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Polystyrene trimethyl ammonium chloride impregnated Rh(o) (Rh@PMe3NCl) as a catalyst and methylating agent for esterification of alcohols through selective oxidation of methanol†

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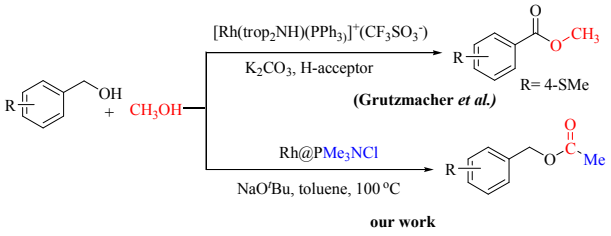
The polystyrene trimethyl ammonium chloride (PMe_3NCl) resin impregnated rhodium(0) nanoparticles (NPs) (Rh@ PMe_3NCl) under basic condition act as cross-dehydrogenative coupling-methylating (CDCM) agent for selective oxidation of methanol and it's *in situ* reaction with benzyl/ alkyl alcohols following methyl transfer to acetate esters synthesis in a tandem approach. Redox property of methanol which restricts oxidation of benzyl/ alkyl alcohols for product formation is critically investigated.

Esters constitute a major class of floral volatiles, as well as, contributing to the aroma of fruits, used primarily as a component of cosmetics, perfumery and can be found in natural products, bulk chemicals, fine chemicals, and polymers.[1] Volatile esters such as 2-phenylethyl acetate and geranyl acetate are primary contributors to the fragrance of roses and many other flowers and served as valuable intermediates in organic synthesis.[2,3] Acetate esters are generally prepared by the reactions of acetic acid and alcohols using acid catalysts, the reaction of activated acid derivatives (acyl chlorides and anhydrides) with alcohols, addition of ketenes to alcohols and O-selective acylation of amino alcohols.[4] But starting from alcohols such type of acetate esters synthesis are unusual, though alcohols are more readily available, easy to handle, cheaper, less toxic and more stable bulk materials than the carbonyl compounds. In recent years, transition metal catalyzed oxidative transformations or cross-dehydrogenative coupling of benzyl alcohols have drawn enormous interest as an alternative approach for the synthesis of esters or amides through a tandem dehydrogenation-functionalization pathway.[5] These "hydrogen-borrowing methodology" using another alcohol as secondary component always leads to the formation of benzoate as the esterification product.

Applying similar concept, Grützmacher and co-workers reported a cationic rhodium complex performing as an active catalyst for the dehydrogenative coupling of primary hydroxyl groups with water, methanol, or amines to furnish carboxylic acids, methyl esters, or amides.[6] Very recently Beller and Lei groups demonstrated oxidative esterification reactions from alcohols using homogeneous palladium catalyst and Ag salts for methyl benzoate as well as self-esterification of benzyl alcohol to benzyl benzoate synthesis.[7,8] In all the previous



Scheme 1. Comparative study of Rh-catalyzed oxidative esterification of benzyl alcohol.

reports, benzyl alcohols first get oxidized into their corresponding benzaldehydes and then coupled with alkyl alcohol to produce benzoate esters. To date, there is no single report of the transition metal catalyzed oxidative esterification of methanol with benzyl or alkyl alcohols for the synthesis of benzyl or alkyl acetates via cross dehydrogenative coupling methylation (CDCM) approaches (Scheme 1). Due to the high oxidation potential of methanal, the oxidation of methanol are very harder to accomplish than most primary benzyl alcohols and also require very harsh oxidative or electrolytic conditions for their oxidations.[9] In the present investigation, the developed heterogeneous rhodium catalyst (Rh@PMe$_3$NCl) has been applied to perform extraordinarily reverse order of reactivity for oxidation of methanol instead of benzyl/ alkyl alcohols for acetate esters synthesis following high degree of selectivity, dehydrogenative oxidation, redox reaction, electrophilic methyl transfer and coupling approaches. The profound mechanistic pathway for the reaction and behavior of catalyst makes the process unprecedented for benzyl/ alkyl acetate esters synthesis from methanol.

