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Authors: Lin Tang, Pengfei Wang, Yang Fan, Xingkun Yang, Changfeng Wan, and Zhenggen Zha

To be cited as: *ChemCatChem* 10.1002/cctc.201601060

Link to VoR: http://dx.doi.org/10.1002/cctc.201601060

A Journal of ChemPubSoc Europe

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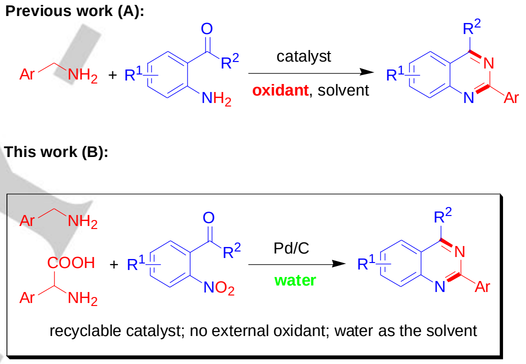
Heterogeneous Palladium-Catalyzed Hydrogen-Transfer Cyclization of Nitroacetophenones with Benzyl Amines: Access to C-N Bonds

Lin Tang,*[a] Pengfei Wang,[a] Yang Fan,[a] Xingkun Yang,[a] Changfeng Wan,*[b] and Zhenggen Zha[c]

Abstract: The first Pd/C-catalyzed oxidative C(sp^3)-H bond amination of *o*-nitroacetophenones with benzyl amines or amino acids by C-N bond cleavage, followed by C-N bond formation via a hydrogen-transfer strategy, has been developed. These transformations proceed smoothly in water, affording the desired quinazolines in moderate to good yields. This protocol represents broad substrate scope, excellent recyclability of the catalyst and good tolerance to air, and does not need additional oxidant, ligand and base, which enables a new and practical avenue for multiple C-N bond formation. Moreover, the hot filtration experiment indicates that heterogeneous palladium nanoparticles during the reaction are active species.

Transition metal-catalyzed direct C-H bond activation has been deemed as a powerful and efficient protocol for C-N bond formation.[1] Accordingly, recent efforts made towards amination of C-H bond with various amino sources via the C-H bond activation strategy have been widely developed.[2,3,4] Since nitro compounds are inexpensive and easily available chemical materials and their reduction is a fundamental and significant transformation in synthesizing various nitrogen-containing medical and synthetic intermediates, transition metal-catalyzed directly oxidative coupling of C-H bond with nitroarenes for constructing C-N bond via a hydrogen-transfer strategy is highly desirable.[5] Additionally, external oxidants are not involved in this strategy. Recently, we[6] and others[7] have successfully developed the hydrogen-transfer strategy for C-N bond construction by use of nitroarenes and alcohols (or amines) as the substrates. However, thus far, the application of this strategy in directly oxidative amination of C(sp^3)-H bond with nitro group through C-N bond cleavage-formation sequence under heterogeneous catalytic system has not been reported.

Quinazolines and their derivatives are regarded as an important class of nitrogen-containing heterocycles because of their extensive appearance in natural products and active molecules.[8] Generally, these compounds were prepared via Bischler cyclization,[9] condensation of *o*-carbonyl anilines with benzaldehydes (or alcohols),[10] Cu-catalyzed coupling of *o*-halobenzoic acids, *o*-halobenzyl halides or *o*-halobenzyl aldehydes with amidines[11] and other alternative approaches.[12] Recently, interesting reactions of benzylamines and *o*-carbonyl anilines were successfully exploited to synthesize 2-arylquinazolines through amination of C(sp^3)-H bond under oxidative conditions (Scheme 1A).[13] As an ongoing effort to synthesize C-N bonds and heterocycles,[6,14] we herein report novel and efficient access to 2,4-disubstituted quinazolines starting from *o*-nitroacetophenones and benzyl amines or amino acids under catalysis of commercially available Pd/C (palladium nanoparticles supported on activated carbon) (Scheme 1B).



Scheme 1. Preparation of 2-arylquinazolines via oxidative C(sp^3)-H bond amination.

