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Cite this: DOI: 10.1039/c0xx00000x

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PAPER

Synthesis of fluorenones by using Pd(II)/Mg-La mixed oxide catalyst

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

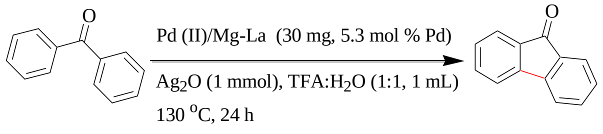
Palladium(II)/magnesium-lanthanum mixed oxide (Pd(II)/Mg-La mixed oxide) catalyst was used in the dehydrogenative cyclization of benzophenones to afford fluorenones. This protocol represents a direct and facile approach for accessing a variety of fluorenone derivatives by means of C-H activation under heterogeneous conditions. The catalyst was recovered by centrifugation and used for three consecutive cycles with nearly consistent activity and selectivity.

1. Introduction

Fluorenones are found in many natural products and medicinally relevant molecules. Generally fluorenone derivatives are known to exhibit extraordinary biological and optical properties.[1] Several methods were developed for the synthesis of fluorenones e.g. oxidation of fluorenol and fluorenes, Friedel-Crafts cyclization of biaryl carboxylic acid derivatives, Pschorr cyclization reaction of 2-haloaryl ketones, cyclization of 2-haloaryl ketones and the cyclocarbonylation of *ortho*-halo biaryls.[2] However, these methods have some disadvantages such as the use of strong acids, strong bases, toxic CO gas and harsh reaction conditions. Larock and coworkers reported the synthesis of fluorenones by an aryl to imidoyl palladium migration process.[3] Daugulis group and J. -C. Hsieh have reported the synthesis of fluorenones from aromatic amides and aryl halides.[4,5] Synthesis of functionalized fluorenones from aromatic aldoxime ethers, aryl halides and benzophenones using Pd(OAc)$_2$ is reported by Cheng and coworkers.[6, 7] Shi et al and others have recently reported the synthesis of fluorenones through dehydrogenative coupling by dual C-H functionalization of benzophenone derivatives using homogeneous palladium acetate catalyst.[8] They have also reported Pd catalyzed synthesis of fluorenones from O-methyl benzaldehyde oxime ethers and aryl boronic acids.[9] Unfortunately, most of these methods involve multistep procedures and requires prefunctionalization of substrate to obtain fluorenones. Hence, a simple route to synthesize fluorenones is highly desirable from the economical and environmental point of view. In the present study, an efficient, straightforward and highly atom economical method is established over Pd(II)/Mg-La mixed oxide catalyst that afforded excellent yields of fluorenone derivatives in a single step under heterogeneous reaction conditions. The fresh and used Pd(II)/Mg-La mixed oxide catalysts are characterized by XRD and TEM analysis and a plausible reaction mechanism is proposed.

2. Results and Discussion

Owing to the industrial prevalence of the heterogeneous catalytic processes over the homogeneous catalytic processes, C-H functionalization using a heterogeneous catalyst constitutes an important area of research in view of its ease of handling, simple workup and regenerability. Earlier, we have demonstrated the catalytic activity of palladium impregnated magnesium lanthanum mixed oxide in the chemoselective hydrogenation of olefinic double bonds [10] and also for the oxidative *sp*^{2} C-H bond acylation with alcohols.[11] Herein, we describe the use of Pd(II)/Mg-La mixed oxide as an efficient heterogeneous and reusable catalyst for dehydrogenative cyclization of readily available benzophenones by dual C-H bond activation to produce industrially important fluorenones (Scheme 1).



Scheme 1 Synthesis of fluorenones over Pd(II)/Mg-La mixed oxide.

