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Palladium-Catalyzed Carbonylative Difunctionalization of C=N Bond of Azaarenes or Imines to Quinazolinones

Xibing Zhou,[a] Yongzheng Ding,[a] and Hanmin Huang*[a,b]

Abstract: By intercepting the acylpalladium species with C=N bond of azaarenes or imines other than free amines or alcohols, the difunctionalization of C=N bond was established via palladium-catalyzed carbonylation/nucleophilic addition sequence. This method is compatible with a diverse range of azaarenes and imines, and allows for the efficient synthesis of a wide range of quinazolinones and derivatives. The synthetic utility has been demonstrated by one-step synthesis of evodiamine and its analogue with inexpensive starting materials.

Quinazolinones are prevalent synthetics and important scaffolds of natural products, which have been widely recognized as “core structures” in drug discovery.[1] They are now known to possess a wide spectrum of biological and pharmacological activities, such as anti-inflammatory, antioxidant, antimicrobial, antipsychotic, and antihypertensive activity, strong analgesic activity, and many effects on the central nervous system (CNS).[2] For example, rutaecarpine, euxylophoricine B, and evodiamine are all effective ingredients of Chinese herbal medicines.[3-4] Additionally, fenquizone[5] and raltitrexed[6] containing this core structure have been on the market or are in clinical trials for the treatment of edema, diuretic, and cancer (Figure 1).

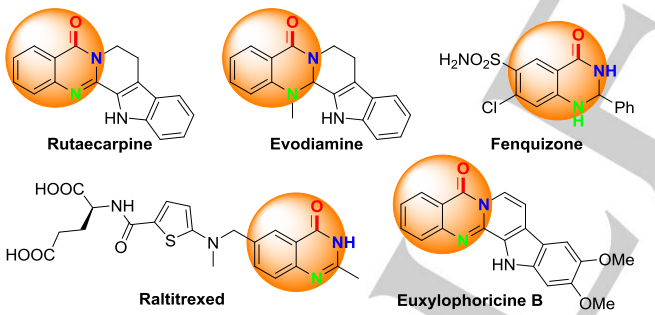
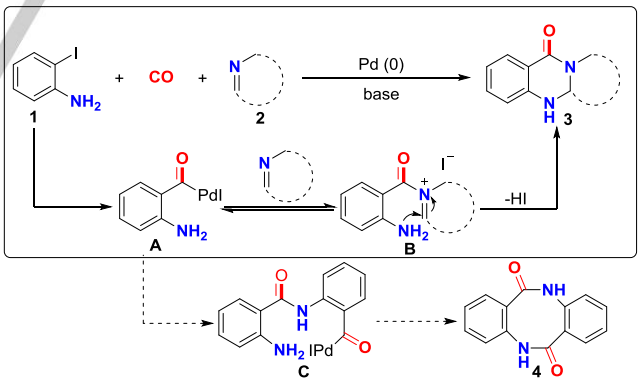


Figure 1. Representive drugs and natural products with quinazolinone core.

Despite their importance, the synthetic methods for making quinazolinones are unsatisfactory. One of the most popular methods is on the basis of condensation reaction with amines and acids or their derivatives as starting materials.[7] Various protocols by combination of Ullmann-type coupling reactions or oxidative coupling with cyclocondensation reaction under harsh conditions have been reported for this method. However, the requirement of a pre-synthesized acid as well as a large amount of dehydrating agents to construct the amide bond limits its practicability and generality. Another alternative method is the transition metal-catalyzed carbonylative coupling reaction with halogenated azaarenes or halogenated imines as coupling partners, which could avoid using acids and dehydrating agents to build the amidic-bond.[8] In these reported reactions, one of the most impressive methods is the intramolecular pyridocarbonylations proceeded via dearomatizing carbonylation of pyridine derivatives.[8e-8g] However, the required halogen or amine prefunctionalization of the imines or azaarenes significantly reduces its synthetic appeal and limits its applications to only a few quinazolinones. Therefore, the development of straightforward methods that enables the construction of complex quinazolinones from simple starting materials would have far-reaching implications for both the synthetic and the medicinal chemistry communities. Although the carbonylative transformation of electron deficient *N*-toluenesulfonyl imines to corresponding 2,3-dihydro-4(1*H*)-quinazolinones have been developed,[9] a general protocol for the synthesis of quinazolinones from simple azaarenes and *N*-alkyl substituted imines would be still desirable.



