C–H Activation

DOI: 10.1002/anie.200705766

Selective Oxidation of Aliphatic C–H Bonds in the Synthesis of Complex Molecules**

*Mathias Christmann**

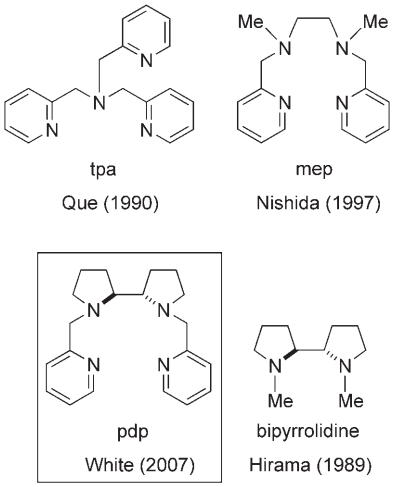
C–H activation · iron · natural products · oxidation

The direct functionalization of C–H bonds, and in particular the controlled oxidation of aliphatic C–H bonds[1,2] is one of the great contemporary challenges in synthetic chemistry.[3] It is known that these transformations can be affected in a stoichiometric fashion by organic peracids,[4] dioxiranes,[5] and oxaziridines,[6] although a catalytic method involving H_2O_2 or O_2 as cheap stoichiometric oxidants is highly desirable. Many biologically-inspired approaches mimic the iron porphyrin (heme) center of cytochrome P450.[7] Outside the protective surroundings of the enzyme, synthetic applications suffer from oxidative degradation of the porphyrin framework. A second member in the class of oxygen activating enzymes, methane monooxygenase (MMO),[8] is capable of oxidizing methane to methanol [Eq. (1)].

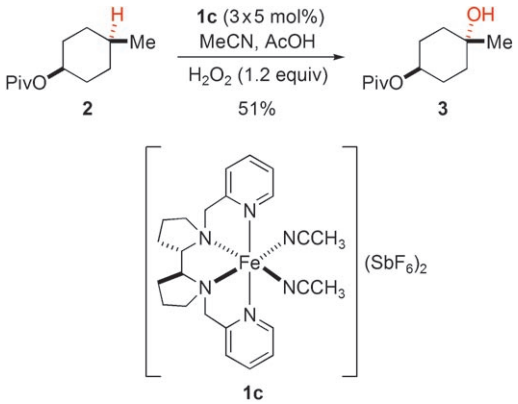
$$CH_4 + O_2 + NADH + H^+ \xrightarrow{MMO} CH_3OH + NAD^+ + H_2O \qquad (1)$$

Since the late 1980s, Que, Jr. and co-workers have developed synthetic models[9] of MMO, and in 1997 they reported $[Fe^{II}(tpa)(MeCN)_2](ClO_4)_2$ as the first nonheme complex to catalyze the stereospecific hydroxylation of alkanes with hydrogen peroxide.[10] In the same year, Nishida et al.[11] introduced the mep ligand, which leads to a higher turnover rate[12] and is capable of forming binuclear μ-oxo, acetate-bridged diiron(III) complexes. The pdp ligand used by White et al., which is discussed below, is a hybrid of the mep ligand, and the bipyrrolidine *N,N′*-dialkyl framework[13] that was developed by Hirama[14] for osmium-catalyzed dihydroxylations.

In 2001, Jacobsen et al. studied $[Fe^{II}(mep)(MeCN)_2](ClO_4)_2$ (**1a**) in the epoxidation of terminal olefins.[15] It was found that changing the counteranion to SbF_6^- leads to improved catalyst performance. Furthermore, the addition of acetic acid[16] was shown to be an essential additive for good substrate-to-catalyst (S/C) ratios. Using 3 mol% of $[Fe^{II}(mep)(MeCN)_2](SbF_6)_2$ (**1b**) and H_2O_2 as the oxidant (1.5 equiv), 1-decene is rapidly epoxidized (5 min, 4 °C, 85% yield).