2.1. Characterization

The Mg-La mixed oxide was synthesized by co-precipitation of Mg- and La nitrates.[12] The Pd-doped Mg-La mixed oxide catalyst (Pd(II)/Mg-La mixed oxide) was prepared by impregnation method (see experimental section, supporting information).The

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

powder X-ray diffraction analysis of the fresh and used **Pd(II)/Mg-La mixed oxide** catalysts revealed the presence of both $La_2O_2(CO_3)$ and PdO phases (Figure 1). Diffraction lines appeared at 2θ = 29.55°, 22.84°, 13.1° [ICDD # 23-0435] and their corresponding 'd' values 0.302, 0.389 and 0.675 nm are attributed to lanthanum oxide carbonate phase. The diffraction peaks are observed due to PdO phase at 2θ = 31.7°, 45.54°, 27.33° with the corresponding 'd' values of 0.282, 0.199, 0.326 nm that are in good agreement with ICDD # 46-1211.

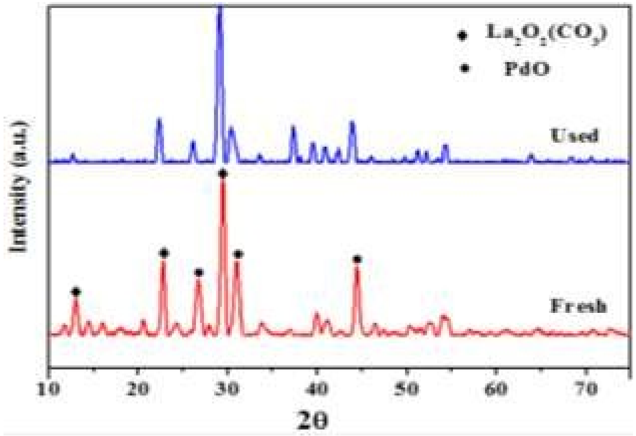


Fig. 1 XRD patterns of the Pd(II)/Mg-La mixed oxide: fresh and used catalysts

The transmission electron microscope (TEM) images of fresh and used (after 1st cycle) Pd(II)/Mg-La mixed oxide catalysts are reported in Figure 1a and Figure 1b. The average Pd particle size is measured from TEM images (Figure 2) and found to be 38 and 43 nm for fresh and used catalysts respectively. The shapes of palladium particles are spherical in both fresh and used samples.

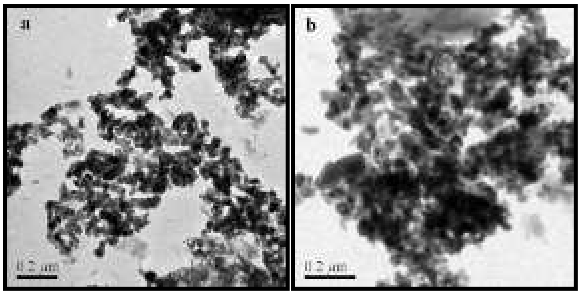


Fig. 2 TEM images of the Pd (II)/Mg-La mixed oxide: [a] fresh and [b] used catalyst (recovered after 1st cycle).

2.2. Dehydrogenative cyclization of benzophenones

In order to optimize the reaction conditions benzophenone was chosen as a model substrate. The reaction of benzophenone using Pd(II)/Mg-La mixed oxide (5.3 mol % of Pd), Ag_2O (1 equiv) and TFA/H_2O (1:1 vol %, 1 mL) at 130 °C for 24 h gave the desired cyclization product i.e. fluorenone with 46% isolated yield (Table 1, entry 1). Encouraged by this result, several optimization studies were conducted by altering the oxidant and solvents. Increasing the quantity of oxidant (Ag_2O, up to 2 equiv.) showed enhanced efficiency in terms of chemical yield (Table 1, entries 1, 2 and 3). Other oxidants such as $Cu(OAc)_2$ and $K_2S_2O_8$ are inactive in the transformation of benzophenone to fluorenone (Table 1, entries 4 and 5). As seen in Table 1, the choice of solvent has a crucial role in the reaction outcome. TFA/water showed excellent cyclization activity (Table 1, entries 7, 9 and 10). However, combination of DMSO and TFA solvents afforded a trace amount of fluorenone. On the other hand, the use of AcOH as a solvent resulted in only 40% yield of the product (Table 1, entries 8 and 11). It is important to note that in the absence of Pd(II)/Mg-La mixed oxide and Ag_2O, the reaction failed to produce any product (Table 1, entries 12 and 13). The **TON is found to be 15.4 which is slightly higher than the earlier report.[7]** The dehydrogenative cyclization of benzophenone is also performed using other heterogeneous catalysts such as Pd(II)/MgO and Pd(II)/La_2O_3 under similar experimental conditions (Table 1, entries 14 and 15). However, both the catalysts afforded lower yields of the product than using Pd(II)/Mg-La mixed oxide catalyst. **Presence of higher number of basic sites on Pd(II)/Mg-La mixed oxide measured by CO_2 pulse chemisorption (Table S1 in SI), seems to increase the electron density on metal sites. As a result of it the catalytic activity of Pd(II)/Mg-La mixed oxide is higher compared to Pd(II)/MgO and Pd(II)/La_2O_3 samples.** Under the optimized reaction conditions, the reactivity of different substituted benzophenones are investigated on Pd(II)/Mg-La mixed oxide catalyst and the results are summarized in Table 2.

