Tetrahedron Letters 54 (2013) 6490–6493

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Alkylation of 2-methylquinoline with alcohols under additive-free conditions by Al_2O_3-supported Pt catalyst

Chandan Chaudhari [a], S. M. A. Hakim Siddiki [b], Ken-ichi Shimizu [a,b,*]

[a] *Catalysis Research Center, Hokkaido University, N-21, W-10, Sapporo 001-0021, Japan*
[b] *Elements Strategy Initiative for Catalysts and Batteries, Kyoto University, Katsura, Kyoto 615-8520, Japan*

ARTICLE INFO

Article history:
Received 22 August 2013
Revised 6 September 2013
Accepted 17 September 2013
Available online 25 September 2013

Keywords:
Alkylation
Alcohols
Methylquinoline
Platinum

ABSTRACT

Supported metal nanoparticle catalysts are studied for alkylation of 2-methylquinoline with benzyl alcohol under additive-free conditions in N_2 atmosphere. Among various metal-loaded Al_2O_3 catalysts and supported Pt catalysts, Pt metal nanocluster loaded-Al_2O_3 pre-reduced in H_2 at 500 °C shows highest yield (82%) of the product (2-phenethyl-quinoline). The catalyst is reusable, shows higher turnover number than a previous homogeneous catalyst, and shows good to moderate yield for alkylation of 2-methylquinoline with various alcohols. The reaction is driven by the borrowing-hydrogen pathway, in which aldehyde formed by dehydrogenation of alcohol undergoes aldol condensation with 2-methylquinoline to give the alkene intermediate which is finally hydrogenated by Pt-H species.

Introduction

Quinolines and their derivatives have great importance in pharmaceutical and agriculture industries.[1,2] Among various methods for synthesizing quinolines,[3] the introduction of alkyl-chain moieties into benzoquinones using methylquinolines as a starting material is of particular importance,[4,5] because methylquinolines are easily accessible. The classical synthetic method of alkylquinolines is the reaction of a 2-methylquinoline with *n*-BuLi, followed by reaction with an alkyl halide. However, the main drawback of this method is the formation of stoichiometric amount of waste salts and use of hazardous reagent. In recent years, much attention has focused on the alkylation reactions using alcohols as alkylating agent driven by the borrowing-hydrogen[6] (or hydrogen-autotransfer[7]) mechanism. It provides excellent protocols for selective C–C bond formations[9–19] such as α-alkylation of ketones,[8] β-alkylation of secondary alcohols,[9–12] and Guerbet-type dimerizations of alcohols.[13–16] In these protocols, alcohol is initially dehydrogenated, then undergoes a functionalization reaction, and finally, re-hydrogenated by in situ formed hydride species. Recently, this methodology has been used for alkylation of more challenging substrates. Kempe and co-workers reported the catalytic alkylation of methyl-N-heteroaromatics by alcohols in the presence of homogeneous catalyst $[IrCl(cod)]_2$ with $Py_2NP(i\text{-}Pr)_2$ ligand under basic condition.[18] Recently, Obora et al. developed a selective alkylation of methylquinolines by alcohols using the $[Ir(OH)(cod)]_2$ complex combined with a phosphine ligand and a base.[19] The reaction provides a simple and atom-economical direct route to alkylquinolines, as the exclusive products, in high yields. However, this method suffers from drawbacks such as low turnover number (TON), necessity of substoichiometric amount (50 mol %) of base, and difficulties in catalyst-product separation and catalyst reuse. As a part of our continuing interest in the heterogeneous catalysis for hydrogen-transfer reactions,[17,20,21] we report herein the first heterogeneous catalytic system for selective alkylation of methylquinolines by alcohols using Pt nanocluster-loaded γ-Al_2O_3 catalyst. This method has advantages over the previous homogeneous system in terms of higher TON, catalyst reusability, and greener (additive-free) conditions.