Scheme 1. Palladium-catalyzed carbonylative difunctionalization of C=N bonds.

The development of catalytic systems for the functionalization of multiple bonds as well as aryl derivatives remains one of the main interests for the chemical and pharmaceutical industries, providing economical and clean methods for various functionalized molecular systems.[10] Among the reported efforts in this area, many attractive procedures have been developed for catalytic difunctionalization of alkene owing to its abundance, diversity and predictable reactivity.[11-12] However, there are few examples of these that bring about the catalytic

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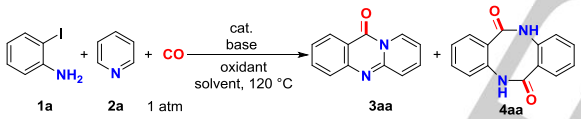
difunctionalization of polar C=N bond, although it would be potentially utilized for the construction of complex nitrogenated compounds. We reasoned that an operationally simple and mechanistically distinct catalytic C=N bond difunctionalization process involving available 2-iodoanilines, imines or azaarenes as well as CO feedstocks would expand the capacity of C=N bond difunctionalization-based strategy to the synthesis of quinazolinones. In previous work,[13] we and others demonstrated that the C=N bond contained in imines or azaarenes could intercept the active acylpalladium species to form *N*-acyliminium ions via reductive elimination.[14] Being aware that *N*-acyliminium ions are capable of undergoing fast nucleophilic addition with a suitable nucleophile to generate the stable amide species, we envisioned that the difunctionalization of C=N bond of imines or azaarenes **2** could be furnished with 2-iodoaniline and CO via the palladium-catalyzed carbonylation and nucleophilic addition sequence. However, the realization of such a process is challenging, since the interception process is reversible and a side reaction for the formation of the cyclic amide **4** from the acylpalladium species **A** may take place to compete with the desired C=N bond difunctionalization reaction (Scheme 1). We believe that the competition would be controlled by tuning the palladium catalyst and reaction condition to affect the rate of the intramolecular nucleophilic addition process. Herein, we report a new strategy for catalytic difunctionalization of C=N bond of azaarenes and imines via palladium catalyzed carbonylation and nucleophilic addition, which leads to the development of an efficient reaction for the construction of quinazolinones.

Table 1. Optimization of Reaction Conditions.[a]

