JOC*Note*
pubs.acs.org/joc

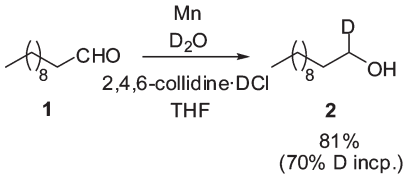
Mn(0)-Mediated Chemoselective Reduction of Aldehydes. Application to the Synthesis of α-Deuterioalcohols

Tania Jiménez,[†] Elisa Barea,[‡] J. Enrique Oltra,[†]
Juan M. Cuerva,[†] and José Justicia*[,†]

[†]*Department of Organic Chemistry and* [‡]*Department of Inorganic Chemistry, Faculty of Sciences, University of Granada, C. U. Fuentenueva s/n, 18071 Granada, Spain*

jjusti@ugr.es

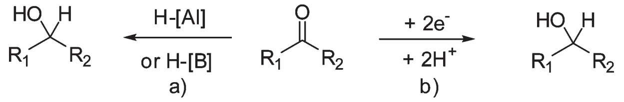
Received August 9, 2010



A mild, simple, safe, chemoselective reduction of different kinds of aldehydes to the corresponding alcohols mediated by the Mn dust/water system is described. In addition to this, the use of D_2O leads to the synthesis of α-deuterated alcohols and constitutes an efficient, inexpensive alternative for the preparation of these compounds.

The synthesis of alcohols from aldehydes is an essential process in organic synthesis[1] and an important step in the preparation of natural products.[2] Consequently, numerous chemical methods have been described to accomplish this basic transformation.[3] Nevertheless, many of them are not chemoselective and also react with ketones and other carbonyl compounds or functional groups, thus limiting their application in polyfunctionalized substrates. Additionally, many of the chemical reagents normally used to reduce aldehydes are caustic, expensive, and/or environmentally unfriendly. Other methods, based on the use of hydrogen as reducing agent, often present problems because of the need for high-pressure apparatus to manipulate the gas. To overcome some of these drawbacks, different boron- and aluminum-based hydrides with good chemoselectivity have been developed (Scheme 1, path a).[3c] Nevertheless, despite their obvious potential interest, their preparation and manipulation is not always simple. Another possibility is the selective transfer of two electrons and two protons to the functionality of the aldehyde (Scheme 1, path b). The main problem with this, however, is the nature of the required SET reagent, usually Na or Li.[3] Within this context, manganese is a cheap, nontoxic, environmentally benign element, which has been extensively used in organic reactions as a coreducing agent. Nevertheless, its own reactivity has hardly been explored.[4] As proton source for this process we were mainly interested in water, an inexpensive, innocuous hydrogen source, because we suspected that its isotopologue, deuterium oxide, might yield the corresponding α-deuterated alcohols and thus turn out to be a cheap alternative to other deuterated reduction reagents.[5]

SCHEME 1. Usual Reagents for Carbonyl Reductions



The main drawback with this approach is that the scarce studies published concerning the behavior of water on manganese surfaces strongly support a dissociative adsorption mechanism and the consequent inactivation of the metal surface.[6] Therefore, a water-compatible regenerating agent able to reactivate the metal surface would be required. Interestingly, the use of manganese dust is combined in titanocene(III)-catalyzed transformations with pyridinium-based hydrochlorides such as 2,4,6-collidinium hydrochloride (2,4,6-Coll·HCl), which are water-compatible additives.[7] We report here that a simple combination of 2,4,6-collidinium hydrochloride and Mn dust in the presence of water is able to carry out an efficient, chemoselective[8] reduction of aldehydes to the corresponding alcohols under extremely safe, mild conditions. It is also important to note that deuterium

---

(1) (a) *Comprehensive Organic Synthesis*, 1st ed.; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 8. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: New York, 2007, p 1786.

(2) (a) Kidwai, M.; Motshra, P.; Mohan, R.; Biswas, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 915–917. (b) Kidwai, M.; Saxena, S.; Mohan, R.; Venkataramanan, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1845–1846.

