Article

Organocatalytic Oxidation of Organosilanes to Silanols

Dimitris Limnios, and Christoforos George Kokotos

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/cs400515w • Publication Date (Web): 26 Aug 2013

Organocatalytic Oxidation of Organosilanes to Silanols

*Dimitris Limnios and Christoforos G. Kokotos**

Laboratory of Organic Chemistry, Department of Chemistry, University of Athens,

Panepistimiopolis 15771, Athens, Greece

KEYWORDS : Green Chemistry, Hydrogen peroxide, Organocatalysis, Oxidation, Perfluoroketones, Silanols

ABSTRACT : The oxidation of organosilanes to silanols constitutes an attractive transformation both for industry and academia. Bypassing the need for stoichiometric oxidants or precious metal catalytic complexes, the first organocatalytic oxidation of silanes has been accomplished. Catalytic amounts of 2,2,2,-trifluoroacetophenone, in combination with the green oxidant H_2O_2, leads to excellent to quantitative yields in short reaction time. A variety of alkyl, aryl, alkenyl and alkynyl substituents can be tolerated providing an easy, cheap, efficient and practical solution to a highly desirable transformation.

INTRODUCTION

Organosilicon compounds are of high interest because they find wide applications as versatile building blocks both in industry and academia.[1] In particular, silanols have been utilized in industry for the production of silicon-based polymeric materials,[2] for the derivatization of

functional groups and as nucleophilic partners in metal-catalyzed cross-coupling reactions in organic synthesis.[3] Organosilanols have been also identified as challenging bioactive agents in experimental pharmacology.[4] Very recently, organosilanols have been employed in catalysis,[5] due to their anion recognition ability.[6] Although the wide application of silanols requires efficient preparative protocols from readily available precursors, current synthetic approaches are only limited to hydrolysis of chlorosilanes, alkali treatment of siloxanes and oxidation of silanes (Figure 1).[7] The latter approach has stimulated the scientific community and early attempts utilized stoichiometric oxidants like peracids,[8a] permanganates,[8b] dioxiranes[8c,d] and oxaziridines.[8e] However, these methods suffer from low yields and selectivities, since undesirable by-products, like disiloxanes are formed. Transition metal catalysis has provided elegant solutions by employing a diverse set of catalytic conditions minimizing the by-product formation. Among the various metals utilized, Rh,[9a,b] Cu,[9c] Re,[9d,e] Pd,[9f] Ir[9g] and W[9h] have been demonstrated to provide efficiently the oxidation of silanes. More recently, Ti-based,[10a] gold-[10b,c] and silver-[10d,e] nanoparticles have been synthesized and employed in the same transformation. Since 2000, organocatalysis, the use of small organic molecules as catalysts for organic transformations, has grown to such an extent that is nowadays considered the third major branch of asymmetric catalysis along with transition metal catalysis and biocatalysis.[11,12] Although much effort has been devoted to invent novel reactivities, researchers on organocatalysis have not been so actively involved in oxidation reactions. Only a number of examples exist in the literature, dealing mainly with the epoxidation reaction.[13-16] Due to their better environmental acceptance and their ability to act without requiring special reaction conditions, non-metal organic oxidants have become available and have been employed in oxidation reactions. Furthermore, in pharmaceutical industry, any contamination in the active pharmaceutical

ingredients coming from metal catalysts is not usually acceptable [very low levels of metals (ppm to ppb) are sometimes tolerated]. Along these lines, we became interested in developing the first organocatalytic protocol that could be efficiently applied in the catalytic oxidation of organosilanes.

(FIGURE 1)