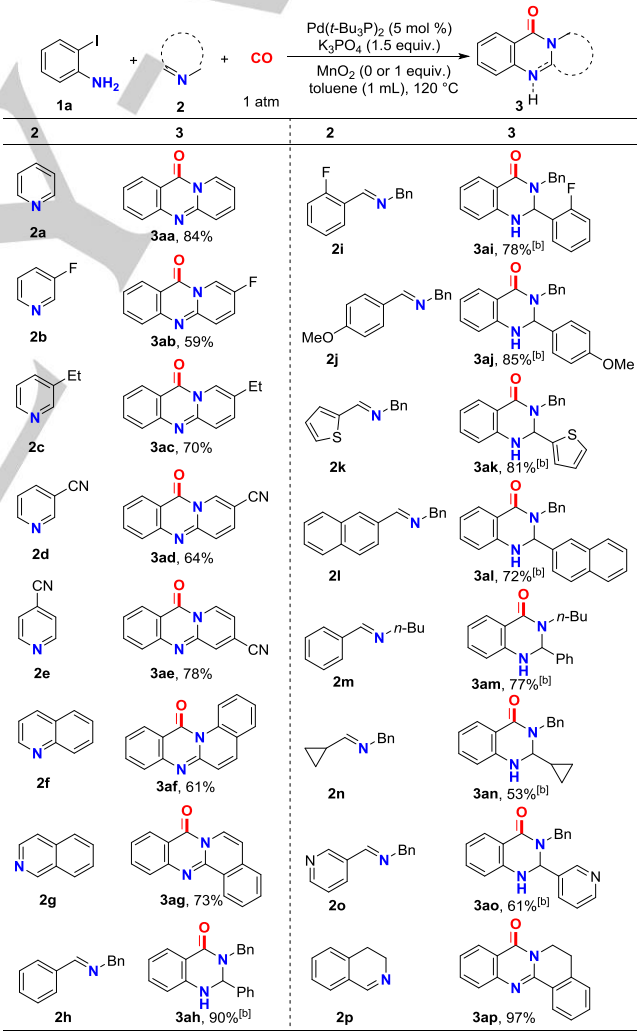


entry	cat. (mol %)	base	oxidant	solvent	yield (%) 3aa	4aa
1	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	-	toluene	49	32
2	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	$Cu(OAc)_2$	toluene	trace	10
3	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	DCP	toluene	trace	36
4	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	MnO_2	toluene	84	7
5	$Pd(MeCN)_2Cl_2$ (5) / PPh_3 (11)	K_3PO_4	MnO_2	toluene	35	17
6	$Pd(MeCN)_2Cl_2$ (5) / PCy_3 (11)	K_3PO_4	MnO_2	toluene	55	31
7	$Pd(MeCN)_2Cl_2$ (5) / DPPF (6)	K_3PO_4	MnO_2	toluene	0	63
8	$Pd(MeCN)_2Cl_2$ (5) / XantPhos (11)	K_3PO_4	MnO_2	toluene	49	27
9	$Pd(MeCN)_2Cl_2$ (5) / *t*-Bu_3P (11)	K_3PO_4	MnO_2	toluene	77	10
10	Pd(*t*-Bu_3P)$_2$ (5)	NEt_3	MnO_2	toluene	59	19
11	Pd(*t*-Bu_3P)$_2$ (5)	Cs_2CO_3	MnO_2	toluene	29	53
12	Pd(*t*-Bu_3P)$_2$ (5)	$NaHCO_3$	MnO_2	toluene	27	66
13	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	MnO_2	anisloe	69	14
14	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	MnO_2	DMA	trace	trace
15	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	MnO_2	1,4-dioxane	63	10
16	Pd(*t*-Bu_3P)$_2$ (5)	K_3PO_4	MnO_2	THF	51	8

[a] Standard conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), CO (1 atm), cat.(5 mol %), base (0.75 mmol), oxidant (0.5 mmol), toluene (1.0 mL), 120 °C, 12 h.

Initially, the palladium catalyzed difunctionalization of C=N bond was investigated with 2-iodoaniline (**1a**) and pyridine (**2a**) under 1 atm of CO. As expected, the desired product **3aa** was obtained in 49% yield by using Pd(*t*-Bu_3P)$_2$ and K_3PO_4 in toluene, together with the side product **4aa** in 32% yield (Table 1, entry 1). To circumvent the formation of byproduct **4aa** and maximize the efficiency of the process, an extensive screening of various reaction parameters was conducted. We assumed that the formation of **3aa** might be accelerated via aromatization in the presence of oxidant. Screening of a variety of oxidants revealed that the most efficient catalytic system was furnished with MnO_2 (Table 1, entries 2-4, and see Supporting Information), in which the desired product **3aa** was obtained in 84% yield with good chemoselectivity. Other phosphine ligands including the commonly used bidentate phosphines and monophosphines were then examined with $Pd(MeCN)_2Cl_2$ as a palladium precursor (Table 1, entries 5−9). The screening experiments demonstrated that the electron-rich and steric hindrance ligands were found to be crucial for obtaining high chemoselectivity and reactivity. Among these, *t*-Bu_3P was the most effective ligand which could deliver the desired quinazolinone **3aa** in 77% yield, together with the byproduct **4aa** in 10% yield. It is worth pointing out that the inverse chemoselectivity was obtained when DPPF served as a ligand. Subsequently, the impact of the base over the reactivity and chemoselectivity of this process was investigated, and it was discovered that K_3PO_4 remained the optimal choice (Table 1, entries 10-12). Additionally, screening of some representative solvents revealed that toluene exhibited the most significant effect to this carbonylative cyclization (Table 1, entries 13-16).

Scheme 2. Substrate scope for azaarenes or imines.[a]



[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), CO (1 atm), Pd(*t*-Bu_3P)$_2$ (5 mol %), K_3PO_4 (0.75 mmol), MnO_2 (0.5 mmol), toluene (1.0 mL), 120 °C, 12 h. Isolated yield. [b] Without MnO_2.