Results and discussion

The structure of Pt species in the standard catalyst, Pt/Al_2O_3 (Pt = 1 wt %) prepared by an impregnation method followed by H_2-reduction at 500 °C, was examined by Pt L_3-edge X-ray absorption near-edge structure (XANES) in Figure 1A and X-ray absorption fine structure (EXAFS) in Figure 1B. XANES features of Pt/Al_2O_3 are close to those of Pt foil. The EXAFS curve-fitting analysis (Table 1) showed that the EXAFS of Pt/Al_2O_3 mainly consists of a Pt–Pt bond at 2.70 Å with coordination number of 6.4. The Pt–Pt distance shorter than that of bulk Pt (2.76 Å) and Pt–Pt coordination number lower than that of bulk Pt (12) are characteristic features of small Pt metal clusters.[22] These features are consistent with the average diameter of Pt metal estimated by CO adsorption experiment (2.3 nm). From these results, it is revealed that

---

* Corresponding author. Tel.: +81 11 706 9240; fax: +81 11 706 9163.
E-mail address: kshimizu@cat.hokudai.ac.jp (K. Shimizu).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.077

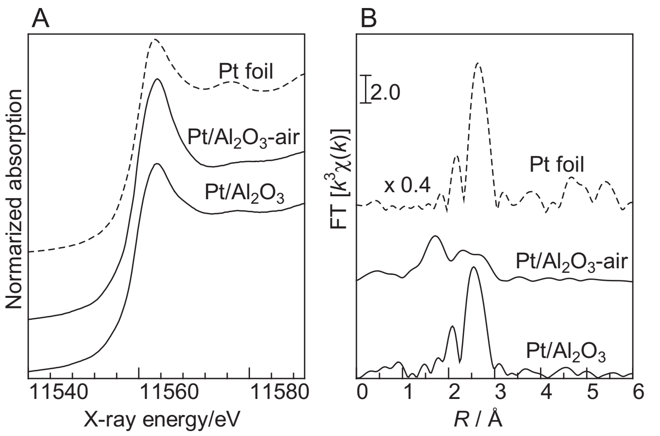


Figure 1. (A) XANES spectra and (B) EXAFS Fourier transforms at Pt L3-edge for Pt catalysts and a reference compound (Pt foil).

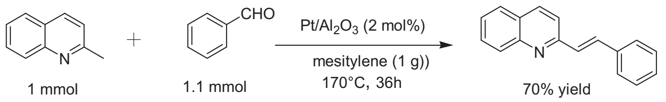
Table 1
Curve-fitting analysis of Pt L_3-edge EXAFS

Sample	Shell	N^a	R^b (Å)	σ^c (Å)	R_f^d (%)
Pt/Al_2O	Pt	6.4	2.70	0.080	1.6
Pt/Al_2O_3–air	O	1.6	2.03	0.071	2.1
	Pt	3.9	2.68	0.094	
Pt foil	Pt	(12)	(2.76)	—	—

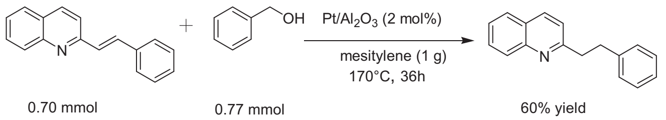
[a] Coordination numbers.
[b] Bond distance.
[c] Debye–Waller factor.
[d] Residual factor.

dominant Pt species in Pt/Al_2O_3 is the metallic Pt nanocluster. The catalyst named Pt/Al_2O_3–air was prepared by exposing the as-reduced Pt/Al_2O_3 catalyst to the ambient conditions for 0.5 h. The EXAFS result of Pt/Al_2O_3–air (Table 1) showed that air-exposure of Pt/Al_2O_3 resulted in an appearance of the Pt-O shell with coordination number of 1.6 and a decrease in the Pt–Pt coordination number from 6.4 to 3.9. The XANES result showed that air-exposure of Pt/Al_2O_3 resulted in an increase in the white line intensity. These results indicate that the metallic Pt species are partially re-oxidized in air.