RESULTS AND DISCUSSION

Among the most promising organic oxidants are perhydrates and dioxiranes.[13a,b] These reagents derive from ketones in conjunction with an oxygen source. Although, in principle, the above-mentioned oxidants can be used catalytically, the vast majority of the literature utilize, in the best case scenario, stoichiometric quantities. In most cases, large excess (over 5 equivalents) is required in order oxidations to reach completion. Attempts to reduce the amount of the reaction promoter to substoichiometric quantities have met with limited success. Indeed, some excellent contributions from the groups of Denmark,[14] Yang[15] and Shi[16] have provided elegant solutions both to racemic and asymmetric epoxidation reactions. To fulfill our expectations for a process that would be acceptable for both academia and industry, we have focused on the development of a general strategy that enables the use of substoichiometric amounts (10 mol%) of a compound as a synthetically versatile and operationally trivial mode of activation of a green oxidant like H_2O_2. Today there is an increasing demand to use oxidants such as H_2O_2, which are environmentally friendly and do not give rise to any waste products. We have been previously involved in the synthesis of activated ketones as potent and selective enzyme inhibitors.[17,18] Coupled with our own previous experience in organocatalysis,[19] we envisaged the use of activated ketones as catalysts. Hydrogen peroxide by itself is a poor oxidant for organic oxidations. Thus, it has to be coupled with a catalyst in order to create a reactive intermediate

that will accelerate the oxidation. We anticipated that an activated ketone has the ability to perform in a similar way to a metal and react with hydrogen peroxide. This intermediate will perform the oxidation of the substrate and will regenerate the catalyst.

A variety of activated ketones were tested as catalysts for the oxidation of triethyl silane to triethyl silanol using H_2O_2 as the oxidant (Scheme 1). Initially, ketoacids **A** and **B**, and ketoester **C** were employed as activated ketones. However, they led to low to moderate yields. Isatin **D** and strained 1,2-diketone **E** did not furnish the desirable results. One of the most important classes of activated ketones is polyfluoroalkyl ketones. These ketones are known to be more activated than ketoacids and ketoesters and they exist in equilibrium with their hydrate form in aqueous environment. From this class of compounds, only some trifluoromethyl ketones have been employed in epoxidation reactions as catalysts. However, more than stoichiometric quantities are usually employed or when substoichiometric amounts are used, lower yields, harsh reaction conditions and longer reaction times are employed.[13] Once 2,2,2-trifluorolacetophenone **F** was employed, excellent yield was obtained after short reaction time (97% yield, 1.5 h). Prolonged reaction time led to quantitative yield. Similar results were obtained, when pentafluoroethyl (**G**) or heptafluoropropyl acetophenone were employed.[20] Decreasing the potency of activation on the carbonyl, either by substituting one fluorine by one chlorine or utilizing a benzyl moiety instead of a phenyl, led to diminished reaction yields. Acetophenone (**J**) or the use of no catalyst led to very low conversions underlying the role of the activated ketone for the catalytic activity.

(Scheme 1)

After optimization,[20] we concluded that 10 mol% of the catalyst **F** in a tert-butanol-aqueous buffer reaction medium can lead to excellent yields after 24 h utilizing 1.1 equivalents of

MeCN:H_2O_2. The substrate scope of the protocol was then explored (Scheme 2). Initially, trialkyl and mixed alkyl silanes were efficiently employed (silanols **2**-**7**). Unsaturated organosilanes bearing triple or double bonds can be utilized once the reaction medium is slightly altered in order to avoid product decomposition (EtOAc instead of tert-butanol). Both aromatic and aliphatic alkynyl substrates were employed leading to high yields (silanols **8** and **9**). Substituting the alkynyl moiety with an alkene led to the isolation of silanol **10** in high yield. Aromatic moieties are also well tolerated. The substitution of an aliphatic alkyl moiety by either a phenyl ring or a heteroaromatic thiophene moiety led to the isolation of silanols **11** and **12** in excellent yields. It has to be highlighted that prolonged reaction time led to decreased yields via decomposition pathways. Further substitution of additional alkyl moieties by aromatic phenyl substituents led to faster reaction, leading to silanols **13** and **14** in almost quantitative yields. An organosilane bearing three TMS moieties was also employed successfully leading to good yield (**15**), although in this case longer reaction time was necessary. Finally, the versatility of this method was also highlighted using diphenylsilane. This substrate usually suffers from the propensity upon oxidation utilizing metal oxidants to form not only the desired silanol **16** but also a mixture of disiloxanes, because a number of reaction pathways can be followed after the first oxidation. Our organocatalytic protocol led to a high yield of silanol **16** and no other by-product could be identified both by NMR and GC-MS analysis of the reaction mixture, although the reaction time and medium were quite crucial for the reaction outcome. Longer reaction time led to decreased yields due to product decomposition to phenol.