As a starting point in their C–H activation studies, White and Chen[17] examined the oxidation of pivalate **2** to the hydroxylated product **3** (Scheme 1). Using catalyst **1b** (5 mol%), compound **3** was obtained in 26% yield at 41% conversion (62% selectivity). It was speculated that rigidifying the mep ligand with Hirama's chiral bipyrrolidine framework should lead to a more selective catalyst system. Consequently, iron(II) complex $[Fe(S,S\text{-pdp})(MeCN)_2]$-



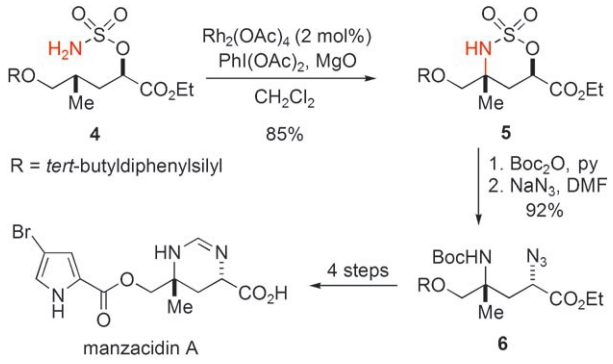
Scheme 1. Oxidation of pivalate **2**.

[*] Dr. M. Christmann
RWTH Aachen, Institute of Organic Chemistry
Landoltweg 1, 52074 Aachen (Germany)
Fax: (+49) 241-809-2127
E-mail: christmann@oc.rwth-aachen.de
Homepage:
http://134.130.101.5/akenders/christmann/Christmann.html

[**] The support of the Fonds der Chemischen Industrie, the DFG (SPP1179), the Dr. Otto Röhm Memorial Foundation, and Professor D. Enders is gratefully acknowledged.

$(SbF_6)_2$ (**1c**) was synthesized and characterized crystallographically. With **1c** as the precatalyst, the yield of **3** increased to 38% (42% conversion, 90% selectivity) and further to 51% upon three consecutive additions of **1c** (5 mol%), acetic acid (AcOH; 0.5 equiv), and H_2O_2 (1.2 equiv) within 30 minutes. The retention of configuration at the tertiary stereocenter supports a concerted rather than a radical mechanism. In an in-depth investigation, White and Chen have developed the catalyst system **1c** into a simple yet highly useful predictive method for the iron-catalyzed oxidation of C–H bonds that is based on steric effects, electronic effects, and directing functional groups (FGs). Before discussing the selectivity rules, a few examples of directed C–H oxidations will be provided.

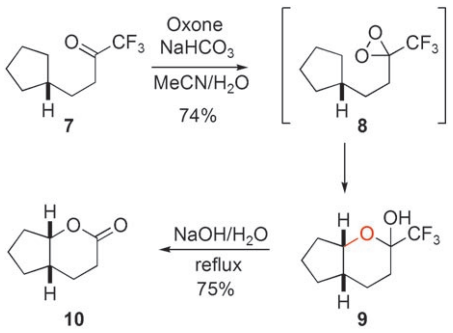
When applying strategic C–H oxidations to complex substrates or target-oriented syntheses, it is important to develop guidelines that allow the prediction of the outcome. The most powerful control element is a reagent directing group, which additionally may be source of the delivered heteroatom. In the total synthesis of callipeltoside[18] and tetrodotoxin[19], intramolecular C–H aminations using carbamates have been deployed.[20] In Du Bois and Wehn's synthesis of manzacidine,[21] a rhodium-catalyzed oxidative insertion of a sulfamate ester (**4**→**5**) retained the configuration at the tertiary stereocenter (Scheme 2). Subsequent *N*-Boc-protection and nucleophilic ring opening with sodium azide yielded intermediate **6**, which was converted into manzacidine in four steps.



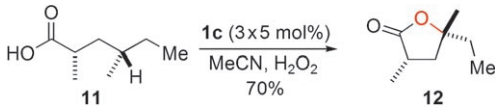
Scheme 2. Oxidative C–H amination. py = pyrdine; Boc = *tert*-butoxycarbonyl.

Alternatively, FGs can be used to deliver the reagent via a highly reactive intermediate. In the example shown in Scheme 3,[22] the carbonyl group in **7** is transformed into the highly reactive dioxirane **8**. Hemiacetal **9** is easily converted into lactone **10** by cleavage of the CF_3 group upon treatment with base. The White catalyst is also effective in FG-directed C–H oxidations (Scheme 4). Successive treatment of **11** with **1c** (3 × 5 mol%) leads to the clean formation of lactone **12** in 70% yield.[23]

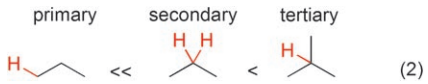
In the absence of directing groups, the following rules provide the basis for predicting the C–H bond reactivity. The oxidation of primary C–H bonds is very slow, and secondary centers are less reactive than tertiary C–H bonds [Eq. (2)]. In



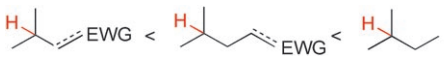
Scheme 3. Functional-group-directed C–H oxidation.



