A general and sustainable *C*-methylation of alcohols, ketones and indoles with methanol by heterogeneous platinum catalyst

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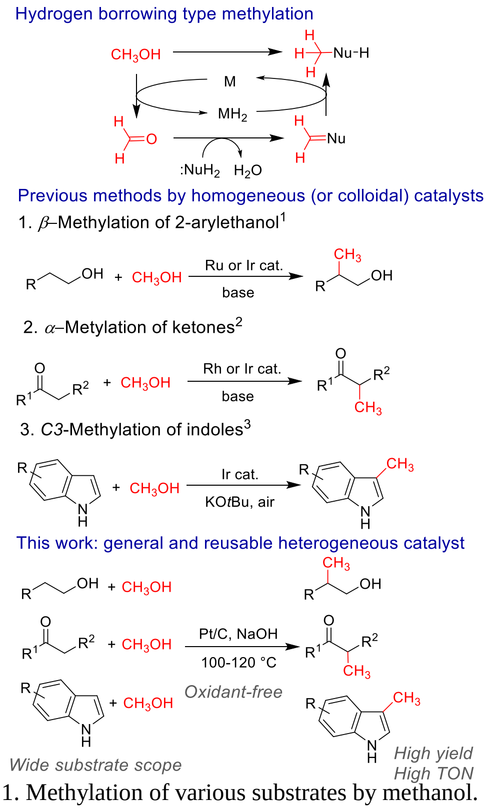
Abstract: We report a versatile, selective and recyclable heterogeneous catalytic method for methylation of C–H bonds by a sustainable C1 resource (methanol) under oxidant-free conditions using a Pt-loaded carbon (Pt/C) catalyst with NaOH. This catalytic system is effective for several methylation reactions including (1) *β*-methylation of primary alcohols (aryl, aliphatic and heterocyclic alcohols) (2) *α*-methylation of ketones and (3) selective *C3*-methylation of indoles. The reactions are driven by borrowing hydrogen mechanism; where alcohols dehydrogenate to aldehydes and subsequently undergo condensation with nucleophiles (aldehydes, ketones or indoles) followed by hydrogenation of the condensation products by Pt-H species to the desired products.

Keywords: Methylation, C-C bond, Pt/C catalyst

1. Introduction

Catalytic formation of C–C/C–N bonds through hydrogen-borrowing methodologies has been received recent attentions in catalysis and organic synthesis. Methylation with methanol in hydrogen-borrowing type reactions is of particular importance, but it is still a challenging reaction. Recently, three types of the catalytic methylation of C–H bonds have been developed using homogeneous catalysts (Scheme 1): (1) Ru-catalyzed β-methylation of 2-arylethanols,[1] (2) Rh-or Ir-catalyzed α-methylation of ketones,[2] (3) Ir-catalyzed C3-methylation of indoles,[3] However, all of these methods suffer from difficulties in catalyst/product separation and catalyst reuse, low turnover number (TON). As a part of our continuing interest in the heterogeneous catalysis for hydrogen-borrowing reactions for C–C bond formation,[4] we report herein a general heterogeneous catalytic system for the three types of methylation reactions in Scheme 1 by using Pt nanoparticles loaded on carbon (Pt/C) with NaOH. This is the first versatile method for methylation of a wide range of substrates by methanol as well as a rare example of heterogeneous catalytic method for the reactions (1)-(3).



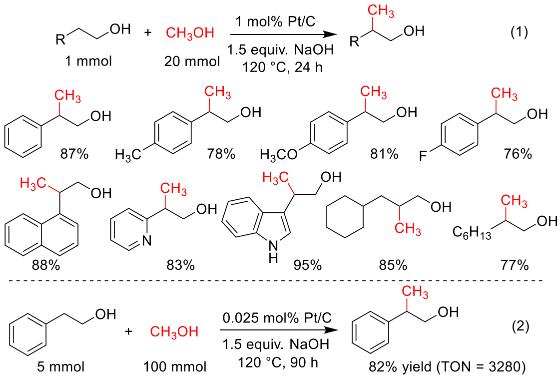
Scheme 1. Methylation of various substrates by methanol.

