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Direct synthesis of quinazolinones by acceptorless dehydrogenative coupling of *o*-aminobenzamide and alcohols by heterogeneous Pt catalysts†

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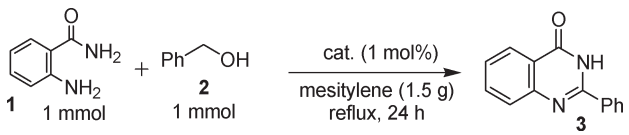
HBEA zeolite-supported Pt metal nanoclusters (Pt/HBEA) effectively catalyze direct dehydrogenative synthesis of quinazolinones from *o*-aminobenzamide and alcohols under promoter-free conditions. This is the first heterogeneous catalytic system for this reaction, which has a turnover number (TON) more than 25 times higher than previous homogeneous catalysts as well as wide scope for aliphatic and aromatic alcohols.

The synthesis of heterocyclic compounds from readily available alcohols is one of the most important branches of organic synthesis.[1–5] Quinazolinones exist in a variety of natural products, and they are important structures in drug development due to their biological and pharmacological activities.[6–17] A number of different synthetic methods for quinazolinones have been reported. Some quinazolinones were synthesized through the coupling between 2-halobenzoic acid derivatives and ammonia sources, including amidines,[9] benzylamines,[10] amino acids[11] and amides,[12] but this method has drawbacks such as a need for stoichiometric amounts of the bases used and the formation of salt wastes. A classical but more general method is the condensation between aldehydes and *o*-aminobenzamides to give aminal intermediates, followed by their oxidation to quinazolinones.[13–17] However, the method has serious drawbacks such as the use of chemically unstable aldehydes and excess amounts of hazardous oxidants ($KMnO_4$,[13] CuCl,[14] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[15] I_2,[16] and MnO_2[17]). Recent reports gave improved catalytic methods using alcohols as more benign and readily available reagents than aldehydes. Wei and a co-worker[18] reported an iodine catalyzed one-pot two-step oxidative system for the cyclization of primary alcohols with *o*-aminobenzamide to quinazolinones using DMSO as the oxidant. The system is convenient, but it produces stoichiometric amounts of dimethyl sulfide as a hazardous byproduct. A ZnI_2-catalyzed oxidative transformation of *o*-aminobenzamide with benzyl alcohols was recently developed by Wu *et al.*,[19] but the method required large amounts of catalyst (10 mol%) and excess amounts of expensive oxidant

Table 1 Quinazolinone synthesis with 5 wt% metal-loaded catalysts[a]



Entry	Catalyst	1 conv. (%)	Yield (%)
1	Pt/TiO_2	87	70
2	Ir/TiO_2	25	11
3	Re/TiO_2	9	0
4	Ru/TiO_2	13	3
5	Pd/TiO_2	11	7
6	Rh/TiO_2	2	0
7	Ni/TiO_2	22	13
8	Cu/TiO_2	0	0
9	Pt/MgO	39	21
10	Pt/Y_2O_3	27	18
11	Pt/CeO_2	5	2
12	Pt/ZrO_2	18	10
13	Pt/Al_2O_3	17	11
14	Pt/SnO_2	5	1
15	Pt/SiO_2	9	6
16	Pt/C	9	5
17	Pt/Nb_2O_5	74	55
18	Pt/SiO_2–Al_2O_3	95	75
19	Pt/HMFI	55	42
20	Pt/HBEA	100	99
21	PtO_x/HBEA	9	0
22[b]	Pt/HBEA–air	75	56
23[c]	HBEA	9	0

[a] The conversion of 1 and the yield of 3 were determined by gas chromatography (GC). The catalysts were pre-reduced in H_2 at 300 °C for 0.5 h except for entries 21 and 23. [b] Pre-reduced Pt/HBEA was exposed to air at room temperature for 0.5 h. [c] 0.1 g HBEA.

