

# Palladium(II)-catalyzed direct annulation of 2-chloronicotinaldehyde with 2-bromothiophenol via novel C(formyl)-C(aryl) coupling strategy

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### Abstract

An efficient and unprecedented method to the synthesis of 1-azathioxanthone derivatives has been developed by means of palladium-catalyzed C(formyl)-C(aryl) coupling followed by SNAr reaction. Optimization study was carried out through different catalyst, ligand, base and solvent. This approach displays various exclusive characteristics such as operational convenience, moderate to good isolated yields and decent functional group tolerance.

### **Graphic Abstract**



Keywords 1-Azathioxanthone  $\cdot$  Cross dehydrohalogenative coupling (CDC)  $\cdot$  C(formyl)-C(aryl) coupling  $\cdot$  Pd(II) catalyst

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### Introduction

The C-H bond activation has been remained a focal point of overwhelming study throughout chronicle of chemical research as it is omnipresent structural motifs in organic compounds [1-8]. The C-H bond having much higher bond dissociation energy is typically thought as the inert bond [9-12]. Thus, harsh reaction condition and multistep procedure is often required for C-H activation process. Unsurprisingly, reorganization of hydrocarbon by C-H bond activation into target molecules is inherently difficult task. The most appealing prospect of C-H functionalization logic is the potential to expand retrosynthetic tree by decreasing the step of reaction in contemporary organic chemistry [13]. Particularly, the direct functionalization of inert formyl C-H bond is susceptible to introduce functionality in complex organic molecule obviating the necessity of pre-functionalization with high atom-economy and energy efficiency [14, 15]. In last two decades, the exploitation of convenient as well as environmentally benign process for the creation of carbon-carbon and carbon-heteroatom (N,O,S) bond via C-H activation is of capital importance [16-20]. Despite tremendous progress being made, the rapid and efficient construction of C(formyl)-C(aryl) bond via formyl C-H activation in the presence of TM-metal catalyst remains a challenging issue. Inspired from previous efforts, we are prompted to functionalize formyl C-H bond through transition metal-catalyzed cross dehydrohalogenative coupling (CDC) reaction. Though we could employ other routes, palladium-catalyzed CDC pathway was thought as indispensable tool owing to its importance in such type of transformations [21–26].

As a feedstock and pervasive functional group, aldehyde represents an ideal starting material for construction of complex organic molecules [27-32]. The designing of innovative synthetic methodology for the functionalization of aldehyde C-H bond is extremely desirable. Nickel-catalyzed arylation of aldehyde has been successful since the pioneering work of Cheng in 2002 (Scheme 1a). Aryl halides were well coupled with aldehyde in the presence of Ni(L<sub>2</sub>)Br<sub>2</sub>/Zn catalytic system [33]. In 2010, Martin and co-worker represented the synthesis of benzocyclobutanone via palladium-catalyzed intramolecular acylation of aryl bromide (Scheme 1b) [34]. Moreover, Suchand and Satyanarayana disclosed Pd(OAc<sub>2</sub>)/ Ag-catalyzed environmentally benign acylation of iodoarenes with aldehyde (Scheme 1c) [35]. Liu et al. had reported the role of  $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ and NiCl<sub>2</sub> in formyl C-H activation for the synthesis of biarylketone (Scheme 1d) [36]. Interestingly, MacMillan and co-worker extended the protocol involving the synergic merger of photo-redox, nickel and hydrogen transfer catalysis for direct formyl C-H functionalization (Scheme 1e) [37]. Very recently, Wang et al. developed a nickel/photo-cocatalyzed acylation of aryl halide with aromatic and aliphatic aldehyde under mild reaction condition (Scheme 1f) [38]. However, most studies in the field of aldehyde C-H bond functionalization is focused on one C-C bond-forming reaction. On the basis of our previous work [39-42] and also motivated by successful reports on TM-catalyzed transformation from other researcher [43-48], we envisaged that two bond-forming palladium-catalyzed



Scheme 1 Comparision of previous work with this work

C(formyl)-C(aryl) coupling followed by SNAr reaction between 2-chloronicotinaldehyde and 2-bromothiophenol may be employed for the synthesis of 1-azathioxanthones (Scheme 1g).

