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An efficient dehydroxymethylation reaction by a palladium catalyst†

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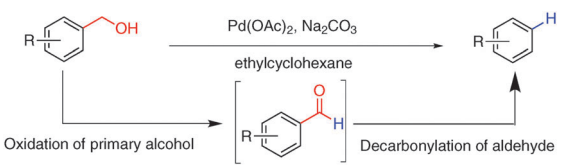
A general method for selective dehydroxymethylation has been discovered by using widely available $Pd(OAc)_2$. The present study offers a new synthetic strategy for the regioselective functionalization by employing the steric, electronic and coordinating nature of the hydroxymethyl ($–CH_2OH$) group temporarily.

The hydroxymethyl group ($–CH_2OH$) can control the stereo- and regiochemical outcome of a reaction through its ability to interact with the incoming reagent or by the complex-induced proximity effect.[1,2] A number of natural products were reported based on a crucial dehydroxymethylation reaction involving two separate catalysts to promote oxidation of alcohol to aldehyde and subsequent decarbonylation.[3] Removal of the hydroxymethyl group in a stepwise manner has also been suggested in biological chemistry.[4] For example, dehydroxymethylation is a key process in DNA demethylase activity which involves (1) oxidation of $R–CH_2OH$ to R–CHO and (2) subsequent decarbonylation of R–CHO to R–H.[4] A single catalyst that can selectively remove the $–CH_2OH$ group, therefore, is expected to have considerable synthetic applications.

Oxidation of alcohol to the corresponding aldehyde has previously been reported in the literature.[5] Although aldehyde decarbonylation was known,[6] only recently we reported a Pd-catalyzed decarbonylation reaction.[7] Subsequently, we envisaged that a dehydroxymethylation reaction might be successful by using palladium (Scheme 1) as it can promote both oxidation[5] and decarbonylation reactions.[7]

Consistent with our expectations, upon optimization, high yields of the desired products from aromatic hydroxymethyl groups were obtained under aerobic conditions with $Pd(OAc)_2$ as the catalyst and Na_2CO_3 as the base. Control experiments in which the metal was omitted resulted in no product formation. This "ligand-free",[9] operationally simple and scalable method is tested with a range of substrates of varying complexity. Notably, a CO scavenger was not required for the smooth functioning of the present protocol.



Scheme 1 Pd-catalyzed removal of the $–CH_2OH$ group.

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Non-functional fused-ring aryl compounds were investigated first and all gave the desired products efficiently (Table 1, **1**–**4**). As anticipated, biphenyl-4-methanol resulted in biphenyl (**6**) in high yield (93%). Various arenes bearing common functional groups such as an ester (**8**), a phenolic –OH (**11**), a cyano[10] (**18**) and even a free amine ($–NH_2$) at the *ortho* position (**15**) were tolerated under the current reaction conditions. These examples demonstrate the power of this strategy to effect selective removal of the hydroxymethyl group.[8b] Electron deficient substrates such as those substituted with nitro (**7** and **12**) and trifluoromethyl (**14**) groups were found to be compatible under the reaction conditions.

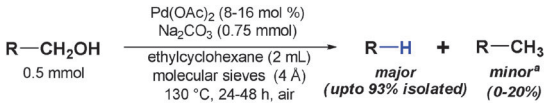
Of interest, 4-benzyloxy benzyl alcohol, which is highly prone to alkyl benzyl ether C–O bond cleavage,[11,12] gave the expected dehydroxymethylation product (**20**) in moderate yield. Benzyl alcohol (**10**) was generated as the major product (60%) from 1,4-phenylenedimethanol.[13] Even a slightly crowded $–CH_2OH$ group (**17**) can be tolerated under the present protocol.[13] The entries in Table 1 demonstrate that the present dehydroxymethylation strategy can be implemented successfully in complex molecular settings with various functional groups.