Scheme 4. Carboxylate-directed oxidative lactonization.

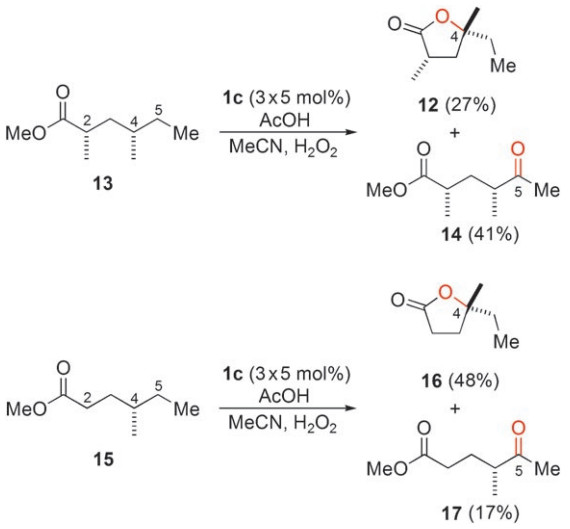


the absence of tertiary carbon centers or limited accessibility, excessive oxidation to the corresponding ketones will occur at the secondary centers. Furthermore, it was found that the proximity of electron withdrawing groups (EWGs) to tertiary centers, such as esters, ketones, and halides, slows down the oxidation [Eq. (3)].

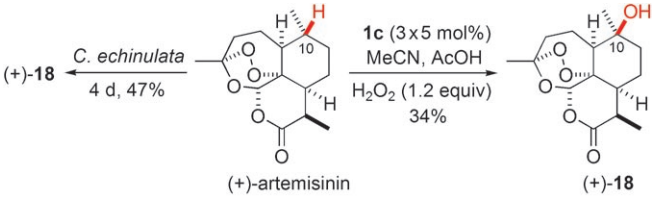


If the directing carboxylate in **11** is replaced by an ester group (**13**), competing oxidation at C4 and C5 was observed, whereas the C2 position is electronically deactivated (Scheme 5). The major product is ketoester **14**, can be explained by shielding of C4 by the C2 methyl group. Consistent with this rationale, removal of the C2 methyl group (**15**) accelerates the oxidation at the C4 position and suppresses the oxidation at C5.

Although the transformations in Scheme 4 and 5 are impressive, the real value of C–H oxidation lies in the predictable introduction of sensitive functional groups into complex molecular frameworks. As a model for the potential application of late-stage C–H oxidation in a total synthesis, the antimalarial natural product (+)-artemisinin was exposed to catalyst **1c**. Of the five tertiary C–H bonds present, only that at C10 was predicted to be reactive; the other tertiary positions are either electronically deactivated or inaccessible to the catalyst.[24] Gratifyingly, under standard conditions, (+)-10β-hydroxyartemisinin **18** was isolated in 34% yield (Scheme 6). Twofold recycling of recovered starting material gave a 54% yield based on the amount of artemisinin initially used. This result compares well to the microbial approach[25] using cultures of *C. echinulata* (4 d, 47% yield).



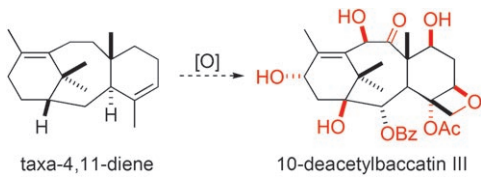
Scheme 5. Electronic and steric control in C–H oxidations.



Scheme 6. Functionalization of (+)-artemisinin.

The role of **1c** as mimic of P450 enzymes may be very useful in the generation of metabolites from drugs and natural products. It is also noteworthy that the endoperoxide is not cleaved under the reaction conditions. The selective late-stage introduction of acid-sensitive tertiary hydroxy groups may offer a strategic advantage that avoids protecting groups.[26] However, it remains to be seen whether catalyst **1c** or further advancements can tolerate olefins and secondary hydroxy groups as two common structural features. Being a close relative of the epoxidation catalyst **1b**, the catalyst **1c** might be capable of sequential oxidative processes. Furthermore, as **1c** is a chiral catalyst, stereochemical differentiation of equally reactive but configurationally distinct C–H bonds seems achievable.