With the optimal reaction conditions identified, investigation into the substrate scope for the present carbonylative cyclization of 2-iodoaniline with a variety of pyridines, imines and other C=N bond containing molecules was pursued. As shown in Scheme 2, the optimized reaction conditions proved to be effective for

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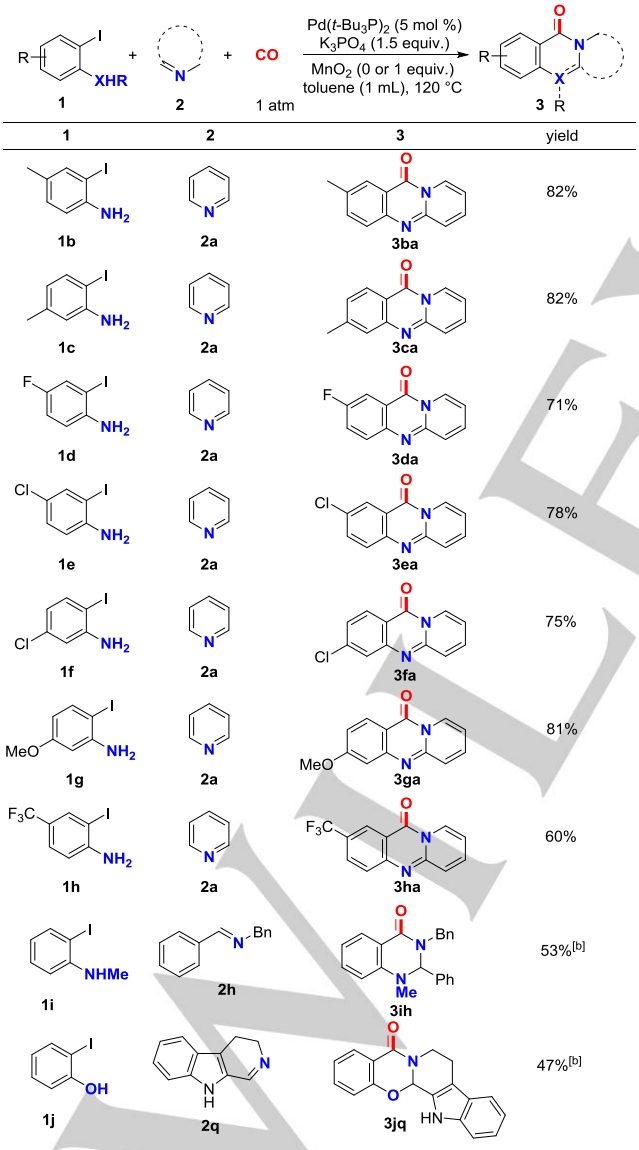
treatment of 2-iodoaniline (**1a**) with a series of pyridines (**2a**-**2e**). Both electron-donating and electron-withdrawing substituents on the pyridine-ring were tolerated to give the corresponding products in moderated to good yields. While the substituents could be located on the *meta*, *para*-position, the pyridine with substituent on the *ortho*-position led to lower activity. It is worth noting that almost no other regioisomers were detected in the reactions of *para*-substituted pyridines (**2b**-**2d**) due to the steric effect. The analogues of pyridine, such as isoquinoline and quinoline, were also suitable substrates (**2f**-**2g**) for the present reaction. The regioselectivity of **2g** might be related to the electropositivity on isoquinoline ring.[7g] However, when the aldimine **2h** was subjected to the reaction conditions, the 3-benzyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one **3ah** was obtained in 77% yield together with trace amount of **4aa** and almost no dehydrogenation product was observed. To our delight, the yield of **3ah** was improved to 90%, when the same

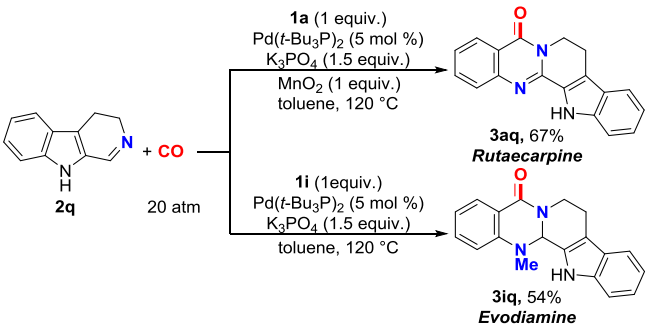
Scheme 3. Substrate scope of 2-iodoanilines.[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), CO (1 atm), Pd(*t*-$Bu_3P)_2$ (5 mol %), K_3PO_4 (0.75 mmol), MnO_2 (0.5 mmol), toluene (1.0 mL), 120 °C, 12 h. Isolated yield. [b] CO (20 atm), without MnO_2.

