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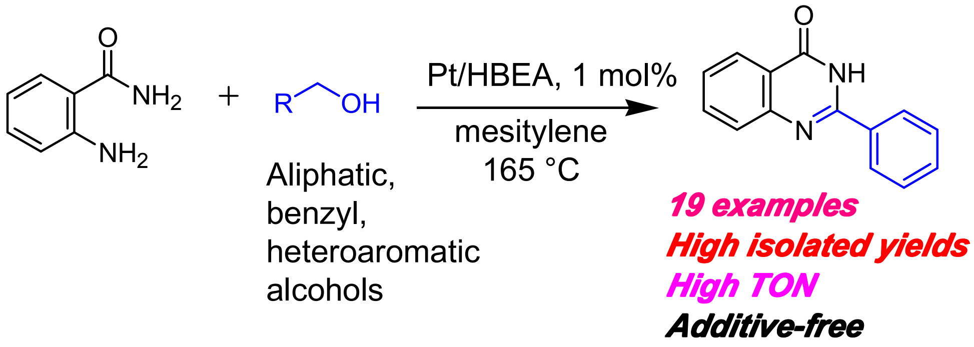
Table of contents



HBEA supported Pt metal nanocluster effectively catalyzes direct dehydrogenative synthesis of quinazolinones from *o*-aminobenzamide and alcohols under promoter-free conditions.

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 nanocluster (Pt/HBEA) effectively catalyzes 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 shows more than 25 times higher turnover number (TON) than previous homogeneous catalysts as well as wide scope of aliphatic and aromatic alcohols.

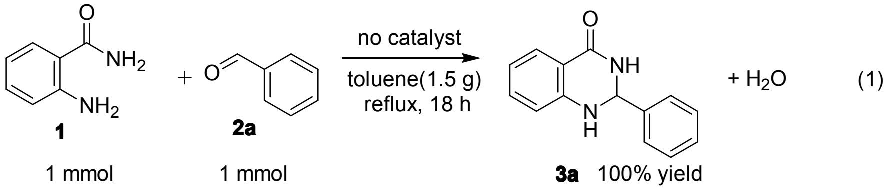
Heterocyclic compounds synthesis from readily available alcohols is one of the most important branch of organic synthesis.[1-5] Quinazolinones exist in a variety of natural products, and they are privileged structures in drug development due to their biological and pharmacological activities.[6-17] A number of different synthetic methods of quinazolinones were reported. Some quinazolinones were synthesized through the couplings between 2-halobenzoic acid derivatives and ammonia sources, including amidines,[9] benzylamines,[10] amino acids[11] and amides,[12] but these methods have drawbacks such as need of stoichiometric amounts of bases and formation of salt wastes. Classical but more general method is 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 uses of chemically unstable aldehydes and excess amounts of hazardous oxidants ($KMnO_4$,[13] CuCl,[14] 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 iodine catalyzed one-pot two-step oxidative system for cyclization of primary alcohols with *o*-aminobenzamide to quinazolinones using DMSO as the oxidant. The system is convenient, but it produces stoichiometric amount of dimethyl sulfide as a hazardous byproduct. ZnI_2-catalyzed oxidative transformation of *o*-aminobenzamide with benzyl alcohols was recently developed by Wu et al.,[19] but the method required large amount of catalyst (10 mol%) and excess amount of expensive oxidant (TBHP). Williams et al.[20] reported the cyclization of primary alcohols with *o*-aminobenzamide to quinazolinones using homogeneous Ru catalyst, but the method required excess amount of oxidant (crotononitrile). Yokoyama et al.[21] reported the synthesis of 4-phenyl-quinazolinones via a domino reaction of *o*-aminobenzamides and benzylalcohols involving benzylation/benzylic C−H amidation methodology catalyzed by 5 mol% of 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 oxidant, and H_2 and H_2O are the byproducts.[22] This method was applied to the syntheses of 2,3-disubstituted natural quinazolinones.[23] However, from practical viewpoint, 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.

