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Palladium-catalyzed ligand-promoted site-selective cyanomethylation of unactivated C(sp^3)–H bonds with acetonitrile†

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The direct cyanomethylation of unactivated sp^3 C–H bonds of aliphatic amides was achieved *via* palladium catalysis assisted by a bidentate directing group with good functional group compatibility. This process represents the first example of the direct cross-coupling of sp^3 C–H bonds with acetonitrile. Considering the importance of the cyano group in medicinal and synthetic organic chemistry, this reaction will find broad application in chemical research.

Introduction

The cyanomethylation of organic molecules is of great research interest to organic and medicinal chemists due to the wide presence of the cyano group in biologically active molecules and the facile conversion of the cyano group into many other functional groups, such as amides, esters, aldehydes, and primary amines.[1] A variety of different synthetic strategies have been developed for the selective introduction of the cyanomethyl group.[2] Among these methods, transition metal-catalyzed cross-couplings with acetonitrile as the coupling partner[3] have attracted considerable attention in recent years due to the avoidance of prefunctionalized substrates such as haloacetonitrile,[4] trimethylsilylacetonitrile,[5] cyanoacetate salts[6] and cyanomethyltributyltin.[7] In 2002, Culkin and Hartwig reported the first cross-coupling reaction of acetonitrile and aryl bromides *via* palladium catalysis.[8] In another study by You and Verkade, aryl chlorides were also demonstrated as effective substrates for this transformation.[9] Furthermore, the direct cross-coupling of benzene with acetonitrile was developed with a palladium catalyst hybridized with a titanium dioxide photocatalyst.[10] However, to date, the direct cross-coupling of sp^3 C–H bonds with acetonitrile has not been discovered. Considering the literature support for the Pd-catalyzed alkylation of unactivated C(sp^3)–H bonds[11] and the reductive elimination of dialkyl palladium(II) species,[11g–i,12] it is envisaged that this process should be feasible if the cyanomethyl group could effectively replace the anion of an alkyl palladium(II) species.

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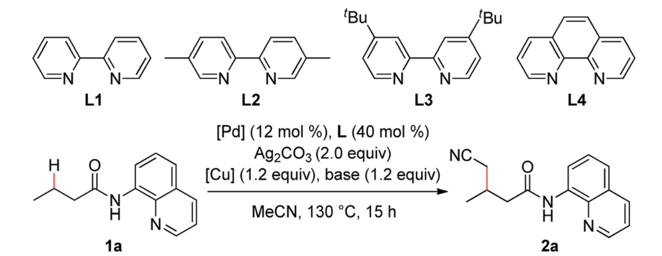
Results and discussion

In the previous reports, it was found that an alkyl arylpalladium(II) species could be formed by the treatment of an arylpalladium(II) species with a cyanomethyl anion in the presence of a ligand. On the basis of these results, the palladium-catalyzed direct cyanomethylation of *N*-(quinolin-8-yl)butyramide (**1a**) with acetonitrile was examined using 2,2′-bipyridine as the ligand, under basic conditions (Table 1, entry 1). Unfortunately, no desired product was observed. A copper(II) salt was then added into the reaction system, because the copper-promoted C–H bond activation of acetonitrile[13] and the transmetalation of an organocopper species onto an organopalladium(II) species[14] have been well documented. As shown in Table 1, copper carboxylates were found to be effective, with $Cu(O_2C^nPr)_2$ providing the best result (entry 3). A series of mono and bidentate ligands[15] were then screened, and it was found out that the reaction yield was improved with 5,5′-dimethyl-2,2′-bipyridine (**L2**) (entry 6). Furthermore, the effect of the palladium catalyst was examined with $Pd(OPiv)_2$ giving the optimal result (entry 9). Further optimization showed that this reaction was significantly improved with CsOPiv as the base (entry 15). In addition, the use of acetonitrile and heptane as the co-solvent could further increase the yield (entry 18). It was also noted that the reaction yield was dramatically decreased in the absence of the ligand, indicating that the ligand plays a role in stabilizing the dialkyl palladium(II) species or the *in situ* generated Pd metal (entry 20). To our delight, the reaction yield could be further improved by increasing the load of palladium catalyst (entry 21).