Table 1 Screening of reaction parameters for dehydrogenative hydrogenation of benzophenone

Entry	Oxidant/Equiv.	Solvent	Yield (%)[a]
1	Ag_2O/1	TFA/H_2O (1:1)	46
2	Ag_2O/1.5	TFA/H_2O (1:1)	60
3	Ag_2O/2	TFA/H_2O (1:1)	82
4	$Cu(OAc)_2$/5	TFA/H_2O (1:1)	-
5	$K_2S_2O_8$/5	TFA/H_2O (1:1)	-
6	Ag_2O/2	H_2O	-
7	Ag_2O/2	Chlorobenzene	-
8	Ag_2O/2	DMSO/TFA(1mmol)	Trace
9	$Cu(OAc)_2$/5	DCE	-
10	Ag_2O/2	DCE	-
11	Ag_2O/2	AcOH	40
12	-	TFA/H_2O (1:1)	-
13	Ag_2O/2	TFA/H_2O (1:1)	-[b]
14	Ag_2O/2	TFA/H_2O (1:1)	60[c]
15	Ag_2O/2	TFA/H_2O (1:1)	55[d]

a Benzophenone (0.5 mmol), Catalyst (30 mg, 5.3 mol % of Pd), TFA/water (1:1 v/v %) solvent (1 mL).

b Without Pd(II)/Mg-La mixed oxide catalyst.

c Using Pd(II)/MgO (5.3 mol % of Pd) .

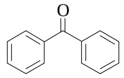
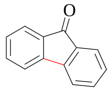
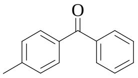
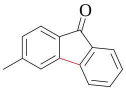
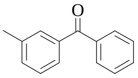
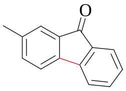
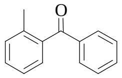
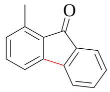
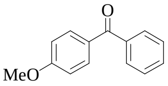
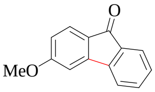
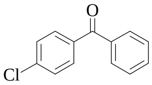
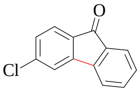
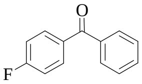
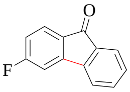
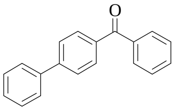
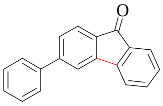
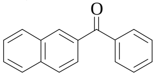
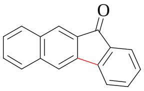
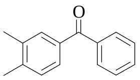
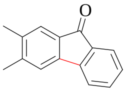
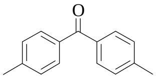
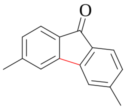
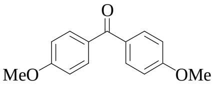
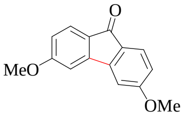
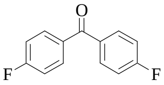
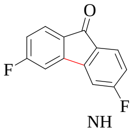
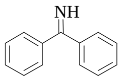
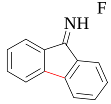
d Using Pd(II)/La_2O_3 (5.3 mol % of Pd).

