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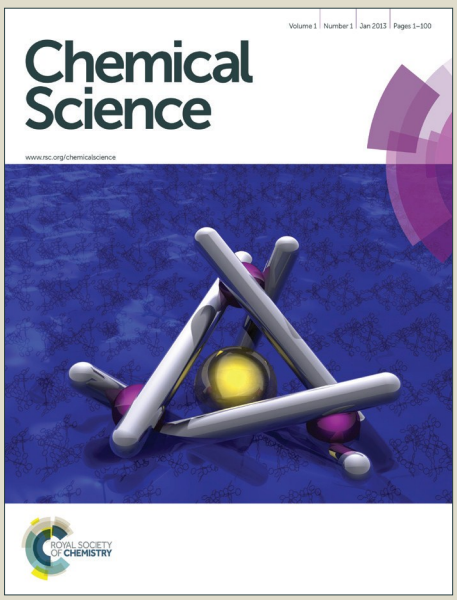

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ARTICLE

Palladium-Catalyzed Ligand-Promoted Site-Selective Cyanomethylation of Unactivated C(sp^3)–H Bonds with Acetonitrile

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

DOI: 10.1039/x0xx00000x

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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 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 applications in chemical research.

Introduction

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 an amide, ester, aldehyde, and primary amine.[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 the 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, direct cross coupling of sp^3 C–H bonds with acetonitrile has not been discovered. Considering the literature support of Pd-catalyzed alkylation of unactivated C(sp^3)–H bond[11] and reductive elimination of dialkyl palladium(II) species,[11g-l,12] it is envisaged that this process is feasible if the cyanomethyl group could effectively replace the anion of an alkyl palladium(II) species.

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 the cyanomethyl anion in the presence of a ligand. On the basis of these results, 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 since the copper-promoted C–H bond activation of acetonitrile[13] and transmetalation of an oragnocopper species onto an oragnopalladium(II) species[14] have been well documented. As shown in the Table 1, copper carboxylates were found 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). Next, 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). Additionally, the use of acetonitrile and heptane as the co-solvent could further increase the yield (entry 18). It was also noticed that the reaction yield was dramatically decreased in the absence of the ligand, indicating that the ligand plays a role in stabilizing an 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).

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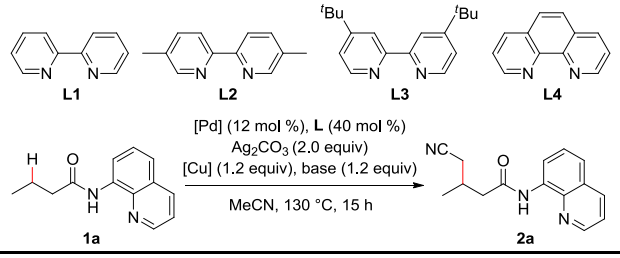
Electronic Supplementary Information (ESI) available: Experimenta ldetails including characterization data, copies of ^1H, ^{13}C NMR and NOESY spectra. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of reaction conditions[a]



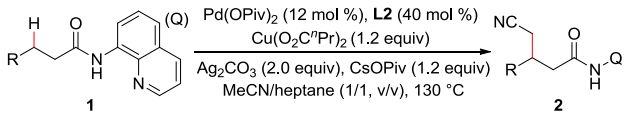
entry	Pd source	Cu source	base	L	yield (%)[b]
1[c]	$Pd(OAc)_2$	-	NaHMDS	**L1**	0
2	$Pd(OAc)_2$	$Cu(OAc)_2$	-	**L1**	11
3	$Pd(OAc)_2$	$Cu(O_2C^nPr)_2$	-	**L1**	20
4	$Pd(OAc)_2$	$Cu(acac)_2$	-	**L1**	trace
5	$Pd(OAc)_2$	CuOAc	-	**L1**	11
6	$Pd(OAc)_2$	$Cu(O_2C^nPr)_2$	-	**L2**	30
7	$Pd(OAc)_2$	$Cu(O_2C^nPr)_2$	-	**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]

