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Pd/Fe₃O₄ supported on nitrogen doped reduced graphene oxide for room temperature isocyanide insertion reactions[†]

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A versatile Pd/Fe₃O₄ supported on N-doped reduced graphene oxide (N-rGO) catalyst was developed to carry out the synthesis of quinazolinones and phenanthridines under extremely mild conditions through isocyanide insertion cascades. The supported Pd/Fe₃O₄ nanoparticles could be easily recovered from the reaction mixture and reused several times without any loss in catalytic activity.

Quinazolinones and phenanthridines are ubiquitous structural motifs found in numerous synthetic and natural products of biological importance.¹⁻² Several alkaloids such as, 2-methyl-4(3H)-quinazolinone,³ bouchardatine,⁴ luotonin (A, B, E),⁵ auranthine,⁶ circumdatin (C, F),⁷ and sclerotigenin⁸ contain these heterocycles as the key structural units of their pharmacophores.

Owing their importance and utility, a number of synthetic routes have been developed to access these heterocycles.⁹ Condensation of 2-aminobenzamide with carboxylic acids using strong dehydrating agents lies amongst the classical syntheses of quinazolinones.¹⁰ In modified versions of this approach, 2-aminobenzamide has been coupled with aldehydes¹¹ or aryl acid chloride.¹² Recently metal catalyzed benzylic C-H amidation,¹³ carbonylative coupling of amines and aryl halides,¹⁴⁻¹⁵ and isocyanide insertion reactions¹⁶ were developed to access quinazolinone derivatives. The reported methods have their own disadvantages such as harsh reaction conditions, high reaction temperature, non-recyclability of the catalyst and expensive ligands. Thus, the development of an easily recoverable and reusable heterogeneous catalytic system for the synthesis of quinazolinones is a challenging task

in this perspective. Herein, we report the preparation of a versatile Pd/Fe₃O₄ supported on N-doped reduced graphene oxide (N-rGO) catalyst and its application for the synthesis of several N-heterocycles from relatively simple starting material under mild conditions through isocyanide insertion cascades (Figure 1). It is worth to mention here that several metal assisted methods for the synthesis of quinazolinones and phenanthridines require harsh conditions and high temperature.¹⁴⁻¹⁸ Whereas our catalytic system provides these heterocycles under very mild condition and at ambient temperature.

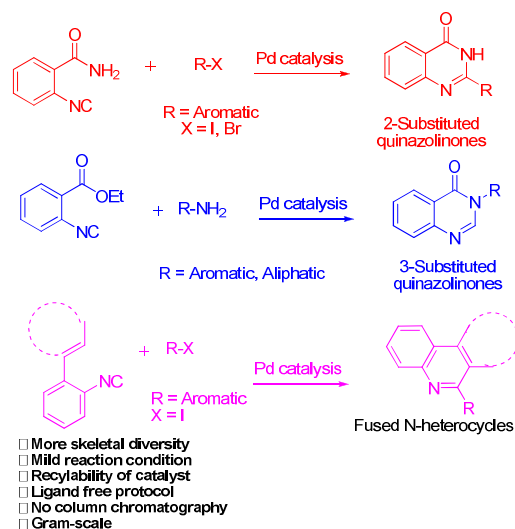


Figure 1. Metal assisted reaction design for isocyanide insertion.

Immobilization of catalytically active transition metals on the heterogeneous support has drawn significant interest over the past decades.¹⁹ Recently, the employment of N-doped reduced graphene oxide (N-rGO) as a metal support was found to be highly promising due to the spin density and charge distribution of carbon atoms influenced by the neighbour nitrogen dopants.²⁰ It induces the high activation of metals on

