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Pd/Cu-Catalyzed Aerobic Oxidative Aromatic C-H Bond Activation/N-Dealkylative Carbonylation towards the Synthesis of Phenanthridinones

prepared tertiary o-arylanilines and CO.

Accepted 00th January 20xx DOI: 10.1039/x0xx00000x

Received 00th January 20xx,

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It is important to achieve diverse functionalization of tertiary anilines due to its importance in biological molecules, pharmaceutical, function materials, ligands. A straightforward Pd/Cu-catalyzed oxidative C-H bond activation/*N*-dealkylative carbonylation of tertiary [1, 1'-biphenyl]-2-anilines towards the synthesis of various biologically important phenanthridin-6(5*H*)ones has been developed. A wide range of functional groups are well tolerated in this transformation. Moreover, O_2 is utilized as the terminal oxidant to promote the oxidative carbonylation process.

Tertiary anilines represent not only core structures in biological molecules, pharmaceutical, function materials and ligands,¹ but also readily accessible starting materials and important building blocks in organic synthesis.² Recently, C-N bond activation³ has attracted more attention and become a hot research topic which provide us a novel tool to achieve the modification of tertiary anilines. To the best of our knowledge, most C-N bond activation of anilines focused on the cross-coupling of Csp²-N bond with organometallic reagents, and electrophilic cyclization.⁴ It still remains a great challenge to achieve diverse functionalization of tertiary anilines. According to our previous work,⁵ it is reliable and efficient to combine the C-N bond activation with C-H oxidative carbonylation to construct important amide derivatives. As a new protocol on the rise, the C-H carbonylation is now widely recognized as a very important and potential tool in organic chemistry, which meets the requirement of "atom economy" and "green chemistry".6 We envisage that phenanthridinone scaffold could be readily constructed starting from o-arylanilines via Pd/Cu-catalyzed aerobic oxidative aromatic C-H bond activation/N-dealkylative carbonylation.

Phenanthridinone is an important scaffold found in many natural products and synthetic compounds with various biological activities (Scheme 1).⁷ Consequently, considerable efforts have been made to develop efficient methods for the synthesis of phenanthridinone derivatives. However, most of these methods involve multistep procedures under harsh reaction conditions.⁸ Through our protocol, phenanthridinones could be constructed in one step from easily

Scheme 1



oxysanguinarine

Our experiment study was initiated by treating N, N-dimethyl-[1, 1'-biphenyl]-2-anilines (1a) in the presence of 1 atm CO/O₂ gas mixture (Table 1). By optimizing various reaction parameters, we found the best results with the combination of a catalytic amount of PdCl₂, Cu(OAc)₂•H₂O, AcOH in a mixed solvent of toluene and DMA using O₂ as the terminal oxidant at 110 °C. Under the optimized conditions, a 80% yield of N-methylphenanthridin-6(5H)one (2a) was obtained after 24 h. No product was detected without the assistance of copper or palladium catalysts (Table 1, entries 2 and 3). Replacing $PdCl_2$ with $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ diminished the reaction yield (Table 1, entries 4 and 5). Additionally, anhydrous Cu(OAc)₂ and Cu(OPiv)₂ showed lower efficiency as well (Table 1, entries 6 and 7). The use of CO/air instead of CO/O2 afforded much less desired carbonylation product (Table 1, entry 8). When DMA was removed, only trace amount of the desired product could be detected (Table 1, entry 9). The variation of the mixed solvent also led to lower yields (Table 1, entries 10 and 11). Inferior result was acquired with a decreased reaction temperature (Table 1, entry 12). Without AcOH, only 42% yield of N-methylphenanthridin-6(5H)one was obtained (Table 1, entry 13).

 Table 1. Palladium / copper-catalyzed oxidative intramolecular Ndealkylative carbonylation of 1a: effects of reaction parameters

ver, O₂ is utilized as *N*-methylcrinasiadine

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1	none	80(75)
2	No Cu(OAc) ₂ •H ₂ O	0
3	No PdCl ₂	0
4	Pd(OAc) ₂ instead of PdCl ₂	17
5	PdCl ₂ (PPh ₃) ₂ instead of PdCl ₂	69
6	$Cu(OAc)_2$ instead of $Cu(OAc)_2 \cdot H_2O$	70
7	Cu(OPiv) ₂ instead of Cu(OAc) ₂ •H ₂ O	69
8	CO/air = 3/ 1	40
9	1.0 mL toluene instead of mixed solvent	0
10	0.2 mL DMSO instead of DMA	68
11	0.2 mL DMF instead of DMA	57
12	90 °C instead of 110 °C	52
13	No AcOH	42

[a] Standard reaction conditions : 1a (0.2 mmol), PdCl₂ (10 mol%), Cu(OAc)₂ •H₂O (30 mol%), AcOH (40 mol%), CO/O₂ =2/1, toluene/DMA =1.0/0.2, 110 °C, 24 h. The yields were determined by GC, and were calibrated using biphenyl as the internal standard.