The initial experiment was carried out with the model reaction of benzylamine (**1a**) with *o*-nitroacetophenone (**2a**) catalyzed by Pd/C in toluene (Table 1). Since hydrogen-transfer reactions are usually performed under alkaline conditions, we employed different bases as the additives. Pleasingly, the corresponding product of **3a** was achieved in 74% when NaOAc was employed (entry 1). However, the reaction was completely suppressed when *t*-BuOK, NaOH or KOH was added (entries 2-4). Interestingly, the reaction proceeded well when K_2CO_3, Na_2CO_3 or $NaHCO_3$ with weaker alkalinity was used (entries 6-8). The obtained results showed that the alkalinity of the additives had a greatly negative impact on aforementioned reaction. As expected, higher yield of 79% was obtained at the absence of additive (entry 9). Further investigations show that reaction temperature of 140 °C and 2 mol% of Pd/C were optimal (entries 10-14). When the reaction took place in water or under air atmosphere, **3a** was still achieved in good yield of 85% or 78% respectively, which indicated the reaction possessed fine tolerance of water and air (entries 15-16). Further studies indicated that 3.0 equiv. of **1a** was optimal (entries 17-18).[15] Since water is the most easily available and nontoxic solvent in organic synthesis,[16] we chose Entry 15 as the optimized conditions.

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[a] Dr. L. Tang, P. Wang, Prof. Dr. Y. Fan, Prof. Dr. X. Yang
College of Chemistry and Chemical Engineering
Xinyang Normal University
Xinyang 464000 (P. R. China)
E-mail: lintang@xynu.edu.cn
[b] Dr. C. Wan
College of Chemistry and Chemical Engineering
Jiangxi Normal University
Nanchang 330022 (P. R. China)
E-mail: wanfeng@jxnu.edu.cn
[c] Prof. Dr. Z. Zha
Department of Chemistry
University of Science and Technology of China
Hefei 230026 (P. R. China)

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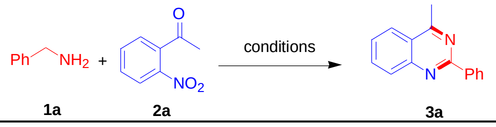
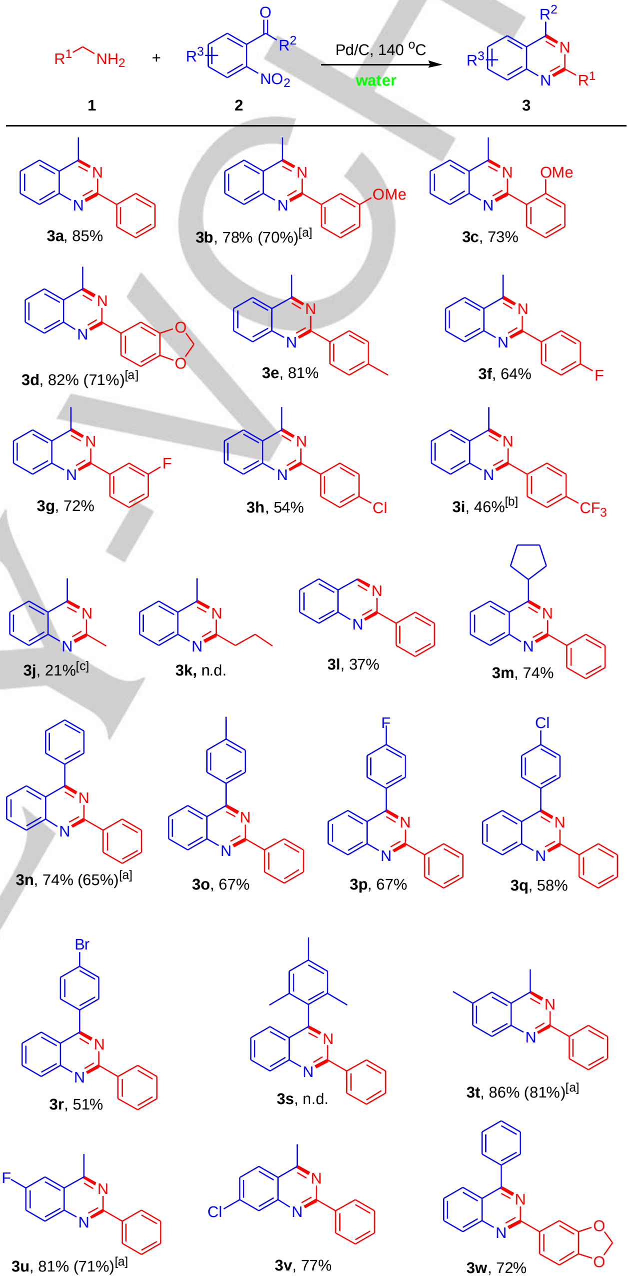
Table 1. Optimization of reaction conditions.[a]