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[†]This paper is dedicated to the memory of Prof. M. S. Hundal
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the graphene surface and allows reactions to occur under mild conditions. Considering the advantages associated with N-rGO support, we immobilized Pd on N-rGO and evaluated its catalytic activity over several isocyanide insertion reactions (For detail synthesis procedure and characterization of the catalyst, see supporting information). In order to achieve magnetically controlled separation of the heterogeneous catalyst from the reaction system, magnetite (Fe_3O_4) particles were also loaded on N-rGO. The morphology and microstructures of $\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$ were unambiguously characterized by scanning electron microscopy (SEM) and high-resolution transmission electron microscopy (HRTEM). Most NPs were effectively dispersed with no agglomeration (Figure 2a). Ordered crystalline structure of N-rGO was demonstrated by interlayer distance 0.37 nm of restored graphitic layers (Figure 2c), which is consistent with the literature.²¹ The atomic scale image by STEM with a probe correction and ~ 0.1 nm point resolution provided the evidence for close proximity between the Pd and the Fe_3O_4 particles. The brighter part (yellow circle) corresponds to Pd atoms (Figure 2b) and the less bright part to Fe atoms (Figure 2b) because the intensity is directly proportional to the square of the atomic number of the elements. X-ray photoelectron spectroscopy (XPS) investigations confirmed that $\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$ contained C, N, Pd, Fe and O as the main elements (Figure S8 in the Supporting Information). The palladium content of the $\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$ was 2.72 wt % (0.25 mmol g^{-1}) as verified by ICP-AES analysis.

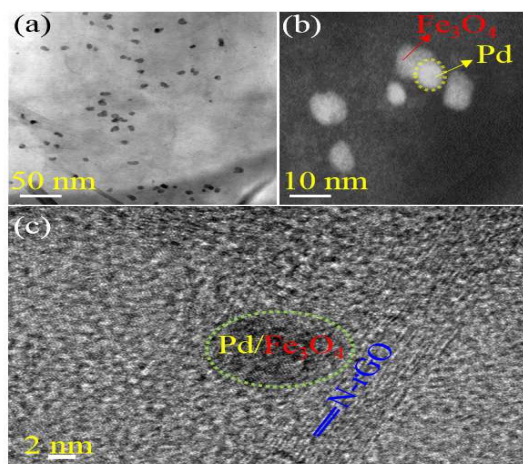


Figure 2. TEM image of $\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$: (a) low resolution; (b) Atomic sensitive HAADF image; (c) high resolution image.

Effort was initiated with benchmark reaction of 2-isocynobenzamide (**1a**) and aryl iodide (**2a**) in the presence of commercially available palladium catalysts (Table 1). Best conversion of the reaction with Pd catalyst was attained in the presence of 10 mol% $\text{Pd}(\text{OAc})_2$ in dioxane at 100°C and the product **3a** was isolated in 41% yield (Table 1, entry 6). To establish an approximate activity ranking among the synthesized catalysts, model reaction was performed with 1 mol% heterogeneous Pd catalysts at 90°C (Table 1, entry 7-11). The highest activity was attained with $\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$ (Table 1, entry 11) as catalyst. However no reaction product **3a** was

isolated, when $\text{Fe}_3\text{O}_4/\text{N-rGO}$ used as a catalyst. Aforementioned catalytic study indicates that the only role of Fe_3O_4 may be in the magnetic separation of catalyst. After 24 h, the product **3a** was isolated in 86% with $\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$ (Table 1, entry 11), in comparison to 72% with $\text{Pd}/\text{N-rGO}$ (Table 1, entry 7). To our delight, model reaction for the synthesis of **3a** was equally compatible at room temperature with $\text{Pd}/\text{N-rGO}$ as a catalyst (Table-1, entry 12). Effect of bases and solvents were investigated using $\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$ as a catalyst. Many bases such as Cs_2CO_3 , K_2CO_3 and K_3PO_4 were used for the optimization studies however, the best results were obtained with Cs_2CO_3 (Table 1, entry 12). Solvent studies suggest that dioxane as solvent furnished the product **3a** with maximum yield (Table 1, entry 12). Better results were not obtained by increasing the amount of synthesized heterogeneous catalyst (Table-1, entry 13). Poor yield of **3a** was obtained when iodo benzene was replaced with bromo benzene (table 1, entry 20) as the coupling partner.