reaction was conducted in the absence of MnO_2. Under this reaction conditions, aldimines bearing fluoro (**2i**) and methoxyl group (**2j**) gave the corresponding 2,3-dihydroquinazolin-4(1*H*)-one in good yields. In addition, thienyl aldimine (**2k**) and naphthyl aldimine (**2l**) could be smoothly converted to the desired product in 81% yield and 72% yield, respectively. Besides the imines derived from benzyl amines, the imine originated from *n*-butylamine could also undergo the carbonylative cyclization reaction to give the corresponding cyclization product in 77% yield (**3am**). The imine **2n** derived from cyclopropanecarbaldehyde proved to be an efficient partner for the present reaction and the desired product was successfully prepared in 53% yield (**3an**). However, imines derived from simple aliphatic aldehydes were not applicable for the present reaction due to their aza-Mannich type self-condensation[15] in the presence of K_3PO_4 at high temperature. It is worth pointing out that when the coupling partner containing both pyridine and imine moieties (**2o**), the difunctionalization of C=N bond occured preferentially on imine-moiety and produced the corresponding product **3ao** in 61% yield. Moreover, 3,4-dihydroisoquinoline (**2p**) was also compatible with this novel reaction, giving the corresponding product **3ap** in 97% yield. However, no desired product was obtained when electro-deficient imine, such as *N*-tosylbenzenemethanimine, was utilized as a coupling partner.

Next, we evaluated the substrate scope with respect to a series of 2-iodoanilines. As shown in Scheme 3, in all cases, the carbonylative cyclization reaction with pyridine proceeded smoothly to afford their corresponding quinazolin-4(3*H*)-ones in good yields. In general, both substituents on the *para* or *meta* position to iodine of the aryl ring, such as alkyl-, alkoxy-, and halogens can survive to efficiently couple with pyridine and CO, while electron-withdrawing groups resulted in a slightly lower yields (**3ba**-**3ha**). Notably, 2-iodo-*N*-methylaniline (**1i**) could react with imine **2g** to give the corresponding product in 53% yield under 20 atm of CO. This method is also compatible with 2-iodophenol to react with 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole **2q** to give evodiamine analogue **3jq** in 47% yield.



Scheme 4. One-step synthesis of rutaecarpine and evodiamine.

The synthetic value of the palladium catalyzed carbonylative cyclization was further demonstrated through its application in the one-step synthesis of evodiamine and its analogue (Scheme 4). Evodiamine is a quinazolinocarboline alkaloid isolated from the fruit of *Evodia rutaecarpa* Bentham, which displays diverse biological activities including anti-inflammatory, antiobesity, and antitumor effects. Because of its broad-spectrum and multi-targeting antitumor profile, evodiamine represents a good

starting point for the development of novel antitumor agents. In a notable example, we obtained rutaecarpine directly from inexpensive and commercially available 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole **2q** and 2-iodoaniline **1a** in 67% yield. In addition, **2q** could react with 2-iodo-*N*-methylaniline to afford the corresponding analogue evodiamine (**3iq**).

On the basis of the above results and precedent reports,[12-13] a tentative catalytic cycle for the formation of quinazolinones was proposed in Figure 2. Initially, the reaction was initiated by the formation of the arylpalladium complex **I** via the oxidative addtion of 2-iodoaniline **1** to Pd(0). Next, migratory insertion of CO into the C-Pd bond of complex I results in the formation of acylpalladium intermediate **II**. The resultant acylpalladium species **II** reacts with imime or pyridine via reductive elimination in the presence of CO to generate *N*-acyliminium salt **III** and regenerate the active Pd(0) species to complete the catalytic cycle. Subsequent nucleophilic addition of the amino group of 2-iodoaniline to *N*-acyliminium salt **III** leads to the formation of 2,3-dihydroquinazolin-4(1*H*)-one.[7g] An alternative reaction pathway is initiated by intermolecular nucleophilic addition of aniline to C=N bond to generate intermediate **IV**, followed by palladium catalyzed intramolecular aminocarbonylation to give 2,3-dihydroquinazolin-4(1*H*)-one **3**.[9] However, because of the relatively poor electrophilicity of azaarenes and *N*-alkyl substituted imines, the rate of intramolecular nucleophilic addition of aniline to *N*-acyliminium salt **III** should be much faster than that of intermolecular nucleophilic addition of aniline to unactivated imine, which indicates **path b** might not be involved in this reaction. It should be noted that the 2,3-dihydroquinazolin-4(1*H*)-one generated from an azaarene could be oxidized by MnO_2 to give the corresponding dehydrogenation product.