Entry	Pd/C [mol %]	Additive	Temp. [°C]	Yield [%][b]
1	5	NaOAc	130	74
2	5	*t*-BuOK	130	n.d.
3	5	NaOH	130	n.d.
4	5	KOH	130	n.d.
5	5	Cs_2CO_3	130	trace
6	5	K_2CO_3	130	65
7	5	Na_2CO_3	130	67
8	5	$NaHCO_3$	130	70
9	5	--	130	79
10	5	--	110	62
11	5	--	140	86
12	5	--	160	87
13	1	--	140	80
14	2	--	140	86
15[c]	2	--	140	85
16[d]	2	--	140	78
17[e]	2	--	140	75
18[f]	2	--	140	84

[a] Reactions conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), toluene (1.0 ml), additive (1.0 equiv.), 24 h, N_2 atmosphere. [b] Isolated yield. [c] Water as the solvent. [d] Air atmosphere. [e] **1a** (0.50 mmol). [f] **1a** (1.0 mmol).

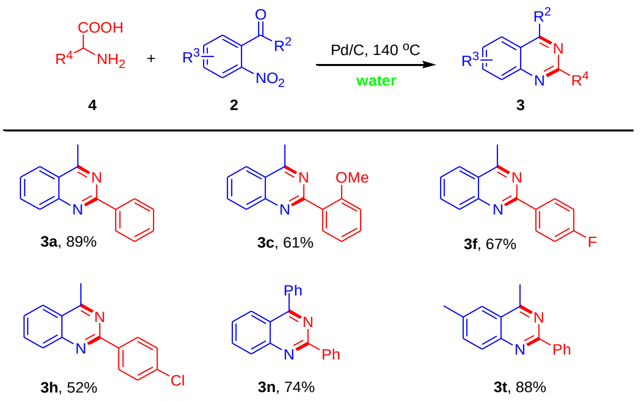
The scope of various benzyl amines with nitroarenes was extended after confirming the optimized conditions (Scheme 2). To our delight, benzylic amines bearing electron-donating groups could proceed smoothly, affording the corresponding products in good yields (**3b**-**3e**). Nevertheless, electron-withdrawing groups on the benzene ring led to slightly lower yields (**3f**, **3g**, **3h**). Besides, only an acceptable yield of **3i** bearing strong electron-withdrawing group was obtained even though the reaction temperature was increased to 160 °C. Substrates of aliphatic amines within two carbon atoms were effective (**3j**, **3k**). Moreover, the desirable products could also be readily achieved when R^2 was replaced by cyclopentyl or substituted aryls (**3m**-**3r**). Nevertheless, low yield of **3l** was obtained, which could be attributed to the decarboxylation of 2-nitrobenzoic acid derived from 2-nitrobenzaldehyde. Additionally, **3s** could not be obtained, perhaps due to the steric hindrance. Good yields of **3t**-**3v** were also achieved when R^3 was methyl, fluoro, or chloro, which indicated that the electronic effect of R^3 had little influence on the above reaction. When we conducted the reaction under an air atmosphere, **3b**, **3d**, **3n**, **3t** and **3u** were still obtained with good yields, which verified that fine tolerance of air was represented in this reaction.



Scheme 2. Reaction conditions: **1** (0.75 mmol), **2** (0.25 mmol), Pd/C (2 mol%), water (1.0 ml), 140 °C, 24 h, N_2 atmosphere; isolated yield. [a] Air atmosphere. [b] 160 °C. [c] 70 wt% ethylamine (1.5 mmol).

The result of **3l** obtained in Scheme 2 indicated the occurrence of decarboxylation. Encouraged by this result, we attempted to employ amino acids as the substrates to synthesize quinazolines via decarboxylative oxidative amination. Pleasingly, these transformations could also proceed smoothly when water was employed as the solvent (Scheme 3).