Using various supported metal nanoparticle catalysts, we carried out catalysts screening study. We adopted the alkylation of 2-methylquinoline (1 mmol) with benzyl alcohol (1.1 mmol) in mesitylene (1 g) under reflux conditions in the presence of 2 mol % of the metal catalyst as a model reaction. Table 2 shows the effect of metal species on the activity of various metal-loaded Al_2O_3. Among various transition metals (Pt, Ir, Re, Rh, Pd, Ag, Ni, Co, and Cu), the Pt catalyst showed the highest yield (82%) of the alkylated product. Table 3 shows the effect of support on the activity of Pt-loaded catalysts. Among various support materials, Al_2O_3 was found to be the best support. From these results, Pt/Al_2O_3 was found to be the most effective catalyst for the alkylation of 2-methylquinoline with benzyl alcohol.



(1)



(2)

Next we studied the scope of substrates for alkylation of 2-methylquinoline (1 mmol) with various alcohols (1.1 mmol) by Pt/Al_2O_3 (Table 4). The substituted benzyl alcohols with electron donating groups (entries 2 and 3) and that with electron withdrawing group (entry 4) gave good yields (70–75%). 4-Fluoro benzyl alcohol (entry 5) resulted in a moderate yield (50%). Aliphatic alcohols such as octanol and hexanol (entries 6 and 7) also resulted in moderate yields (60–63%). Note that, unlike the homogeneous Ir catalyst reported by Obora,[19] our system does not require additives and excess molar amount of 2-methylquinoline.

We studied leaching test and reusability study for the Pt/Al_2O_3-catalyzed alkylation of 2-methylquinoline with benzyl alcohol. The reaction was completely terminated by removal of the catalyst from the reaction mixture after 4 h; further heating of the filtrate for 36 h under the reflux condition did not increase the yield. ICP-AES analysis of the filtrate confirmed that the content of Pt in the solution was below the detection limit. These results confirm that the reaction is attributed to the heterogeneous catalysis of Pt/Al_2O_3. Figure 2 shows the results of catalyst reuse. After the reaction of cycle 1 (Table 4, entry 1), we separated catalyst from reaction mixture by centrifugation. The separated catalyst was dried at 90 °C at 12 h and then reduced in H_2 at 500 °C for 0.5 h. The recovered catalyst was reused at least four times without marked indication of catalyst deactivation. The total TON for the five cycles was 195. This value is an order of magnitude higher than that of the homogeneous Ir (TON = 18.4 for the same reaction).[19]

In analogy to the proposed mechanism for the C-3 alkylation of indole with alcohols,[19] the present reaction may proceed through the hydrogen-borrowing pathway (Fig. 3). The time course of the reaction (Fig. 4) shows a profile characteristic to a consecutive reaction mechanism via the unreduced intermediate, phenylethenylquinoline, detected by GC–MS analysis; the intermediate formed at an initial induction period is consumed to give the

Table 2
Alkylation of 2-methylquinoline with benzyl alcohol with 1 wt % metal-loaded Al_2O_3[a]

Entry	Catalysts	Conv. (%)	Yield (%)
1	Pt/Al_2O_3	83	82
2	Ir/Al_2O_3	79	53
3	Re/Al_2O_3	47	6
4	Rh/Al_2O_3	39	31
5	Pd/Al_2O_3	29	32
6	Ag/Al_2O_3	15	5
7	Ni/Al_2O_3	7	4
8	Co/Al_2O_3	0	0
9	Cu/Al_2O_3	0	0

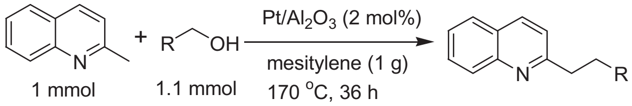
[a] Conditions: 2-methylquinoline (1 mmol), benzyl alcohol (1.1 mmol), metal (0.02 mmol), mesitylene (1 g), 170 °C, 36 h.