Last few years our group has been working in the area of solid supported transition metal (SS-Pd, -Pt, -Rh and -Ru) NPs development as heterogeneous catalyst and their applications in different organic transformations.[10] In this study, Rh@PMe$_3$NCl (formerly reported as SS-Rh) was synthesized following our previous report[11] and characterized by Transmission electron microscopy

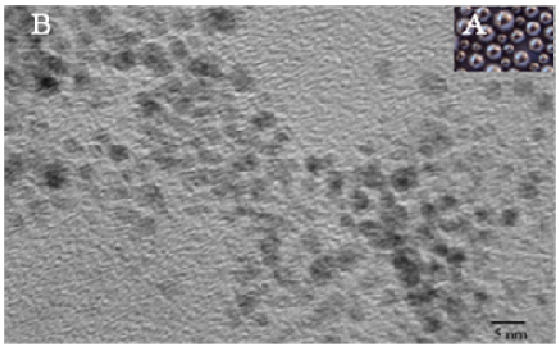


Fig. 1 A. Rh@PMe$_3$NCl; B. TEM image of Rh@PMe$_3$NCl before use

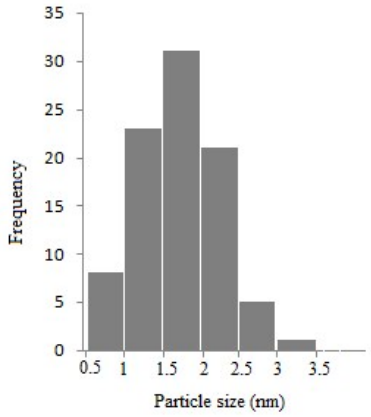


Fig 2. Histogram of Rh@PMe$_3$NCl representing the distribution of Rh(0) nanoparticles before use

(TEM) (Fig. 1(B)), Energy dispersive x-ray (EDX) (Fig. 3), FTIR (Fig. 4), single crystal analysis, Hg(0) poisoning test and ICP-AES analysis (supporting information).

The high resolution transmission electron micrograph (HRTEM) was performed to analyze the morphological feature of Rh@PMe$_3$NCl (Fig. 1(B)). The sample for TEM analysis was prepared following the same process as described for SS-Rh.[10] HRTEM study of Rh@PMe$_3$NCl

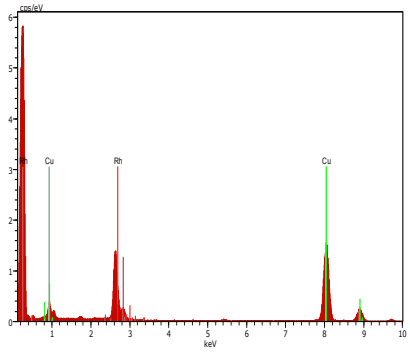


Fig. 3 Energy Dispersive X-ray spectroscopy (EDX) of Rh@PMe$_3$NCl

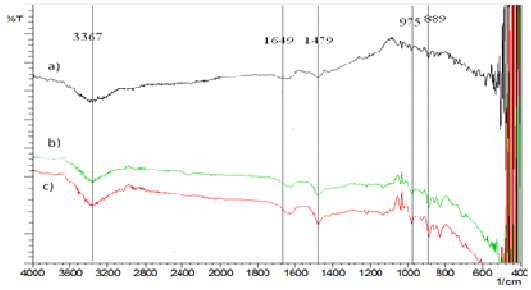
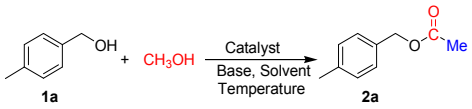


Fig 4. FTIR spectra of prepared samples a) PMe$_3$NCl b) Rh@PMe$_3$NCl before reaction c) Rh@PMe$_3$NCl after use.