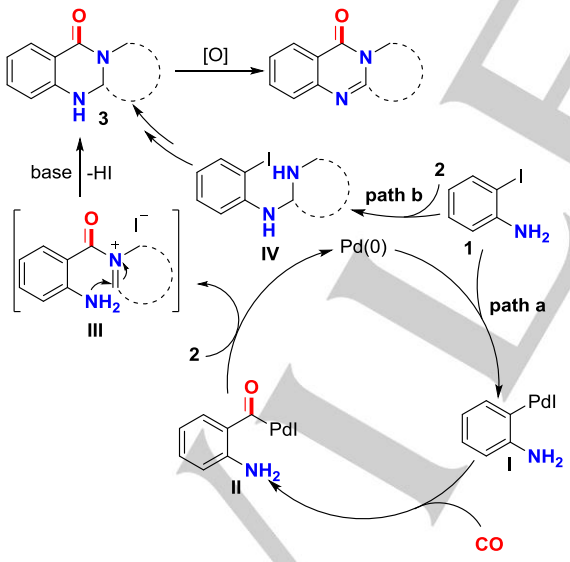


Figure 2. Proposed mechanism.

In summary, we have successfully developed a new and efficient C=N bond difunctionalization protocol for the direct synthesis of quinazolinones from simple starting materials via palladium-catalyzed carbonylative cyclization reactions. Both azaarenes and imines coud be ultilized as coupling partners to give a wide range of quinazolinones in good to excellent yields. The reaction could be performed under 1 atm of CO and can also be employed in the one-step synthesis of evodiamine and its analogues with inexpensive starting materials. Further investigations on gaining a detailed mechanistic understanding of this reaction and the application of this strategy in other reactions are currently in progress.

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Keywords: palladium • carbonylation • quinazolinone • cyclization • difunctionalization

[1] a) J. Bartroli, E. Turmo, M. Algueró, E. Boncompte, M. L. Vericat, L. Conte, J. Ramis, M. Merlos, J. García-Rafanell, J. Forn, *J. Med. Chem.*,**1998**, *41*, 1869-1882; b) S. B. Mhaske, N. P. Argade, *Tetrahedron* **2006**, *62*, 9787-9826; c) A. Maity, S. Mondal, R. Paira, A. Hazra, S. Naskar, K. B. Sahu, P. Saha, S. Banerjee, N. B. Mondal, *Tetrahedron Lett.* **2011**, *52*, 3033-3037.

[2] a) N. J. Liverton, D. J. Armstrong, D. A. Claremon, D. C. Remy, J. J. Baldwin, R. J. Lynch, G. Zhang, R. J. Gould, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483-486; b) N. Malecki, P. Carato, B. Rigo, J.-F. Goossens, R. Houssin, C. Bailly, J.-P. Hnichart, *Bioorg. Med. Chem.* **2004**, *12*, 641-647; c) Z. Ma, Y. Hano, T. Nomura, *Heterocycles* **2005**, *65*, 2203-2219; d) D. Arora, H. Kumar, D. Malhotra, M. Malhotra, *Pharmacologyonline* **2011**, *3*, 659-668; e) K. Nepali, S. Sharma, R. Ojha, K. L. Dhar, *Med. Chem. Res.* **2013**, *22*, 1-15; f) A. Chawla, C. Batra, *Int. Res. J. Pharm.* **2013**, *4*, 49-58.

[3] J. B. Koepfli, J. F. Mead, J. A. Brockman, *J. Am. Chem. Soc.* **1947**, *69*, 1837-1837.

[4] a) J. Bergman, S. Bergman, *J. Org. Chem.* **1985**, *50*, 1246-1255; b) F. Pin, S. Comesse, A. Daïch, *Tetrahedron* **2011**, *67*, 5564-5571; c) B. A. Granger, K. Kaneda, S. F. Martin, *Org. Lett.* **2011**, *13*, 4542-4545; d) G. Huang, D. Roos, P. Stadtmüller, M. Decker, *Tetrahedron Lett*. **2014**, *55*, 3607-3609.

[5] C. Ferrando, J. M. Foy, F. W. Pratt, I. R. Purvis, *J. Pharm. Pharmacol.* **1981**, *33*, 219-222.