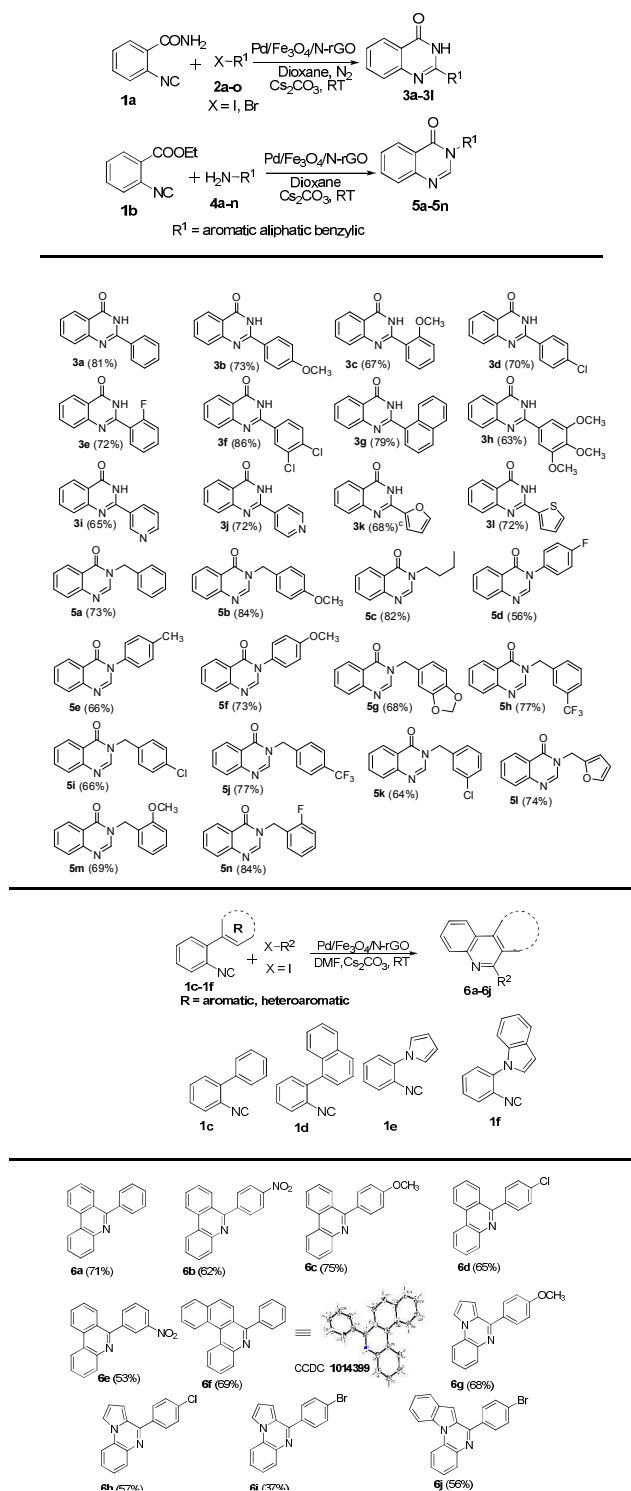
Table 1. Optimization of reaction condition for the formation of quinazolinone **3a**.^a

Entry	Catalyst	Solvent	Base	Yield ^b	
1	-	Dioxane	Cs_2CO_3	0	
2	$\text{Pd}(\text{Ph}_3)_4$	Dioxane	Cs_2CO_3	36	
3	$\text{Pd}(\text{MeCN})_2\text{Cl}_2$	Dioxane	Cs_2CO_3	12	
4	$\text{Pd}_2(\text{dba})_3$	Dioxane	Cs_2CO_3	26	
5	PdCl_2	Dioxane	Cs_2CO_3	Trace	
6	$\text{Pd}(\text{OAc})_2$	Dioxane	Cs_2CO_3	41	
7	$\text{Pd}/\text{N-rGO}$	Dioxane	Cs_2CO_3	72	
8	$\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	Cs_2CO_3	NR	
9	Pd^{2+}/GO	Dioxane	Cs_2CO_3	29	
10	Pd/C	Dioxane	Cs_2CO_3	12	
11	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	Cs_2CO_3	86	
12 ^c	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	Cs_2CO_3	84	
13 ^d	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	Cs_2CO_3	84	
14	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	K_2CO_3	51	
15	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	K_3PO_4	56	
17	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	DMSO	Cs_2CO_3	56	
18	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	DMF	Cs_2CO_3	63	
19	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Toluene	Cs_2CO_3	38	
20 ^{e,f}	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	Cs_2CO_3	14	
21 ^{e,g}	$\text{Pd}/\text{Fe}_3\text{O}_4/\text{N-rGO}$	Dioxane	Cs_2CO_3	77	