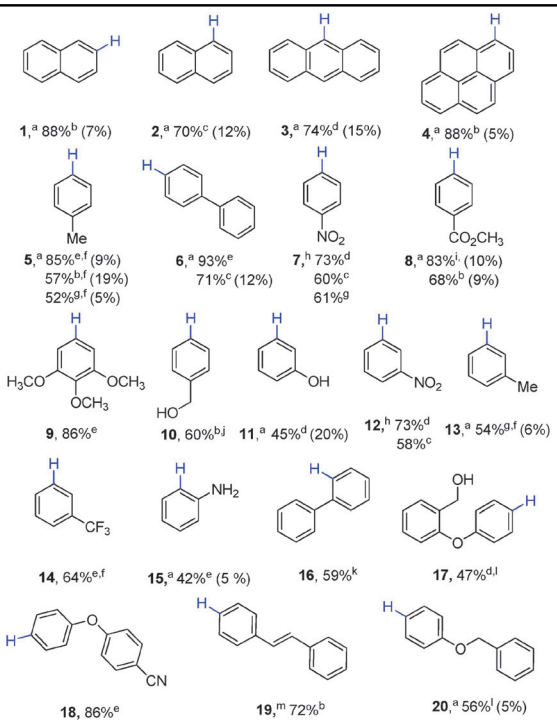
Lower product yields, as seen in few cases, can be attributed to incomplete conversion of $R–CH_2OH$, generation of R–CHO (*vide infra*) and/or due to the formation of $R–CH_3$.[13] Side-products $R–CH_3$ were successfully isolated (entries **1**, **6** and **11**). In all other cases, yields of the minor products were determined based on GC-results. We also found that amounts of these side-products vary with catalyst loadings.[13]

To examine and explore the scope of the present method further, heterocyclic and aliphatic derivatives were evaluated under the optimized conditions (Table 2). In general, the reactions were as effective as that of the aryl-CH_2OH derivatives to yield the desired product. High yields using quinoline (**21**), azaindole (**24**) and dibenzo[*b*,*d*]thiophene (**28**) containing substrates were observed. Five membered heterocyclic substrates with two heteroatoms (**23** and **25**) performed well under these reaction conditions. In addition, the more challenging substrates such as 2-hydroxymethyl indole (**22**) and 2-hydroxymethyl benzo[*b*]thiophene (**26**) gave the desired product in preparatively useful yields. As we anticipated, the *N*-protected azaindole (**24**) has performed better than the unprotected indole (**22**). Simple alkane (**32** and **33**) and alkenyl (**30** and **31**) substrates were also dehydroxymethylated despite their propensity to undergo β-H elimination and formation of homo-coupled side products.

Since hydroxymethyl groups are found in biologically and pharmaceutically relevant compounds,[2] we decided to test our

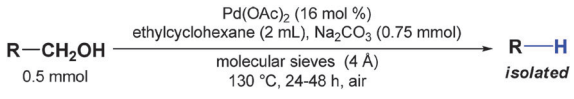
Table 1 Scope of dehydroxymethylation reactions[13]

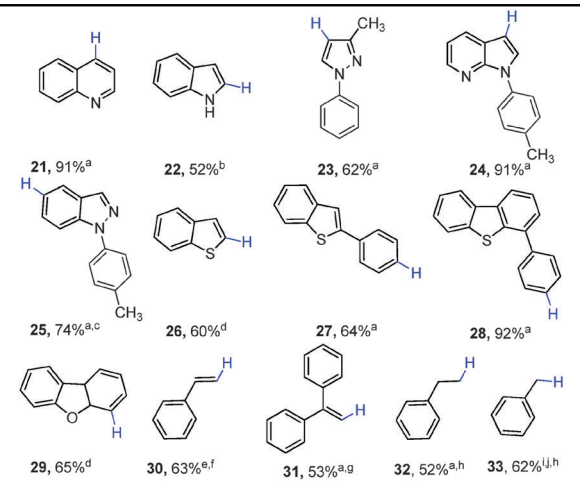




[a] Minor products, R–CH_3, are depicted in parentheses. [b] 36 h. [c] 48 h. [d] 12 mol% Pd, 24 h, cyclohexane. [e] 16 mol% Pd, 48 h, cyclohexane. [f] GC yield. [g] 8 mol% Pd, 24 h, cyclohexane. [h] Aniline was detected (7–14%). [i] 12 mol% Pd, 36 h, cyclohexane. [j] 8% benzene and 4% PhCHO. [k] 20 mol% Pd, 48 h, cyclohexane. [l] 24 h. [m] 1,2-Diphenylethane was detected (20%).