With the optimized reaction conditions in hand, a substrate scope study on linear aliphatic amides was then carried out. As shown in Table 2, the direct cyanomethylation of unbranched amides provided the desired products in moderate to good yields (**2a–f**). In addition, a variety of functional groups, such as the alkenyl, chloro, ester, phenyl and thienyl groups, were well

Table 1 Optimization of the reaction conditions[a]



Entry	Pd source	Cu source	Base	L	Yield[b] (%)
1[c]	$Pd(OAc)_2$	—	NaHMDS	**L1**	0
2	$Pd(OAc)_2$	$Cu(OAc)_2$	—	**L1**	11
3	$Pd(OAc)_2$	$Cu(O_2C^nPr)_2$	—	**L1**	20
4	$Pd(OAc)_2$	$Cu(acac)_2$	—	**L1**	Trace
5	$Pd(OAc)_2$	CuOAc	—	**L1**	11
6	$Pd(OAc)_2$	$Cu(O_2C^nPr)_2$	—	**L2**	30
7	$Pd(OAc)_2$	$Cu(O_2C^nPr)_2$	—	**L3**	23
8	$Pd(OAc)_2$	$Cu(O_2C^nPr)_2$	—	**L4**	21
9	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	—	**L2**	34
10	$PdCl_2$	$Cu(O_2C^nPr)_2$	—	**L2**	22
11	$Pd(MeCN)_2Cl_2$	$Cu(O_2C^nPr)_2$	—	**L2**	26
12	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	K_3PO_4	**L2**	25
13	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	KOAc	**L2**	49
14	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	KOPiv	**L2**	52
15	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	CsOPiv	**L2**	56
16[d]	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	CsOPiv	**L2**	69
17[e]	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	CsOPiv	**L2**	73
18[f]	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	CsOPiv	**L2**	76(72)[g]
19[h]	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	CsOPiv	**L2**	68
20[f]	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	CsOPiv	—	9
21[i]	$Pd(OPiv)_2$	$Cu(O_2C^nPr)_2$	CsOPiv	**L2**	85(80)[g]

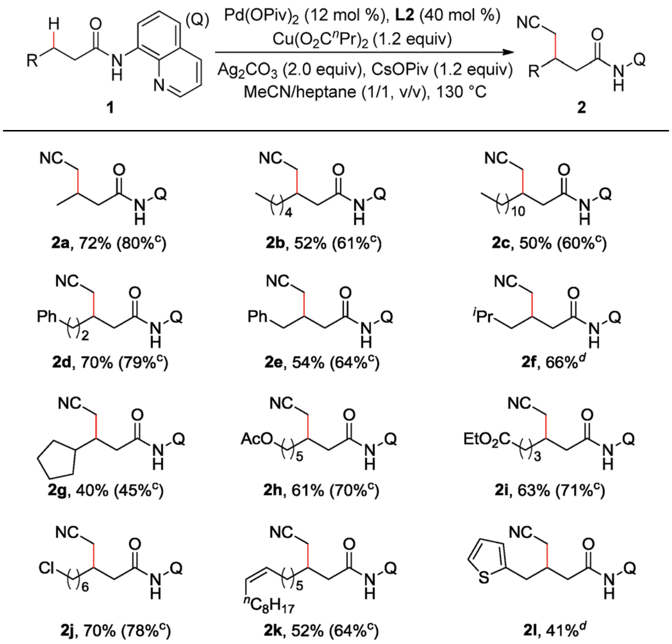
[a] Reaction conditions: **1a** (0.3 mmol), Pd source (0.036 mmol), **L** (0.12 mmol), Cu source (0.36 mmol), Ag_2CO_3 (0.6 mmol), base (0.36 mmol), MeCN (3.0 mL), air (1 atm), 130 °C, 15 h unless other noted. [b] Yields are based on **1a**, determined by ^{1}H-NMR using dibromomethane as the internal standard. [c] NaHMDS (1 M in THF, 1.5 mL) was used. [d] MeCN/toluene (1.5 mL/1.5 mL). [e] MeCN/hexane (1.5 mL/1.5 mL). [f] MeCN/heptane (1.5 mL/1.5 mL). [g] Isolated yield. [h] MeCN/cyclohexane (1.5 mL/1.5 mL). [i] $Pd(OPiv)_2$ (0.045 mmol).

tolerated under the catalytic system, allowing for the further manipulation of the original products. Furthermore, there is an apparent steric effect for this reaction because a lower yield was obtained with substrates bearing a substituent on γ-carbon (**2g**).