^a reaction conditions: 2-isocynobenzamide **1a** (1.2 mmol, slow addition), aryl iodide **2a** (1.0 mmol), Pd catalyst (10 mol% homogeneous Pd catalyst, 1 mol% heterogeneous Pd catalyst), and base (2.0 mmol) in solvents (5 mL) under N_2 for 24h (Entry 1-6, Temp = 100°C , Entry 7-11, Temp. = 90°C . Entry

12-19, Temp = RT. ^bIsolated yield. ^cRoom temperature. ^dCatalyst loading was 2 mol%. ^e Bromo benzene was used in place of iodobenzene. ^freaction time 36h. ^gTemperature was 90°C. NR = no reaction, RT = room temperature

Figure 3. Evaluation of the substrate scope.^{a,b}



^aReaction conditions: *ortho*-functionalized aromatic isocyanides (**1a-1f**), aryl iodide (**2a-2o**) or amine (**4a-4n**) (1.0 mmol), Pd/Fe₃O₄/N-rGO catalyst (1

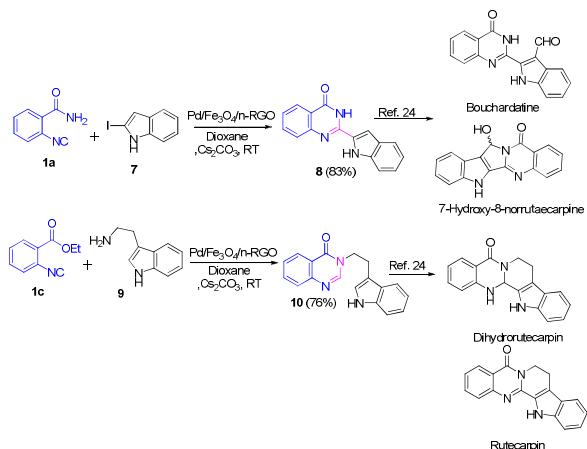
mol%), and base (2.0 mmol) in solvents (5 mL) for 24h at RT. ^bIsolated yield. ^cReaction was completed in 14h.

In heterogeneous catalysis, the reusability of the catalyst is an important issue from the economic and sustainability point of view. The durability of the catalyst was evaluated by using the model reaction substrate followed by its separation from the reaction mixture with an external permanent magnet (Fig.S11). The synthesized catalyst maintained the recyclability in the range of 84, 85, 84, 81, 76% yields for 5 run pre-treatment, with good results.

With the optimized reaction condition, next we surveyed the generality of the palladium mediated coupling process. The methodology reported here was found to be compatible with both electron donating and -withdrawing groups on the phenyl ring of **2** in good to excellent yield as shown in Figure 3. However the yields of quinazolinones were slightly lower with electron donating aromatic iodides (Figure 3, entries **3b**, **3c** and **3h**). Having established a good scope with substituted aryl halides, application of the method to heteroaryl halides (Figure 3, entries **3i**, **3j**, **3k** and **3l**) was also performed. Gratifyingly the conditions optimized for aryl iodides, provided equally significant isolated yields (68-72%) for heteroaryl iodides without any further optimization. Formally divalent carbon atom on isocyanides facilitates the reaction with amines in the presence of metal catalyst known to form amidines.²² Having demonstrated the concept of using an isocyanide insertion approach for 2-substituted quinazolinone synthesis, we enhanced the application to 3-substituted quinazolinones (Figure 3, entries **5a-n**) using suitable *ortho*-substituted aromatic isocyanide and amines. It is important to note here, the developed catalyst was equally compatible for the synthesis of 3-substituted quinazolinones (14 compounds) from the reaction of ethyl 2-isocyanobenzoate (**1b**) and various aliphatic, aromatic and benzylic amines in good to excellent yields.