(3) (a) Greeves, N. *Comprehensive Organic Synthesis*, 1st ed.; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 8, pp 1−24. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH: New York, 1999. (c) Kidwai, M.; Bansal, V.; Saxena, A.; Shankar, R.; Mozumdar, S. *Tetrahedron Lett.* **2006**, *47*, 4161–4165. and references cited therein.

(4) For a recent review of its properties, activation, and synthetic applications see: Concellón, J. M.; Rodríguez-Solla, H.; del Amo, V. *Chem.—Eur. J.* **2008**, *14*, 10184–10191.

(5) The typical price of D_2O (99.90 atom % D, 100 mL) is about €47.70, while $NaBD_4$ (98 atom % D, 5 g, €176), $LiAlD_4$ (98 atom % D, 5 g, €90.30), and D_2 (99.9 atom % D, 25 L, €221.50) are considerably more expensive.

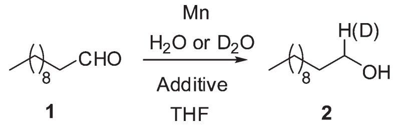
(6) Flugge, J. C.; Watson, L. M.; Fabian, D. J.; Affrossman, S. *Surf. Sci.* **1975**, *49*, 61–76.

(7) (a) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101–103. (b) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltenmeyer, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909–2910. (c) Gansäuer, A.; Ndene, N.; Lauterbach, T.; Justicia, J.; Winkler, I.; Mück-Lichtenfeld, C.; Grimme, S. *Tetrahedron* **2008**, *64*, 11839–11845. (d) Gansäuer, A.; Fleckhaus, A.; Lafont, M. A.; Okkel, A.; Kotsis, K.; Anoop, A.; Neese, F. *J. Am. Chem. Soc.* **2009**, *131*, 16989–16999. (e) Estévez, R. E.; Oller-López, J. L.; Robles, R.; Melgarejo, C. R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2006**, *8*, 5433–5436. (f) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cárdenas, D. J.; Buñuel, E.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5522–5526. (g) Gansäuer, A.; Fan, C.-A.; Piestert, F. *J. Am. Chem. Soc.* **2008**, *130*, 6916–6917. (h) Paradas, M.; Campaña, A. G.; Estévez, R. E.; Álvarez de Cienfuegos, L.; Jiménez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2009**, *74*, 3616–3619.

(8) For an overview concerning the importance of chemoselectivity in organic chemistry see: Afagh, N. A.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2010**, *459*, 262–310.

DOI: 10.1021/jo1015618

TABLE 1. Reduction of 1 with a Mn Dust/Water System in the Presence of Different Ammonium and Pyridium Salts



entry	additive	hydrogen source	solvent	yield
1	2,4,6-Coll·HCl	H_2O	THF	81%
2	2,4,6-Coll·HBF_4	H_2O	THF	12%
3	2,6-Lut·HCl	H_2O	THF	50%
4	Py·HCl	H_2O	THF	11%
5	Et_3N·HCl	H_2O	THF	traces
6	NH_4Cl	H_2O	THF	traces
7	PPTS	H_2O	THF	traces
8	2,4,6-Coll·DCl[13]	D_2O	THF	81%[a]

[a] 70% of deuterium incorporation.

oxide can be used as a hydrogen atom source instead of water to yield the corresponding α-deuterated alcohols.

Initially we studied the reduction reaction of decanal (**1**) (1 mmol), a prototypical aldehyde, using different ammonium and piridynium salts (2 mmol), Mn dust (8 mmol),[9] and water (10 mmol)[10] in THF[11] (Table 1, entries 1−7). The best results were obtained with 2,4,6-Coll·HCl as regenerating agent for the Mn surface. The success of this additive is related in some cases to the very low solubility of the other additives in THF (entries 4−6) and, apparently, with the nature of the counteranion in the manganese(II) salt generated (entries 2 and 7). 2,6-Lutidine hydrochloride (2,6-Lut·HCl), which is slightly less soluble than 2,4,6-Coll·HCl, also triggered the reaction, but produced somewhat lower yields (see entry 3). As we expected, the substitution of water and 2,4,6-Coll·HCl for their deuterium analogues afforded a good yield of 1-deuteriodecanol (**2*d***) with a high incorporation of deuterium (Table 1, entry 8).[12] This result also reflects unequivocally that the hydrogen atom required in the reduction process comes from water.