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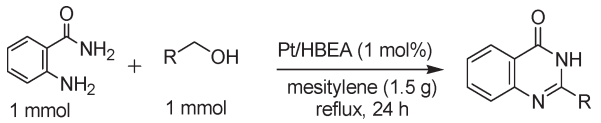
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cy00092g

Table 2 Alkylation of *o*-aminobenzamide with different alcohols using Pt/HBEA



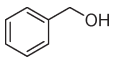
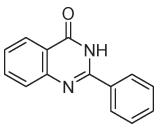
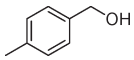
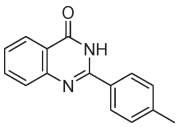
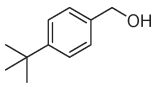
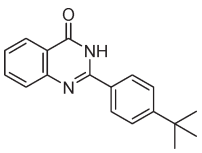
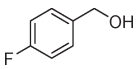
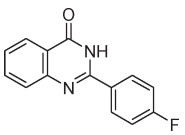
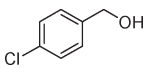
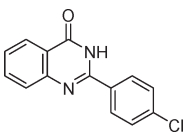
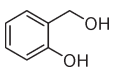
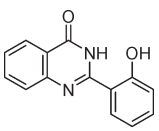
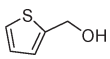
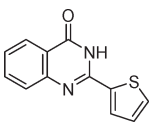
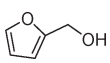
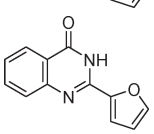
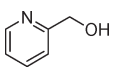
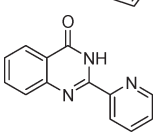
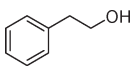
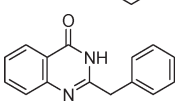
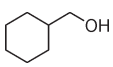
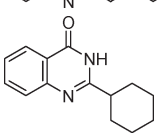
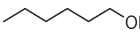
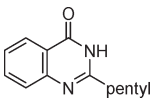
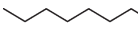
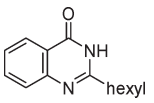
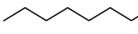
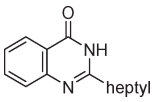
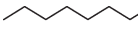
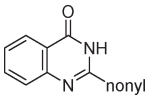
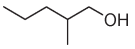
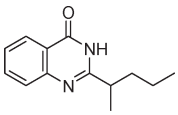
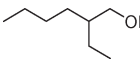
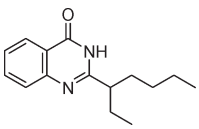
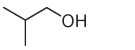
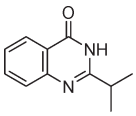
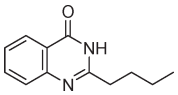
Entry	Alcohol	Product	Isolated yield (%)
1			95(99)[a]
2[b]			(95)[a]
3			86
4			90
5			82
6			76[a]
7			72[a]
8			75
9			65[a]
10			78
11			85
12			93

Table 2 *(continued)*

Entry	Alcohol	Product	Isolated yield (%)
13			90
14			95
15			95
16			92
17			88
18			80
19			78
20			90[a]

[a] GC yield. [b] Pt = 0.001 mmol, 80 h.

(*tert*-butyl hydroperoxide (TBHP)). Williams *et al.*[20] reported the cyclization of primary alcohols with *o*-aminobenzamide to quinazolinones using a homogeneous Ru catalyst, but the method required excess amounts of oxidant (crotononitrile). Yokoyama *et al.*[21] reported the synthesis of 4-phenyl-quinazolinones *via* a domino reaction of *o*-aminobenzamides and benzylalcohols involving a benzylation/benzylic C–H amidation methodology catalyzed by 5 mol% homogeneous Pd catalyst. However, the method required an expensive ligand and was limited to benzylalcohols. Compared with the above methods, $[Cp^*IrCl_2]_2$-catalyzed cyclization of primary alcohols with *o*-aminobenzamides to quinazolinones developed by Zhou and Fang is more atom-efficient, because it does not require an oxidant, and H_2 and H_2O are the byproducts.[22] This method was applied to the synthesis of 2,3-disubstituted natural quinazolinones.[23] However, from a practical viewpoint, the turnover number (TON) of the system is still low. As a part of our continuing interest in heterogeneous Pt nanocluster catalysis for acceptorless dehydrogenation of alcohols and dehydrogenation-driven coupling reactions *via* hydrogen-transfer methodologies,[24–27] we report herein the first heterogeneous catalytic system for acceptorless cyclization of primary alcohols with *o*-aminobenzamide to quinazolinones using Pt-loaded HBEA zeolite.