The sulfur-containing heterocycles play significant role in the field of photoelectric material owing to higher resonance energy associated with sulfur atom than other heteroatom [49, 50]. Particularly, 1-azathioxanthones are effective sensitizers for europium and terbium luminescence [51]. As a consequence, much effort has been devoted in the development of novel synthetic strategy to generate substituted 1-azathioxanthones. Up to now, the synthetic approaches mostly relied on i) Yb(OTf)<sub>3</sub>/TfOH-catalyzed intramolecular cyclization of phenylthiopyridine acid under solvent free conditions [52], ii) CaF-mediated annulation process of 3-(trimethylsilyl)pyridin-2-yl triflate with 2-mercaptobenzoate [53], and iii) the cyclization of (2-fluorophenyl)(2-halophenyl)methanones with N<sub>2</sub>S·9H<sub>2</sub>O [54]. In spite of existing methods, a conceptually general route which utilize easily accessible starting substrate is still highly demanded. To the best of our knowledge, herein we report first palladium-catalyzed synthesis of 1-azathioxanthone derivatives through aldehyde C-H activation.

### **Result and discussion**

At the outset of our investigation, we carried out an optimization study for the exemplary reaction utilizing 2-chloronicotinaldehyde and 2-bromothiophenol as the model substrate. The optimized reaction condition for palladium-catalyzed synthesis of 1-azathioxanthones is shown in Table 1. A series of control experiments were executed to understand this reaction intensively. Expectedly, when the reaction was performed without a Pd catalyst, no desired conversion was observed (Table 1, entry 1). It was ascertained that Pd(0) catalysts like  $Pd_2(dba)_3$  or  $Pd(PPh_3)_4$ with K<sub>2</sub>CO<sub>3</sub> as base in dimethylformamide (DMF) solvent at 130 °C temperature under  $N_2$  atmosphere afford the hypothesized product in very poor yield (Table 1, entries 2-3). Much to our delight, when Pd(II) complexes along with ligands were applied as catalytic system, resultant transformation was achieved in moderate yield (Table 1, entries 4-6). Among different Pd(II) catalysts examined, PdCl<sub>2</sub> gave the best outcome (Table 1, entry 6). Successively, effect of different ligands were also evaluated in the system. L1, L3, L4 and L5 were failed to give improved performance when compared with the result of entry no.7 (Table 1, entries 6–10). Here, we observed that picolinamide ligand were efficient to generate the satisfactory yield of desired product via formyl C-H functionalization, while other ligand like BINAP and phenanthroline was ineffective in this reaction. The employment of base cesium carbonate  $(Cs_2CO_3)$  in DMF solvent is found most operative. Other bases such as Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, KO<sup>t</sup>Bu and NaOAc were less efficient or inefficient in driving this conversion (Table 1, entries 11-15). DMF was the optimal solvent, and the yield was significantly lowered when other solvent like 'PrOH, toluene or dioxane was used (Table 1, entries 16–18). The same experiment was also carried out under air atmosphere to check the feasibility of reaction but it results in trace amount of yield (Table 1, entry 19). Thus, the annulation reaction of 2-chloronicotinaldehyde with 2-bromothiophenol was conducted using PdCl<sub>2</sub> (10 mol%), L2 (20 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (4 equiv.) in DMF at 130 °C temperature under N<sub>2(g)</sub> atmosphere for 20 h.

With the optimized reaction condition in hand, the substrate scope with respect to both coupling partner was discovered. We started to investigate the scope of various 2-chloronicotinaldehyde by using 2-bromothiophenol as coupling partner (Table 2, 1a-1i). Significantly, different alkyl substituents were well tolerated, providing the possibility of further derivatization. Here, we could not found noticeable effect of steric hindrance associated with alkyl group on quantity of yield (Table 2, 1a-1c).



Table 1	Optimization	of the	reaction	conditions. <sup>a</sup>
	opumnation	01 0110	reaction	conditionor

<sup>a</sup>Reaction condition: 1a (0.8 mmol, 1 equiv.), 2a (2.0 mmol, 2.5 equiv.), Pd(II) catalyst (10 mol%), L2 (20 mol%), Cs2CO3 (4 equiv.) in 6.0 ml of solvent for 20 hours at 130oC under N2(g) atmosphere

<sup>b</sup>Isolated yield

<sup>c</sup>Reaction carried out at 100 °C

<sup>d</sup>Reaction carried out under air atmosphere

Examination under standard condition showed that the substrate with electron releasing substitution on pyridine ring afforded relatively lower yield than those with electron withdrawing substitution (Table 2, 1d-1i). Notably, in the case of 2-chloro-1-methyl-1H-pyrrole-3-carbaldehyde and 2-chlorothiophene-3-carbaldehyde, the coupling-cyclization reaction also worked well, affording the desired products 3j-3 k