2. Experimental

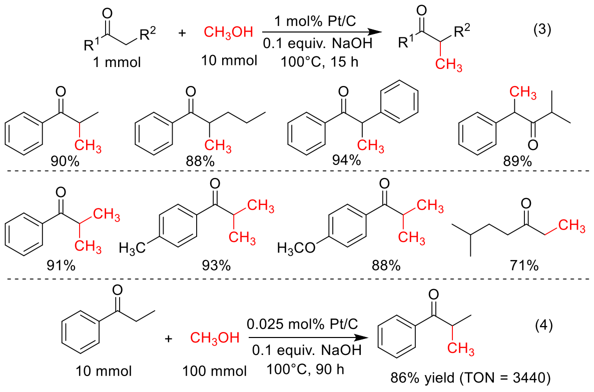
The catalyst was prepared by impregnating supports with an aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ followed by pre-reduction in H_2 at 300 °C. After reduction, the catalyst in the closed glass tube sealed with a septum inlet was cooled to room temperature under H_2. Methanol (10 or 20 mmol) was injected to the pre-reduced catalyst inside the glass tube through a septum inlet. Then the septum was tentatively removed under air, and 1mmol of substrate (alcohols, ketones, or indoles), NaOH (0.1 or 1.5 mmol), *n*-dodecane (0.25 mmol) and a magnetic stirrer bar were put in the tube. Then, the tube was inserted to a stainless autoclave (28 cm^3). After being sealed, the autoclave was charged with 1 bar N_2 and heated at 100 ˚C or 120 ˚C under stirring (500 rpm). After completion of the reaction, the catalyst was removed by filtration and the products were isolated by column chromatography with silica gel 60 (spherical, 40-100 μm, Kanto Chemical Co. Ltd.) using hexane/ethyl acetate (9/1) as eluting solvent. The products were identified by ^{1}H and ^{13}C NMR and GC-MS equipped with the same column as GC.

3. Results and discussion

Various Pt-loaded catalysts were screened for model methylation reactions of 2-phenylethanol/ propiophenone/indole with methanol. Carbon supported Pt metal (Pt/C) showed the highest yield of corresponding methylated products. Substrate scope for *β*-methylation of primary alcohols were effective for various alcohols (aryl, aliphatic and heterocyclic) as shown in scheme 2. The same catalytic system was effective for mono-methylation of aromatic and aliphatic ketones at *α*-position and bis-methylation for terminal ketones as in scheme 3.

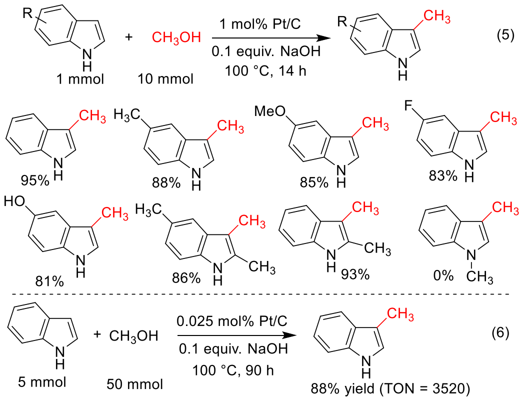


Scheme 2. *β*-Methylation of primary alcohols.



Scheme 3. *α*-Methylation of ketones.

Pt/C was reusable for several times without a marked loss of its activity. The TON of the methylation of 2-phenylethanol and propiophenone were studied as shown in eqn. (2) (TON = 3280) and eqn. (3) (TON = 3440) respectively. These TON values are higher than that of the previously reported catalyst for the methylation of 2-phenylethanol (TON of 435) and propiophenone (TON of 95). Selective *C3* methylation of indoles were demonstrated with different indole derivatives in very good to high yields as in scheme 4. Methylation of indole eqn. (6) shows two orders of magnitude higher TON than homogeneous system.[3]



Scheme 3. Selective *C3*-methylation of indoles.

4. Conclusions

We have developed a general heterogeneous catalytic method for selective *β*-methylation of primary alcohols, *α*-methylation of ketones, *C3*-methylation of indoles using methanol as a C1 feedstock; where all the reactions proceed through borrowing-hydrogen methodology. Pt^0 sites on the Pt metal particles are responsible for dehydrogenation of methanol to formaldehyde and NaOH catalyzed the condensation reaction, finally unsaturated intermediates hydrogenated by Pt-H species on the catalyst. Compared with the previous homogeneous catalytic system, our method has the following advantages: (1) recyclable catalyst, (2) wider substrate scope, (3) higher TON, (4) easy catalyst/product separation (5) oxidant free and first example of *β*-methylation for primary aliphatic alcohols.

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