Using these optimized conditions we extended our study to the reduction of different carbonyl compounds to determine their scope and chemoselectivity. To this end we submitted different types of aldehyde and ketones to the reduction reaction. The results are set out in Table 2.

Different kinds of aldehydes (aliphatic, aromatic, and α,*β*-unsaturated) were reduced under these conditions to give moderate-to-good yields. In entries 1−4 aromatic aldehydes were efficiently reduced and no traces of the corresponding pinacol coupling products were detected. This suggests that the quantity of the corresponding ketyl radical in solution was very low.[14] Interestingly, the *E* stereochemistry of geranial (**7**) and farnesal (**8**) (entries 5 and 6) was completely preserved. When aliphatic, aromatic, and α,*β*-unsaturated ketones **11**−**13** (entries 9−11) were submitted to the same reaction conditions, on the other hand, no reduction products were observed. Consequently ketoaldehyde **15** (entry 13) afforded good yields of the corresponding ketoalcohol **35**. The only exception was *tert*-butyl cyclohexanone **14** (entry 12), which gave low quantities of *cis*-cyclohexanol **34** (20%). This could be related to the strain associated with this functionalized cyclohexane ring. In fact it is known that cyclohexanone is reduced by sodium borohydride 355 times faster than di-*n*-hexyl ketone.[15] Interestingly, other compounds that are prone to react with the typical hydride-based reduction reagents,[3] such as esters (entry 14), amides (entry 15), nitriles (entry 21), primary halides and mesilates (entry 16 and 22), or epoxides (entry 19), do not react under these conditions. Bearing in mind the presence of water and a Brönsted acid, it is worth noting that acidic labile groups, such as epoxides and O-MEM functionalities, also afford good yields of the corresponding alcohols (entries 19 and 22). Although hydrogen gas is also generated by the reaction of 2,4,6-collidinium hydrochloride and Mn dust, this reducing agent is unable to react with the C−C multiple bonds present in aldehydes **19**, **20**, and **22** (entries 17, 18, and 20). This excellent chemical profile may contribute to a precise control over the individual reactivity of functional groups within a complex molecular architecture, allowing the use of less protective groups, which constitutes an important objective in modern organic chemistry.[16]

As mentioned above, the substitution of D_2O for water may allow the preparation of α-deuterated alcohols, constituting an efficient and inexpensive alternative to known processes for the preparation of this kind of compound.[5,12] To check the synthetic usefulness of our reaction in the synthesis of these compounds we submitted a set of aldehydes to our reduction conditions in the presence of D_2O. The results are set out in Table 3.

To our satisfaction, the results obtained in the reduction of aldehydes **3**, **8**−**10**, **18**, **19**, and **21** with D_2O as the deuterium source were on the whole fairly good. The yields were slightly lower than those obtained with water as the hydrogen source. The formation of nondeuterated alcohols was probably due to the presence of adventitious water in the solvent or to a hydrogen atom transfer from THF. Thus, when aldehyde **1** was reduced in deuterated THF in the presence of D_2O, complete deuterium incorporation was observed (99% D incorporation).[17] In any case, these reaction conditions constitute a useful procedure for the preparation of α-deuterated alcohols of different kinds.

---

(9) Although strictly only 1 equiv of Mn dust is required, we found that 8 equiv gives better, more reliable results (see the S.I.). Interestingly, the excess of Mn dust and Coll·HCl could be reused up to four times with excellent results.

(10) Methanol and ethanol can also be used but with lower yields (52% and 34%, respectively).

(11) The reaction was also tried in other common solvents such as acetone, DMF, acetonitrile, benzene, and hexane but the reaction did not take place. The reaction took place in other polar solvents such as MeOH (52%) or EtOH (34%), but with lower yields.