Furthermore, the scope of α-substituted aliphatic amides was studied under the modified reaction conditions (Table 3). As expected, propanamides bearing a linear, branched, or cyclic alkyl group were shown to be effective substrates (**3a–h**). It is worth mentioning that this reaction showed high site-selectivity by favouring the sp^3 C–H bonds of the methyl group over those of the methylene groups, including that of the relatively reactive benzylic sp^3 C–H bond (**3c**). Furthermore, the cyclic sp^3 C–H bond could also be functionalized, albeit with a moderate yield (**3k**). Amides with α-tertiary carbon (**3l**) were inappropriate substrates and could be quantitatively recovered under current conditions.

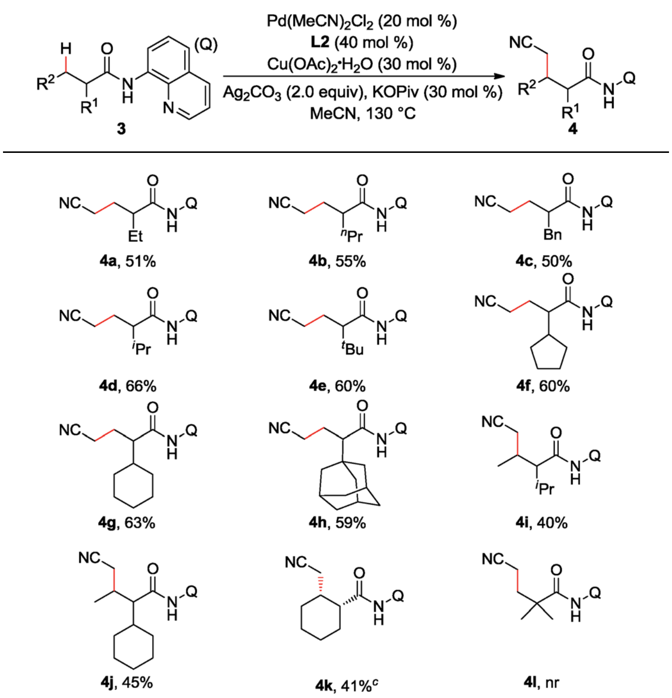
To provide some insights into the catalytic cycle, we carried out mechanistic studies into this process. It has been reported

Table 2 Scope of the linear aliphatic amides[a,b]

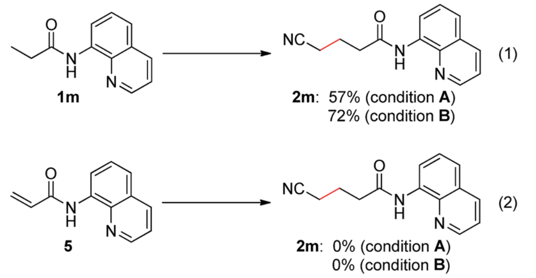


[a] Reaction conditions: **1** (0.3 mmol), $Pd(OPiv)_2$ (0.036 mmol), **L2** (0.12 mmol), $Cu(O_2C^nPr)_2$ (0.36 mmol), Ag_2CO_3 (0.6 mmol), CsOPiv (0.36 mmol), MeCN (1.5 mL), heptane (1.5 mL), and air (1 atm), 130 °C, 15 h. [b] Isolated yield. [c] $Pd(OPiv)_2$ (0.045 mmol). [d] $Pd(OPiv)_2$ (0.06 mmol). Q = 8-quinolinyl.

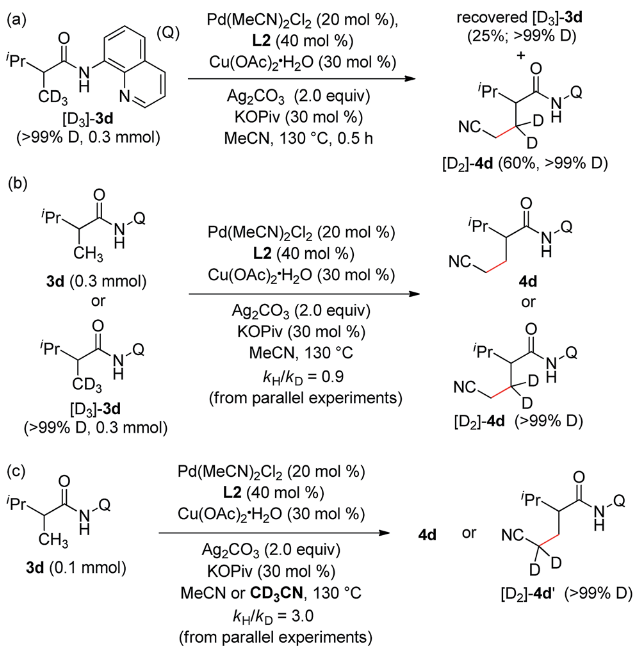
Table 3 Scope of the α-substituted aliphatic amides[a,b]