Table 1. Optimization of methodology for acetate ester synthesis.[a]



1a **2a**

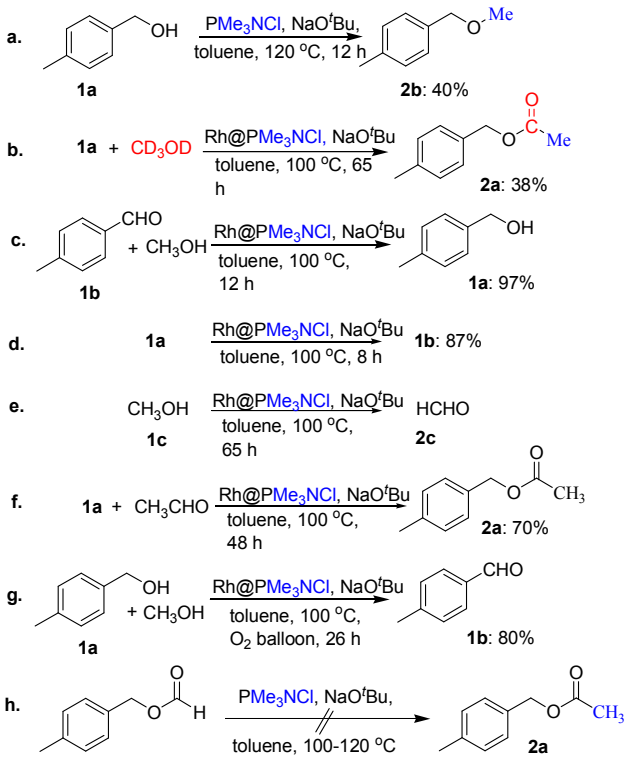
Entry	Catalyst (mol% Rh)	Base	Solvent	Temp. (°C)	Yield [%][b]
1	Rh@PMe$_3$NCl (2)	K_2CO_3	Toluene	100	n.d
2	Rh@PMe$_3$NCl (2)	Na_2CO_3	Toluene	100	n.d
3	Rh@PMe$_3$NCl (2)	KF	Toluene	100	n.r
4	Rh@PMe$_3$NCl (2)	Et_3N	Toluene	100	n.d
5	Rh@PMe$_3$NCl (2)	KOH	Toluene	100	62
6	Rh@PMe$_3$NCl (2)	KO^{t}Bu	Toluene	100	27
7	Rh@PMe$_3$NCl (1)	NaO^{t}Bu	Toluene	100	45
8	**Rh@PMe$_3$NCl (2)**	**NaO^{t}Bu**	**Toluene**	**100**	**64**
9	Rh@PMe$_3$NCl (3)	NaO^{t}Bu	Toluene	100	64
10	Rh/C (2)	NaO^{t}Bu	Toluene	100	n.r
11	$RhCl_3$ (2)	NaO^{t}Bu	Toluene	100	n.r
12	[(RhCp*Cl$_2$)$_2$] (2)	NaO^{t}Bu	Toluene	100	n.r
13	Rh@PMe$_3$NCl (2)	NaO^{t}Bu	DMF	100	n.r
14	Rh@PMe$_3$NCl (2)	NaO^{t}Bu	Acetonitrile	100	n.r
15	Rh@PMe$_3$NCl (2)	NaO^{t}Bu	PEG-400	100	n.d
16	Rh@PMe$_3$NCl (2)	NaO^{t}Bu	Toluene	80	32
17	Rh@PMe$_3$NCl (2)	NaO^{t}Bu	Toluene	110	57

[a]All reactions were carried out with *p*-Me benzyl alcohol (1 eqv.), methanol (1.2 mL), base (3 eqv.), toluene (1.5 mL) and time = 65 hours.[b]Isolated yield (2a); n.r.= no reaction; n.d.= not detected.

revealed that the average particle size distribution of Rh(0) over the matrix was found to be in the range of 1-2 nm (Fig. 2).

Meanwhile, Energy dispersive x-ray (EDX) spectrum indicated the existence of rhodium in the analyzed region. The FTIR studies of PMe_3NCl and Rh@PMe_3NCl (before and after use) were shown in Figure 4. A broad absorption band, characteristic of aromatic C-C double bond, centred at around 1649 cm^{-1} in Fig. 4 a) was shifted to a lower wavenumber region, 1625 cm^{-1} in both Fig. 4 b) and c) indicating the weak Π-bond interaction of resin backbone with the Rh-centre in the prepared catalyst. No significant structural change of Rh@PMe_3NCl surface was observed after methylation reaction through FTIR study.