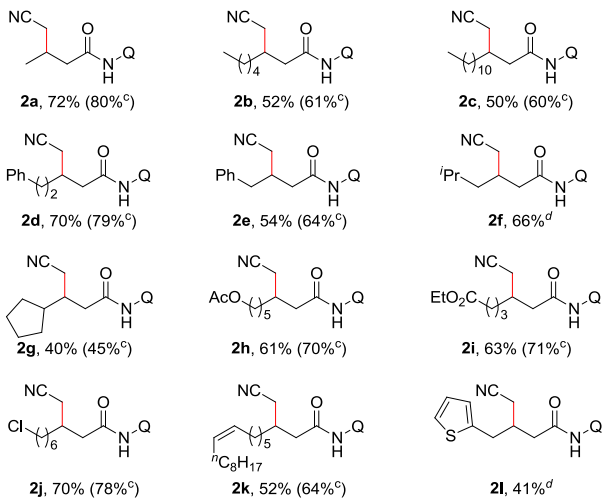
[a] Reaction conditions: **1a** (0.3 mmol), Pd source (0.036 mmol), **L** (0.12 mmol), Cu source (0.36 mmol), Ag_2CO_3 (0.6 mmol), base (0.36 mmol), MeCN (3.0 mL), air (1 atm), 130 °C, 15 h unless other noted. [b] Yields are based on **1a**, determined by ^{1}H-NMR using dibromomethane as the internal 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).

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

Next, 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 effective substrates (**3a**-**h**). It is worth mentioning that this reaction showed high site-selectivity by favoring the sp^3 C–H bonds of the methyl group over those of the methylene groups including the relatively reactive benzylic sp^3 C–H bond (**3c**). Furthermore, cyclic sp^3 C–H bond could also be functionalized, albeit with a moderate yield (**3k**). Amide with α-tertiary carbon (**3l**) was an inappropriate substrate which could be quantitatively recovered under current conditions.

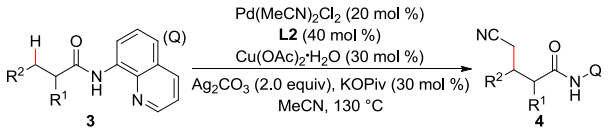
Table 2 Scope of linear aliphatic amides[a,b]

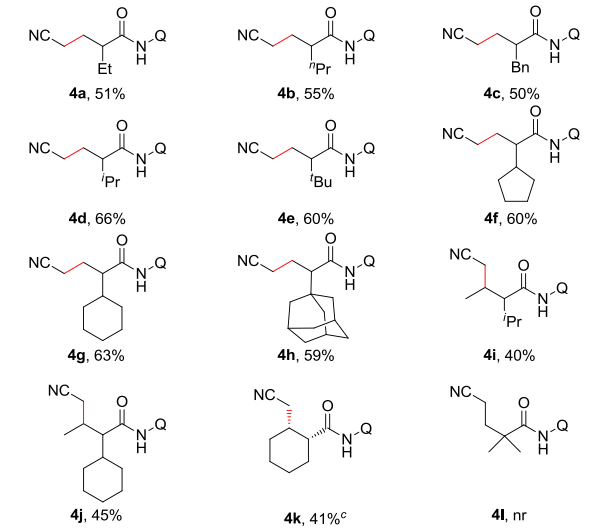




[a] Reaction conditions: **1** (0.3 mmol), $Pd(OPiv)_2$ (0.036 mmol), **L2** (0.12 mmol), $Cu(O_2C^nPr)_2$ (0.36 mmol), Ag_2CO_3 (0.6 mmol), CsOPiv (0.36 mmol), MeCN (1.5 mL), heptane (1.5 mL), air (1 atm), 130 °C, 15 h. [b] Isolated yield. [c] $Pd(OPiv)_2$ (0.045 mmol). [d] $Pd(OPiv)_2$ (0.06 mmol).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

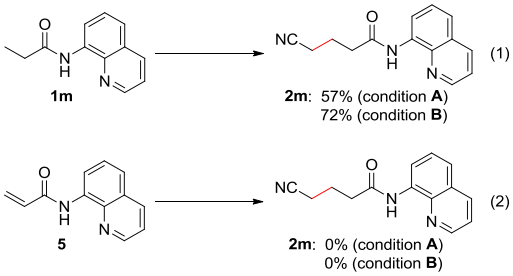
Table 3 Scope of α-substituted aliphatic amides[a,b]





