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Ligand-Promoted Non-Directed C–H Cyanation of Arenes

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Abstract

We herein report the first example of a 2-pyridone accelerated non-directed C–H cyanation with an arene as the limiting reagent. This protocol is compatible with a broad scope of arenes, including advanced intermediates, drug molecules, and natural products. A kinetic isotope experiment ($k_H/k_D = 4.40$) indicates that the C–H bond cleavage is the rate-limiting step. Also, the reaction is readily scalable, further showcasing the synthetic utility of this method.

Graphical Abstract

Keywords

cyanation; C–H activation; palladium; 2-pyridone

Cyanoarenes are abundant in natural products, drug molecules, and advanced synthetic intermediates.¹ The cyano functional group is highly versatile in organic synthesis and can be readily converted to carboxyl, carbonyl, amino, and other heterocyclic groups.² Thus, installation of cyano groups in a direct and facile manner is of high interest. However,

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introduction of cyano groups onto arenes have traditionally relied heavily on the Sandmeyer reaction and other transition-metal-mediated cross-coupling reactions with aryl halides.³ The use of highly reactive diazonium intermediate and the requirement to prefunctionalize arenes render these traditional methods undesirable and inefficient, often with limited scope and functional group tolerance.

On the other hand, direct C–H cyanation of arenes offers a potentially superior alternative. In the past decade, tremendous efforts have been devoted to the development of directed C–H cyanation of arenes. Pyridines, pyrimidines, and oximes have been employed as directing groups for *ortho* C–H cyanation with Pd, Ru, Rh, and Co catalysts (Fig. 1a).⁴ A *meta*-selective C–H cyanation has been realized using a U-shaped template.⁵ More recently, two examples of non-directed C–H cyanation of arenes through radical pathways have also been achieved (Fig. 1b).⁶ In a continuing effort to improve the reactivity and selectivity of non-directed C–H functionalizations of arenes, we have successively discovered 2,6-dialkyl pyridine ligands⁷ that can accelerate non-directed C–H olefination of electron-deficient arenes and electron-deficient 2-pyridone ligands⁸ that can enable C–H olefination with arenes as the limiting reagent (Fig. 1c).

Guided by these ligand developments, we wondered whether these ligands could be used to enable C–H cyanation. We began our study by treating the model substrate mesitylene (1.0 equiv.) with Pd(OAc)₂ (10 mol%), AgCN (1.1 equiv., cyanide source), and AgOAc (3.0 equiv.) in HFIP (solvent) at 100 °C. Encouragingly, the desired C(sp²)–H cyanation product was detected in 18% yield. We first evaluated several mono-dentate pyridine-based ligands (**L1–L3**), which have been shown to promote C–H activation.⁹ However, only trace amounts of product were observed. Based on our previous studies on non-directed C(sp²)–H olefination promoted by electron-deficient 2-pyridone ligands, we set out to extensively screen 2-pyridone ligands for this non-directed C(sp²)–H cyanation reaction. The addition of a simple 2-pyridone ligand suppressed the reactivity (**L4**). To our delight, the use of 5-nitro-2-pyridone, which has previously demonstrated efficiency for γ -C(sp³)–H arylation,¹⁰ slightly increased the yield to 25% (**L5**). Incorporation of a trifluoromethyl or a nitro group at the 3 position of **L5** led to lower yields (**L6**, **L7**). A significant drop in reactivity was observed with 3-nitro-2-pyridone (**L8**). Intriguingly, the yield increased to 77% when a trifluoromethyl group was installed at the 5-position of **L8** (**L9**). The replacement of 5-CF₃ in **L9** with 5-Cl further improved the yield to 87% (**L10**). However, the use of 3,5-dichloro-2-pyridone resulted in loss of reactivity (**L11**). These results suggest that this cyanation reaction is exceptionally sensitive to the steric and electronic environments of the 2-pyridone ligands. Other structural variations of 2-pyridone ligands resulted in low reactivity (**L12–L15**) (Table 1).