(Scheme 2)

We then turned our attention in elucidating the reaction mechanism. A number of experiments were performed in order to shed more light on the reactive intermediates and key-active species.

In the absence of H_2O_2, no reaction occurred. H_2O_2 was not capable by itself or in the combination with the catalyst to perform the oxidation, because in the absence of MeCN, oxidation did not take place (Scheme 3, **A**). Furthermore, when only 0.5 equivalent of MeCN was employed, then only 48% of the oxidation occurs.[20] We assume that there is an intermediate oxidant, which is a peroxycarboximidic acid, similar to the intermediate that Payne and coworkers have proposed in their epoxidation reaction.[21] Furthermore, this intermediate oxidant is also not capable of promoting the reaction by itself, since in the absence of the catalyst only 29% yield is obtained (Scheme 3, **A**). In our belief, H_2O_2 which is not capable of performing the oxidation by itself, has to react with acetonitrile to afford the more reactive oxidant intermediate, which in turn is not capable of performing the full oxidation but in the presence of the hydrate form of the catalyst can react and form the final oxidant which performs the reaction. Evidence that supports the peroxycarboximic acid intermediate is the observation of acetamide formation at the end of the reaction both by GC-MS analysis and ^{1}H-NMR. At this stage, the crucial role of the pH of the solution has to be highlighted in order the peroxycarboximic acid intermediate to be generated (see Supporting Information). The reaction outcome was independent from the addition of the radical traps, like Tempo, AIBN and BHT, indicating that this protocol does not contain any radical intermediates (Scheme 3, **B**). Stemming from previous knowledge acquired in our laboratory for fluoroketones,[17] ^{19}F NMR experiments showed that although in organic solvents the equilibrium lied towards the ketone form, in the aqueous medium of the reaction, the hydrate was the main form (Scheme 3, **C**, see also SI). Following the reaction mixture by ^{19}F-NMR, IR and MS spectroscopy, new species containing fluorine were identified (Scheme 3, **C**). Although 2,2,2-trilfuoroacetophenone exists in the keto form in organic solvents, in the D_2O-buffer solution, the hydrate form is the predominant species (Scheme 3, **C**). Upon addition of *t*-

BuOH and MeCN, no change was observed. Once H_2O_2 was added, immediately a new peak was observed in ^{19}F-NMR. This is presumably compound **IV**, a perhydrate since the same compound was obtained when no MeCN was added in the reaction mixture (Scheme 3, **C**, bottom). It seems that MeCN has a dual role in the oxidation via the formation of the peroxycarboxymidic acid. First, it helps in the formation of higher concentrations of the perhydrate via oxidation and secondly the perhydrate with the peroxycarboximidic acid forms the active oxidant species. If no silane was added, the perhydrate was slowly transformed to a new compound, which is assumed to be the corresponding dihydroperoxide. This compound is capable of promoting the oxidation, but its oxidation reaction rate is slower (24% yield, 1 h; 94% yield, 24 h). Monitoring the reaction mixture leads to the conclusion that the perhydrate is decaying while the concentration of the dihydroperoxide increases.

(Scheme 3)

Taking into consideration these data, the following catalytic cycle is proposed (Figure 2). Initially the perfluoroalkyl ketone is hydrated in the presence of water leading to its hydrate form **I**. Once the optimum pH is utilized, acetonitrile and H_2O_2 react to form peroxycarboximidic acid **II**. The hydrate form of the perfluoroalkyl ketone is oxidized by H_2O_2 and **II** forming perhydrate **IV** and leaving as by-product from the peroxycarboximidic acid, acetamide **III**. The presence of a new intermediate after addition of acetonitrile and H_2O_2 in the solution of the catalyst in the reaction medium was identified by ^{19}F-NMR (see SI). Perhydrate **IV** then reacts with **II** forming the active oxidant species of the oxidation.[22] Upon addition of the silane, the oxidation occurs to the corresponding silanol. Finally, the silanol derivative is obtained and at the same time recycling of the catalyst occurs through generation of the hydrate **I**. If no silane is added in the reaction medium, perhydrate is transformed to another species, the dihydroperoxide, which is

capable of promoting the oxidation but in a slower rate (based on the observation of ^{19}F-NMR, see SI).