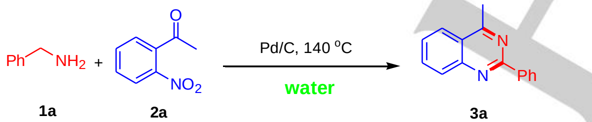
Reactions of different amino acids with *o*-nitroacetophenones, regardless of electron-donating groups or electron-withdrawing groups, yielded the corresponding products in moderate to good yields (**3a**, **3c**, **3f**, **3h**, **3n** and **3t**). It is a pity that the reaction was inactive when R^4 was an alkyl.



Scheme 3. Reaction conditions: **4** (0.75 mmol), **2** (0.25 mmol), Pd/C (2 mol%), water (1.0 ml), 140 °C, 24 h, N_2 atmosphere; isolated yield.

We could easily recover this heterogeneous catalyst through straightforward physical separation. The recyclability of heterogeneous catalysts is one of the most important advantages. Therefore, reuse of the catalyst for the synthesis of **3a** was performed (Table 2). To our delight, **3a** still was obtained in 71% yield at the fifth run, which indicates that the catalyst possesses an excellent recyclability in this reaction.

Table 2. Recycling of the catalyst for the synthesis of **3a**.[a]



Run	1	2	3	4	5
Yield [%][b]	85	81	78	74	71

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), Pd/C (2 mol%), water (1.0 ml), 140 °C, 24 h, N_2 atmosphere. [b] Isolated yield.

Pd/C might produce homogeneous active species of Pd during the reaction. To verify the active species, the hot filtration experiment in the reaction of **1a** with **2a** in toluene under standard conditions was carried out (Figure 1). Once Pd/C was removed, the reaction could not take place even though 14 ug/ml leaching form of Pd nanoparticles was detected by ICP (inductively coupled plasma) analysis. In addition, TEM (transmission electron microscopy) analysis signified that the particle size of the obtained catalyst was about 4.12 nm.[17] The above experiments absolutely proved that heterogeneous Pd nanoparticles were the active species.

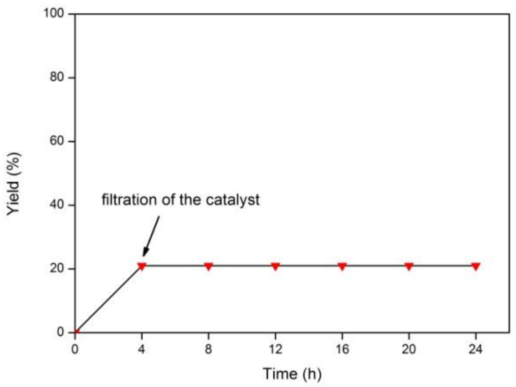
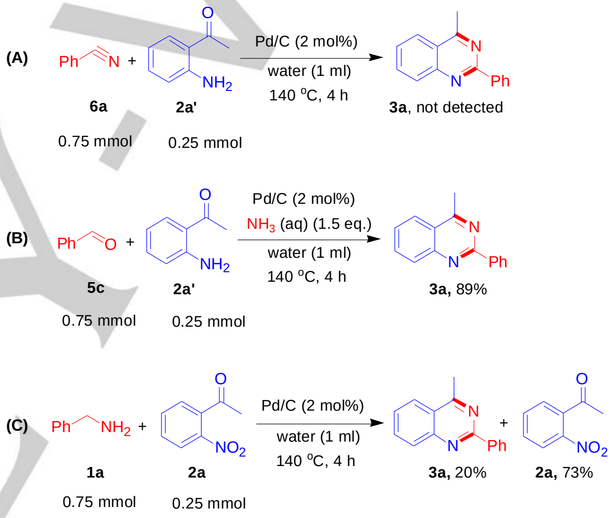