With the optimal ligand **L10** identified, we next examined different cyanide sources and their loadings (Table 2). We first tested several commercially available cyanide salts and found that increasing the loading of AgCN to 2.0 equivalents from 1.1 equivalents decreased yield to 50% from 84%, presumably due to palladium catalyst deactivation by excess cyanide coordination.¹¹ Screening of two other cyanide sources showed that CuCN and Zn(CN)₂ gave lower yields. Other reaction parameters have also been examined, such as oxidants, solvents, and temperature. Further, minimal products were afforded with KCN,

$K_3Fe(CN)_6$, and TMSCN as the cyanation reagents. Oxidants other than AgOAc only provided trace products, while other variations of the reaction parameters resulted in inferior reactivity.

With the optimal reaction conditions established, we next explored the scope of arenes for this non-directed cyanation reaction. Extensive screening of 2-pyridone ligands proved that **L9** gave similar even higher yields than **L10** in some cases, thus both of the two ligands were used to explore the substrate scope of this reaction. Electron neutral to rich arenes such as simple benzene, alkyl substituted benzenes, and alkoxy benzenes consistently afforded the mono-cyanated products in good yields (**2a–2q**, **2t–2u**). The mono selectivity could be explained by the electron-deficient nature of cyanated arenes. Mono-alkylated arenes were cyanated at the less sterically hindered *meta* and *para* positions, providing *meta*- and *para*-isomers as the main products (**2b–2d**). Arenes with bulkier substituents such as *tert*-butyl group (**2d**) afforded considerably better *para* site selectivity. Di-alkylated and tri-alkylated arenes all provided the mono-cyanated products in good yields with various selectivities depending on the substitution patterns of the alkylated arenes (**2e–2h**). Strong electron-donating substituents such as alkoxy groups, only provide *ortho*- and *para*-cyanated isomers, owing to its electronic effect. The bulkier silyl-protected phenol gave *para*-cyanated product as the main isomer because of steric effect (**2p** and **2q**). Naphthalene also provided the cyanated products in 73% yield, with a 2.0/1.0 selectivity ratio (α/β) (**2l**). This non-directed cyanation occurred selectively on the relative electron-rich arene for diaryl substrates (**2m**). For 2-chloroanisole and 3-chloroanisole (**2n** and **2o**), the yields dropped to only 20% under the same conditions due to the electron-withdrawing effect of the chloride on the benzene ring. However, heating up the reaction to 120 °C improved yields to 64% and 50% respectively. Electron-deficient arenes such as chlorobenzene and methyl benzoate, are unreactive to this reaction condition, thus 8.0 equiv. of arenes and 1.0 equiv. of cyanide were used to secure 45% and 50% yields respectively (**2s** and **2t**).

To further examine the practicality of this reaction, we also examined cyanation on advanced intermediates and biologically relevant substrates (**2v–2x**, **2ab–2ac**). Gladly, O, S, N-heterocycles could be cyanated in good yields. Interestingly, for both dibenzofuran and dibenzothiophene, cyanation proceeded selectively at the 4 position, while olefination occurred at the 2 position in our previous studies for non-directed olefination.^{ref} This suggests that electronic effect is more important to selectivity compared to steric effect in this cyanation reaction. Some natural products and drug molecules can also be cyanated under the optimal conditions in moderate to good yields (**2z**, **2aa**, **2ad**). 2-Alkyl/aryl anisoles were observed to give better selectivity (**2ae–2aj**), which could be rationalized by a combination of electronic effect and steric effect (Table 3).

To further showcase the synthetic utility of this method, non-directed cyanation of mesitylene (**1h**) was carried out on 10.0 mmol scale, yielding the desired product in 62% yield (Fig. 2a).

To gain insight into the reaction mechanism, we carried out kinetic isotope effect (KIE) experiments. Intermolecular one-pot and parallel experiments provided a P_H/P_D value of

4.29 and a k_H/k_D value of 4.40, respectively, which suggest that the C–H activation step is rate-limiting step (Fig. 2b).

A plausible catalytic cycle is outlined in Figure 4. 2-pyridone ligand functions as an analogue of OAc and accelerates C–H cleavage to form intermediate **II**. Ligand Exchange of CN^- between AgCN and Pd complex intermediate **II** forms **III**. Then reductive elimination from **III** provides the desired product (Fig. 3).