Next, the scope of the 2-isocyanobiphenyl (**1c**), 1-(2-isocyanophenyl)naphthalene (**1d**), 1-(2-isocyanophenyl)-1H-pyrrole (**1e**), and 1-(2-isocyanophenyl)-1H-indole (**1f**) for the isocyanide insertion and C-H activation cascade reaction was explored using various aryl iodides. Following the optimized protocol, a number of nitrogen heterocycles (Figure 3, entries **6a-6j**) were synthesized in moderate to high yields (37-75%) at room temperature, which is otherwise reported at 100°C using high palladium loading and additives.²³ Unambiguous proof for the structure of phenanthridines was obtained by single crystal X-ray analysis of the compound **6f** (See supporting information).

To further illustrate the versatility of the developed protocol, 2-isocyanobenzamide (**1a**) was undergo cross-coupling reaction with 2-iodoindole (**7**) for the synthesis of 2-(1H-indol-2-yl)quinazolin-4(3H)-one (**8**), which can be converted to the rutaecarpine-type alkaloids bouchardatine and 7-hydroxy-8-norrutaecarpine (Scheme 1). Furthermore, the reaction of 2-isocyanobenzoate (**1c**) with tryptamine (**9**) furnished quinazolinone (**10**) in 73% yield which is an important intermediate for the synthesis of natural product dihydrorutecarpin and rutecarpin (Scheme 1).²⁴



Scheme 1. Formal synthesis of bouchardatine, 7-hydroxy-8-norrutacarpine, dihydrorutecarpin, and rutecarpin via isocyanide insertion.

Conclusions

In summary, an efficient and mild palladium-catalyzed method for the isocyanide insertion cascade was first developed. This protocol provided a new avenue for developing quinazolinones with different substitutions via C-C and C-N bond-forming reactions of aromatic isocyanides. Most notably, this is the first report of aromatic isocyanide insertion coupling using heterogeneous catalyst. This study opens up the possibilities of utilizing Pd/Fe₃O₄/n-RGO as recyclable catalyst in the vast area of isocyanide insertion reactions for the synthesis of valuable intermediates and heterocycles under mild conditions.