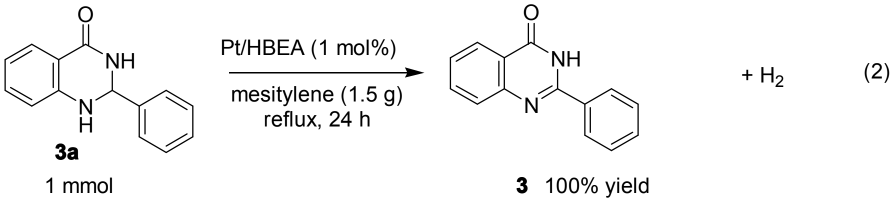
We chose the reaction of equimolar amount of benzylalcohol and *o*-aminobenzamide as a model system in order to optimize catalytic conditions. Table 1 (entries 1-8) summarizes the results of the initial catalyst screening test under the same reaction conditions (reflux in mesitylene for 24 h under N_2) 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 results of support effect 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 the quinazolinone **3** (99%) at 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 an unreduced catalyst precursor, PtO_x/HBEA (platinum oxides-loaded HBEA) was also inactive (entry 21). Considering the Pt metal diameter of 1.5 nm (CO adsorption experiment), these results suggest that both Pt metal nanoclusters and acid sites of HBEA are required for this catalytic system. The catalyst named Pt/HBEA–air, prepared by exposing Pt/HBEA to the ambient conditions for 0.5 h, showed lower yield (56%) than as-reduced Pt/HBEA (99%). This suggests that the metallic Pt^0 species on the surface of Pt nanoparticles are the active species and re-oxidation of them by O_2 under ambient conditions results in decrease in the catalyst 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 26% yield of **3** (t = 3 h). Then, further heating of the filtrate for 21 h under the reflux conditions did not increase the product yield. 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 general applicability of the present catalytic system. Table 2 shows the isolated yields of 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 alcohols. The reaction of a sterically hindered *o*-substituted benzylalcohol (entry 7) also proceeded in good yield. Heteroaromatic alcohol with thienyl (entry 8), furanyl (entry 9) and pyridinyl (entry 10) groups were also tolerated with good yields (75%, 65% and 78%). 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 quinazolinones. Considering the fact that previous methods[18-22] did not tolerate branched aliphatic alcohols, our system is the first general method of quinazolinones synthesis from aliphatic alcohols. Unfortunately reaction with hydrogen acceptable group having alcohol, 4-pentene-1-ol (entry 20) was not successful, high yield (90%) of quinazolinone was obtained with complete reduction of the terminal double bond; which is due to the availability of byproduct hydrogen in the reaction system through PtH species. Using small amount of the catalyst (0.1 mol%), cyclization of *o*-aminobenzamide to quinazolinones with benzylalcohol (entry 2) gave 95% yield, corresponding to TON of 950. Table 3 compares catalytic activity of our heterogeneous system with those of previous homogeneous systems for direct quinazolinone synthesis from *o*-aminobenzamide and benzylalcohol. TON of Pt/HBEA is more than 25 times higher than those of previous catalytic systems, which clearly demonstrate the higher catalytic efficiency of the present system.

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





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 shows wide scope of alcohols and more than 25 times higher TON than the previous homogeneous catalytic systems (with expensive organic ligands or excess amount of oxidant), and hence the method provides one of the most environmentally benign catalytic routes to quinazolinones from readily available substrates.

Acknowledgment

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Notes and references

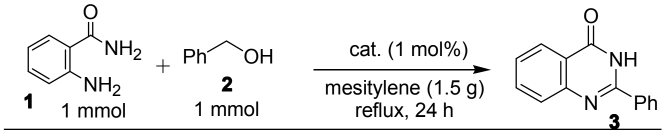
1 C. Gunanathan, D. Milstein, *Science*, **2013**, *341*, 249.

2 R. Yamaguchi, K. Fujita, M. Zhu, *Heterocycles*, **2010**, *81*, 1093.

3 Y. Obora, Y. Ishii, *Synlett*, **2011**, *1*, 30.

4 G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.*, **2010**, *110*, 1611.
5 K. Fujita, 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.*, **200**3, *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**, *6*5, 2061.
15 Y. Mitobe, S. Ito, T. Mizutani, T. Nagase, N. Sato and S. Tokita, *Bioorg. Med. Chem. Let*t., **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.