In summary, we have developed the first example of a Pd-catalyzed non-directed cyanation of arenes, enabled by an electron-deficient 2-pyridone ligands. The reaction features broad substrate scope and high functional group compatibility, exemplified by successful C–H cyanation of a range of complex molecules. Currently, we are attempting to achieve better site selectivity for non-directed C–H activation through ligand design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. Fleming FF, Yao L, Ravikumar PC, Funk L, Shoo BC. J. Med. Chem 2010, 53, 7902. [PubMed: 20804202]
- [2]. (a)Hyland J, O'Connor C. J. Chem. Soc., Perkin Trans 2 1973, 223;(b)Swain C, J. Am. Chem. Soc 1947, 69, 2306;(c)Das B, Reddy C, Kumar D, Krishnaiah M, Narender R, Synlett 2010, 2010, 391;(d)Finholt AE, Jacobson EC, Ogard AE, Thompson P, J. Am. Chem. Soc 1955, 77, 4163; (e)Rappoport Z, The Chemistry of the Cyano Group, Inter- science, New York, 1970.
- [3]. (a)Sekiya A, Ishikawa N, Chem. Lett 1975, 4, 277;(b)Takagi K, Okamoto T, Sakakibara Y, Ohno A, Oka S, Hayama N, Bull. Chem. Soc. Jpn 1975, 48, 3298;(c)Dalton JR, Regen SL, J. Org. Chem 1979, 44, 4443;(d)Akita Y, Shimazaki M, Ohta. Synthesis 1981, 1981, 974;(e)Chatani N, Hanafusa T, J. Org. Chem 1986, 51, 4714;(f)Sato N, Suzuki MJ, Heterocycl. Chem 1987, 24, 1371;(g)Nair V, Purdy DF, Sells TB, J. Chem. Soc., Chem. Commun 1989, 878;(h)Takagi K, Sasaki K, Sakakibara Y, Bull. Chem. Soc. Jpn 1991, 64, 1118;(i)Tschaen DM, Desmond R, King AO, Fortin MC, Pipik B, King S, Verhoeven TR, Synth. Commun 1994, 24, 887.
- [4]. For selected examples of Pd, Ru, Rh, Co-catalyzed directed $C(sp^2)$ –H cyanation, see:(a)Jia XF, Yang DP, Zhang SH, J. Cheng, Org. Lett 2009, 11, 4716; [PubMed: 19764735] (b)Jia XF, Yang DP, Wang WH, Luo F, Cheng J, J. Org. Chem 2009, 74, 9470; [PubMed: 19938811] (c)Mishra A, Vats TK, Deb I, J. Org. Chem 2016, 81, 6525; [PubMed: 27408980] (d)Chaitanya M, Anbarasan P, Org. Lett 2015, 17, 3766; [PubMed: 26196156] (e)Gong TJ, Xiao B, Cheng W-M, Sun W, Xu J, Liu Z-J, Liu L, Fu Y, J. Am. Chem. Soc 2013, 135, 10630; [PubMed: 23822812] (f)Yu D-G, Gensch T, Azambuja F, Vasquez-Céspedes S, Glorius F, J. Am. Chem. Soc 2014, 136, 17722. [PubMed: 25472496]
- [5]. Bag S, Jayarajan R, Dutta U, Chowdhury R, Mondal R, Maiti D, Angew. Chem. Int. Ed 2017, 56, 12538;Angew. Chem 2017, 129, 12712.
- [6]. (a)Mcmanus JB, Nicewicz DA, J. Am. Chem. Soc 2017, 139, 2880; [PubMed: 28177237] (b)Shu Z, Ji W, Wang X, Zhou Y, Zhang Y, Wang J, Angew. Chem. Int. Ed 2014, 53, 2186;Angew. Chem 2014, 126, 2218.
- [7]. Zhang Y-H, Shi B-F, Yu J-Q, J. Am. Chem. Soc 2009, 131, 5072. [PubMed: 19296661]