Unintentionally, in some trial reactions we observed that methanol in presence of Rh@PMe_3NCl, NaO^{t}Bu in toluene at 100 ^oC behaved as a redox reagent and it reduced benzaldehyde to benzyl alcohol as major product with minor quantity of benzyl acetate. The minor unexpected leads of benzyl acetate opened up opportunity for thinking its in-depth possibility. In a second attempt, when benzyl alcohol was treated with methanol in presence of Rh@PMe_3NCl (2 mol% Rh), NaO^{t}Bu (1 eqv.) in toluene under closed condition at 100 ^oC giving unexpected major product of benzyl acetate (Scheme 1). First time such an observation where benzyl alcohol remained unoxidized in the reaction mixture and methanol get oxidized and finally unexpected benzyl acetate formed as major product was reported. To fix the methodology, all the related parameters (catalyst, base, solvent and temperature) were extensively investigated for the acetates synthesis (Table 1). The best optimized condition was found to be *p*-Me benzyl alcohol (1eqv.), methanol (1.2 mL), NaO^{t}Bu (3 eqv.), Rh@PMe_3NCl (2 mol% Rh), toluene (1.5 mL) at 100 ^oC under closed refluxing condition in 65 hours afforded the corresponding acetate product **2a** in 64% yield (Table 1, entry 8).



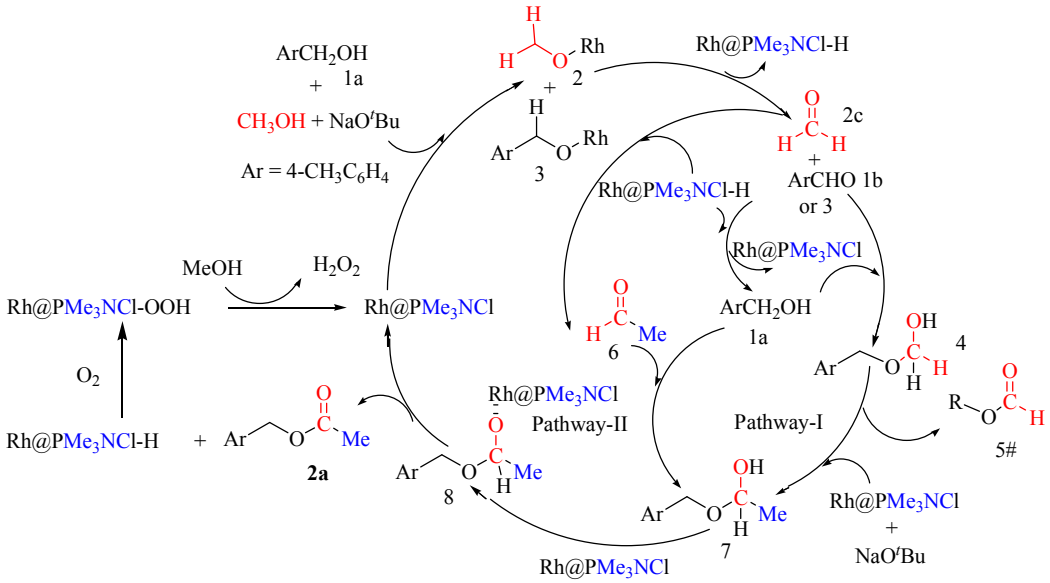
Scheme 2. Set of reactions performed to proof the mechanism.