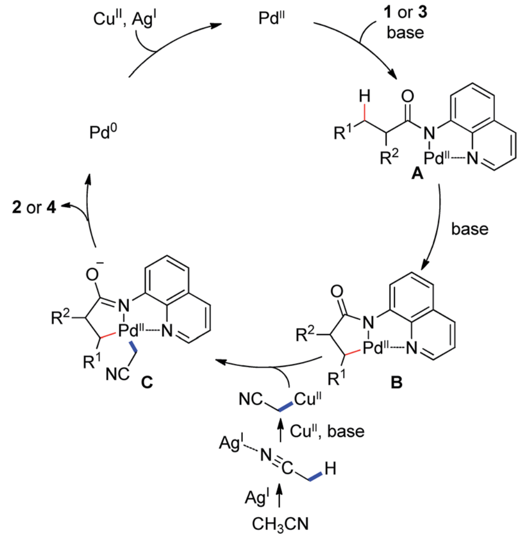
[a] Reaction conditions: **1** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (0.06 mmol), **L2** (0.12 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.09 mmol), Ag_2CO_3 (0.6 mmol), KOPiv (0.09 mmol), MeCN (2.0 mL), air (1 atm), 130 °C, 1 h. [b] Isolated yield. [c] $Pd(OPiv)_2$ (0.06 mmol), **L2** (0.12 mmol), $Cu(O_2C^nPr)_2$ (0.36 mmol), Ag_2CO_3 (0.6 mmol), CsOPiv (0.36 mmol), MeCN (1.5 mL), heptane (1.5 mL), air (1 atm), 130 °C, 15 h. Q = 8-quinolinyl.



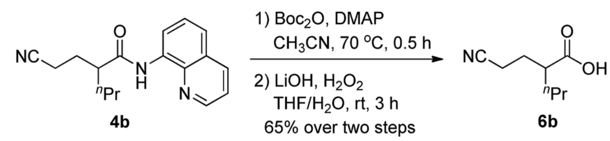
Scheme 1 Control experiments on the reaction mechanism. Condition A: **1m** or **5** (0.3 mmol), $Pd(OPiv)_2$ (0.036 mmol), **L2** (0.12 mmol), $Cu(O_2C^nPr)_2$ (0.36 mmol), Ag_2CO_3 (0.6 mmol), CsOPiv (0.36 mmol), MeCN (1.5 mL), heptane (1.5 mL), air (1 atm), 130 °C, 15 h. Condition B: **1m** or **5** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (0.06 mmol), **L2** (0.12 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.09 mmol), Ag_2CO_3 (0.6 mmol), KOPiv (0.09 mmol), MeCN (2.0 mL), air (1 atm), 130 °C, 1 h.



Scheme 2 Deuterium-labelling experiments.



Scheme 3 Proposed reaction mechanism.



Scheme 4 Removal of the directing group.

that aliphatic esters and nitriles could undergo dehydrogenation to form the corresponding α,β-unsaturated derivatives.[16] Therefore, a sequential dehydrogenation/1,4-addition process could potentially occur in this reaction and could provide the desired products. To clarify this, *N*-(quinolin-8-yl)acrylamide (**5**) was prepared and subjected to the reaction conditions (Scheme 1). It turned out that no desired product (**2m**) was obtained, and thus the dehydrogenation/1,4-addition process could be excluded.

To further probe the reaction mechanism, a series of deuterium-labelling experiments were carried out. As shown in Scheme 2, no apparent H/D exchange was observed with deuterium-labelled 2,3-dimethyl-*N*-(quinolin-8-yl)butanamide (D_3-**3d**) (Scheme 2a), indicating that the sp^3 C–H bond cleavage is an irreversible step under the current reaction conditions. Furthermore, no obvious kinetic isotope effect was observed for **3d** (*vs.* D_3-**3d**) based on the early relative rate of the parallel reactions (Scheme 2b), whereas a primary isotope effect with regard to acetonitrile (MeCN *vs.* CD_3CN) was obtained (Scheme 2c), suggesting that the sp^3 C–H bond cleavage of acetonitrile is the rate-limiting step in the catalytic process.