(Figure 2)

Conclusions

In conclusion, the first highly selective organocatalytic oxidation protocol of organosilanes to silanols is described. Perfluoroalkyl aryl ketones can be employed as catalysts (10 mol%) in a such a reaction leading to excellent to quantitative yields in short reaction times. To our knowledge, this is the first example of such a catalytic oxidation utilizing a cheap and commercially available metal-free organic molecule. The substrate scope of the reaction is very general and a variety of alkyl, alkenyl, alkynyl, aryl and heteroaryl substituents can be tolerated. The mechanism of the reaction was studied and active intermediates are proposed.

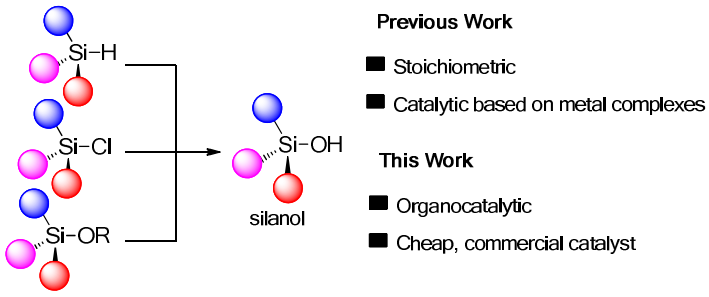


Figure 1. Approaches for the synthesis of silanols.