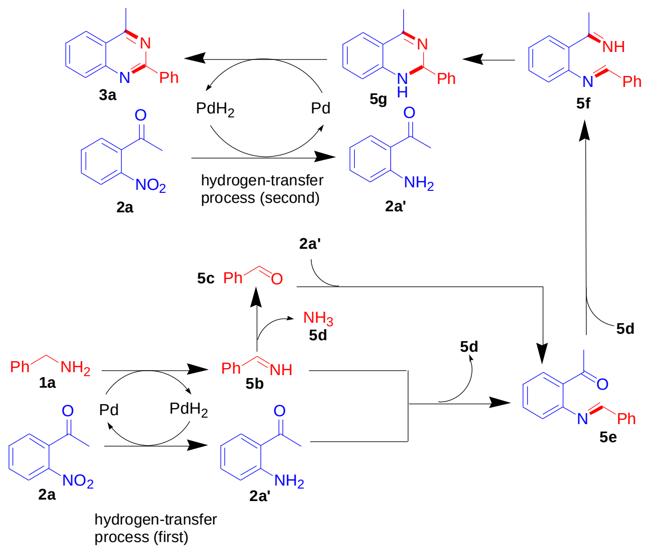
Figure 1. Hot filtration experiment.



Scheme 4. Control experiments.

To gain insight into the possible information on the quinazoline forming pathway, several control experiments were conducted as shown in Scheme 4. Firstly, **3a** could not be observed when the reaction of **6a** with **2a'** proceeded for 4 h under standard conditions (A).[18] While the reaction of **5c** with **2a'** was performed in the presence of nitrogen source, 89% of **3a** could be achieved (B). The results obtained in (A) and (B) revealed that the reaction proceeded via routes A instead of B.[19] When **1a** reacted with **2a** for 4 h, only 20% of **3a** was obtained and 73% of **2a** was recovered, which indicated that route C could hardly take place and this hydrogen-transfer process was the rate-determining step (C).

Based on control experiments and previous reports,[7c,14c,20] we propose a plausible reaction mechanism as shown in Scheme 5. First of all, dehydrogenation of benzylamine (**1a**) can produce imine (**5b**) as well as the palladium-hydride species (PdH_2), which reduces **2a** into **2a'** in situ. This hydrogen-transfer process is regarded as the rate-determining step. Then, **5b** can be converted to **5c** by C-N cleavage with liberation of **5d**. The condensation of **5c** or **5b** with **2a'** can give **5e**. The C-N bond formation reaction of **5e** with **5d** undergoes condensation, followed to generate **5g** by cyclization. Afterwards, the final product **3a** can be achieved from **5g** and **2a** via the second hydrogen-transfer process. **1a** and **5g** serve as the hydrogen donor (reductant) and **2a** serves as the hydrogen acceptor (oxidant) in the catalytic system.



Scheme 5. Proposed reaction mechanism.

In conclusion, an efficient and novel synthetic method for cascade preparation of quinazolines under the catalysis of Pd/C via a hydrogen-transfer strategy has been developed. By taking the advantage of this heterogeneous catalytic system, two C-N bonds are formed through intermolecular oxidative amination of $C(sp^3)$-H Bonds with nitro group by C-N bond cleavage-formation sequence, and decarboxylative amination is also accomplished when amino acids are employed as the substrates. Prominent superiorities, such as broad substrate scope, no involvement of external oxidant, ligand, base and organic solvent, recyclable catalyst and fine tolerance of air, were represented in the reaction. Further studies on reaction mechanism and its applications are currently underway in our laboratory.

Experimental Section

General reaction procedures for the synthesis of 3a and recycling of the catalyst

Water (1.0 ml) was added to the mixture of **2a** (0.25 mmol), **1a** (0.75 mmol), and 10% Pd/C (2 mol%) in a Schlenk tube. The tube was vacuumized to remove the air, refilled with N_2 and sealed. Then, the mixture was heated to 140 °C for 24 h. When the reaction was finished, the mixture was extracted with EtOAc and separated by centrifugation. Then, the obtained solid catalyst was dried under vacuum and heated at 120 °C before it was used in the next run. The organic layer was removed in vacuo. The obtained residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 30:1) to give the final product.

General procedures for hot filtration experiment

Toluene (1.0 ml) was added to the mixture of **2a** (0.25 mmol), **1a** (0.75 mmol), and 10% Pd/C (2 mol%) in a Schlenk tube. The tube was vacuumized to remove the air, refilled with N_2 and sealed. Then, the mixture was heated to 140 °C for 4 h. The catalyst was recovered by filtration. The filtrate was refilled with N_2 and was kept reacting for desired time (8, 12, 16, 20 and 24 h). After reaction, the content of Pd was detected by ICP analysis and the yield was detected by GC analysis.