On the basis of the abovementioned observations and the previous studies,[11–14] a plausible reaction mechanism is proposed (Scheme 3), involving the coordination of amide **1** or **3** to a Pd^{II} species, followed by a ligand exchange process, giving rise to the palladium intermediate **A.** Irreversible sp^3 C–H bond activation of this intermediate under basic conditions generates the cyclometalated palladium(II) complex **B.** Transmetalation of the complex **B** with the cyanomethyl copper(II) species, possibly from a silver-promoted process of acetonitrile, affords the dialkyl palladium intermediate **C**, which provides the final product **2** or **4** upon reductive elimination.

To further broaden the synthetic application of this methodology, removal of the 8-quinolylamino directing group of **4b** was carried out based on the reported two-step process,[11l] and the C–N bond of amide was selectively cleaved to deliver the desired acid product **6b** in a 65% yield without affecting the cyano group (Scheme 4).

Conclusions

In summary, a highly regioselective cyanomethylation of aliphatic amides with an 8-aminoquinolinyl group as the directing moiety was developed *via* a palladium-catalyzed cross dehydrogenative coupling process. This process exhibited a predominant preference for methyl C–H bonds over methylene C–H bonds with good functional group tolerance. Mechanistic studies were carried out that excluded the possibly sequential dehydrogenation/Michael addition process. Detailed mechanistic studies of this reaction and expansion of the substrate scope[17] are currently ongoing in our laboratory.

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Notes and references

1 For selected reviews, see: (*a*) F. F. Fleming, *Nat. Prod. Rep.*, 1999, **16**, 597–606; (*b*) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902–7917; (*c*) R. López and C. Palomo, *Angew. Chem., Int. Ed.*, 2015, **54**, 13170–13184; for a selected book, see: (*d*) Z. Rappoport, *The Chemistry of the Cyano Group*, Wiley-Interscience, London, 1970.

2 (*a*) S. P. Khanapure and E. R. Biehl, *J. Org. Chem.*, 1990, **55**, 1471–1475; (*b*) N. Kumagai, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 13632–13633; (*c*) B. Anxionnat, D. G. Pardo, G. Ricci and J. Cossy, *Org. Lett.*, 2011, **13**, 4084–4087; (*d*) J. Velcicky, A. Soicke, R. Steiner and H. Schmalz, *J. Am. Chem. Soc.*, 2011, **133**, 6948–6951; (*e*) T. Wu, X. Mu and G. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 12578–12581; (*f*) G.-W. Wang, A.-X. Zhou, J.-J. Wang, R.-B. Hu and S.-D. Yang, *Org. Lett.*, 2013, **15**, 5270–5273; (*g*) S. Chakraborty, Y. J. Patel, J. A. Krause and H. Guan, *Angew. Chem., Int. Ed.*, 2013, **52**, 7523–7526; (*h*) J. Shen, D. Yang, Y. Liu, S. Qin, J. Zhang, J. Sun, C. Liu, C. Liu, X. Zhao, C. Chu and R. Liu, *Org. Lett.*, 2014, **16**, 350–353; (*i*) A. Bunescu, Q. Wang and J. Zhu, *Chem.–Eur. J.*, 2014, **20**, 14633–14636; (*j*) P. J. Lindsay-Scott, A. Clarke and J. Richardson, *Org. Lett.*, 2015, **17**, 476–479; (*k*) A. D. Mamuye, L. Castoldi, U. Azzena, W. Holzera and V. Pace, *Org. Biomol. Chem.*, 2015, **13**, 1969–1973.

3 For a selected review, see: D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234–245.

4 For selected examples, see: (*a*) T. Frejd and T. Klingstedt, *Synthesis*, 1987, 40–42; (*b*) A. Nortcliffe, N. P. Botting and D. O'Hagan, *Org. Biomol. Chem.*, 2013, **11**, 4657–4671; (*c*) O. M. Ali, A. E.-G. E. Amr and E. E. Mostafa, *Res. Chem. Intermed.*, 2014, **40**, 1545–1556.

5 For selected examples, see: (*a*) F. Diaba, C. L. Houerou, M. Grignon-Dubois and P. Gerval, *J. Org. Chem.*, 2000, **65**, 907–910; (*b*) L. Wu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 15824–15832; (*c*) T. Mukaiyama and M. Michida, *Chem. Lett.*, 2007, **36**, 1244–1245; (*d*) C. Verrier, S. Oudeyer, I. Dez and V. Levacher, *Tetrahedron Lett.*, 2012, **53**, 1958–1960; (*e*) Y.-C. Fan, G.-F. Du, W.-F. Sun, W. Kang and L. He, *Tetrahedron Lett.*, 2012, **53**, 2231–2233.