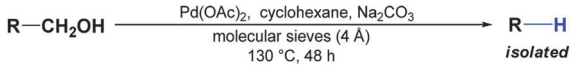
Table 2 Heterocyclic and aliphatic substrates[13]

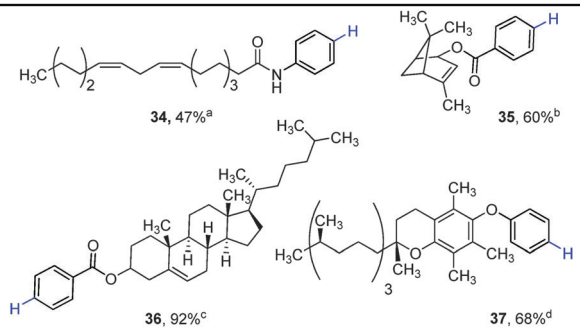




[a] Cyclohexane, 48 h. [b] 24 h. [c] 5% aldehyde isolated. [d] 36 h. [e] 12 mol% Pd, 24 h, cyclohexane. [f] 10% ethylbenzene and 5% 3-phenylpropan-1-1-ol were detected. [g] 10% homocoupled product. [h] GC yield. [i] 30 mol% Pd. [j] 5% ethylbenzene was detected.

Table 3 Application to natural product derivatives[13]





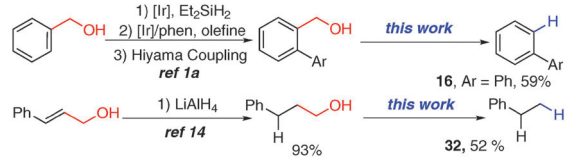
[a] 20 mol% Pd, 29% recovered starting material. [b] 20 mol% Pd, 20% recovered starting material. [c] 20 mol% Pd. [d] 50 mol% Pd, isolated respective aldehyde 28%, 5% recovered starting material.

method in complex settings (Table 3). In this context, a substrate derived from cholestan-3-ol of the steroid cholesterol family that comprises seven contiguous stereo centers was selectively dehydroxymethylated in an excellent yield (**36**).[13] Natural product derived substrates containing (multiple) alkene and an amide (**34**) or an ester (**35**) can further reinforce the utility of this method in complex molecular settings.[13]

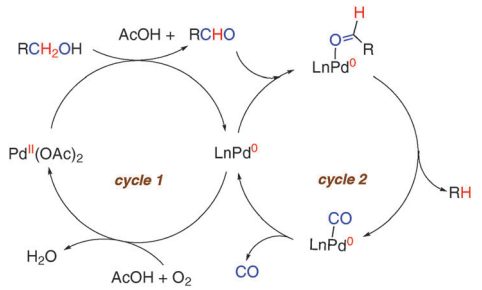
Having tested a dehydroxymethylation reaction in complex natural product derivatives, we sought to apply the protocol in diverse synthetic transformations. In this respect, one can synthesize biphenyl from benzyl alcohol by implementing the dehydroxymethylation strategy in the final step (Scheme 2).[1b] Ethylbenzene can be generated from cinnamyl alcohol by taking advantage of the present protocol (Table 2).[2,14] These results (Scheme 2) highlight the importance of the –CH_2OH functional as a directing group[2] and demonstrate the use of it in suitable settings.

Catalytic "cycle 1" can be suggested based on the well-established literature involving oxidation of alcohol to aldehyde under similar conditions (Scheme 3).[5] "Cycle 2" is proposed based on our previous work on Pd-catalyzed decarbonylation reaction under similar conditions.[7,15]

Consistent with the proposal in Scheme 3, we have isolated aldehyde as the by-product (*e.g.* 4% entry **10**, 28% entry **37**, 5% entry **25**) under the reaction conditions. A high catalyst loading is needed since two catalytic cycles operate in sync to generate the desired dehydroxymethylated product.[13] On a related note, neither the corresponding carboxylic acid from dehydroxymethylation reaction was detected in any case (Tables 1–3,) nor an appreciable amount of decarboxylation product was observed by reacting the respective carboxylic acids under present conditions.[13] Moreover, when 1-naphthalene–CD_2OH was subjected to

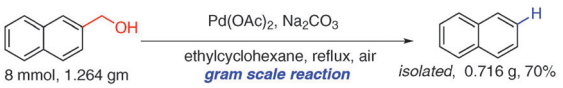


Scheme 2 Synthetic application.[13]



Scheme 3 Proposed catalytic cycles.