(12) For some selected examples of the synthesis of 1-deuterioalcohols see: (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211–5213. (b) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352–2355. (c) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275–6278. (d) Keck, G. E.; Krishnamurthy, D. *J. Org. Chem.* **1996**, *61*, 7638–7639. (e) Junk, T.; Catallo, W. J. *Chem. Soc. Rev.* **1997**, *26*, 401–406. (f) Morelli, C. F.; Cairoli, P.; Marigolo, T.; Speranza, G.; Manitto, P. *Tetrahedron: Asymmetry* **2009**, *20*, 351–354.

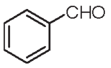
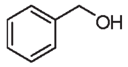
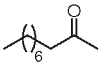
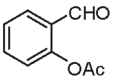
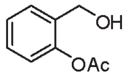
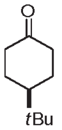
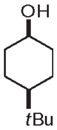
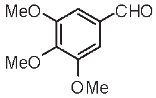
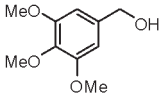
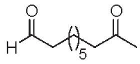
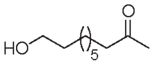
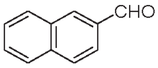
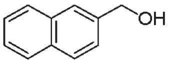
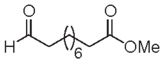
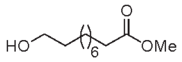
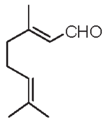
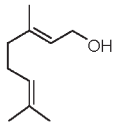
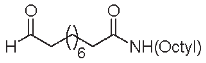
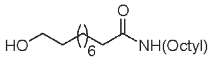
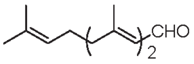
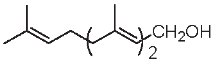
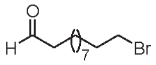
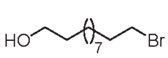
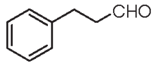
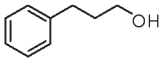
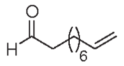
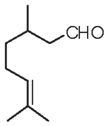
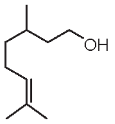
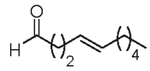
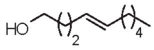
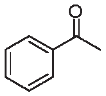
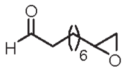
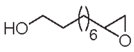
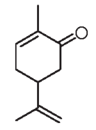
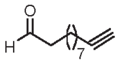
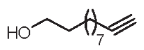
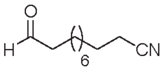
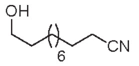
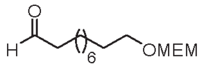
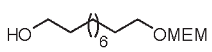
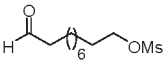
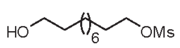
(13) Coll·DCl was prepared from commercial 2,4,6-collidine and DCl 7 N in D_2O.

(14) (a) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717–5718. (b) Gansäuer, A. *Chem. Commun.* **1997**, 457–458. (c) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070–2071. (d) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2673–2676. (e) Hirao, T.; Hatano, B.; Asahara, M.; Muguruma, Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, *39*, 5247–5248. (f) Dunlap, M. S.; Nicholas, K. M. *J. Organomet. Chem.* **2001**, *630*, 125–131. (g) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923–1927.

(15) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, 1st ed.; Wiley-Interscience: New York, 1994; pp 731−732.

(16) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404–408.

TABLE 2. Reduction of Aldehydes 3−10, Ketones 11−14, and Polyfunctionalyzed Aldehydes 15−25 with a Mn Dust/Water System under the Optimized Reaction Conditions

Entry	Aldehyde	Product	Yield	Entry	Aldehyde	Product	Yield
1	 **3**	 **26**	50%	11	 **13**	No reaction	-
2	 **4**	 **27**	73%	12	 **14**	 **34**	20%
3	 **5**	 **28**	72%	13	 **15**	 **35**	85%
4	 **6**	 **29**	71%	14	 **16**	 **36**	79%
5	 **7**	 **30**	61%	15	 **17**	 **37**	89%
6	 **8**	 **31**	69%	16	 **18**	 **38**	87%
7	 **9**	 **32**	65%	17	 **19**	 **39**	84%
8	 **10**	 **33**	65%	18	 **20**	 **40**	100%[a]
9	 **11**	No reaction	-	19	 **21**	 **41**	88%
10	 **12**	No reaction	-	20	 **22**	 **42**	91%
				21	 **23**	 **43**	87%
				22	 **24**	 **44**	85%[a]
				22	 **25**	 **45**	83%[a]

[a] Yield based on recovered starting material.