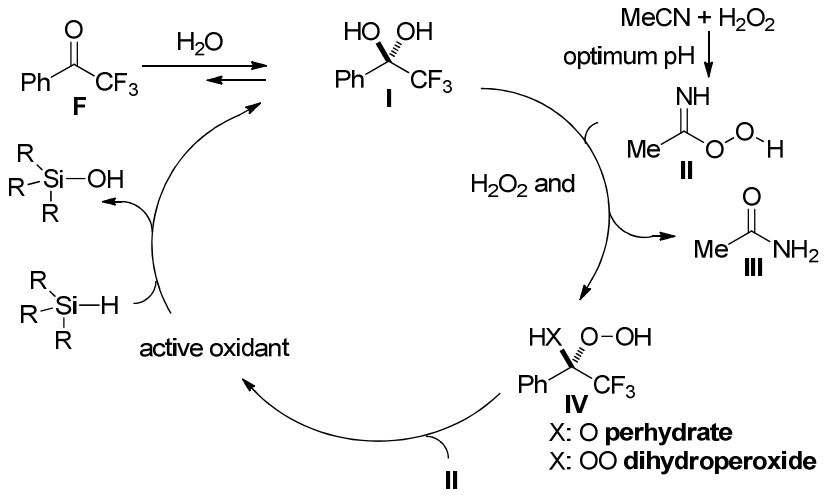
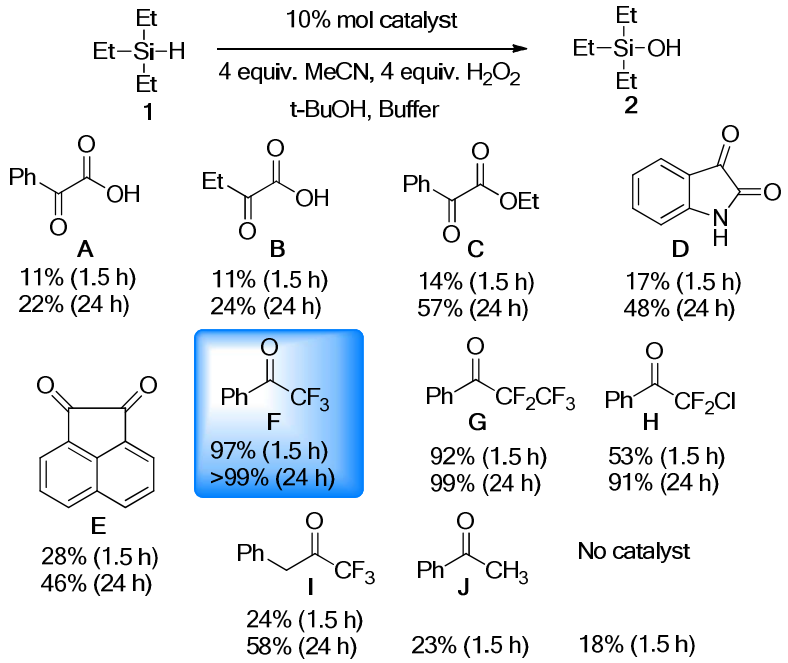
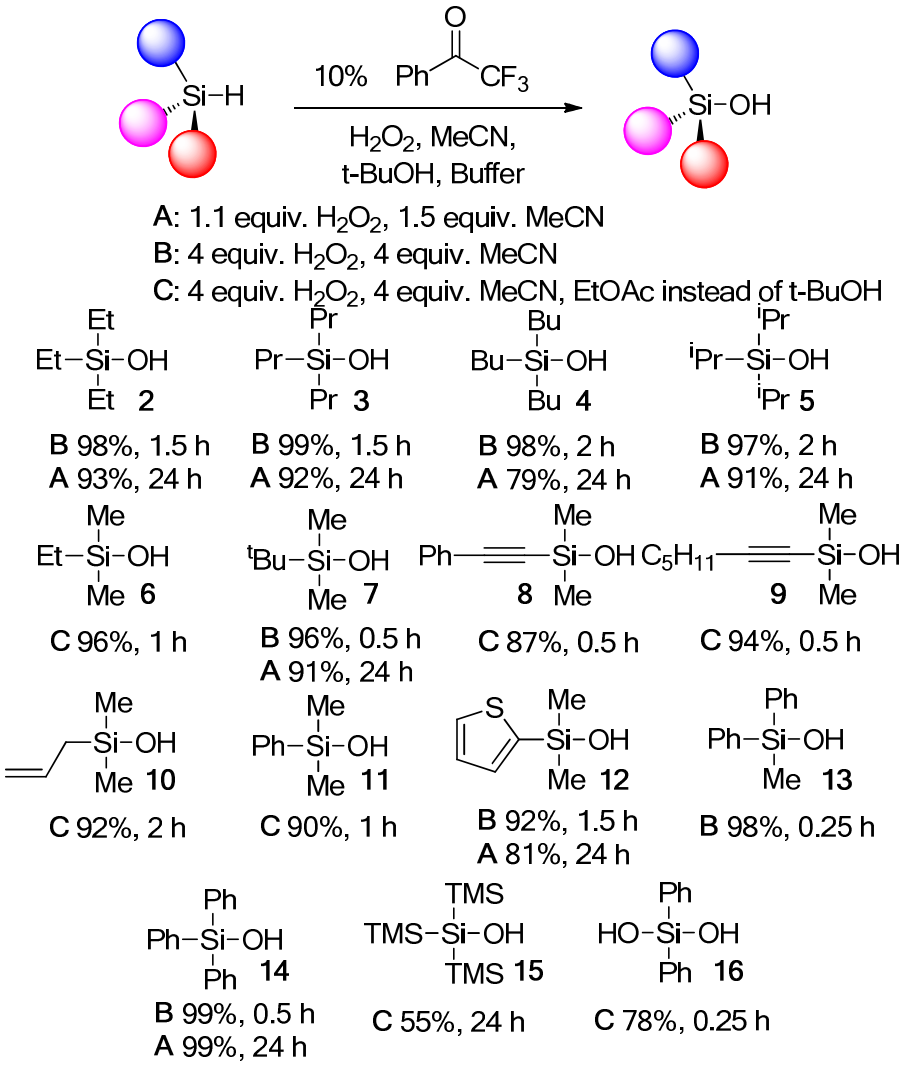