Table 3 Catalysts for direct quinazolinone synthesis from *o*-aminobenzamide and benzylalcohol

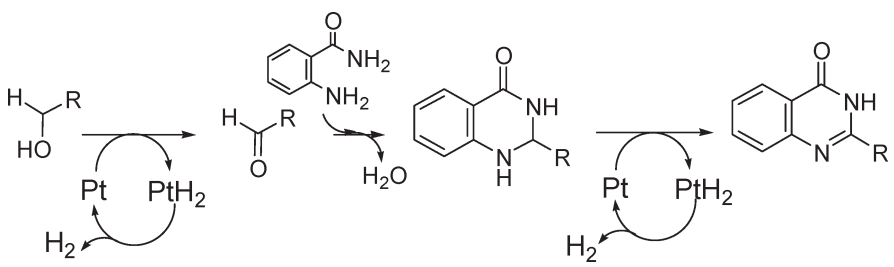
Catalyst	mol%	Oxidant	*T* (°C)	*t* (h)	Yield (%)	TON	Ref.
Pt/HBEA	0.1		165	80	95	950	This study
$Ir[Cp^*IrCl_2]_2$	2.5		140	36	93	37	22
$Pd(OAc)_2$/TPPMS[a]	5		120	16	93	19	21
$Ru(PPh_3)_3(CO)(H)_2$/Xantphos	5	2.5 eq. crotononitrile	115	24	72	14	20
ZnI_2	10	4 eq. TBHP	110	16	90	9	19

[a] sodium (diphenylphosphino) benzene-3-sulfonate

We chose the reaction of equimolar amounts of benzylalcohol and *o*-aminobenzamide as a model system in order to optimize the catalytic conditions. Table 1 (entries 1–8) summarizes the results of the initial catalyst screening test under the same reaction conditions (reflux in mesitylene for 24 h under N_2) using various transition metal (Pt, Ir, Re, Ru, Pd, Rh, Ni, Cu) catalysts supported on TiO_2 pre-reduced in H_2 at 300 °C. Among the catalysts tested, Pt/TiO_2 showed the highest conversion of amide to the corresponding quinazolinone, **3**. Entries 9–20 show the effect of the support on Pt-loaded catalysts pre-reduced at 300 °C. Among the various supports (TiO_2, MgO, Y_2O_3, CeO_2, ZrO_2, Al_2O_3, SnO_2, SiO_2, C, Nb_2O_5, SiO_2–Al_2O_3, HMFI, HBEA), HBEA (entry 20) gave the highest yield of quinazolinone **3** (99%) with 100% conversion of *o*-aminobenzamide. Acidic supports such as TiO_2, Nb_2O_5, SiO_2–Al_2O_3, and HMFI also gave good yields (42–75%). HBEA itself (entry 23) was completely inactive for this reaction and the unreduced catalyst precursor, PtO_x/HBEA (platinum oxide-loaded HBEA) was also inactive (entry 21). Considering the Pt metal diameter of 1.8 nm (CO adsorption experiment), these results suggest that both Pt metal nanoclusters and the acidic sites of HBEA are required for this catalytic system. The catalyst, named Pt/HBEA–air, prepared by exposing Pt/HBEA to ambient conditions for 0.5 h, gave a lower yield (56%) than as-reduced Pt/HBEA (99%). This suggests that the metallic Pt^0 species on the surface of the Pt nanoparticles are the active species and re-oxidation of them by O_2 under ambient conditions results in a decrease in the catalyst's activity.