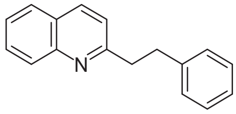
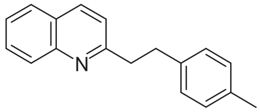
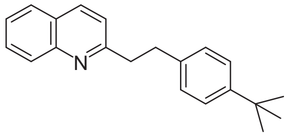
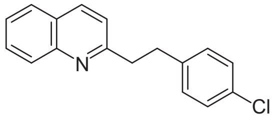
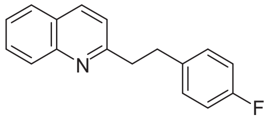
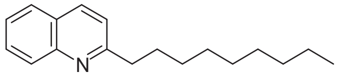
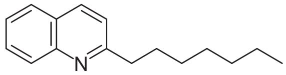
Table 3
Alkylation of 2-methylquinoline with benzyl alcohol with 1 wt % Pt-loaded catalysts[a]

Entry	Catalysts	Conv. (%)	Yield (%)
1	Pt/Al_2O_3	83	82
2	Pt/Nb_2O_5	50	20
3	Pt/C	12	7
4	Pt/BEA	5	1
5	Pt/ZrO_2	15	1
6	Pt/CeO_2	10	0
7	Pt/MgO	8	0
8	$PtOx/Al_2O_3$	45	40
9	Pt/Al_2O_3-air	18	5

[a] Conditions: 2-methylquinoline (1 mmol), benzyl alcohol (1.1 mmol), Pt (0.02 mmol), mesitylene (1 g), 170 °C, 36 h.

Table 4
Alkylation of 2-methylquinoline with alcohols with Pt/Al_2O_3[a]



Entry	Product	Yield (%)
1		82 (75)
2		72 (65)
3		70 (60)
4		75 (70)
5		50 (42)
6[b]		63 (55)
7[b]		60 (50)

[a] Conditions: 2-methylquinoline (1 mmol), alcohol (1.1 mmol) , Pt (0.02 mmol), mesitylene (1 g), 170 °C, 36 h. Isolated yields are in parentheses.

[b] Undecane (1 g) as solvent, 200 °C, 36 h.

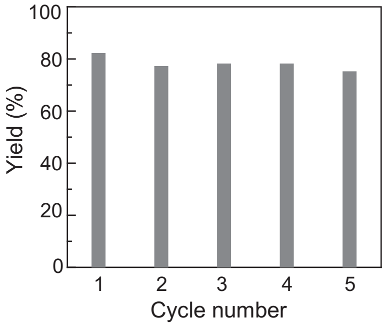


Figure 2. Recycle study for alkylation of 2-methylquinoline with alcohols with Pt/Al_2O_3.

hydrogenated product. As shown in Eq. 1, the reaction of benzaldehyde and 2-methylquinoline with Pt/Al_2O_3 under N_2 resulted in the formation of the unreduced intermediate, phenylethenylquinoline, in 70% yield. As shown in Eq. 2, the transfer hydrogenation of phenylethenylquinoline by benzyl alcohol with Pt/Al_2O_3 gave the hydrogenated product in 60% yield. From these considerations, we propose a possible catalytic cycle shown in Figure 3. First, hydrogen transfer from alcohol to a Pt° site on a Pt metal cluster, gives aldehyde and Pt-H species. Then, Al_2O_3-catalyzed aldol

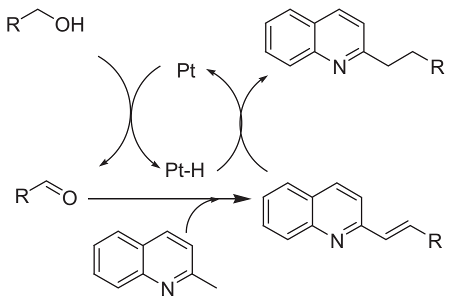


Figure 3. Presumable catalytic cycle for Pt/Al_2O_3-catalyzed alkylation of 2-methylquinoline with alcohols.