Scheme 2. Palladium/copper-catalyzed intramolecular oxidative *N*-dealkylative carbonylation of tertiary biphenyl-2-anilines **1**.



1 (0.2 mmol), PdCl₂ (10 mol%), Cu(OAC)₂ •H₂O (30 mol%), AcOH (40 mol%), CO/O₂ =2/1, toluene/DMA =1.0/0.2, 110 $^{\circ}$ C, 24 h. Isolated yield.

With the optimized conditions in hand, the carbonylation of a variety of tertiary [1, 1'-biphenyl]-2-anilines was tested (Scheme 2). In general, electron-donating substituents on aniline ring of biphenyl-2-amine derivatives were well tolerated under the current conditions (2b, 2c and 2d). The site of methyl has less influence on the yield. On the other hand, strong electron-withdrawing groups lowered the yield (2e and 2f). Substrate substituted with halogens including Cl and Br furnished the corresponding carbonylation products in good yields (2g, 2h and 2i), which can provide useful handles for further synthetic transformations.

Scheme 3. Palladium/copper-catalyzed intramolecular oxidative *N*-dealkylative carbonylation of biphenyl-2-amine derivatives **1**.



1 (0.2 mmol), PdCl₂ (10 mol%), Cu(OAc)₂ •H₂O (30 mol%), AcOH (40 mol%), CO/O₂ = 2/1, toluene/DMA =1.0/0.2, 110 °C, 24 h. Isolated yield. ^a *N*, *N*-diethyl-[1, 1'-biphenyl]-2-amine as the substrate. ^b *N*-methyl-*N*-ethyl-[1, 1'-biphenyl]-2-amine as the substrate. ^c *N*, *N*-dibenzyl-[1, 1'-biphenyl]-2-amine as the substrate.

Furthermore, this protocol could also be applied to tertiary biphenyl-2-anilines with substitutes on the other benzene ring (Scheme 3). Halogens like -F, -Cl are well tolerated, which provided the opportunities of further functionalization (2j and 2k). The reaction underwent smoothly to give the corresponding lactams in high yields with electron-rich groups (2m and 2n). When electron deficient *N*, *N*-dimethyl-4'-(trifluoromethyl)biphenyl-2-amine was used, 40% yield of desired product was obtained (2l). The position of the substituted groups have little influence on this reaction (2o and 2p). In addition, the carbonylation product was attained in moderate to good yield by utilizing *N*, *N*-dimethyl-2-(naphthalen-1-yl)aniline (2q).

Scheme 4 Application of palladium/copper-catalyzed intramolecular oxidative *N*-dealkylative carbonylation



When *N*, *N*-diethyl-[1, 1'-biphenyl]-2-amine **1r** was utilized as the substrate, the desired product could be obtained in 72% yield (Scheme 3). While the standard reaction of tertiary [1, 1'-biphenyl]-2-anilines **1s** gave the mixture of 2r/2a(1.15/1) which indicated that methyl group was easier to remove. On the other hand, when we used *N*, *N*-dibenzyl-[1, 1'-biphenyl]-2-amine **1t** as the substrate, only 35% desired product was obtained. At the meantime, we got 65% benzaldehyde as the by-product which showed that the alkyl group was transferred to aldehyde after C-N bond activation. After testing different heteroaryl substituted tertiary anilines *N*, *N*-dimethyl-2-(thiophen-2-yl)aniline and 2-(furan-2-yl)-*N*, *N*-dimethylaniline, we get 35% and 47% yields respectively.