The heterogeneous nature of this catalytic system is confirmed by the following results. For the standard reaction, Pt/HBEA was removed from the reaction mixture at a 26% yield of **3** (t = 3 h). Further heating of the filtrate for 21 h under the reflux conditions did not increase the product yield. Inductively coupled plasma (ICP) analysis of the filtrate confirmed that the content of Pt in the solution was below the detection limit.

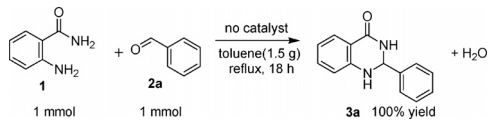
Under the optimized conditions with Pt/HBEA, we studied the general applicability of the present catalytic system. Table 2 shows the isolated yields of the quinazolinones from *o*-aminobenzamide with various primary alcohols using 1 mol% of the catalyst. Both electron rich (entries 3, 4, 7) and electron poor (entries 5, 6) benzylalcohols were tolerated to give excellent isolated yields (82–95%) with 100% conversions of *o*-aminobenzamide and the alcohols. The reaction of a sterically hindered *o*-substituted benzylalcohol (entry 7) also proceeded in good yield. Heteroaromatic alcohols with thienyl (entry 8), furanyl (entry 9) and pyridinyl (entry 10) groups were also tolerated with good yields (75%, 65% and 78%, respectively). It is important to note that various aliphatic alcohols, including linear and branched aliphatic alcohols (entries 11–19), were tolerated, giving 100% conversion of *o*-aminobenzamide and good to excellent isolated yields (78–95%) of the quinazolinones. Considering the fact that previous methods[18–22] did not tolerate branched aliphatic alcohols, our system is the first general method of quinazolinone synthesis from aliphatic alcohols. Although the reaction with the hydrogen acceptor group containing alcohol (4-pentene-1-ol (entry 20)) was not successful, a high yield (90%) of quinazolinone was obtained with complete reduction of the terminal double bond due to the availability of hydrogen as a byproduct in the reaction system through the PtH species. Using small amounts of the catalyst (0.1 mol%), cyclization of *o*-aminobenzamide to quinazolinones with benzylalcohol (entry 2) gave 95% yield, corresponding to a TON of 950. Table 3 compares the catalytic activity of our heterogeneous system with those of previous homogeneous systems for direct quinazolinone synthesis from *o*-aminobenzamide and benzylalcohol. The TON of Pt/HBEA is more than 25 times higher than those of previous



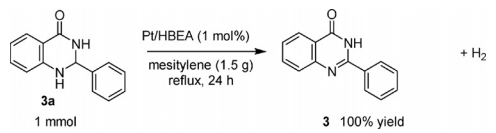
Scheme 1 Possible mechanism for Pt/HBEA-catalyzed quinazolinone formation.

catalytic systems, which clearly demonstrates the higher catalytic efficiency of the present system.

As proposed in a previous paper on oxidant-free quinazolinone formation from *o*-aminobenzamide and alcohols by an Ir-complex,[22] the present reaction can proceed through a dehydrogenative coupling pathway (Scheme 1), which is evidenced by the following results. First, we have reported that supported Pt metal clusters catalyze acceptor-free dehydrogenation of alcohols.[24] Second, the reaction of benzaldehyde and *o*-aminobenzamide under catalyst-free conditions resulted in the quantitative formation of the condensation product, aminal **3a** (eqn (1)). Aminal **3a**, which was then isolated, was dehydrogenated by Pt/HBEA under N_2 to give quinazolinone **3** in a quantitative yield (eqn (2)). Based on these results, we propose a possible mechanism of the present catalytic system in Scheme 1. The reaction begins with the Pt-catalyzed dehydrogenation of the primary alcohol to the aldehyde accompanied by the generation of H_2. Then, non-catalytic condensation of the aldehyde and *o*-aminobenzamide gives aminal **3a**, which undergoes Pt-catalyzed dehydrogenation to quinazolinone **3**. We studied the temperature effect for the model reaction from Table 1 and found that the lower temperature reaction at 150 °C slows down the dehydrogenation of aminal **3a** (eqn (2)) to quinazolinone **3**.



