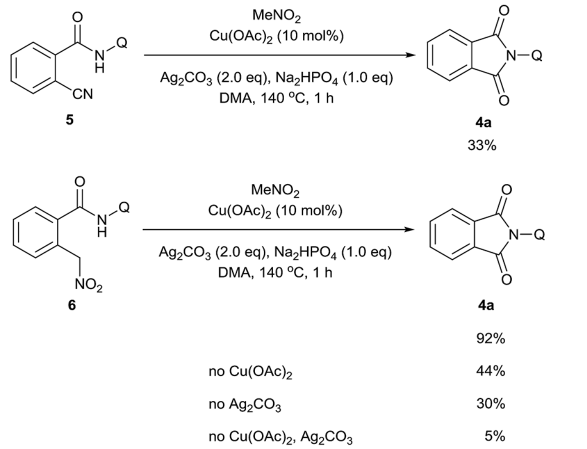
Scheme 3 Scope of sp^2 C–H carbonylation. Reaction conditions: **3** (0.3 mmol), $Cu(OAc)_2$ (10 mol%), Ag_2CO_3 (2 eq.), Na_2HPO_4 (1 eq.), $MeNO_2$ (0.5 mL), DMA (2 mL), 140 °C, 24 h. [a]165 °C, 48 h.

To gain some insights into this novel transformation mechanism, a series of deuterium-labelling experiments were performed. As shown in Scheme 4, evident H/D exchange of the substrate was found when the deuterium-labelled 2,2-diethyl-*N*-(quinolin-8-yl)pentanamide (D_3-**1d**) was subjected to the standard conditions, indicating that the sp^3 C–H bond cleavage is a reversible step. In addition, regular **2d** was obtained in 92% yield from the subjection of [D/H]-**2d** to the current reaction system, suggesting that the keto–enol tautomerism might account for the fast H/D exchange of the product [D/H]-**2d**. In contrast, no apparent H/D exchange was observed when the deuterium-labelled *N*-(quinolin-8-yl)benzamide (D_5-**3a**) was subjected to the standard conditions, indicating that the sp^2 C–H bond cleavage is an irreversible step. Furthermore, a secondary kinetic isotope effect was observed for **3a** based on the early relative rate of parallel reactions, indicating that the sp^2 C–H cleavage of **3a** should not be the rate-determining step. Finally, the addition of 4 equivalents of $H_2{}^{18}O$ to the reaction of **3a** resulted in 60% of ^{18}O incorporation into **4a**, suggesting that water may be the source of oxygen in the carbonyl group.

A series of control experiments were carried out to further probe the transformation pathway (Scheme 5). The cyano compound **5**, a potential intermediate that was previously



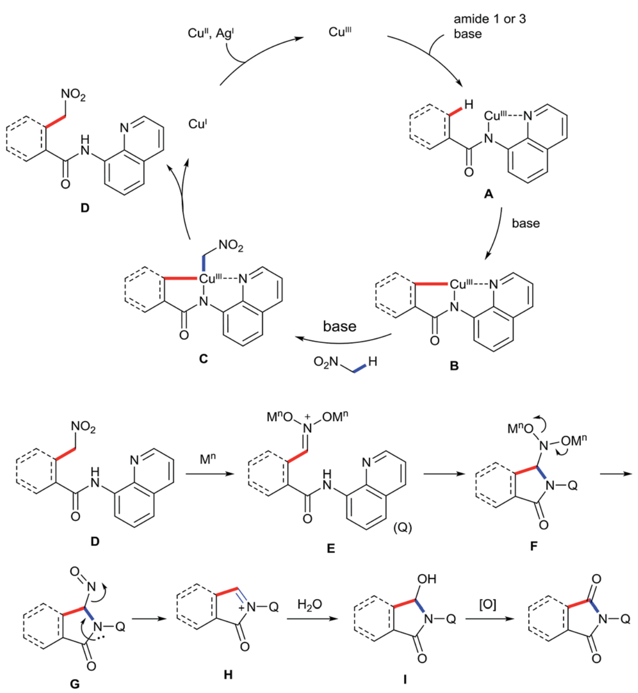
Scheme 4 Kinetic isotope effect studies.



Scheme 5 Control experiments.

reported in the copper-catalyzed cyanation of 2-phenylpyridine with nitromethane[10b] was subjected to the reaction system and afforded the carbonylation product in 33% yield. On the other hand, the phthalimide product **4a** was obtained in 92% yield from the originally proposed nitromethyl product **6**, indicating that it is likely the major intermediate in this catalytic process. We then investigated the transformation from **6** to the product **4a** with a number of control experiments. It was found that either $Cu(OAc)_2$ or Ag_2CO_3 could promote the reaction, whereas only a small amount of product was formed without any metal. We thus infer that the metal salts should act as Lewis acid catalysts in this process.

On the basis of the abovementioned results and previous reports,[5–9,16] a plausible mechanism for the observed transformation is proposed and is depicted in Scheme 6. The reaction is believed to be initiated by coordinating the Cu^{III} species to the bidentate ligand, followed by ligand exchange under basic conditions to generate intermediated **A**. Cyclometalation of **A** through a sp^2 or sp^3 C–H activation process affords intermediate **B.** Subsequently, ligand exchange of **B** with nitromethane in the presence of the base affords intermediate **C**, which undergoes reductive elimination to give the intermediate **D.** Formation of iminium ion **E** in the presence of a Lewis acid, followed by a sequence of the intramolecular addition and the loss of the nitroso group gives rise to the imine intermediate **H.** Finally, the addition of water and the subsequent oxidation provide the desired product.