Acknowledgements

The authors are grateful to the National Natural Science Foundation of China (21602190, 21402068), the Foundation of Henan Educational Committee (17A150049), the Nanhu Scholars Program for Young Scholars of XYNU, and the Doctoral Research Foundation of Xinyang Normal University (15025, 15124).

Keywords: palladium • quinazolines • heterogeneous catalysis • hydrogen-transfer strategy • amination

[1] For selected reviews, see: a) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874; b) M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901; c) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun*. **2014**, *50*, 29; d) O. V. Zatolochnaya, V. Gevorgyan, *Nat. Chem.* **2014**, *6*, 661; e) A. Armstrong, J. C. Collins, *Angew. Chem. Int. Ed*. **2010**, *49*, 2282; f) J. L. Jeffrey, R. Sarpong, *Chem. Sci*. **2013**, *4*, 4092; g) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev*. **2011**, *40*, 1926; h) D. N. Zalatan, J. Du Bois, *Top. Curr. Chem*. **2010**, *292*, 347; i) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417.

[2] For C-H bond amination with azides, see selected examples: a) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari, T. H. Warren, *Angew. Chem. Int. Ed.* **2008**, *47*, 9961; b) V. Lyaskovskyy, A. I. O. Suarez, H. Lu, H. Jiang, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.* **2011**, *133*, 12264; c) E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 591; d) J. Kim, J. Kim, S. Chang, *Chem. Eur. J.* **2013**, *19*, 7328; e) K. Sun, R. Sachwani, K. J. Richert, T. G. Driver, *Org Lett.* **2009**, *11*, 3598; f) O. Villanueva, N. M. Weldy, S. B. Blakey, C. E. MacBeth, *Chem. Sci*. **2015**, *6*, 6672; g) J. R. Suárez, J. L. Chiara, *Chem. Commun*. **2013**, *49*, 9194.

[3] For selected examples of transition-metal-catalyzed C-H bond amination with *N*-substituted amino sources, see: a) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; b) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1694; c) T. Kawakami, K. Murakami, K. Itami, *J. Am. Chem. Soc.* **2015**, *37*, 2460; d) K.-H. Ng, A. S. C. Chan, W.-Y. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862; e) K.-H. Ng, Z. Zhou, W.-Y. Yu, *Org. Lett*. **2012**, *14*, 272; f) J. He, T. Shigenari, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 6545; g) M. Shang, S.-H. Zeng, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *Org. Lett.* **2013**, *15*, 5286; h) T. Matsubara, S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 646; i) F. Sun, Z. Gu, *Org. Lett*. **2015**, *17*, 2222; j) K.-H. Ng, Z. Zhou, W.-Y. Yu, *Chem. Commun*. **2013**, *49*, 7031.

[4] For selected examples of transition-metal-catalyzed C–H/N–H bond dehydrogenative amination, see: a) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1466; b) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 7652; c) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7; d) L. D. Tran, J. Roane, O. Daugulis, *Angew. Chem. Int. Ed.* **2013**, *52*, 6043; e) M. Shang, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 3354; f) Q. Li, S.-Y. Zhang, G. He, Z. Ai, W. A. Nack, G. Chen, *Org. Lett.* **2014**, *16*, 1764; g) H. Kim, K. Shin, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 5904; h) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt,

Nature **2014**, *510*, 129; i) Á. M. Martínez, N. Rodríguez, R. G. Arrayás, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 2801; j) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; k) L. L. Chng, J. Yang, Y. Wei, J. Y. Ying, *Chem. Commun.* **2014**, *50*, 9049; l) J. J. Neumann, S. Rakshit, T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2009**, *48*, 6892; m) K. Sun, X. Wang, L. Liu, J. Sun, X. Liu, Z. Li, Z. Zhang, G. Zhang, *ACS Catal.* **2015**, *5*, 7194; n) X. Jin, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2012**, *48*, 4974.

[5] a) Y. Liu, Y. Lu, M. Prashad, O. Repic, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 217; b) S. Chandrasekhar, S. J. Prakash, C. L. Rao, *J. Org. Chem.* **2006**, *71*, 2196.