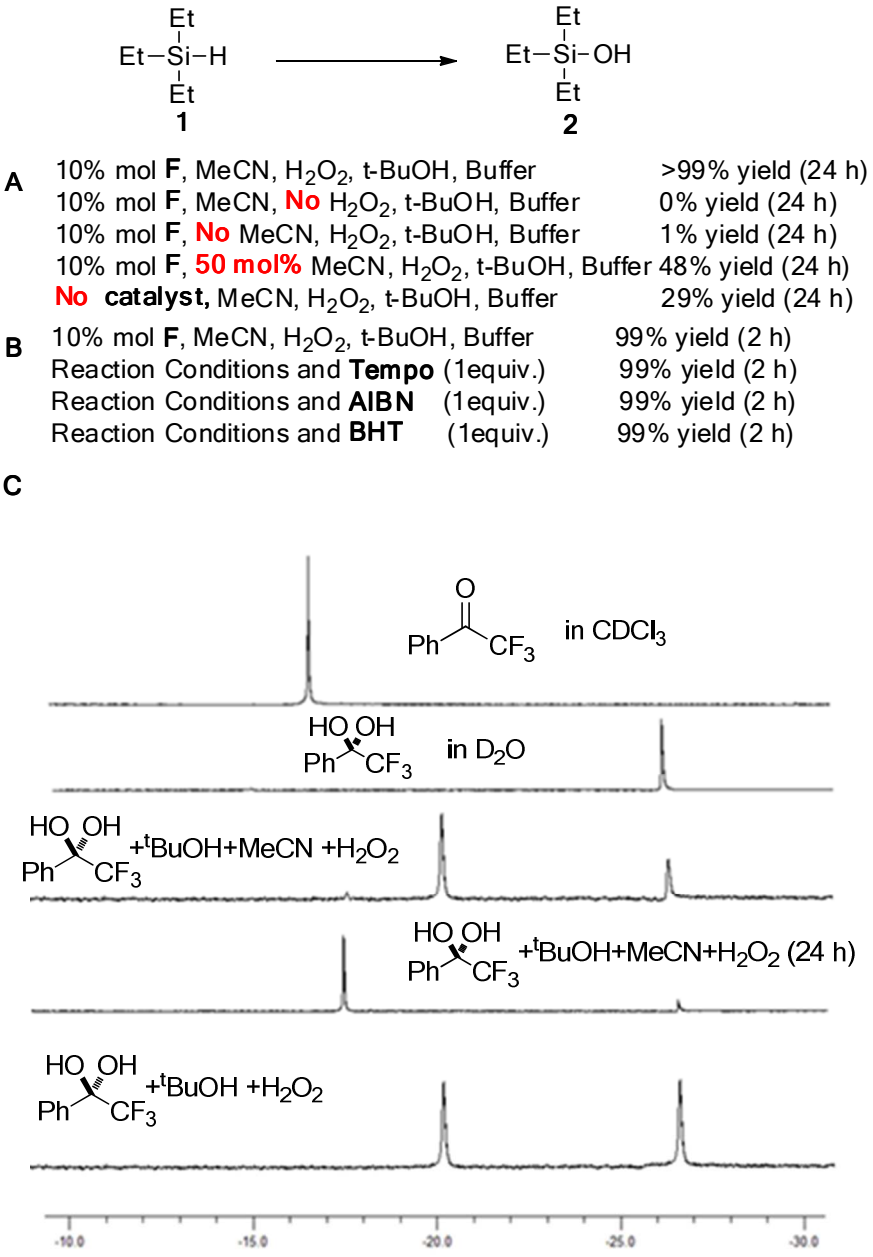
Figure 2. Proposed catalytic cycle of the oxidation.



Scheme 1. Catalyst screening for the organocatalytic oxidation of triethyl silane to silanol.



Scheme 2. Substrate scope of the organocatalytic oxidation of organosilanes.



Scheme 3. **A**. Control experiments to probe the reaction mechanism. **B**. Experiments to rule out the possibility of radical intermediates. **C**. ^{19}F-NMR experiments to probe the active oxidant species.

AUTHOR INFORMATION

Corresponding Author

* Tel: +30 210 7274281. E-mail: ckokotos@chem.uoa.gr

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors gratefully acknowledge the Operational Program "Education and Lifelong Learning" for financial support through the NSRF program "ΕΝΙΣΧΥΣΗ ΜΕΤΑΔΙΔΑΚΤΟΡΩΝ ΕΡΕΥΝΗΤΩΝ" (PE 2431)" co-financed by ESF and the Greek State.

ASSOCIATED CONTENT

Supporting Information

Experimental Procedures, Catalyst and Conditions Optimization including NMR and GC data, as well as mechanistic investigations. This information is available free of charge via the Internet at htpp://pubs.acs.org/.

REFERENCES

(1) For books, see: (a) Ojima, I., Li, Z., Zhu, J. In *The Chemistry of Organic Silicon Compounds*, Rappoport, S., Apeloig, Y., Eds.; Wiley: New York, 1998; (b) Colvin, E. W. In *Silicon Reagents in Organic Synthesis*, Academic Press, London, 1988.