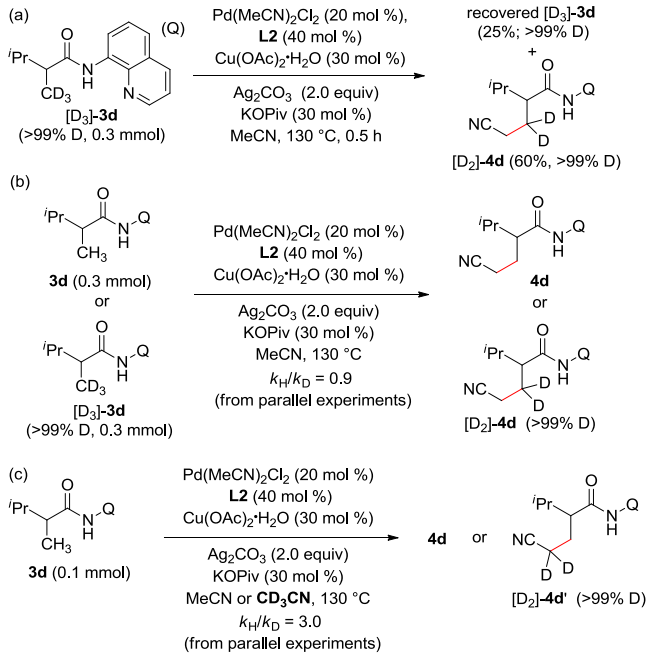
[a] Reaction conditions: **1** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (0.06 mmol), **L2** (0.12 mmol), $Cu(OAc)_2·H_2O$ (0.09 mmol), Ag_2CO_3 (0.6 mmol), KOPiv (0.09 mmol), MeCN (2.0 mL), air (1 atm), 130 °C, 1 h. [b] Isolated yield. [c] $Pd(OPiv)_2$ (0.06 mmol), **L2** (0.12 mmol), $Cu(O_2C^nPr)_2$ (0.36 mmol), 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.

To provide some insights into the catalytic cycle, we carried out the mechanistic studies of this process. It has been reported 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 to provide the desired products. To clarify this, *N*-(quinolin-8-yl)acrylamide (**5**) was prepared and subjected into 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.



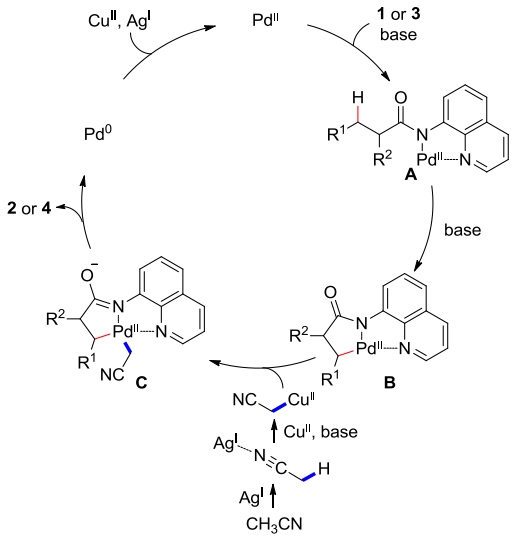
Scheme 1 Control experiments on reaction mechanism. Condition **A**: **1m** or **5** (0.3 mmol), $Pd(OPiv)_2$ (0.036 mmol), **L2** (0.12 mmol), $Cu(O_2C^nPr)_2$ (0.36 mmol), Ag_2CO_3 (0.6 mmol), CsOPiv (0.36 mmol), MeCN (1.5 mL), heptane (1.5 mL), air (1 atm), 130 °C, 15 h. Condition **B**: **1m** or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

To further probe the reaction mechanism, a series of deuterium-labeling 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 2, a), indicating that the sp^3 C–H bond cleavage is an irreversible step under current reaction conditions. Furthermore, no obvious kinetic isotope effect was observed for **3d** (vs D_3-**3d**) based on the early relative rate of parallel reactions (Scheme 2, b), while a primary isotope effect with regard to acetonitrile (MeCN vs CD_3CN) was obtained (Scheme 2, c), suggesting that the sp^3 C–H bond cleavage of acetonitrile is the rate-limiting step in the catalytic process.



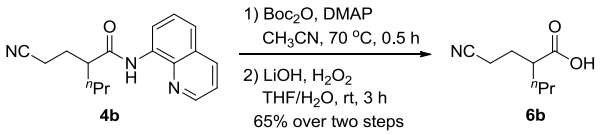
Scheme 2 Deuterium labeling experiments.

On the basis of the above observations and the previous studies,[11-14] a plausible reaction mechanism is proposed (Scheme 3). Coordination of amide **1** or **3** to a Pd^{II} species followed by a ligand exchange process gives rise to the palladium intermediate **A**. Irrreversible 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.



Scheme 3 Proposed reaction mechanism.

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 65% yield without affecting the cyano group.



Scheme 4 Removal of the directing group.

Conclusions

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

Acknowledgements

The authors gratefully acknowledge financial support for this research from NSF CHE-1350541 and Indiana University-Purdue University Indianapolis. Ke Yang is also grateful for financial support from NSFC (No. 21332005) and the Jiangsu Innovation Programs (P. R. China).

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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.

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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.

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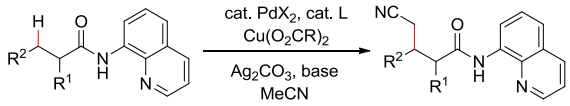

The direct coupling of unactivated sp^3 C–H bonds in aliphatic amides with acetonitrile was achieved via palladium catalysis.