[6] a) L. Tang, X. Guo, Y. Yang, Z. Zha, Z. Wang, *Chem. Commun.* **2014**, *50*, 6145; b) L. Tang, Y. Yang, L. Wen, S. Zhang, Z. Zha, Z. Wang, *Org. Chem. Front.* **2015**, *2*, 114; c) L. Tang, X. Zhao, G. Zou, Y. Zhou, X. Yang, *Asian J. Org. Chem.* **2016**, *5*, 335.

[7] For selected examples, see: a) A. M. Rasero-Almansa, A. Corma, M. Lglesias, F. Sánchez, *ChemCatChem* **2014**, *6*, 1794; b) M. Wu, X. Hu, J. Liu, Y. Liao, G.-J. Deng, *Org. Lett.* **2012**, *14*, 2722; c) A. Porcheddu, M. G. Mura, L. D. Luca, M. Pizzetti, M. Taddei, *Org. Lett.* **2012**, *14*, 6112; d) J. Kim, S. H. Hong, *Org. Lett.* **2014**, *16*, 4404; e) S. P. Shan, T. T. Dang, A. M. Seayad, B. Ramalingam, *ChemCatChem* **2014**, *6*, 808; f) T. B. Nguyen, J. L. Bescont, L. Ermolenko, A. Al-Mourabit, *Org. Lett.* **2013**, *15*, 6218; g) Y. Liu, W. Chen, C. Feng, G.-J. Deng, *Chem. Asian J.* **2011**, *6*, 1142; h) C.-H. Tang, L. He, Y.-M. Liu, Y. Cao, H.-Y. He, K.-N. Fan, *Chem. Eur. J.* **2011**, *17*, 7172; i) M. Kumar, Richa, S. Sharma, V. Bhatt, N. Kumar, *Adv. Synth. Catal.* **2015**, *357*, 2862; j) F. Xie, M. Zhang, H. Jiang, M. Chen, W. Lv, A. Zheng, X. Jian, *Green Chem.* **2015**, *17*, 279; k) B. Xiong, Y. Li, W. Lv, Z. Tan, H. Jiang, M. Zhang, *Org. Lett.* **2015**, *17*, 4054; l) S. Sabater, J. A. Mata, E. Peris, *Chem. Eur. J.* **2012**, *18*, 6380; m) T. B. Nguyen, P. Retailleau, A. Al-Mourabit, *Org. Lett.* **2013**, *15*, 5238.

[8] a) B. A. Foster, H. A. Coffrey, M. J. Morin, F. Rastinejad, *Science* **1999**, *286*, 2507; b) R. Gundla, R. Kazemi, R. Sanam, R. Muttineni, J. A. R. P. R. Dayam, N. Neamati, *J. Med. Chem.* **2008**, *51*, 3367; c) D. W. Fry, A. J. Kraker, A. McMichael, L. A. Ambroso, J. M. Nelson, W. R. Leopold, R. W. Connors, A. J. Bridges, *Science* **1994**, *265*, 1093.

[9] a) A. Witt, J. Bergman, *Curr. Org. Chem.* **2003**, *7*, 659; b) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron* **2005**, *61*, 10153.

[10] a) F. Portela-Cubillo, J. S. Scott, J. C. Walton, *Chem. Commun.* **2008**, 2935; b) R. Sarma, D. Prajapati, *Green Chem.* **2011**, *13*, 718; c) Z. Chen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang, H. Wu, *J. Org. Chem.* **2013**, *78*, 11342; d) Y. C. Chen, D. Y. Yang, *Tetrahedron* **2013**, *69*, 10438.

[11] a) C. Huang, Y. Fu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun.* **2008**, 6333; b) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem, Int. Ed.* **2009**, *48*, 348; c) V. L. Truong, M. Morrow, *Tetrahedron Lett.* **2010**, *51*, 758; d) C. C. Malakar, A. Baskakova, J. Conrad, U. Beifuss, *Chem. Eur. J.* **2012**, *18,* 8882.