(2) Lickiss, P. D. *Adv. Inorg. Chem.*, **1995**, *42*, 147-262.

(3) For a book, see: Denmark, S. E., Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A., Diederich, F., Eds; Wiley-VHC: Weinheim, 2004; (b) For a recent use of silanols as cross-coupling partner, see: Zhou, H.; Moberg, C. *J. Am. Chem. Soc.*, **2012**, *134*, 15992-15999.

(4) For a recent review, see: Franz, A. K.; Wilson, S. O. *J. Med. Chem.*, **2013**, *56*, 388-405.

(5) Tran, N. T.; Wilson, S. O.; Franz, A. K. *Org. Lett.*, **2012**, *14*, 186-189.

(6) Kondo, S.; Harada, T.; Tanaka, R.; Unno, M. *Org. Lett.*, **2006**, *8*, 4621-4624.

(7) For a recent review, see: (a) Jeon, M.; Han, J.; Park, J. *ACS Catal.*, **2012**, *2*, 1539-1549. For selected examples on the synthesis of enantioenriched silanols, see: (b) Igawa, K.; Takada, J.; Shimono, T.; Tomooka, K. *J. Am. Chem. Soc.*, **2008**, *130*, 16132-16133; (c) Igawa, K.; Yoshihiro, D.; Ichikawa, N.; Kokan, N.; Tomooka, K. *Angew. Chem. Int. Ed.*, **2012**, *51*, 12745-12748.

(8) (a) Sommer, L. H.; Ulland, L. A.; Parker, G. A. *J. Am. Chem. Soc.*, **1972**, *94*, 3469-3471; (b) Al-Shali, S. A. I.; Eaborn, C.; Fattah, F. A.; Najim, S. T. *J. Chem. Soc., Chem. Commun.*, **1984**, 318-319; (c) Adam, W.; Mello, R.; Curci, R. *Angew. Chem. Int. Ed.*, **1990**, *29*, 890-891; (d)

Grabovskii, S. A.; Kabalnova, N. N.; Shereshovets, V. V.; Chatgilialoglu, C. *Organometallics* **2002**, *21*, 3506-3510; (e) Cavivvhioli, M.; Montanari, V.; Resnati, G. *Tetrahedron Lett.* **1994**, *35*, 6329-6330.

(9) (a) Shi, M.; Nicholas, K. M. *J. Chem. Res.*, **1997**, 400-401; (b) Lee, M.; Ko, S.; Chang, S. *J. Am. Chem. Soc.*, **2000**, *122*, 12011-12012; (c) Schubert, U.; Lorenz, C. *Inorg. Chem.*, **1997**, *36*, 1258-1259; (d) Adam, W.; Mitchell, C. M.; Saha-Moller, C. R.; Weichold, O. *J. Am. Chem. Soc.*, **1999**, *121*, 2097-2103; (e) Ison, E. A.; Corbin, R. A.; Abu-Omar, M. M. *J. Am. Chem. Soc.*, **2005**, *127*, 11938-11939; (f) Barnes, G. H.; Daughenbaugh, N. E. *J. Org. Chem.*, **1966**, *31*, 885-887; (g) Lee, Y.; Seomoon, D.; Kim, S.; Han, H.; Chang, S.; Lee, P. H. *J. Org. Chem.*, **2004**, *69*, 1741-1743; (h) Ishimoto, R; Kamata, K.; Mizuno, N. *Angew. Chem. Int. Ed.*, **2009**, *48*, 8900-8904.

(10) (a) Adam, W.; Garcia, H.; Mitchell, C. M.; Saha-Moller, C. R.; Weichold, O. *Chem. Commun.*, **1998**, 2609-2610; (b) Mitsudome, T.; Noujima, A.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.*, **2009**, 5302-5304; (c) Asao, N.; Ishikawa, Y.; Hatakeyama, N.; Meggenbateer, Yamamoto, Y.; Chen, M.; Zhang, W.; Inoue, A. *Angew. Chem. Int. Ed.*, **2010**, *49*, 10093-10095; (d) Mitsudome, T.; Arita, S.; Mori, H.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Angew. Chem. Int. Ed.*, **2008**, *47*, 7938-7940; (e) Kikukawa, Y.; Kuroda, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.*, **2012**, *51*, 2434-2437.