DOI: 10.1039/C6CC08701A

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To demonstrate the utility of this new protocol, we also developed a short route toward *N*-methylcrinasiadine, one of the important alkaloids derived from amaryllidaceae which might have cytotoxicities. According to the previous works, multistep procedures under harsh reaction conditions or complex substrates were involved.⁹ Through our protocol, we could achieve this product in 70% yield form easy-prepared corresponding tertiary aniline (Scheme 4).

Based on the above observations and previous reports, we proposed the following catalytic cycle for this intramolecular oxidative C-H bond activation/*N*-dealkylative carbonylation reaction (Scheme 5). Taking the reaction of **1a** as an example, the Pd-catalyzed aerobic C-N bond activation of **1a** slowly releases the intermediate **I**(SI). Then, Pd(II) complex **I** undergoes sequential CO insertion to generate the key intermediate **II**, followed by oriented C-H bond activation to achieve seven-membered palladacycle **III**. Finally, reductive elimination occurs to form the product **2a**, and releases the Pd(0) species, which is re-oxidized by O₂ with the assistance of the copper co-catalyst to regenerate Pd(II) complex.

Scheme 5 Proposed mechanism



Conclusions

In conclusion, we have developed a novel palladium/coppercatalyzed intramolecular aerobic oxidative C-H bond activation/*N*dealkylative carbonylation reaction of tertiary biphenyl-2-amines. This transformation provides an effective and straightforward protocol towards the synthesis of biologically and synthetically useful phenanthridinones from widely available substrates. Moderate to good yields were obtained and a variety of functional groups were tolerated as well. Therefore, we anticipate that this work will contribute substantially to the development of next generation carbonylation of amines.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (21390400, 21520102003, 21272180, 21302148), the Hubei Province Natural Science Foundation of China (2013CFA081), the Research Fund for the Doctoral Program of Higher Education of China (20120141130002), and the Ministry of Science and Technology of China (2012YQ120060). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