2.3. Substrate scope

Benzophenones substituted with 4- and/or 3-methyl groups gave the corresponding fluorenone derivatives in 72 and 70% yields respectively [Table 2, entries 2 and 3]. However, the 2-substituted benzophenone resulted in a moderate yield~50% [Table 2, entry

4]. Similarly, 4-methoxy and 4.4′-dimethoxy substituted benzophenones have afforded the corresponding fluorenone products of about 66 and 72% yields within 22 h [Table 2, entries 5 and 12]. It is interesting to note that the Pd(II)/Mg-La mixed oxide is also compatible with chloro and fluoro substituted benzophenones [Table 2, entries 6 and 7].

Table 2 Dehydrogenative cyclization of different benzophenone derivatives.

Entry	Substrate	Product	Time (h)	Yield (%)
1			24	82
2			20	72
3			22	70
4			40	50[b]
5			22	66
6			24	85
7			24	60
8			22	77
9			22	50
10			24	60
11			22	72
12			22	72
13			24	70
14			40	50[b]

Reaction conditions: [a]Substrate (0.5 mmol), Pd(II)/Mg-La mixed oxide catalyst (30 mg, 5.3 mol % of Pd), Ag_2O (2 equiv., 1mmol), TFA/Water (1:1 v/v %, 1 mL) at 130 °C. [b]GC yields.

The 4-phenyl and 4, 4′-difluoro substituted benzophenones afforded fluorenones with 77 and 70% yields respectively [Table 2, entries 8 and 13]. The 3, 4-dimethyl and 4, 4′-dimethyl substituted benzophenones are also examined under the standard reaction conditions which gave fluorenones yields of about 60 and 72% respectively [Table 2, entries 10 and 11]. Under the optimized reaction conditions 2-benzonapthanone is also transformed to benzofluorenone with 50% yield [Table 2, entry 9]. Apart from benzophenone, the benzophenone imine also afforded the desired cyclization product of about 50% yield [Table 2, entry 14]. All the products were carefully characterized by ^1H and ^{13}C NMR spectroscopy.

2.4. Recyclability

The recyclability of the catalyst was examined using benzophenone at 130 °C using 1:1 v/v % of TFA/water as solvent and the results are shown in Figure 3. The activity graph illustrates that the catalyst can be used for 3 consecutive cycles.

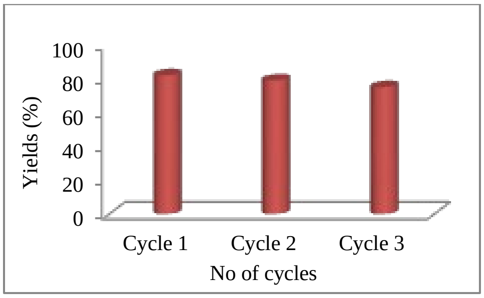


Fig. 3 Recyclability of catalyst.

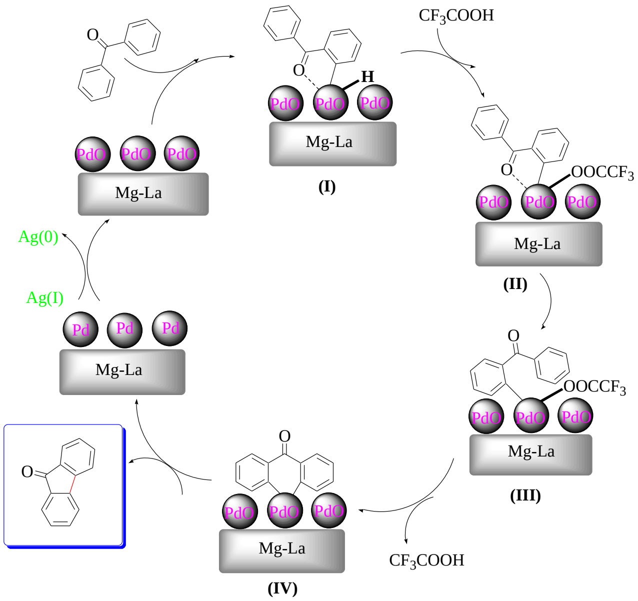
In the recyclability studies, catalyst was recovered by simple centrifugation method. The recovered catalyst was washed with alkali and distilled water, air-dried and reused directly for the next cycle without any further purification. The ICP-MS analysis showed that the Pd content in the fresh and the used catalysts were about 9.6% and 9.0% respectively.