The efficient syntheses of highly oxidized and complex molecular frameworks such as 10-deacetylbaccatin III, a precursor of the anticancer drug paclitaxel (Taxol), offers a formidable challenge to the synthetic chemist's imagination.[27] It seems very possible that C–H activation plays a major role in this pursuit (Scheme 7). White's systematic investigations document a departure in the application of C–H oxidations towards natural product synthesis. The outcome is predictable and does not require directing or activating groups. In addition, the use of a nontoxic metal combined with H_2O_2 as oxidant renders the overall process environmentally benign. It may be hoped that collaborative efforts of inorganic and organic chemists in the field of biomimetic oxidation catalysis remain fruitful.



Scheme 7. Possible approach to the synthesis of 10-deacetylbaccatin III. Bz = benzoyl.

[1] *Handbook of C-H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**.
[2] A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439.
[3] S. Tanase, E. Bouwman, *Adv. Inorg. Chem.* **2006**, *58*, 29.
[4] H.-J. Schneider, W. Müller, *J. Org. Chem.* **1985**, *50*, 4609.
[5] R. Mello, M. Fiorentino, C. Fusco, R. Curci, *J. Am. Chem. Soc.* **1989**, *111*, 6749.
[6] D. D. DesMarteau, A. Donadelli, V. Montanari, V. A. Petrov, G. Resnati, *J. Am. Chem. Soc.* **1993**, *115*, 4897.
[7] B. Meunier, *Chem. Rev.* **1992**, *92*, 1411.
[8] a) B. J. Wallar, J. D. Lipscomb, *Chem. Rev.* **1996**, *96*, 2625; b) M. Merkx, D. A. Kopp, M. H. Sazinsky, J. L. Blazyk, J. Müller, S. J. Lippard, *Angew. Chem.* **2001**, *113*, 2860; *Angew. Chem. Int. Ed.* **2001**, *40*, 2782.
[9] R. E. Norman, S. Yan, L. Que, Jr., G. Backes, J. Ling, J. Sanders-Loehr, J. H. Zhang, C. J. O'Connor, *J. Am. Chem. Soc.* **1990**, *112*, 1554.
[10] C. Kim, K. Chen, J. Kim, L. Que, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 5964.
[11] T. Okuno, S. Ito, S. Ohba, Y. Nishida, *J. Chem. Soc. Dalton Trans.* **1997**, 3547.
[12] K. Chen, L. Que, Jr., *Chem. Commun.* **1999**, 1375.
[13] Optically pure 2,2′-bipyrrolidine can be obtained by photodimerization of pyrrolidine (Crabtree) followed by resolution with tartaric acid: a) R. R. Ferguson, C. G. Boojamra, S. H. Brown, R. H. Crabtree, *Heterocycles* **1989**, *28*, 121; b) T. Oishi, M. Hirama, L. R. Sita, S. Masamune, *Synthesis* **1991**, 789; c) S. E. Denmark, J. Fu, M. J. Lawler, *Org. Synth.* **2006**, *83*, 121.
[14] a) M. Hirama, T. Oishi, S. Ito, *J. Chem. Soc. Chem. Commun.* **1989**, 665.
[15] M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194.
[16] For pertinent discussion concerning the effect of acetic acid, see: R. Mas-Ballesté, L. Que, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 15964.
[17] M. S. Chen, M. C. White, *Science* **2007**, *318*, 783.
[18] B. M. Trost, J. L. Gunzner, O. Dirat, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396.
[19] A. Hinman, J. Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 11510.
[20] C. G. Espino, J. Du Bois, *Angew. Chem.* **2001**, *113*, 618; *Angew. Chem. Int. Ed.* **2001**, *40*, 598.
[21] P. M. Wehn, J. Du Bois, *J. Am. Chem. Soc.* **2002**, *124*, 12950.
[22] M.-K. Wong, N.-W. Chung, L. He, X.-C. Wang, Z. Yan, Y.-C. Tang, D. Yang, *J. Org. Chem.* **2003**, *68*, 6321.
[23] For carboxylic acid directing groups, the addition of acetic acid was omitted.
[24] In less obvious situations, DFT calculations or X-ray structures were used to estimate site-specificity.
[25] J. Zhan, H. Guo, J. Dai, Y. Zhang, D. Guo, *Tetrahedron Lett.* **2002**, *43*, 4519.
[26] For an insightful discussion, see: P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404.
[27] A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477.