[12] a) H. Yuan, W. J. Yoo, H. Miyamura, S. Kobayashi, *Adv. Synth. Catal.* **2012**, *354*, 2899; b) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2010**, *12*, 3963; c) J. Ju, R. Hua, J. Su, *Tetrahedron* **2012**, *68*, 9364; d) W. Zhang, F. Guo, F. Wang, N. Zhao, L. Liu, J. Li, Z. Wang, *Org. Biomol. Chem.* **2014**, *12*, 5752; e) Y. Yan, Y. Xu, B. Niu, H. Xie, Y. Liu, *J. Org. Chem.* **2015**, *80*, 5581.

[13] a) B. Han, C. Wang, R.-F. Han, W. Yu, X.-Y. Duan, R. Fan, X.-L. Yang, *Chem. Commun.* **2011**, *47*, 7818; b) J. Zhang, D. Zhu, C. Yu, C. Wan, Z. Wang, *Org. Lett.* **2010**, *12,* 2841.

[14] a) C. Wan, J. Zhang, S. Wang, J. Fan, Z. Wang, *Org. Lett.* **2010**, *12*, 2338; b) C. Wan, L. Gao, Q. Wang, J. Zhang, Z. Wang, *Org. Lett.* **2010**, *12*, 3902; c) L. Tang, H. Sun, Y. Li, Z. Zha, Z. Wang, *Green Chem.* **2012**, *14*, 3423; d) L. Tang, X. Guo, Y. Li, S. Zhang, Z. Zha, Z. Wang, *Chem. Commun.* **2013**, *49*, 5213.

[15] See the supporting information for possible reactions starting from **1a.**

[16] For selected examples of organic reactions in water, see: a) Y. R. Shen, V. Ostroverkhov, *Chem. Rev.* **2006**, *106*, 1140; b) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68; c) M. B. Gawande, V. D. B. Bonifácio, R Luque, P. S. Branco, R. S. Varma, *Chem. Soc. Rev.* **2013**, *42*, 5522; d) L. Tang, Y. Yang, L. Wen, X. Yang, Z. Wang, *Green Chem.* **2016**, *18*, 1224.

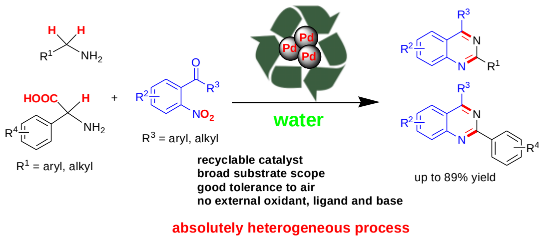
[17] See Figure S1 for TEM analysis in the supporting information.

[18] The reported method for the synthesis of quinazolines through the reaction of **5a** and **2a**, see: M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv H. Jiang, *Org. Lett.* **2014**, *16*, 6028.

[19] See possible reaction routes for the synthesis of **3a** in the supporting information.

[20] a) A. Zanardi, J. A. Mata, E. Peris, *Chem. Eur. J.* **2010**, *16*, 10502; b) A. Corma, T. Ródenas, M. J. Sabater, *Chem. Eur. J.* **2010**, *16*, 254; c) L. Andrews, L. Manceron, M. E. Alikhani, X. F. Wang, *J. Am. Chem. Soc.* **2000**, *122*, 11011; d) J. Cossy, D. Belotti, *Org. Lett.* **2002**, *4*, 2557; e) J. W. Kim, K. Yamaguchi, N. Mizuno, *J. Catal.* **2009**, *263*, 205; f) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden, J. M. J. Williams, *Angew. Chem. Int. Ed.* **2009**, *48*, 7375; g) W. He, L. Wang, C. Sun, K. Wu, S. He, J. Chen, P. Wu, Z. Yu, *Chem. Eur. J.* **2011**, *17*, 13308; h) I. Kim, S. Itagaki, X. Jin, K. Yamaguchi, N. Mizuno, *Catal. Sci. Technol.* **2013**, *3*, 2397.

An efficient synthesis of quinazolines catalyzed by recyclable Pd/C via a hydrogen-transfer strategy is reported. Based on this heterogeneous catalytic system, two C-N bonds are formed through intermolecular oxidative amination of C(sp^3)-H Bonds with nitro group by C-N bond cleavage-formation sequence, and decarboxylative amination is also accomplished when amino acids are employed as the substrates.



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