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Notes and references

- D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; (b) S. B. Mhaske, N. P. Argade, *Tetrahedron*, 2006, **62**, 9787.
- M. M. Ghorab, *IL Farmco*, 2000, **55**, 249; (b) D. S. Bradley, *Tetrahedron Lett.*, 2001, **42**, 1851; (c) A. Kumar, M. Tyagi, V. K. Shrivastava, *Indian J. Chem.*, 2003, **42B**, 2142; (d) N. R. El-Brollosy, M. F. Abdel-Megeed, A. R. Genady, *Alex J. Pharm. Sci.*, 2003, **17**, 17; (e) H. J. Hess, T. H. Cronin, A. Scriabine, *J. Med. Chem.*, 1968, **11**, 140.
- S. Yoshida, T. Aoyagi, S. Harada, N. Matsuda, T. Ikeda, H. Naganawa, M. Hamada, T. Takeuchi, *J. Antibiot.*, 1991, **44**, 111.
- C. Wattanapiromsakul, P. I. Forster, P. G. Waterman, *Phytochemistry*, 2003, **64**, 609.
- Z. Z. Ma, Y. Hano, T. Nomura, Y. Chen, *J. Heterocycles*, 1997, **46**, 541.
- S. E. Yeulet, P. G. Mantle, J. N. Bilton, H. S. Rzepa, R. N. Sheppard, *J. Chem. Soc. Perkin Trans. 1*, 1986, 1891-1894.
- J. R. Dai, B. K. Carte, P. J. Sidebottom, A. L. Yew, S. W. Ng, Y. Huang, M. S. Butler, *J. Nat. Prod.* 2001, **64**, 125.
- B. K. Joshi, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *J. Nat. Prod.*, 1999, **62**, 650-652.
- M. Rueping, A. P. Antonchick, E. Sugiono, K. Grenader, *Angew. Chem. Int. Ed.* 2009, **48**, 908; (b) J. F. Liu, P. Ye, B. Zhang, G. Bi, K. Yu, L. Sargent, D. Yohannes, C. M. Baldino, *J. Org. Chem.*, 2005, **70**, 6339; (c) M. Ramanathan, S.-T. Liu, *J. Org. Chem.* 2015, **80**, 5329; (d) D. Zhao, Y. R. Zhou, Q. Shen, J. X. Li, *RSC Adv.*, 2014, **4**, 6486; (e) H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046; (f) Y.-F. Chen, J.-C. Hsieh, *Org. Lett.* 2014, **16**, 4642; (g) X.-F. Wu, L. He, H. Neumann, M. Beller, *Chem. Eur. J.* 2013, **19**, 12635.
- A. V. Purandare, A. Gao, H. Wan, J. Somerville, C. Burke, C. Seachord, W. Vaccaro, J. Wityak, M. A. Poss, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2669.
- D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153.
- T. M. Potewar, R. N. Nadaf, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *Synth. Commun.* 2005, **35**, 231.
- H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046.
- L. He, H. Li, H. Neumann, M. Beller, X.-F. Wu, *Angew. Chem. Int. Ed.* 2014, **53**, 1420.
- X.-F. Wu, L. He, H. Neumann, M. Beller, *Chem. Eur. J.* 2013, **19**, 12635.
- X. Jiang, T. Tang, J.-M. Wang, Z. Chen, Y.-M. Zhu, S.-J. Ji, *J. Org. Chem.* 2014, **79**, 5082.
- (a) A. V. Lygin, A. D. Meijere, *Angew. Chem. Int. Ed.*, 2010, **49**, 9094; (b) G. Qiu, G. Liu, S. Pu, J. Wu, *Chem. Commun.*, 2012, **48**, 2903; (c) D. Zhao, T. Wang, J.-X. Li, *Chem. Commun.*, 2014, **50**, 6471.
- B. Liu, Y. Li, H. Jiang, M. Yin, H. Huang, *Adv. Synth. Catal.* 2012, **354**, 2288.
- (a) D. Wang, D. Astruc, *Chem. Rev.*, 2014, **114**, 6949; (b) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* 2006, **348**, 609.
- (a) D. R. Dreyer, C. W. Bielawski, *Chem. Sci.*, 2011, **2**, 1233; (b) C. L. Su, K. P. Loh, *Acc. Chem. Res.*, 2013, **46**, 2275; (c) X. K. Kong, C. L. Chen, Q. W. Chen, *Chem. Soc. Rev.*, 2014, **43**, 2841; (d) S. Navalon, A. Dhakshinamoorthy, M. Alvaro, H. Garcia, *Chem. Rev.*, 2014, **114**, 6179; (e) C. L. Su, M. Acik, K. Takai, J. Lu, S. J. Hao, Y. Zheng, P. P. Wu, Q. L. Bao, T. Enoki, Y. J. Chabal, K. P. Loh, *Nat. Commun.*, 2012, **3**, 1298; (f) D. R. Dreyer, H. P. Jia, C. W. Bielawski, *Angew. Chem. Int. Ed.*, 2010, **49**, 6813.
- A. K. Singh, K. C. Basavaraju, S. Sharma, S. Jang, C. P. Park, D.-P. Kim, *Green Chem.*, 2014, **16**, 3024; (b) G.-Y. Jeong, A. K. Singh, S. Sharma, K. W. Gyak, R. A. Maurya, D.-P. Kim, *NPG Asia Materials*, 2015, **7**, e173.
- (a) M. Lazar, R. J. Angelici, *J. Am. Chem. Soc.*, 2006, **128**, 10613; (b) T. Vlaar, R. C. Cioc, P. Mampuy, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chem. Int. Ed.*, 2012, **51**, 13058.
- J. Li, Y. He, S. Luo, J. Lei, J. Wang, Z. Xie, Q. Zhu, *J. Org. Chem.* 2015, **80**, 2223.
- J. Bergman, S. Bergman, *J. Org. Chem.* 1985, **50**, 1246.