Scheme 4 Proposed pathways[5] for generation of R–CH_3.



Scheme 5 Large scale reaction.

the reaction conditions, 1-naphthalene–CD_2H was detected by GC-MS (~5%).[13] These observations helped us to suggest a mechanism for the generation of minor products under the present conditions (Scheme 4).[5] Note that in the absence of any exogenous ligand, substrates under study such as R–CH_2OH or R–CHO, which are generated during the course of the reaction, may act as the ligand for palladium.[9]

Additionally, the reaction proved to be scalable, with 2-naphthalenemethanol on a gram scale, delivering 70% of the desired product (Scheme 5). Aside from the wide substrate scope and functional group tolerance, it is worth noting that this method works under air and without any need for solvent purification.

We are presently studying the detailed mechanism of this reaction and also working on increasing the turnover number of the catalyst. Nevertheless, the results of this work have demonstrated that the selective cleavage of the –CH_2OH group can be conducted by simply using widely available $Pd(OAc)_2$.[16] The scope of the reaction is broad, allowing the dehydroxymethylation of aryl substrates, as well as the extension of this protocol to heteroaromatic and aliphatic moieties. The present study also offers a new synthetic strategy for the regioselective functionalization by employing the steric, electronic and coordinating nature of the –CH_2OH group temporarily. This advance clearly impacts one of the limitations of the existing practice of dehydroxymethylation, which usually required two separate catalytic systems.