3. Plausible reaction mechanism

A plausible reaction mechanism is proposed and reported in Scheme 2 in conjugation with earlier reports.[6,7] In the first step Pd particle activates the *ortho*-C-H of benzophenones to form (I). In the next step, the activated hydrogen is replaced by trifluoroacetate group which would form (II) as it is expected to be in equilibrium with palladium aryl s-complex in (III). Subsequently the six membered palladium complex (IV) may be formed by activating the second hydrogen of benzophenone. Reductive elimination of (IV) produces Pd(0) and fluorenone. Finally Pd(0) species reacts with Ag(I) to regenerate the active Pd(II) species for further cycles. The XRD analysis Pd(II)/Mg-La mixed oxide also confirmed the presence of PdO phase in used catalyst.

4. Conclusions

In summary, we have developed a simple and effective route for the synthesis of various fluorenone derivatives using a heterogeneous reusable Pd(II)/Mg-La mixed oxide catalyst. Utilization of inexpensive, readily available starting materials, low catalyst loading, H_2O as a solvent, short reaction time and avoiding the use of base are significant advantages in this investigation. Both electron rich and electron poor substrates have been screened in this study and obtained good to excellent yields towards various fluorenones.



Scheme 2 Plausible reaction mechanism of Pd(II)/Mg-La mixed oxide catalyzed synthesis of fluorenones.

Acknowledgements

RK and MS thank the CSIR, New Delhi for the award of Senior Research Fellowship. BV thank UGC for Junior Research Fellowship, SSP thank the RMIT for financial support.

Notes and references

‡ Typical procedure for synthesis of fluorenones by using Pd(II)/Mg-La mixed oxide catalyst: A 10 mL round bottom flask was charged with benzophenone (91.1 mg, 0.5 mmol), Pd(II)/Mg-La mixed oxide (30 mg, 5.3 mol % of Pd), Ag_2O (231.7 mb, 2 equiv., 1mmol) and TFA/H_2O (1:1 v/v %, 1 mL). The round bottom flask was kept stirring at 130 °C for 24 h. After the completion of the reaction, as monitored by TLC, the catalyst was separated by simple centrifugation, washed with distilled water for 5 times times, dried at 100 °C and directly used for the next cycle without any further purification. The reaction mixture was cooled and extracted with dichloromethane (3x5 mL). The combined filtrate was dried with Na_2SO_4 then concentrated and separated on a silica gel column using hexane/EtOAc (15:1) as eluent gave the corresponding pure fluorenone product with 82% yield.

References

1 (*a*) M. L. Greenlee, J. B. Laub, G. P. Rouen, F. DiNinno, M. L. Hammond, J. L. Huber, J. G. Sundelof and G. G. Hammond, *Bioorg. Med. Chem. Lett*., 1999, **9**, 3225-3230; (*b*) P. J. Perry, M. A. Read, R. T. Davies, S. M. Gowan, A. P. Reszka, A. A. Wood, L. R. Kelland and S. Neidle, *J. Med. Chem*., 1999, **42**, 2679-2684; (*c*) M. T. Tierney and M. W. Grinstaff, *J. Org. Chem.*, 2000, **65**, 5355-5359; (*d*) E. Gonza lez-Cantalapiedra, O. de Frutos, C. Atienza, C. Mateo and A. M. Echavarren, *Eur. J. Org. Chem*., 2006, **6**, 1430-1443; (*e*) D. A. Shultz, J. C. Sloop and G. Washington, *J. Org. Chem*., 2006, **71**, 9104-9113; (*f*) K. Itami, K. Tonogaki, T. Nokami, Y. Ohashi and J. -I. Yoshida, *Angew. Chem., Int. Ed*., 2006, **45**, 2404-2409; (*g*) H. Usta, A. Facchetti and J. T. Marks, *Org. Lett*., 2008, **10**, 1385-1388.