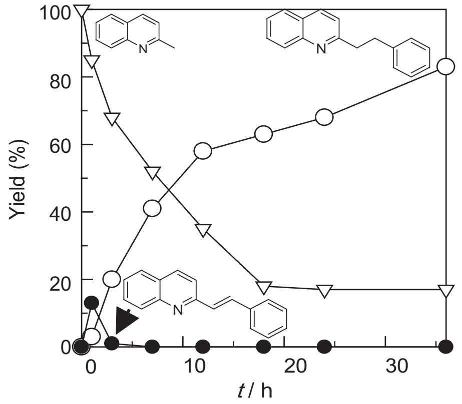


Figure 4. Time-yield profile for the alkylation of 2-methylquinoline (1 mmol) with benzyl alcohol (1.1 mmol) in mesitylene (1 g) under reflux conditions in the presence of 1 mol % of Pt/Al_2O_3: yields of unreacted 2-methylquinoline (▽), 2-phenethyl-quinoline (○), and phenylethenylquinoline (●).

condensation of aldehyde and 2-methylquinoline gives alkenylquinoline, which is hydrogenated by the Pt-H species to give alkylated quinoline.

In summary we have shown that γ-Al_2O_3 supported Pt metal nanoclusters catalyze the alkylation reaction of 2-methylquinoline with various alcohols under additive free conditions. Considering the fact that the previous system using a homogeneous Ir catalyst with 50 mol % *t*-BuOK and 20 mol % Ph_3P is the only successful catalytic method of the title reaction, our method provides the most environmentally benign catalytic system for this reaction because of the following advantages: (1) high TON, (2) easy catalyst/product separation, (3) catalyst reuse, (4) no need of additives, and excess molar amount of 2-methylquinoline.

Acknowledgment

This work was supported by a MEXT program 'Elements Strategy Initiative to Form Core Research Center' (since 2012), Japan.

Supplementary data

Supplementary data (general method, characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.077.

References and notes

1. Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891.
2. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.
3. Robinson, B. *Chem. Rev.* **1963**, *63*, 373–401.

4. Robert, V. S.; Jimmy, W. C. *J. Org. Chem.* **1990**, *55*, 2237–2240.
5. Parekh, V.; Ramsden, J. A.; Wills, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1549–1556.
6. Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. *J. Adv. Synth. Catal.* **2007**, *349*, 1555–1575.
7. Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358–2364.
8. Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72–73.
9. Cho, C. S.; Kim, B. T.; Kim, H. S.; Kim, T. J.; Shim, S. C. *Organometallics* **2003**, *22*, 3608–3610.
10. Martinez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8982–8987.
11. Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7*, 4017–4019.
12. Kose, O.; Saito, S. *Org. Biomol. Chem.* **2010**, *8*, 896–900.
13. Matsu-ura, T.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2006**, *71*, 8306–8308.
14. Koda, K.; Matsu-ura, T.; Obora, Y.; Ishii, Y. *Chem. Lett.* **2009**, *38*, 838–839.
15. Obora, Y.; Anno, Y.; Okamoto, R.; Matsu-ura, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 8618–8622.
16. Ogo, S.; Onda, A.; Yanagisawa, K. *Appl. Catal. A* **2011**, *402*, 188–195.
17. Shimizu, K.; Sato, R.; Satsuma, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 3982–3986.
18. Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924–925.
19. Obora, Y.; Ogawa, S.; Yamamoyo, N. *J. Org. Chem.* **2012**, *77*, 9429–9433.
20. Shimizu, K.; Kon, K.; Onodera, W.; Yamazaki, H.; Kondo, J. N. *ACS Catal.* **2013**, 112–117.
21. Shimizu, K.; Sawabe, K.; Satsuma, A. *Catal. Sci. Technol.* **2011**, *1*, 331–341.
22. Frenkel, A. I.; Hills, C. W.; Nuzzo, R. G. *J. Phys. Chem. B* **2001**, *105*, 12689–12703.