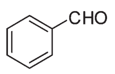
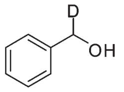
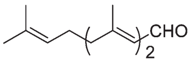
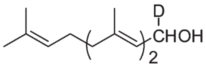
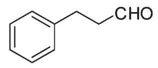
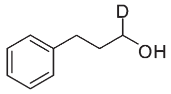
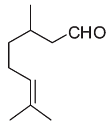
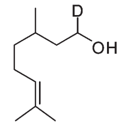
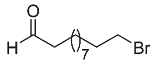
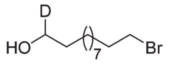
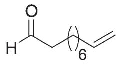
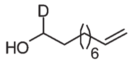
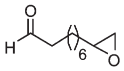
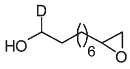
Although other similar aldehyde/ketone chemoselective reductions with a metal in aqueous media have been described,[18] they are based on the difference between the reduction potentials of both functional groups. In fact, single electron transfer (SET) reactions could provide monosubstituted hydroxy radical intermediates or dianionic species adsorbed on the manganese surface, which can subsequently lead to the corresponding alcohols via a reaction with hydrogen atom donors or proton sources. The absence of pinacol coupling products or their corresponding Michael adducts with methyl acrylate, which could not be detected in this reaction, suggests that free ketyl radicals are not involved in this transformation. Moreover, the chemoselectivity observed in this reaction is apparently incompatible with a selectivity based only on reduction potentials, bearing in mind that aromatic ketones are not reduced by this protocol.[19] It would seem that the higher steric hindrance of ketones compared to

---

(17) The deuterium incorporation of 99% in THF-d_8 suggests that THF is also donating hydrogen atoms under the described conditions, although less efficiently than water, taking into account the molar relationship. In fact, control experiments showed that in the absence of water THF is also able to promote the reaction albeit in lower yield and higher reaction times

(18) (a) Hazarika, M. J.; Barua, N. C. *Tetrahedron Lett.* **1989**, *30*, 6567–6570. (b) Wang, W.-B.; Shi, L.-L.; Huang, Y.-Z. *Tetrahedron Lett.* **1990**, *31*, 1185–1186. (c) Baruah, R. N. *Tetrahedron Lett.* **1992**, *33*, 5417–5418. (d) Bordoloi, M.; Sharma, R. P.; Chakraborty, V. *Synth. Commun.* **1999**, *29*, 2501–2506. (e) Desai, D. G.; Swami, S. S.; Nandurdikar, R. S. *Synth. Commun.* **2002**, *32*, 931–933.

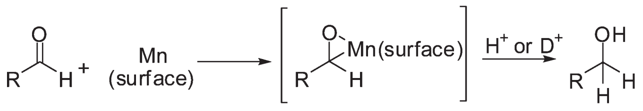
TABLE 3. Synthesis of α-Deuterated Alcohols via the Reduction of Aldehydes 3, 6, 8−10, 18, 19, and 21 with Mn Dust/D_2O

Entry	Aldehyde	Product	Yield (%-D incorp.)
1	 **3**	 **26d**	40% (55%)
2	 **8**	 **31d**	71% (67%)
3	 **9**	 **32d**	62% (59%)
4	 **10**	 **33d**	72% (69%)
5	 **18**	 **38d**	75% (72%)
6	 **19**	 **39d**	71% (69%)
7	 **21**	 **41d**	80% (68%)

aldehydes may prevent an efficient η^2-type interaction between the carbonyl group and the metal surface.[20,21] Therefore, we propose that the experimental results are better explained by a double reduction process of the corresponding aldehyde by η^2-interaction between the carbonyl group and the Mn surface, followed by two protonation steps (see Scheme 2).[22]