(11) For books, see: (a) Berkessel, A., Groger, H. In *Asymmetric Organocatalysis – From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis*, Berkessel, A. Groger, H., Eds; Wiley-VCH: Weinheim, 2005; (b) Dalko, P. I. In *Enantioselective Organocatalysis Reactions and Experimental Procedure*, Dalko, P. I., Ed; Wiley-VCH: Weinheim, 2007.

(12) For selected reviews, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569; (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743; (c) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304-308; (d) Barbas, C.F. III *Angew. Chem. Int. Ed.*, **2008**, *47*, 42-47.

(13) For reviews, see: (a) Adam, W.; Saha-Moller, C. R.; Ganespure, P. A. *Chem. Rev.* **2001**, *101*, 3499-3548; (b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958-3987. For other oxidation studies in organocatalysis, see: (c) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.*, **2006**, *128*, 8412-8413.

(14) (a) Denmark, S. E.; Wu, Z. ; Crudden, C. M. ; Matsuhashi, H. *J. Org. Chem.*, **1997**, *62*, 8288-8289; (b) Denmark, S. E. ; Matsuhashi, H. *J. Org. Chem.*, **2002**, *67*, 3479-3486.

(15) Yang, D. *Acc. Chem. Res.*, **2004**, *37*, 497-505.

(16) (a) Wang, Z.-X.; Tu, Y. ; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.*, **1997**, *119*, 11224-11235; (b) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.*, **2000**, *122*, 11551-11552.

(17) (a) Yaksh, T. L.; Kokotos, G.; Svensson, C. I.; Stephens, D.; Kokotos, C. G.; Fitzsimmons, B.; Hadjipavlou-Litina, D.; Hua, X. Y.; Dennis, E. A. *J. Pharmacol. Exp. Ther.*, **2006**, *316*, 466-475; (b) Kokotos, C. G.; Baskakis, C.; Kokotos, G. *J. Org. Chem.*, **2008**, *73*, 8623-8626; (c) Kokotos, G.; Hsu, Y.-H.; Burke, J.; Baskakis, C.; Kokotos, C. G.; Magrioti, V.; Dennis, E. A. *J. Med. Chem.*, **2010**, *53*, 3602-3610.

(18) For a review, see: Dennis, E. A.; Cao, J.; Hsu, Y.-H.; Magrioti, V.; Kokotos, G. *Chem. Rev.*, **2011**, *111*, 6130-6185.

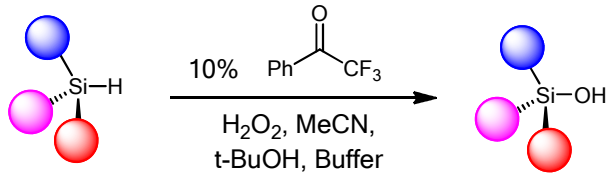
(19) (a) Kokotos, C. G.; Limnios, D.; Triggidou, D.; Trifonidou, M.; Kokotos, G. *Org. Biom. Chem.*, **2011**, *9*, 3386-3395; (b) Tsakos, M.; Kokotos, C. G. *Eur. J. Org. Chem.*, **2012**, 576-580; (c) Kokotos, C. G. *J. Org. Chem.*, **2012**, *77*, 1131-1135; (d) Trifonidou, M.; Kokotos, C. G. *Eur. J. Org. Chem.*, **2012**, 1563-1568; (e) Tsakos, M.; Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.*, **2012**, *354*, 740-746; (f) Tsakos, M.; Elsegood, M. R. J.; Kokotos, C. G. *Chem. Commun.*, **2013**, *49*, 2219-2221; (g) Kokotos, C. G. *Org. Lett.*, **2013**, *15*, 2406-2409.

(20) For full catalyst screening, reaction optimization and mechanistic experiments, see suporting information.

(21) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.*, **1961**, *26*, 659-663.

(22) For a possible structure of the active oxidant species, see Supporting Information.

Table of Contents (TOC) and Abstract Graphic



alkyl, aryl, alkenyl, alkynyl high to quantitative yields