To prove the detailed mechanistic study, a set of reactions have been intended for the CDCM esterification reactions. In an attempt, when **1a** was treated with PMe_3NCl (without Rh catalyst), NaO^{t}Bu in toluene at 120 ^oC, the reaction gave 1-(methoxymethyl)-4-methylbenzene (**2b**) as the sole product which indicated that with nucleophilic centre, PMe_3NCl resin behaved as a methylating agent (Scheme 2, (**a**)). In another study, when **1a** was treated with CD_3OD under standard condition, **2a** was isolated as the major product which indicated that one methyl group was transferred from Rh@PMe_3NCl (Scheme 2, (**b**)). Interestingly, when *p*-Me benzaldehyde (**1b**) was treated with methanol under standard condition, it gave major *p*-Me benzyl alcohol (**1a**) in 97% yield as reduced product (Scheme 2, (**c**)).While performing the reaction in the absence of methanol, **1a** was quantitatively oxidized through *β*-hydride elimination to **1b** in 87% yield (Scheme 2, (**d**)), which indicated that methanol behaved as a redox reagent under this standard catalytic conditions. In a controlled reaction, formation of formaldehyde (**2c**) from methanol (**1c**) in reaction mixture was detected by GC analysis (Scheme 2, (**e**)) and supporting information). Interestingly, when **1a** was treated with acetaldehyde under the same condition, the reaction ended with **2a** as the major product in 70% yield (Scheme 2, (**f**)). However, when the reaction of benzyl alcohol 1a and methanol under standard Rh@PMe_3NCl catalytic condition was performed in presence of O_2 balloon, the reaction ended with benzaldehyde 1b in 80% yield as oxidized product and no desired acetate ester was formed (Scheme 2, (g)). Similarly, while conducting the same reaction under N_2 atmosphere, the acetate 2a was obtained in 10% yield. Therefore, the traces of oxygen play a crucial role in obtaining the desired acetate **2a**.

In the proposed mechanism, initially methanol and benzyl alcohol co-ordinates to the rhodium followed by *β*-hydride elimination to produce **2c** (Scheme 2, (**e**)) and *p*-Me benzaldehyde in traces (detected by GCMS) (Scheme 3). Further, the liberated hydride either reduce the *p*-Me benzaldehyde to the corresponding alcohol (proved in Scheme 2, (**c**)) in a redox cycle or force to convert rhodium co-ordinated benzyl alcohol (**3**) to **1a** (Scheme 3), which further reacts with formaldehyde (**2c**) to generate the respective hemiacetal **4** (confirmed from byproduct 5 detected by GCMS, Scheme 3). Formation of hemiacetal **7** may occur through two different pathways. In one possible Pathway-I, hemiacetal **4** transforms into another hemiacetal **7** through *in situ* electrophilic methyl transfer from Rh@PMe_3NCl in presence of base. However, treatment of *p*-Me benzylformate with PMe_3NCl under basic conditions did not led to the formation of desired ester **2a** indicating methyl transfer could not take place at this stage (proved in Scheme 2, (**h**)). In an alternative mode, formaldehyde **2c** may get converted into acetaldehyde **6** through the methyl transfer from Rh@PMe_3NCl, which directly reacts with the benzyl alcohol (**1a**) to generate the hemiacetal **7** (Pathway-II, Scheme 3 and proved in Scheme 2, (**f**)). Finally, the hemiacetal **7** through co-ordination with Rh@PMe_3NCl followed by *β*-hydride elimination gives rise to acetate **2a** as the esterification product. The result obtained from Scheme 2(**g**), it is obvious that the role of O_2 provided in the mechanism is to regenerate active catalyst for the catalytic cycle only.

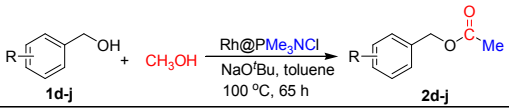
The standard experimental condition was then applied to a variety of substituted benzyl alcohols and no such significant electronic and steric effect was observed on product yields (Table 2, entries 1-6). 1-Naphthyl methanol (**1j**) also gave the desired product **2j** in 62% yield indicating the steric control had no role on the outcome of the reaction (Table 2, entry 7). Conversely, for all the reactions in Table 2, no methyl benzoate was detected by GCMS.

The protocol for the oxidative esterification of benzyl alcohols with methanol was extended to the aliphatic primary and allylic alcohols with the optimized catalyst system. Both the electron donating and withdrawing aliphatic primary alcohols (saturated and unsaturated) were efficiently participated in the oxidative esterification reactions and



Scheme 3. Probable mechanism of acetate ester synthesis. #By-product detected by GCMS for compound **1q** (supporting information).