- [8]. Wang P, Verma P, Xia G-Q, Shi J, Qiao JX, Tao S, Cheng PTW, Poss MA, Farmer ME, Yeung K-S, Yu J-Q, Nature 2017, 551, 489. [PubMed: 29168802]
- [9]. For selected examples of pyridine-based ligands promoted C–H activation, see:(a)Wasa M, Chan KSL, Zhang X-G, He J, Miura M, Yu J-Q, J. Am. Chem. Soc 2012, 134, 18570; [PubMed: 23116159] (b)Li S, Zhu R-Y, Xiao K-J, Yu J-Q, Angew. Chem. Int. Ed 2016, 55, 4317;Angew. Chem 2016, 128, 4389.
- [10]. Zhu R-Y, Li Z-Q, Park HS, Senanayake CH, Yu J-Q, J. Am. Chem. Soc 2018, 140, 3564. [PubMed: 29481072]
- [11]. Erhardt S, Grushin VV, Kilpatrick AH, Macgregor SA, Marshall WJ, Roe DC, J. Am. Chem. Soc 2008, 130, 4828. [PubMed: 18336024]

(a) Transition-Metal-Catalyzed Directed C(sp²)-H Cyanation (b) Non-Directed C(sp²)-H Cyanation (c) Ligand-Accelerated Non-Directed C(sp²)-H Olefination of Arenes

(d) This Work

Figure 1.

(a) Previous work about transition-metal-catalyzed directed C(sp²)-H cyanation. (b) Non-directed cyanation of arenes via radical mechanism (c) Ligand-accelerated non-directed C(sp²)-H olefination of arenes. (d) Ligand-accelerated non-directed C(sp²)-H cyanation of arenes.

Figure 2.

(a) Scale-up reaction. (b) Primary kinetic isotope effect.

Figure 3.
Proposed mechanism

Table 1.

Ligand Evaluation^{a,b}

without ligand				
18%	L1 trace	L2 trace	L3 trace	
L4 < 10%	L5 25%	L6 21%	L7 < 10%	
L8 < 10%	L9 77%	L10 87%	L11 < 10%	
L12 16%	L13 trace	L14 trace	L15 trace	

^[a] Conditions: mesitylene (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol%), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures.

^[b] The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

Table 2.

Optimization of Reaction Conditions^{a,b,c}

Entry	Variations from the 'Standard Conditions'	Total Yield (%)
1	none	84
2	2.0 equiv. AgCN	50
3	1.1 equiv. CuCN	67
4	2.0 equiv. CuCN	39
5	0.6 equiv. Zn(CN) ₂	37
6	1.0 equiv. Zn(CN) ₂	32
7	1.1 equiv. KCN	trace
8	0.2 equiv. K ₃ Fe(CN) ₆	18
9	0.5 equiv. K ₃ Fe(CN) ₆	6
10	1.1 equiv. TMSCN	trace
11	no AgOAc	trace
12	1.0 equiv. AgOAc	45
13	2.0 equiv. AgOAc	50
14	2.0 equiv. Cu(OAc) ₂	trace
15	2.0 equiv. CuBr ₂	trace
16	CHCl ₃ as solvent instead of HFIP	trace
17	CHCl ₃ /HFIP = 1/1	30
18	45 mol% ligand	68
19	80 °C	60
20	120 °C	72

[a] Conditions: *o*-xylene (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol%), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures.

[b] The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

[c] The product was isolated as a mixture of two isomers: 3-cyano and 4-cyano *o*-xylene.

Table 3.

Substrate Scope^{a,b}

Late-stage functionalization

2y40 %^f **2z**67%^f **2aa**57%^f **2ab**75%^g
(m/p = 1.0/6.7) **2ac**73%^g
(m/p = 1.0/6.3) **2ad**41%^f
(m/p = 1.0/1.0)

2-Alkyl/aryl-1-alkoxyl substrates

2ae56%^f
(o/p = 1.0/7.3) **2af**75%^f
(o/p = 1.0/10.0) **2ag**81%^f
(o/p = 1.0/9.7) **2ah**51%^f
(o/p = 1.0/9.8) **2ai**31%^f
(o/p = 1.0/7.8) **2aj**72%^f
(o/p = 1.0/8.0)

[a] Conditions: **1** (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), **L9** (20 mol%), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures.

[b] The product was isolated as mixture of regio-isomers.

[c] 3.0 equiv. of benzene were used.

[d] 8.0 equiv. of substrates were used.

[e] The reaction was conducted at 120 °C.

[f] 15 mol% Pd(OAc)₂ were used instead of 10 mol%.

[g] 20 mol% Pd(OAc)₂ were used instead of 10 mol%.

[h] **L10** was used instead of **L9**.

[i] The reaction was conducted at 90 °C for 12 h.