Table 2 (continued)						
Entry	1	2	3	Yield		
9	NC NC CHO 1i	Br HS 2a	NC NC NS 3i	70%		
10	CHO N I 1j	Br HS 2a		56%		
11	CHO S CI 1k	Br HS 2a	S S Sk	53%		
12	CHO N CI	Br HS 2a		77%		
13	The second secon	Br HS 2a	O N S 3m	79%		
14	MeO N CI 1n	Br HS 2a	MeO N N S 3n	70%		
( 15	D <sub>2</sub> N CHO 10	Br HS 2a	$O_2N$ $V$ $S$	73%		
16	CHO CI 1a	Br HS 2b	O N S 3p	76%		
17	CHO CI	Br HS 2c	O N S 3q	75%		

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in good yields (Table 2, 1j-1 k). We subsequently replaced 2-chloronicotinaldehyde by 2-chloro3-formylquinoline to highlight the versatility of reaction (Table 2, 1 1-10). Interestingly, condensed quinolines were obtained by the treatment of 2-chloro3-formylquinoline with 2-bromothiophenol. Such type of condensed N-heterocycles are imperative molecules for material science applications. Next we used the optimal reaction condition in the synthesis of 1-azathioxanthones derivatives by reacting substituted 2-bromothiophenol with 2-chloronicotinaldehyde (Table 2, 2b-2 h). Substituents such as alkyl, alkoxy, nitro, triflouroalkyl on 4th position of 2-bromothiophenol produce the corresponding product in good yield. In short, it was noted that all the combinations which were screened gave the anticipated product regardless of electron donating group and electron withdrawing group at R or R' (Table 2).

On the basis of previous literature [55, 56] and result obtained from experiments, a plausible mechanistic route is represented in Scheme 2. Initially,  $PdCl_2$  was converted to transient palladium intermediate ( $Z_1$ ) by the coordination with two N donor atom of **L2** ligand in DMF solvent. Then,  $Z_1$  underwent ligand exchange with  $Cs_2CO_3$  to form intermediate ( $Z_2$ ), releasing cesium-halide. Organopalladium complex ( $Z_3$ ) will be formed upon the interaction of aryl aldehyde with  $Z_2$  via aldehyde C-H activation. Oxidative addition of  $Z_3$  to C–Br bond of 2-bromothophenol generated adduct  $Z_4$ .



Scheme 2 Proposed mechanism

Succeedingly,  $Z_4$  experienced reductive elimination to produce  $Z_5$  [2-chloropyridin-3-yl)(2-mercaptophenyl)methanone]. Finally, intramolecular aromatic nucleophilic substitution of  $Z_5$  with  $Cs_2CO_3$  base afforded the desired product 1-azathioxanthone.

### Conclusion

We have revealed strategy of palladium-catalyzed annulation of 2-chloronicotinaldehyde with 2-bromothiophenol which provides an efficient protocol for construction of 1-azathioxanthone in good to higher yield under fairly mild reaction condition. The strategy shows noticeable tolerance of various functional groups that are attached to both substrates. Further studies on detailed mechanistic insight and synthesis of valuable advance materials based on the present methodology are in progress.

### **Experimental section**

#### **General information**

2-Chloronicotinaldehydes, 2-bromothiophenols, palladium catalysts, ligands, base and solvents were purchased commercially and were used as received without any further purification. All reactions were supervised by thin-layer chromatography using Merck 60 F254 precoated silica gel plates (0.25 mm thickness). Column chromatography was performed using 60-120 and 200-400 mess silica from Spectrochem PVT.LTD., Mumbai, India. The newly synthesized compounds were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and elemental analysis. Melting points were determined using open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a 400 MHz FT NMR, Avance III Bruker model spectrometer using DMSO-d6 as a solvent, and assigned in parts per million ( $\delta$ ). <sup>1</sup>H NMR chemical shifts were given on the  $\delta$  scale (ppm) and were referenced to internal TMS. All coupling constants (J values) were denoted in Hertz (Hz). Multiplicities were reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet. The high-resolution mass spectrum (HRMS) was recorded on a Bruker Daltonics MicroTof. Elemental analysis (C, H, N) was carried out using a Heraeus CarloErba 1180 CHN analyzer (Hanau, Germany).