Scheme 6 Plausible carbonylation reaction mechanism.

Conclusions

In summary, a novel copper-promoted site-selective carbonylation of sp^2 or unactivated sp^3 C–H bonds has been established using nitromethane as the carbonyl source with the assistance of an 8-aminoquinolyl auxiliary. Preliminary mechanistic experiments suggested that the substrate undergoes a dehydrogenative coupling with nitromethane, followed by a Nef type reaction to form the carbonylation product. To the best of our knowledge, it is the first example of unactivated C–H bond functionalization integrated with the Nef reaction. Further studies toward understanding the detailed mechanism and potential application of this transformation are in process.

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Notes and references

1 For selected recent reviews, see: (*a*) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (*b*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*c*) H. M. Davis, J. Du Bois and J.-Q. Yu, *Chem. Soc. Rev.*, 2011, **40**, 1855; (*d*) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (*e*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*f*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (*g*) M. C. White, *Science*, 2012, **335**, 807; (*h*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (*i*) J. Li, S. De Sarkar and L. Ackermann, *Top. Organomet. Chem.*, 2016, **55**, 217.

2 For selected recent reviews, see: (*a*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*c*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*d*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062; (*e*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013,

52, 11726; (*f*) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886.

3 M. Kitahara, N. Umeda, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2011, **133**, 2160.

4 For selected recent reviews, see: (*a*) M. Miura, T. Satoh and K. Hirano, *Bull. Chem. Soc. Jpn.*, 2014, **87**, 751; (*b*) K. Hirano and M. Miura, *Chem. Commun.*, 2012, **48**, 10704; (*c*) K. Hirano and M. Miura, *Top. Catal.*, 2014, **57**, 878; (*d*) J. Dong, Q. Wu and J. You, *Tetrahedron Lett.*, 2015, **56**, 1591; For examples, see: ; (*e*) M. Nishino, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2012, **51**, 6993; (*f*) M. Nishino, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2013, **52**, 4457; (*g*) R. Odani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2013, **78**, 11045; (*h*) R. Odani, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2014, **53**, 10784; (*i*) R. Odani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2015, **80**, 2384.

5 Z. Wang, J. Ni, Y. Kuninobu and M. Kanai, *Angew. Chem., Int. Ed.*, 2014, **53**, 3496.

6 C. Wang, Y. Yang, D. Qin, Z. He and J.-S. You, *J. Org. Chem.*, 2015, **80**, 8424.

7 X. Wu, Y. Zhao, G. Zhang and H. Ge, *Angew. Chem., Int. Ed.*, 2014, **53**, 3706.

8 X. Wu, Y. Zhao and H. Ge, *Chem.–Asian J.*, 2014, **9**, 2736.

9 X. Wu, Y. Zhao and H. Ge, *Chem. Sci.*, 2015, **6**, 5978.

10 (*a*) E. M. Vogl and S. L. Buchwald, *J. Org. Chem.*, 2002, **67**, 106; (*b*) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (*c*) R. R. Walvoord, S. Berritt and M. C. Kozlowski, *Org. Lett.*, 2012, **14**, 4086; (*d*) R. R. Walvoord and M. C. Kozlowski, *J. Org. Chem.*, 2013, **78**, 8859; (*e*) K. F. VanGelder and M. C. Kozlowski, *Org. Lett.*, 2015, **17**, 5748.

11 (*a*) D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234; (*b*) A. Bunescu, Q. Wang and J.-P. Zhu, *Chem.–Eur. J.*, 2014, **20**, 14633; (*c*) C. Chatalova-Sazepin, Q. Wang, G. M. Sammis and J.-P. Zhu, *Angew. Chem., Int. Ed.*, 2015, **54**, 5443; (*d*) A. Bunescu, Q. Wang and J.-P. Zhu, *Angew. Chem., Int. Ed.*, 2015, **54**, 3132; (*e*) Y. Liu, K. Yang and H. Ge, *Chem. Sci.*, 2016, **7**, 2804.

12 For selected recent reviews, see: (*a*) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; (*b*) C. C. C. Johansson and T. J. Colacot, *Angew. Chem., Int. Ed.*, 2010, **49**, 676, For selected recent examples, see: ; (*c*) W. Zhu, D. Zhang, N. Yang and H. Liu, *Chem. Commun.*, 2014, **50**, 10634; (*d*) H.-L. Wang, M. Shang, S.-Z. Sun, Z.-L. Zhou, B. N. Laforteza, H.-X. Dai and J.-Q. Yu, *Org. Lett.*, 2015, **17**, 1228.

13 For recent examples of C–H carbonylation, see: (*a*) S. Inoue, H. Shiota, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 6898; (*b*) E. J. Yoo, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 17378; (*c*) J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Org. Lett.*, 2011, **13**, 5326; (*d*) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 8070; (*e*) X. Wu, Y. Zhao and H. Ge, *J. Am. Chem. Soc.*, 2015, **137**, 4924.

14 W. E. Noland, *Chem. Rev.*, 1955, **55**, 137.

15 For examples of using DMPU in C–H functionalization, see: (*a*) Q. Chen, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 428; (*b*) L. Ilies, Q. Chen, X.-M. Zeng and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 5221; (*c*) Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, *Org. Lett.*, 2011, **13**, 3232.

16 E. E. Van Tamelen and R. J. Asd Thiede, *J. Am. Chem. Soc.*, 1952, **74**, 2615.