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



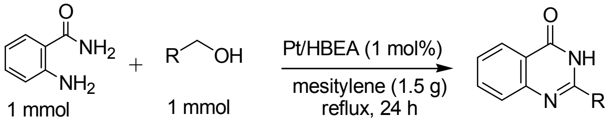
entry	catalyst	**1** conv.(%)	yield (%)
1	Pt/TiO_2	87	70
2	Ir/TiO_2	25	11
3	Re/TiO_2	9	0
4	Ru/TiO_2	13	3
5	Pd/TiO_2	11	7
6	Rh/TiO_2	2	0
7	Ni/TiO_2	22	13
8	Cu/TiO_2	0	0
9	Pt/MgO	39	21
10	Pt/Y_2O_3	27	18
11	Pt/CeO_2	5	2
12	Pt/ZrO_2	18	10
13	Pt/Al_2O_3	17	11
14	Pt/SnO_2	5	1
15	Pt/SiO_2	9	6
16	Pt/C	9	5
17	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

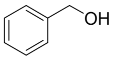
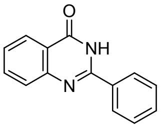
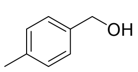
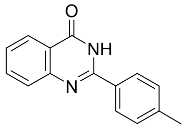
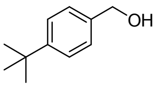
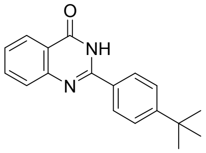
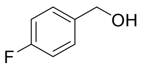
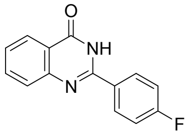
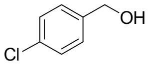
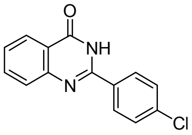
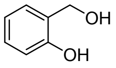
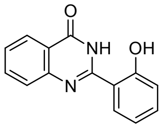
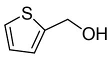
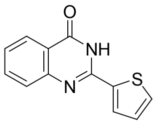
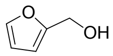
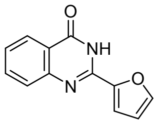
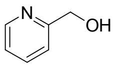
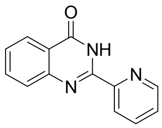
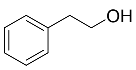
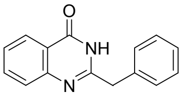
[a] Conversion of **1** and yield of **3** were determined by GC. Catalysts were pre-reduced in H_2 at 300 °C for 0.5 h except for entries 21 and 23.

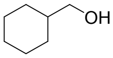
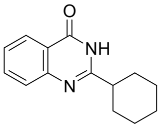
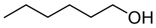
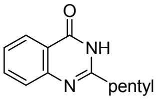
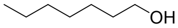
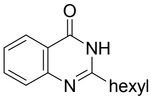
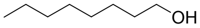
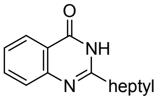
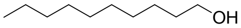
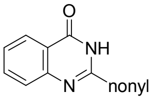
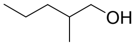
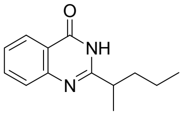
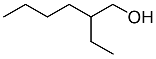
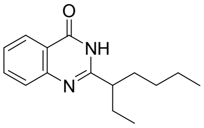
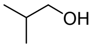
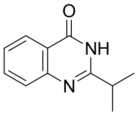
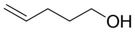
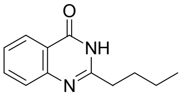
[b] Pre-reduced Pt/HBEA was exposed to air at room temperature for 0.5 h.

[c] 0.1 g HBEA.

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



entry	alcohols	products	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

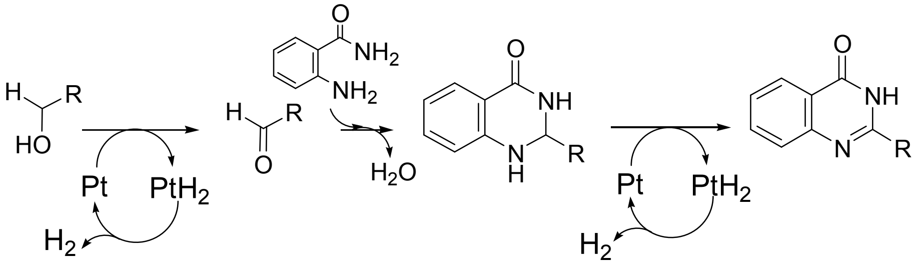
12			93
13			90
14			95
15			95
16			92
17			88
18			80
19			78
20			90[a]

[a] GC yield.

[b] Pt = 0.001 mmol, 80 h.

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	17
Pd(OAc)$_2$ /TPPMS	5		120	16	93	19	15
Ru(PPh$_3$)$_3$(CO)(H)$_2$ /Xantphos	5	2.5 eq. crotononitrile	115	24	72	14	16
ZnI$_2$	10	4 eq. TBHP	110	16	90	9	14



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