### General procedure for the synthesis of 5H-thiochromeno[2,3-b]pyridin-5-one

A mixture of 2-chloronicotinaldehydes (0.113 g, 0.8 mmol, 1 equiv.), 2-bromothiophenols (0.378 g, 2 mmol, 2.5 equiv.),  $PdCl_2$  (0.017 g, 0.08 mmol, 10.0 mol%), L2 (0.029 g, 0.16 mmol, 20 mol%) and cesium carbonate (1.04 g, 3.2 mmol, 4.0 equiv.) were dissolved in DMF (6.0 ml). The reaction mixture was stirred at 130 °C for 20 h under N<sub>2</sub> atmosphere and the progress of reaction was monitored continuously by TLC with ethyl acetate: hexane (3:4) eluent system. After the completion of reaction, crude was poured into crushed ice and then filtered the reaction mixture. Afterward, reaction mixture was subjected to solvent extraction by adding 20 ml of ethyl acetate. The organic layer was separated, dried over anhydrous MgSO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography to obtain anticipated product. Characterization data of compound 3a-3t are mentioned in the supplementary file.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11164-021-04536-1.

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#### References

- 1. R.H. Crabtree, J. Organometal. Chem. 689, 4083 (2004)
- 2. R.G. Bergman, Nature 446, 391 (2007)
- 3. P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, Chem. Rev. 119, 2192 (2018)
- 4. T. Bruckl, R.D. Baxter, Y. Ishihara, P.S. Baran, Acc. Chem. Res. 45, 826 (2012)
- 5. Y. Yang, J. Lan, J. You, Chem. Rev. 117, 8787 (2017)
- 6. L. Revathi, L. Ravindar, W.-Y. Fang, K. P. Rakesh, H.-L Qin, Adv. Syn. Catal. 360, 4652 (2018)
- 7. A. Shamsabadi, V. Chudasama, Org. Biomol. Chem. 17, 2865 (2019)
- 8. G. Rani, V. Luxami, K. Paul, Chem. Comm. 56, 12479 (2020)
- 9. D.F. McMillen, D.M. Golden, Ann. Rev. Phys. Chem. 33, 493 (1982)
- 10. J.A. Labinger, J.E. Bercaw, Nature 417, 507 (2002)
- 11. S.J. BlanksBy, G.B. Ellison, Acc. Chem. Res. 36, 255 (2003)
- 12. X.-S. Xue, P. Ji, B. Zhou, J.-P. Cheng, Chem. Rev. 117, 8622 (2017)
- 13. W.R. Gutekunst, P.S. Baran, Chem. Soc. Rev. 40, 1976 (2011)
- 14. K. Matcha, A.P. Antonchick, Angew. Chem. 125, 2136 (2013)
- 15. L. Yu, M. Wang, L. Wang, Tetrahedron **70**, 5391 (2014)
- 16. Y. Park, Y. Kim, S. Chang, Chem. Rev. 117, 9247 (2017)
- 17. Z. Dong, Z. Ren, S.J. Thompson, Y. Xu, G. Dong, Chem. Rev. 117, 9333 (2017)
- N.V. Tzouras, I.K. Stamatopoulos, A.T. Papastavrou, A.A. Liori, G.C. Vougioukalakis, Coordination Chem. Rev. 343, 25 (2017)
- 19. J. Ck Chu, T. Rovis, Angew. Chem. Int. Ed. 57, 62 (2018)
- 20. Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi, J.-A. Ma, Chem. Soc. Rev. 48, 4921 (2019)
- 21. C. Aouf, E. Thiery, J.L. Bras, J. Muzart, Org. Lett. 11, 4096 (2009)
- 22. J. Zhao, H. Fang, C. Xie, J. Han, G. Li, Y. Pan, Asian J. Org. Chem. 2, 1044 (2013)
- 23. A. Dey, M.A. Ali, S. Jana, S. Samanta, A. Hajra, Tetrahedron Lett. 58, 313 (2017)
- 24. B.V. Pipaliya, A.K. Chakraborti, J. Org. Chem. 82, 3767 (2017)
- 25. J. Zhang, Y. Zhuang, Y. Ma, X. Yang, M. Szostak, Adv. Syn. Catal. 361, 5709 (2019)
- 26. V.N. Shinde, N. Bhuvanesh, A. Kumar, H. Joshi, Organometallics 39, 324 (2020)
- 27. M.A. Sprung, Chem. Rev. 26, 297 (1940)
- 28. S. Guillarme, K. Plé, A. Banchet, A. Liard, A. Haudrechy, Chem. Rev. 106, 2355 (2006)
- 29. A. Maruani, M.T.W. Lee, G. Watkins, A.R. Akhbar, H. Baggs, A. Shamsabadi, D.A. Richards, V. Chudasama, RSC Adv. 6, 3372 (2016)
- 30. W.S. Hamama, M.E. Ibrahim, A.A. Gooda, H.H. Zoorob, RSC Adv. 8, 8484 (2018)
- 31. G. Pandey, S. Koley, R. Talukdar, P.K. Sahani, Org. Lett. 20, 5861 (2018)
- 32. W. Wang, K. Lu, Y. Qin, W. Yao, D. Yuan, S. A. Pullarkat, L. Xu, M. Ma, Tetrahedron 131145 (2020)
- 33. Y.-C. Huang, K.K. Majumdar, C.-H. Cheng, J. Org. Chem. 67, 1682 (2002)
- 34. P. Álvarez-Bercedo, A. Flores-Gaspar, A. Correa, R. Martin, J. Am. Chem. Soc. 132, 466 (2010)
- 35. B. Suchand, G. Satyanarayana, J. Org. Chem. 81, 6409 (2016)
- 36. M.D. Vu, M. Das, X.-W. Liu, Chem. Eur. J. 23, 15899 (2017)
- 37. X. Zhang, D.W.C. MacMillan, J. Am. Chem. Soc. 139, 11353 (2017)
- 38. P. Fan, C. Zhang, L. Zhang, C. Wang, Org. Lett. 22, 3875 (2020)
- 39. M.I. Morja, J.J. Patel, P.M. Chauhan, K.H. Chikhalia, Tetrahedron 76, 131348 (2020)
- 40. P.M. Chauhan, M.I. Morja, M. Asamdi, K.H. Chikhalia, Tetrahedron Lett. 61, 152601 (2020)
- 41. M. Asamdi, M.M. Shaikh, P.M. Chauhan, K.H. Chikhalia, Tetrahedron 74, 3719 (2018)
- 42. M.M. Shaikh, A.P. Patel, S.P. Patel, K.H. Chikhalia, New J. Chem. 43, 10305 (2019)
- 43. I. Nakamura, Y. Yamamoto, Chem. Rev. 104(2127), 21278 (2004)
- 44. M. Zhang, Adv. Syn. Catal. 351(2243), 2243 (2009)
- 45. S. Guin, S.K. Rout, A. Banerjee, S. Nandi, B.K. Patel, Org. Lett. 14, 5294 (2012)