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Notes and references

1 (*a*) E. M. Simmons and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 17092–17095; (*b*) K. M. Engle, T. S. Mei, M. Wasa and J. Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802.
2 A. H. Hoveyda, D. A. Evans and G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307–1370.
3 (*a*) J. E. Baldwin and A. P. Kostikov, *J. Org. Chem.*, 2010, **75**, 2767–2775; (*b*) F. A. Khan and B. Rout, *Tetrahedron Lett.*, 2006, **47**, 5251–5253; (*c*) S. Ikeda, M. Shibuya and Y. Iwabuchi, *Chem. Commun.*, 2007, 504–506; (*d*) W. J. Koot and S. V. Ley, *Tetrahedron*, 1995, **51**, 2077–2090; (*e*) K. G. Liu, A. Chougnet and W. D. Woggon, *Angew. Chem., Int. Ed.*, 2008, **47**, 5827–5829; (*f*) G. S. Weatherhead, G. A. Cortez, R. R. Schrock and A. H. Hoveyda, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5805–5809; (*g*) K. G. Liu and W. D. Woggon, *Eur. J. Org. Chem.*, 2010, 1033–1036.
4 (*a*) K. I. Ladwein and M. Jung, *Angew. Chem., Int. Ed.*, 2011, **50**, 12143–12145; (*b*) M. Munzel, D. Globisch and T. Carell, *Angew. Chem., Int. Ed.*, 2011, **50**, 6460–6468; (*c*) T. Pfaffeneder, B. Hackner, M. Truss, M. Munzel, M. Muller, C. A. Deiml, C. Hagemeier and T. Carell, *Angew. Chem., Int. Ed.*, 2011, **50**, 7008–7012; (*d*) M. Munzel, D. Globisch, C. Trindler and T. Carell, *Org. Lett.*, 2010, **12**, 5671–5673.
5 (*a*) K. M. Gligorich and M. S. Sigman, *Angew. Chem., Int. Ed.*, 2006, **45**, 6612–6615; (*b*) M. S. Sigman and D. R. Jensen, *Acc. Chem. Res.*, 2006, **39**, 221–229; (*c*) B. A. Steinhoff, S. R. Fix and S. S. Stahl, *J. Am. Chem. Soc.*, 2002, **124**, 766–767; (*d*) M. J. Schultz, C. C. Park and M. S. Sigman, *Chem. Commun.*, 2002, 3034–3035; (*e*) B. A. Steinhoff and S. S. Stahl, *Org. Lett.*, 2002, **4**, 4179–4181; (*f*) M. J. Schultz, S. S. Hamilton, D. R. Jensen and M. S. Sigman, *J. Org. Chem.*, 2005, **70**, 3343–3352; (*g*) M. Hayashi, K. Yamada and S. Nakayama, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1501–1503; (*h*) F. Batt, C. Gozzi and F. Fache, *Chem. Commun.*, 2008, 5830–5832; (*i*) T. Nishimura, N. Kakiuchi, M. Inoue and S. Uemura, *Chem. Commun.*, 2000, 1245–1246.
6 (*a*) T. Iwai, T. Fujihara and Y. Tsuji, *Chem. Commun.*, 2008, 6215–6217; (*b*) T. C. Fessard, S. P. Andrews, H. Motoyoshi and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2007, **46**, 9331–9334; (*c*) B. Morandi and E. M. Carreira, *Synlett*, 2009, 2076–2078; (*d*) M. Kreis, A. Palmelund, L. Bunch and R. Madsen, *Adv. Synth. Catal.*, 2006, **348**, 2148–2154.
7 (*a*) A. Modak, A. Deb, T. Patra, S. Rana, S. Maity and D. Maiti, *Chem. Commun.*, 2012, **48**, 4253–4255; (*b*) Akanksha and D. Maiti, *Green Chem.*, 2012, **14**, 2314–2320.
8 (*a*) Just recently, a Rh-catalyzed photocatalytic alcohol decarbonylation has been developed H.-A. Ho, K. Manna and A. D. Sadow, *Angew. Chem., Int. Ed.*, 2012, **51**, 8607–8610. Our Pd-catalyzed method is found to be complementary to this report. The Rh-catalyzed method is efficient with aliphatic substrates, whereas a much better substrate scope of aromatic and heteroaromatic moieties is obtained with $Pd(OAc)_2$; (*b*) The Rh-catalyzed method[8a] failed completely (yield, 0%) with substituted benzyl alcohol (4-X–$C_6H_4CH_2OH$; X = NO_2, CO_2Me, *etc.*), whereas our method produces acceptable yields of the expected product (Table 1, entries **7**, **8**, *etc.*).
9 *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, Germany, 2nd edn, 2004.
10 M. Tobisu, R. Nakamura, Y. Kita and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 3174–3175.
11 (*a*) P. Alvarez-Bercedo and R. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 17352–17353; (*b*) A. G. Sergeev and J. F. Hartwig, *Science*, 2011, **332**, 439–443; (*c*) M. Tobisu, K. Yamakawa, T. Shimasaki and N. Chatani, *Chem. Commun.*, 2011, **47**, 2946–2948; (*d*) T. Mesganaw, N. F. Fine Nathel and N. K. Garg, *Org. Lett.*, 2012, **14**, 2918–2921; (*e*) N. Barbero and R. Martin, *Org. Lett.*, 2012, **14**, 796–799.
12 B. A. Ellsworth, W. Meng, M. Patel, R. N. Girotra, G. Wu, P. M. Sher, D. L. Hagan, M. T. Obermeier, W. G. Humphreys, J. G. Robertson, A. Y. Wang, S. P. Han, T. L. Waldron, N. N. Morgan, J. M. Whaley and W. N. Washburn, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4770–4773.
13 See ESI†.
14 F. A. Hochstein and W. G. Brown, *J. Am. Chem. Soc.*, 1948, **70**, 3484–3486.
15 Note that mechanistically Rh-catalyzed methods are different compared to the Pd-catalyzed process discussed here[8]. (*a*) D. Morton and D. J. Colehamilton, *J. Chem. Soc., Chem. Commun.*, 1987, 248–249; (*b*) D. Morton, D. J. Colehamilton, I. D. Utuk, M. Panequesosa and M. Lopezpoveda, *J. Chem. Soc., Dalton Trans.*, 1989, 489–495; (*c*) E. Delgadolieta, M. A. Luke, R. F. Jones and D. J. Colehamilton, *Polyhedron*, 1982, **1**, 839–840; (*d*) J. H. Park, Y. Cho and Y. K. Chung, *Angew. Chem., Int. Ed.*, 2010, **49**, 5138–5141.
16 A patent on this work has been filed, Indian Patent Application No: 3280/MUM/2011.