Notes and references

- (a)D. W. Old, J. P. Wolfe and S. L. Buchwald, J. Am. Chem. Soc., 1998, 120, 9722-9723; (b)A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi and S. L. Buchwald, J. Am. Chem. Soc., 1999, 121, 4369-4378; (c)M. C. Harris, O. Geis and S. L. Buchwald, J. Org. Chem., 1999, 64, 6019-6022; (d)J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, J. Am. Chem. Soc., 1999, 121, 9550-9561.
- 2 (a)Z. Li and C.-J. Li, J. Am. Chem. Soc., 2004, 126, 11810-11811; (b)S.-I. Murahashi, T. Nakae, H. Terai and N. Komiya, J. Am. Chem. Soc., 2008, 130, 11005-11012; (c)Y.-D. Du, C.-W. Tse, Z.-J. Xu, Y. Liu and C.-M. Che, Chem. Commun., 2014, 50, 12669-12672; (d)S. S. Kahandal, S. R. Kale, M. B. Gawande, R. Zboril, R. S. Varma and R. V. Jayaram, RSC Adv., 2014, 4, 6267-6274; (e)H. Veisi, A. Sedrpoushan, P. Mohammadi, A. R. Faraji and S. Sajjadifar, RSC Adv., 2014, 4, 25898-25903; (f)R. K. Kawade, D. B. Huple, R.-J. Lin and R.-S. Liu, Chem. Commun., 2015, 51, 6625-6628; (g)Y. Tan, W. Yuan, L. Gong and E. Meggers, Angew. Chem. Int. Ed., 2015, 54, 13045-13048; (h)T. Hering, B. Mühldorf, R. Wolf and B. König, Angew. Chem. Int. Ed., 2016, 55, 5342-5345; (i)N. Kennedy, P. Liu and T. Cohen, Angew. Chem. Int. Ed., 2016, 55, 383-386; (j)N. Koukabi, S. Otokesh, E. Kolvari and A. Amoozadeh, Dyes Pigments, 2016, 124, 12-17.
- 3. (a)R. M. Laine, D. W. Thomas and L. W. Cary, J. Am. Chem. Soc., 1982, 104, 1763-1765; (b)E. I. Solomon, U. M. Sundaram and T. E. Machonkin, Chem. Rev., 1996, 96, 2563-2606; (c)M. Gandelman and D. Milstein, Chem. Commun., 2000, 1603-1604; (d)T. Hosokawa, T. Kamiike, S.-I. Murahashi, M. Shimada and T. Sugafuji, Tetrahedron Lett., 2002, 43, 9323-9325; (e)B. Zou, H.-F. Jiang and Z.-Y. Wang, Eur. J. Org. Chem., 2007, 2007, 4600-4604; (f)S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, Org. Lett., 2010, 13, 522-525; (g)J. Luo, M. Wu, F. Xiao and G. Deng, Tetrahedron Lett., 2011, 52, 2706-2709; (h)X. Zhao, D. Liu, H. Guo, Y. Liu and W. Zhang, J. Am. Chem. Soc., 2011, 133, 19354-19357; (i)Y. Xie, J. Hu, Y. Wang, C. Xia and H. Huang, J. Am. Chem. Soc., 2012, 134, 20613-20616; (j)J. Hu, Y. Xie and H. Huang, Angew. Chem. Int. Ed., 2014, 53, 7272-7276; (k)K. Ouyang, W. Hao, W.-X. Zhang and Z. Xi, Chem. Rev., 2015, 115, 12045-12090; (1)G. Zhang, B. Gao and H. Huang, Angew. Chem. Int. Ed., 2015, 54, 7657-7661; (m)Q. Wang, Y. Su, L. Li and H. Huang, Chem. Soc. Rev., 2016, 45, 1257-1272; (n)R. Shi, H. Zhang, L. Lu, P. Gan, Y. Sha, H. Zhang, Q. Liu, M. Beller and A. Lei, Chem. Commun., 2015, 51, 3247-3250.
- (a)S. B. Blakey and D. W. C. MacMillan, J. Am. Chem. Soc., 2003, 125, 6046-6047; (b)J. Shearer, C. X. Zhang, L. Q. Hatcher and K. D. Karlin, J. Am. Chem. Soc., 2003, 125, 12670-12671; (c)D. Yue and R. C. Larock, Org. Lett., 2004, 6, 1037-1040; (d)S. Ueno, N. Chatani and F. Kakiuchi, J. Am. Chem. Soc., 2007, 129, 6098-6099; (e)Y. Kuninobu, M. Nishi and K. Takai, Chem. Commun., 2010, 46, 8860-8862; (f)L.-G. Xie and Z.-X. Wang, Angew. Chem. Int. Ed., 2011, 50, 4901-4904; (g)B. Yao, Q. Wang and J. Zhu, Angew. Chem. Int. Ed., 2012, 51, 12311-12315; (h)B. Yao, Q. Wang and J. Zhu, Angew. Chem. Int. Ed., 2012, 51, 5170-5174; (i)X.-F. Xia, L.-L. Zhang, X.-R. Song, Y.-N. Niu, X.-Y. Liu and Y.-M. Liang, Chem. Commun., 2013, 49, 1410-1412; (j)B. Yao, Q. Wang and J. Zhu, Angew. Chem. Int. Ed., 2013, 52, 12992-12996; (k)W. Hao, W. Geng, W.-X. Zhang

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Page 4 of 4

and Z. Xi, *Chem. Eur. J.*, 2014, **20**, 2605-2612; (I)J. Sheng, S. Li and J. Wu, *Chem. Commun.*, 2014, **50**, 578-580.