2 (*a*) R. A. Fernandes and P. Kumar, *Tetrahedron Lett*., 2003, **44**, 1275-1278; (*b*) W. Qian, E. Jin, W. Bao and Y. Zhang, *Angew. Chem., Int. Ed*., 2005, **44**, 952-955; (*c*) A. Dhakshinamoorthy and M. Alvaro, H. Garcia, *J. Catal*., 2009, **267**, 1-4; (*d*) D. Saio, T. Amaya and T. Hirao, *Adv. Synth. Catal*., 2010, **352**, 2177-2182; (*e*) M. S. Yusubov, A. A. Zagulyaeva and V. V. Zhdankin, *Chem. Eur. J.*, 2009, **15**, 11091-11094; (*f*) L. G. Wade, K. J. Acker, R. A. Earl and R. A. Osteryoung, *J. Org. Chem*., 1979, **44**, 3723-3724; (*g*) C. S. Yi, K.-H. Kwon and D. W. Lee, *Org. Lett*., 2009, **11**, 1567-1569; (*h*) S. Reim, M. Lau and P. Langer, *Tetrahedron Lett*., 2006, **47**, 6903-6905; (*i*) J. Barluenga, M. Trincado, E. Rubio and J. M. Gonza lez, *Angew. Chem., Int. Ed*., 2006, **45**, 3140-3143; (*j*) A. A. Pletnev and R. C. Larock, *Tetrahedron Lett*., 2002, **43**, 2133-2136; (*k*) D. Tilly, S. S. Samanta, A. De, A.-S. Castanet and J. Mortier, *Org. Lett*., 2005, **7**, 827-830; (*l*) G. A. Olah, T. Mathew, M. Farnia and S. Prakash, *Synlett*, 1999, **7**, 1067-1068; (*m*) Z. Yu and D. Velasco, *Tetrahedron Lett*., 1999, **40**, 3229-3232; (*n*) J. N. Moorthy and S. Samanta, *J. Org. Chem*., 2007, **72**, 9786-9789; (*o*) G. Qabaja and G. B. Jones, *J. Org. Chem*., 2000, **65**, 7187-7194; (*p*) N. Chatani, A. Kamitani, M. Oshita, Y. Fukumoto and S. Murai, *J. Am. Chem. Soc*., 2001, **123**, 12686-12687; (*q*) M. A. Campo and R. C. Larock, *Org. Lett*., 2000, **2**, 3675-3677; (*r*) X. Zhang and R. C. Larock, *Org. Lett.*, 2005, **7**, 3973-3976; (*s*) J. P. Waldo, X. Zhang, F. Shi and R. C. Larock, *J. Org. Chem*., 2008, **73**, 6679-6685.

3 J. Zhao, D. Yue, M. A. Campo and R. C. Larock, *J. Am. Chem. Soc*. 2007, **129**, 5288-529.

4 D. Shabashov, J. R. M. Maldonado and O. Daugulis, *J. Org. Chem*., 2008, **73**, 7818-7821.

5 J. -C. Wan, J. -M. Huang, Y. -H. Jhan and J. -C. Hsieh, *Org. Lett*., 2013, **15**, 2742-2745.

6 V. S. Thirunavukkarasu, K. Parthasarathy and C. -H. Cheng, *Angew. Chem*., 2008, **120**, 9604-9607.

7 P. Gandeepan, C. -H. Hung and C. -H. Cheng, *Chem. Commun*., 2012, **48**, 9379-9381.

8 H. Li, R. -Y. Zhu, W. -J. Shi, K. -H. He and Z. J. Shi, *Org. Lett*., 2012, **14**, 4850-4853.

9 C. -L. Sun, N. Liu, B. -J. Li, D. -G. Yu, Y. Wang and Z. -J. Shi, *Org. Lett*., 2010, **12**, 184-187.

10 M. L. Kantam, R. Kishore, J. Yadav, M. Sudhakar and A. Venugopal, *Adv. Synth. Catal*., 2012, **354**, 663-669.

11 R. Kishore, M. L. Kantam, J. Yadav, M. Sudhakar, S. Laha and A. Venugopal, *J. Mol. Catal. A: Chem.*, 2013, **379**, 213-218.

12 (a) A. Cwik, Z. Hella, F.Figueras, *Tetrahedron Lett*., 2006, **47**, 3023–3026.