[6] G. Cocconi, D. Cunningham, E. Van Cutsem, E. Francois, B. Gustavsson, G. van HazelD Kerr, K. Possinger, S. M. Hietschold, *J. Clin. Oncol.* **1998**, *16*, 2943-2952.

[7] a) C. Huang, Y. Fu, H. Fu, Y. Jiang, Y. Zhao, *Chem. Commun.* **2008**, 6333-6335; b) X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem. Int. Ed.* **2009**, *48*, 348-351; c) M. Sharma, S. Pandey, K. Chauhan, D. Sharma, B. Kumar, P. M. S. Chauhan, *J. Org. Chem.* **2012**, *77*, 929-937; d) L. Colis, G. Ernst, S. Sanders, H. Liu, P. Sirajuddin, K. Peltonen, M. DePasquale, J. C. Barrow, M. Laiho, *J. Med. Chem.* **2014**, *57*, 4950-4961; e) D. Zhao, T. Wang, J.-X. Li, *Chem. Commun*. **2014**, *50*, 6471-6474; f) J. Sun, Q. Tan, W. Yang, B. Liu, B. Xu, *Adv. Synth. Catal.* **2014**, *356*, 388-394; g) Y. Yang, C. Zhu, M. Zhang, S. Huang, J. Lin, X. Pan, W. Su, *Chem. Commun.* **2016**, *52*, 12869-12872.

[8] a) Z. Zheng, H. Alper, *Org. Lett.* **2008**, *10*, 829-832; b) B. Ma, Y. Wang, J. Peng, Q. Zhu, *J. Org. Chem.* **2011**, *76*, 6362-6366; c) X.-F. Wu, L. He, H. Neumann, M. Beller, *Chem.-Eur. J.* **2013**, *19*, 12635-12638; d) J. Chen, K. Natte, A. Spannenberg, H. Neumann, P. Langer, M. Beller, X.-F. Wu, *Angew. Chem. Int. Ed.* **2014**, *53*, 7579-7583; e) D. Liang, Y. He, Q. Zhu, *Org. Lett.* **2014**, *16*, 2748-2751; f) T. Xu, H. Alper, *Org. Lett.* **2015**, *17*, 1569-1572; g) Z. Xie, S. Luo, Q. Zhu, *Chem. Commun.* **2016**, *52*, 12873-12876.

[9] K. Okuro, H. Alper, *Tetrahedron Lett.* **2012**, *53*, 2540-2542;

[10] a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, 98, 675-704; b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695-705; c) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **2004**, *43*, 3368-3398; d) V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.* **2007**, *46*, 1910-1923; e) R. I.

McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981-3019; f) R. Chinchilla, C. Nájera, *Chem. Rev.* **2014**, 114, 3, 1783-1826; g) L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 7, 2596-2697; h) X. Zeng, *Chem. Rev.* **2013**, *113*, 6864-6900.

[11] For leading reviews, see: a) J. P. Wolfe, *Eur. J. Org. Chem.* **2007**, 571-582; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318-5365; c) K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.* **2008**, *6*, 4083-4088; d) K. Muñiz, *Angew. Chem. Int. Ed.* **2009**, *48*, 9412-9423; e) S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009-3019; f) P. A. Sibbald, *Palladium-catalyzed oxidative difunctionalization of alkenes: New reactivity and new mechanisms*, ProQuest, UMI Dissertation Publishing, **2011**; g) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464-3484; h) E. M. Beccalli, G. Broggini, S. Gazzola, A. Mazza, *Org. Biomol. Chem.* **2014**, *12*, 6767-6789; i) G. Yin, X. Mu, G. Liu, *Acc. Chem. Res.* **2016**, *49*, 2413-2423; j) X.-W. Lan, N.-X. Wang, Y. Xing, *Eur. J. Org. Chem.* **2017**, 5821-5851; k) Z. J. Garlets, D. R. White, J. P. Wolfe, *Asian J. Org. Chem.* **2017**, *6*, 636-653; l) J.-S. Zhang, L. Liu, T. Chen, L.-B. Han, *Chem. Asian J.* **2018**, *13*, 2277-2291.