- X.-F. Wu, Transition Metal-Catalyzed Heterocycle Synthesis via CH Activation (Wiley, New York, 2015)
- 47. R. Santhoshkumar, C.-H. Cheng, Chem. A Eur. J. 25, 9366 (2019)
- 48. M. Choury, A.B. Lopes, G. Blond, M. Gulea, Molecules 25, 3147 (2020)
- 49. M.E. Cinar, T. Ozturk, Chem. Rev. 115, 3036 (2015)
- 50. J. Li, S. Yang, W. Wu, H. Jiang, Org. Chem. Frontiers 7, 1395 (2020)
- P. Atkinson, K.S. Findlay, F. Kielar, R. Pal, D. Parker, R.A. Poole, H. Puschmann, S.L. Richardson, P.A. Stenson, A.L. Thompson, J. Yu, Org. Biomol. Chem. 4, 1707 (2006)
- 52. J. Li, C. Jin, W. Su, Heterocycles **81**, 2555 (2010)
- 53. Y. Fang, R.C. Larock, Tetrahedron 68, 2819 (2012)
- 54. K. Kobayashi, T. Komatsu, K. Nakagawa, E. Hara, S. Yuba. Heterocycles: an international journal for reviews and communications in heterocyclic chemistry **87**, 2577 (2013)
- 55. T. Wakaki, T. Togo, D. Yoshidome, Y. Kuninobu, M. Kanai, ACS Catal. 8, 3123 (2018)
- 56. A. Patel, M. Shaikh, K.H. Chikhalia, Tetrahedron 75, 236 (2019)

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