In conclusion, a mild, selective, safe, and economic method for the reduction of aldehydes to alcohols based on a Mn/water system is described. This method allows the reduction of aldehydes of different kinds (aliphatic, aromatic, α,β-unsaturated) to afford good-to-excellent yields of alcohols and almost complete chemoselectivity. Ketones and other groups, normally reactive toward typical hydride-based reduction reagents, do not react under these conditions, providing a satisfactory, mild alternative for the reduction of aldehydes, which may well be of interest in the synthesis of polyfunctionalized substrates. Additionally, the use of D_2O instead of water allows the synthesis of α-deuterated alcohols, thus constituting an efficient and inexpensive alternative to the processes currently used for the preparation of these kinds of compounds. At the moment, we are working in the determination of the mechanistic aspects of this reaction.

SCHEME 2. Mechanistic Proposal for the Reduction of Aldehydes by the Mn Dust/H_2O System



Experimental Section

General Procedure for the Reduction of Aldehydes in the Presence of Water/D_2O. Completely deoxygenated THF (20 mL) was added to a mixture of Coll·HCl (2 mmol) and Mn dust (Acros, 317442500) (8 mmol) under an Ar atmosphere. A solution of aldehyde (1 mmol) and water or D_2O (10 mmol) in 1 mL of THF was then added. The almost neutral mixture (pH 6) was stirred for 8−10 h at rt. AcOEt was added and the organic layer was washed with a saturated solution of acidic $KHSO_4$ (pH 1)[23] before being dried with anhyd Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (EtOAc/hexane) to give the corresponding alcohol. Products **2**, **26**−**45**, **26d**, **31d**−**33d**, **38d**−**39d**, and **41d** were purified by flash chromatography on silica gel (hexane: EtOAc) and characterized by spectroscopic techniques.[24] The yields obtained are reported in Tables 1−3.

Acknowledgment. We thank the Spanish MICINN (project CTQ2008-06790) and the Regional Government of Andalucía (projects P09-FQM-4571 and P07-FQM-3213) for financial support. T.J. and E.B. thank the Spanish MICINN for FPU fellowship and a "Ramon y Cajal" contract. J.J. thanks the University of Granada for his "Reincorporación de Doctores" contract. Finally we thank Dr. J. Trout of the University of Granada Scientific Translation Service for revising our English text.

Supporting Information Available: General experimental details, synthesis of aldehydes **17** and **23**−**25**, and ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(19) In a competitive experiment with a mixture of decanal (**1**) and benzaldehyde (**3**) we obtained a 1:2 relationship of the corresponding alcohols **2** and **26**. Bearing in mind the reported reduction potentials of benzaldehyde (−0.85 V vs SCE) and aliphatic aldehydes (−1.5 to −1.9 V vs SCE), chemoselectivity cannot be exclusively based on the difference between such reduction potentials: Joyce-Pruden, C.; Pross, J. K.; Li, Y. *J. Org. Chem.* **1992**, *57*, 5087–5091.

(20) (a) Huang, Y.-H.; Gladysz, J. *J. Chem. Educ.* **1988**, *65*, 298–303. (b) Adams, R. D.; Chen, G.; Chen, L.; Wu, W.; Yin, J. *J. Am. Chem. Soc.* **1991**, *113*, 9406–9408.

(21) It is known that metal hydrides are generated on transition metal surfaces from their interaction with water molecules and they could potentially be used in reduction reactions. This possibility remains unexplored, however, probably owing to their fleeting existence. Nevertheless, this posible mechanism cannot be completely ruled out: Thiel, P. A.; Madey, T. E. *Surf. Sci. Rep.* **1987**, *7*, 211–385.

(22) The possible deuterium atom in the hydroxyl group is removed by aqueous workup of the reaction or by D/H exchange with environmental humidity.

(23) Owing to the acid workup is only required to remove the 2,4,6-collidine obtained during the process, other acid solutions with different pH values or even water can also be used for the workup of this reaction.

(24) All new compounds are fully described in the Supporting Information.