6 (*a*) R. Shang, D.-S. Ji, L. Chu, Y. Fu and L. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 4470–4474; (*b*) P. Y. Yeung, K. H. Chung and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 2912–2915.

7 M. Kosugi, M. Ishiguro, Y. Negishi, H. Sano and T. Migita, *Chem. Lett.*, 1984, 1511–1512.

8 D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 9330–9331.

9 (*a*) J. You and J. G. Verkade, *Angew. Chem., Int. Ed.*, 2003, **42**, 5051–5053; (*b*) J. You and J. G. Verkade, *J. Org. Chem.*, 2003, **68**, 8003–8007.

10 H. Yoshida, Y. Fujimura, H. Yuzawa, J. Kumagai and T. Yoshida, *Chem. Commun.*, 2013, **49**, 3793–3795.

11 For selected reviews, see: (*a*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (*c*) H. Li, B.-J. Lia and Z.-J. Shi, *Catal. Sci. Technol.*, 2011, **1**, 191–206; (*d*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726–11743; (*e*) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064; (*f*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107–1295; for selected examples, see: (*g*) X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634–12635; (*h*) D.-H. Wang, M. Wasa, R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 7190–7191; (*i*) B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 4882–4886; (*j*) L. D. Tran and O. Daugulis, *Angew. Chem., Int. Ed.*, 2012, **51**, 5188–5191; (*k*) S.-Y. Zhang, G. He, W. A. Nack, Y.-S. Zhao, Q. Li and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 2124–2127; (*l*) S.-Y. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 12135–12141; (*m*) K. Chen, F. Hu, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 3906–3911; (*n*) E. T. Nadres, G. I. F. Santos, D. Shabashov and O. Daugulis, *J. Org. Chem.*, 2013, **78**, 9689–9714; (*o*) K. Chen and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 11950–11954; (*p*) R.-Y. Zhu, J. He, X.-C. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 13194–13197; (*q*) B. Wang, X. Wu, R. Jiao, S.-Y. Zhang, W. A. Nack, G. He and G. Chen, *Org. Chem. Front.*, 2015, **2**, 1318–1321.

12 For selected examples, see: (*a*) M. R. Netherton, C. Dai, K. Neuschütz and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 10099–10100; (*b*) J. H. Kirchhoff, C. Dai and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 1945–1947; (*c*) J. H. Kirchhoff, M. R. Netherton, I. D. Hills and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 13662–13663; (*d*) J. Zhou and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 12527–12530.

13 For selected examples, see: (*a*) Y. Suto, N. Kumagai, S. Matsunaga, M. Kanai and M. Shibasaki, *Org. Lett.*, 2003, **5**, 3147–3150; (*b*) A. Bunescu, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2015, **54**, 3132–3135; (*c*) C. Chatalova-Sazepin, Q. Wang, G. M. Sammis and J. Zhu, *Angew. Chem., Int. Ed.*, 2015, **54**, 5443–5446; (*d*) Y. Suto, R. Tsuji, M. Kanai and M. Shibasaki, *Org. Lett.*, 2005, **7**, 3757–3760.

14 For selected reviews, see: (*a*) P. Espinet and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2004, **43**, 4704–4734; (*b*) C. Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya and P. Espinet, *ACS Catal.*, 2015, **5**, 3040–3053; for selected examples, see: (*c*) V. Farina, S. Kapadia, B. Krishnan, C. Wang and L. S. Liebeskind, *J. Org. Chem.*, 1994, **59**, 5905–5911; (*d*) M. Eckhardt and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 13642–13643; (*e*) S. P. H. Mee, V. Lee and J. E. Baldwin, *Angew. Chem., Int. Ed.*, 2004, **43**, 1132–1136.

15 With monodentate ligands (80 mol%), such as pyridine, 2,6-lutidine and quinolone, the reactions give only trace amount of product **2a** under similar conditions as entry 7 in Table 1.

16 Y. Chen, J. P. Romaire and T. R. Newhouse, *J. Am. Chem. Soc.*, 2015, **137**, 5875–5878.

17 Attempt to use higher nitriles with secondary α-carbon such as propionitrile, butyronitrile and benzyl cyanide as coupling partners was unsuccessful under current conditions. Besides, the coupling of sp^2 C–H of benzamides with CH_3CN using 8-quinolylamino as the directing group was not achieved under similar conditions.