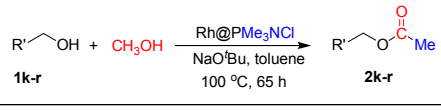
Table 2. Rh@PMe$_3$NCl catalyzed CDCM reaction of substituted benzyl alcohols with methanol for acetates synthesis.[a]



Entry	Substrate	Product	Yield[%][b]
1	1d	2d	61
2	1e	2e	60
3[c]	1f	2f	70
4	1g	2g	60
5	1h	2h	57
6	1i	2i	66
7	1j	2j	62

[a]Reaction conditions: Substituted benzyl alcohols, 1d–j (1 eqv.), NaO^{t}Bu (3 eqv.), methanol (1.2 mL), Rh@PMe$_3$NCl (2 mol% Rh) in toluene (2 mL).[b]Isolated yields. [c]KOH (3 eqv.) used as base.

Table 3. Rh@PMe$_3$NCl catalyzed CDCM reaction of aliphatic primary alcohols with methanol for acetates synthesis.[a]



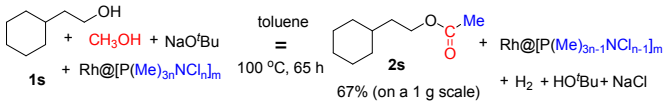
Entry	Substrate	Product	Yield [%][b]
1	1k	2k	62
2	1l	2l	65
3	1m	2m	62
4	1n	2n	60
5	1o	2o	65
6	1p	2p	67
7	1q	2q	66
8	1r	2r	65

[a]Reaction conditions: aliphatic primary alcohols, 1k–r (1 eqv.), NaO^{t}Bu (3 eqv.), methanol (1.2 mL), Rh@PMe$_3$NCl (2 mol% Rh) in toluene (2 mL).
[b]Isolated yields.

converted into the corresponding acetates with comparable yields (Table 3, entries 1-8) and no self oxidative esterification product was observed.[12]

To see the applicability of the method for oxidative esterification following CDCM reaction of methanol with **1s** was recognized under

standard condition for the gram scale synthesis of acetate ester **2s** in 67% yield (Scheme 4).



Scheme 4. Gram scale synthesis of acetate ester. #The generalized form of Rh@[P(Me)$_{3n}$NCl$_n$]$_m$ has been mentioned as Rh@[P(Me)$_3$NCl in the manuscript to avoid confusion (detail provided in supporting information).

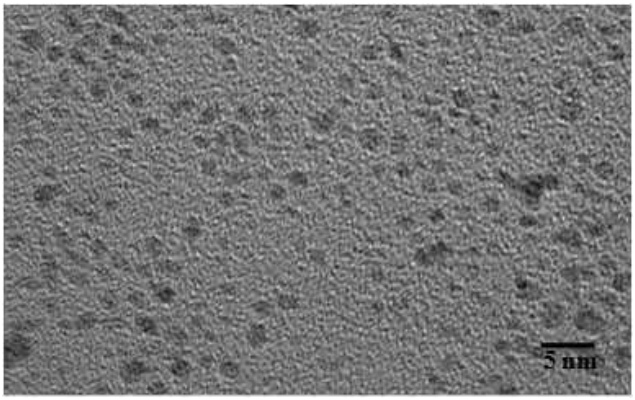


Fig 5. TEM image of Rh@PMe$_3$NCl after six cycles of esterification

In the recyclability experiment, TEM study of Rh@PMe$_3$NCl after six cycles of reaction showed the presence of Rh NPs in the solid matrix (Fig. 5). Moreover, inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis of the crude reaction mixture indicated that after six cycles of reaction, only 0.336 ppm of Rh in total was leached into the reaction mixture (supporting information).

Conclusions

In conclusion, Rh@PMe$_3$NCl NPs as heterogeneous catalyst played a remarkable role for CDCM esterification of benzyl and alkyl alcohols with methanol to generate acetate esters without using any additives or hydrogen acceptors. The process proceeded via preferential dehydrogenative oxidation reaction of methanol in comparison to the activated benzyl and long-chain aliphatic primary alcohols and resulted into the exclusive formation of acetate esters indicating a high degree of selectivity. The unprecedented methodology demonstrated herein is a new findings considering basic scientific approach and could be attractive for future implementation of the process for hydrogen generation from methanol.

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Notes and references

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†Electronic supplementary information (ESI) available: Experimental procedures, preparation and characterization of Rh@PMe$_3$NCl catalyst and full spectroscopy data for all compounds are provided .

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