[12] For leading references on carbonylative difunctionalization of alkenes: a) L. S. Hegedus, G. F. Allen, D. J. Olsen, *J. Am. Chem. Soc.* **1980**, *102*, 3583-3587; b) Y. Tamaru, T. Kobayashi, S.-I. Kawamura, H. Ochiai, Z.-I. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 4479-4482; c) Y. Tamaru, M. Hojo, H. Higashimura, Z. Yoshida, *J. Am. Chem. Soc.* **1988**, *110*, 3994-4002; d) H. Harayama, A. Abe, T. Sakado, M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1997**, *62*, 2113-2122; e) T. Shinohara, M. A. Arai, K. Wakita, T. Arai, H. Sasai, *Tetrahedron Lett.* **2003**, *44*, 711-714; f) T. Tsujihara, T. Shinohara, K. Takenaka, S. Takizawa, K. Onitsuka, M. Hantanaka, H. Sasai, *J. Org. Chem.* **2009**, *74*, 9274-9279; g) J. Cheng, X. Qi, M. Li, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2015**, *137*, 2480-2483; h) M. Li, F. Yu, X. Qi, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2016**, *55*, 13843-13848; i) X. Qi, F. Yu, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 12692-12696; j) M. Li, F. Yu, P. Chen, G. Liu, *J. Org. Chem.* **2017**, *82*, 11682-11690; k) J.-B. Peng. F.-P. Wu, D. Li, H.-Q. Geng, X. Qi, J. Ying, X.-F. Wu. *ACS Catal.* **2019**, *9*, 2977-2983.

[13] For selected examples, see: a) S. Kacker, J. S. Kim, A. Sen, *Angew. Chem. Int. Ed*. **1998**, *37*, 1251-1253; b) R. D. Dghaym, R. Dhawan, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2001**, *40*, 3228-3230; c) J. L. Davis, R. Dhawan, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2004**, *43*, 590-594; d) R. Dhawan, B. A. Arndtsen, *J. Am. Chem. Soc.* **2004**, *126*, 468-469; e) A. R. Siamaki, B. A. Arndtsen, *J. Am. Chem. Soc.* **2006**, *128*, 6050-6051; f) D. A. Black, R. E. Beveridge, B. A. Arndtsen, *J. Org. Chem.* **2008**, *73*, 1906-1910; g) S. Bontemps, J. S. Quesnel, K. Worrall, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8948-8951; h) H. Yu, G. Zhang, H. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 10912-10916; i) G. M. Torres, J. S. Quesnel, D. Bijou, B. A. Arndtsen, *J. Am. Chem. Soc.* **2016**, *138*, 7315-7324; j) H. Erguven, D. C. Leitch, E. N. Keyzer, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2017**, *22*, 6078-6082; k) J. Tjutrins, B. A. Arndtsen, *Chem. Sci*. **2017**, *8*, 1002-1007; k) X. Zhou, A. Chen, W. Du, Y. Wang, Y. Peng, H. Huang, *Org. Lett.* **2019**, *21,* 9114-9118.

[14] a) G. Zhang, B. Gao, H. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 7657-7661; b) Y. Hu, Z. Shen, H. Huang, *ACS Catal.* **2016**, *6*, 6785-6789; c) Y. Hu, H. Huang, *Org. Lett.* **2017**, *19*, 5070-5073; d) B. Gao, H. Huang, *Org. Lett.* **2017**, *19*, 6260-6263; e) J. Zhu, B. Gao, H. Huang, *Org. Biomol. Chem.* **2017**, *15*, 2910-2913; f) B. Gao, G. Zhang, X. Zhou, H. Huang, *Chem. Sci.* **2018**, *9*, 380-386; g) X. Zhou, G. Zhang, B. Gao, H. Huang, *Org. Lett.* **2018**, *20*, 2208-2212; h) S. Zou, B. Gao, Y. Huang, T. Zhang, H. Huang, *Org. Lett.* **2019**, *21*, 6333-6336.

[15] W. S. Emerson, S. M. Hess, F. C. Uhle, *J. Am. Chem. Soc.* **1941**, *63*, 872-872.

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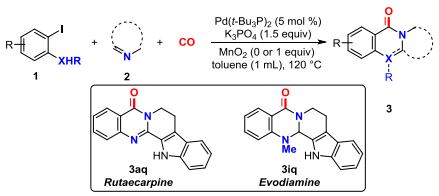

The palladium-catalyzed carbonylative difunctionalization of C=N bond of azaarenes or imines is described for the first time, which provides a reliable and rapid approach to quinazolinones. The synthetic utility of this reaction has further been demonstrated by its application to one-step syntheses of rutaecarpin and evodiamine from inexpensive and commercially available materials.