- R. Shi, L. Lu, H. Zhang, B. Chen, Y. Sha, C. Liu and A. Lei, *Angew. Chem. Int. Ed.*, 2013, **52**, 10582-10585.
- (a)Q. Liu, G. Li, J. He, J. Liu, P. Li and A. Lei, Angew. Chem. Int. 6. Ed., 2010, 49, 3371-3374; (b)H. Zhang, D. Liu, C. Chen, C. Liu and A. Lei, Chem. Eur. J., 2011, 17, 9581-9585; (c)Q. Liu, H. Zhang and A. Lei, Angew. Chem. Int. Ed., 2011, 50, 10788-10799; (d)H. Zhang, R. Shi, P. Gan, C. Liu, A. Ding, Q. Wang and A. Lei, Angew. Chem. Int. Ed., 2012, 51, 5204-5207; (e)X. Fang, R. Jackstell and M. Beller, Angew. Chem. Int. Ed., 2013, 52, 14089-14093; (f)X.-F. Wu, H. Neumann and M. Beller, ChemSusChem, 2013, 6, 229-241; (g)W. Li, C. Liu, H. Zhang, K. Ye, G. Zhang, W. Zhang, Z. Duan, S. You and A. Lei, Angew. Chem. Int. Ed., 2014, 53, 2443-2446; (h)L. Wang, Y. Wang, C. Liu and A. Lei, Angew. Chem. Int. Ed., 2014, 53, 5657-5661; (i)A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, Nature, 2014, 510, 129-133; (j)S. Li, G. Chen, C.-G. Feng, W. Gong and J.-Q. Yu, J. Am. Chem. Soc., 2014, 136, 5267-5270; (k)W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu and A. Lei, Angew. Chem. Int. Ed., 2015, 54, 1893-1896
- (a)J.-H. Li, L. Serdyuk, D. V. Ferraris, G. Xiao, K. L. Tays, P. W. Kletzly, W. Li, S. Lautar, J. Zhang and V. J. Kalish, *Biorg. Med. Chem. Lett.*, 2001, **11**, 1687-1690; (b)Z. Tu, W. Chu, J. Zhang, C. S. Dence, M. J. Welch and R. H. Mach, *Nucl. Med. Biol.*, 2005, **32**, 437-443; (c)S. Patil, S. Kamath, T. Sanchez, N. Neamati, R. F. Schinazi and J. K. Buolamwini, *Biorg. Med. Chem.*, 2007, **15**, 1212-1228; (d)D. C. Hegan, Y. Lu, G. C. Stachelek, M. E. Crosby, R. S. Bindra and P. M. Glazer, *Proc. Natl. Acad. Sci.*, 2010, **107**, 2201-2206.
- (a)Q. J. Zhou, K. Worm and R. E. Dolle, J. Org. Chem., 2004, 69, 5147-5149; (b)M. A. Yawer, I. Hussain, I. Iqbal, A. Spannenberg and P. Langer, *Tetrahedron Lett.*, 2008, 49, 4467-4469; (c)S. Pimparkar and M. Jeganmohan, *Chem. Commun.*, 2014, 50, 12116-12119; (d)S.-M. Lu and H. Alper, J. Am. Chem. Soc., 2005, 127, 14776-14784; (e)D. Liang, Z. Hu, J. Peng, J. Huang and Q. Zhu, *Chem. Comm.*, 2013, 49, 173-175; (f)R. G. G. Leenders and H. W. Scheeren, *Tetrahedron Lett.*, 2000, 41, 9173-9175; (g)T. Harayama, H. Akamatsu, K. Okamura, T. Miyagoe, T. Akiyama, H. Abe and Y. Takeuchi, J. Chem. Soc., Perkin Trans. 1, 2001, 523-528; (h)M. Feng, B. Tang, N. Wang, H.-X. Xu and X. Jiang, Angew. Chem. Int. Ed., 2015, 54, 14960-14964; (i)T. Cailly, F. Fabis and S. Rault, *Tetrahedron*, 2006, 62, 5862-5867; (j)B. O. Ashburn, R. G. Carter and L. N. Zakharov, J. Org. Chem., 2008, 73, 7305-7309.
- (a)G. Cahiez, C. Chaboche, F. Mahuteau-Betzer and M. Ahr, Org. Lett., 2005, 7, 1943-1946; (b)T. Harayama, Y. Kawata, C. Nagura, T. Sato, T. Miyagoe, H. Abe and Y. Takeuchi, Tetrahedron Lett., 2005, 46, 6091-6094; (c)R. Sanz, Y. Fernandez, M. P. Castroviejo, A. Perez and F. J. Fananas, Eur. J. Org. Chem., 2007, 2007, 62-69; (d)C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, Chem. Sci., 2010, 1, 331-336; (e)T. Harayama, C. Nagura, T. Miyagoe, Y. Kawata, H. Abe and Y. Takeuchi, Heterocycles, 2010, 81, 2609-2616; (f)S.-K. Hua, Q.-P. Hu, J. Ren and B.-B. Zeng, Synthesis, 2013, 45, 518-526; (g)S. Pimparkar and M. Jeganmohan, Chem. Commun., 2014, 50, 12116-12119; (h)M. Feng, B. Tang, N. Wang, H.-X. Xu and X. Jiang, Angew. Chem., Int. Ed., 2015, 54, 14960-14964; (i)W. Shen, J. Li, C. Zhang, M. Shi and J. Zhang, Chem.

Asian J., 2016, **11**, 1883-1886; (j)M. Feng, B. Tang, H.-X. Xu and X. Jiang, Org. Lett., 2016, **18**, 4352-4355.

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