(1)



(2)

In summary we have developed the first heterogeneously catalyzed direct synthesis of quinazolinones from primary alcohols with *o*-aminobenzamide under additive-free conditions using the HBEA-supported Pt nanocluster catalyst. This method works for a wide scope of alcohols and shows more than a 25 times higher TON than the previous homogeneous catalytic systems (with expensive organic ligands or excess amounts of oxidant), and hence the method provides one of the most environmentally benign catalytic routes to quinazolinones from readily available substrates.

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Notes and references

1 C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 249.
2 R. Yamaguchi, K. Fujita and M. Zhu, *Heterocycles*, 2010, **81**, 1093.
3 Y. Obora and Y. Ishii, *Synlett*, 2011, **1**, 30.
4 G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611.
5 K. Fujita and R. Yamaguchi, *Synlett*, 2005, **4**, 560.
6 S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787.
7 Z.-Z. Ma, Y. Hano, T. Nomura and Y.-J. Chen, *Heterocycles*, 1997, **46**, 541.
8 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.
9 C. Huang, Y. Fu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun.*, 2008, 6333.
10 W. Xu, Y. Jin, H. Liu, Y. Jiang and H. Fu, *Org. Lett.*, 2011, **13**, 1274.
11 W. Xu and H. Fu, *J. Org. Chem.*, 2011, **76**, 3846.
12 L. Xu, Y. Jiang and D. Ma, *Org. Lett.*, 2012, **14**, 1150.
13 T. Hisano, M. Ichikawa, A. Nakagawa and M. Tsuji, *Chem. Pharm. Bull.*, 1975, **23**, 1910.
14 R. J. Abdel-Jalil, H. M. Aldoqum, M. T. Ayoub and W. Voelter, *Heterocycles*, 2005, **65**, 2061.
15 Y. Mitobe, S. Ito, T. Mizutani, T. Nagase, N. Sato and S. Tokita, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4075.
16 M. Bakavoli, A. Shiri, Z. Ebrahimpour and M. Rahimizadeh, *Chin. Chem. Lett.*, 2008, **19**, 1403.
17 C. Balakumar, P. Lamba, D. P. Kishore, B. L. Narayana, K. V. Rao, K. Rajwinder, A. R. Rao, B. Shireesha and B. Narsaiah, *Eur. J. Med. Chem.*, 2010, **45**, 4904.
18 W. Ge, X. Zhu and Y. Wei, *RSC Adv.*, 2013, **3**, 10817.
19 M. Sharif, J. Opalach, P. Langer, M. Beller and X.-F. Wu, *RSC Adv.*, 2014, **4**, 8.
20 A. J. A. Watson, A. C. Maxwell and J. M. Williams, *Org. Biomol. Chem.*, 2012, **10**, 240.
21 H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046.
22 J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730.
23 J. Fang and J. Zhou, *Org. Biomol. Chem.*, 2012, **10**, 2389.
24 K. Kon, S. M. A. H. Siddiki and K. Shimizu, *J. Catal.*, 2013, **304**, 63.
25 S. M. A. H. Siddiki, K. Kon and K. Shimizu, *Chem.–Eur. J.*, 2013, **19**, 14416.
26 C. Chaudhari, S. M. A. H. Siddiki and K. Shimizu, *Tetrahedron Lett.*, 2013, **54**, 6490.
27 K. Shimizu, K. Ohshima, Y. Tai, M. Tamura and A. Satsuma, *Catal. Sci. Technol.*, 2012, **2**, 730.