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Green Diacetoxylation of Alkenes in a Microchemical System

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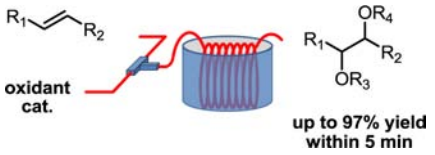
ABSTRACT



The palladium-catalyzed diacetoxylation and trifluoromethanesulfonic acid-catalyzed diacetoxylation using inexpensive and environmentally friendly hydrogen peroxide and peracetic acid were successfully conducted with the help of microchemical technology. Excellent yield and selectivity were achieved in significantly shortened reaction times without the decomposition of explosive oxidants and further transformation of unstable products, offering a safe and efficient alternative to traditional methods for alkene diacetoxylation.

The vicinal difunctionalization of alkenes plays an important role in organic chemistry. The transformation is generally achieved using osmium catalysts or *m*-chloroperbenzoic acid (*m*-CPBA) on a laboratory-scale.[1] However, the catalyst and oxidant pose inherent problems such as high toxicity and cost or formation of troublesome byproducts. The requirements for good chemical processes include minimizing waste, designing safe control, and diminishing energy consumption.[2] Accordingly, alternative oxidants and catalytic systems have been challenging areas of research. Hydrogen peroxide and peracetic acid are obviously cheap and clean oxidants because they only release water or acetic acid, which can be easily removed by distillation in the purification step.[3] However, these ideal reagents are very unstable and may lead to highly exothermic explosion in the presence of heat or infinitesimal amounts of metallic impurities.[4] Oxidations under extremely mild conditions were certainly preferred because hot spots caused by self-decomposition can instantly spoil the entire reaction.[5]

Microchemical technology offers noticeable innovation compared with traditional batch reactions.[6] The ease with which reaction parameters can be controlled is manifested in improved selectivity and reaction yield. Scaling out can

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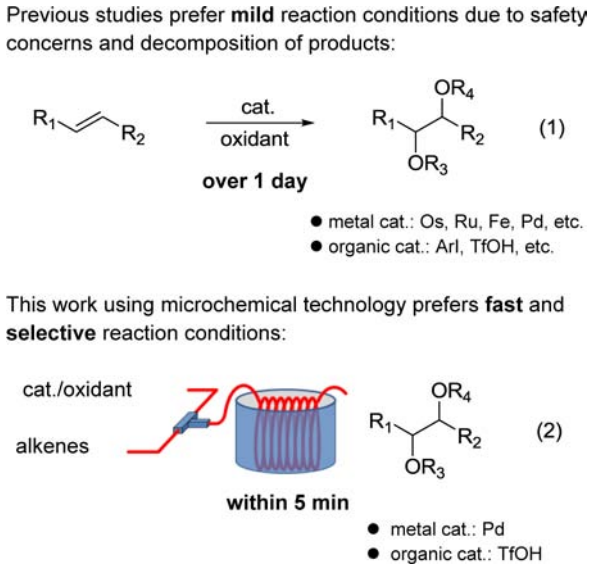
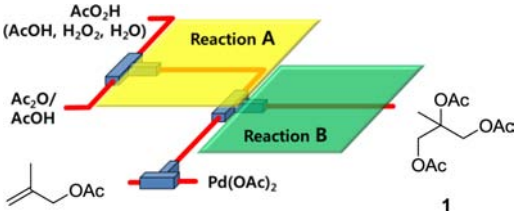
also be achieved by systems arranged in a row. Furthermore, hazardous and unstable chemicals can be applied in various reactions without safety hazards.[4b,7] Recently, Yoshida's research group serialized various reactions via flash chemistry using reactive organic lithium reagents.[8] The reactions involving unstable short-lived reactive intermediates are perfectly controlled under the sophisticated regulations of residence time and temperatures.

Scheme 1. Diacetoxylation of Alkenes



Herein, we report safe microchemical processes for the diacetoxylation of several alkenes which showed advantage of shortened and optimal reaction time. High heat-exchange efficiency in the microchemical system allowed highly exothermic reactions to be performed under isothermal conditions, and the formation of hot spots and accumulation of reaction heat were suppressed. It afforded high yields and selectivities at elevated temperature. Excellent microchemical reactions for alkene diacetoxylation are summarized in Scheme 1. Although use of mild reaction conditions has been the most important issue in previous studies because of explosive oxidants and unstable products, this is not the case in this microchemistry. Fast and selective reaction conditions were preferable in our study, providing the diacetoxylation products in good yields and selectivities within 5 min residence time.

Table 1. Pd-Catalyzed Diacetoxylation of 2-Methylallyl Acetate in a Microreactor[a]



entry	ratio (AcO_2H/Ac_2O)[b]	reaction A time (min), temp (°C)	reaction B time (min), temp (°C)	conv[c] (%)	yield[c] (%)
1	1:0	–, –	5, rt	8	
2	1:0	–, –	5, 50	38	9.5
3	1:0	–, –	5, 65	59	19.5
4	1:3	5, rt	5, rt	15	6.75
5	1:3	5, 50	5, 50	80	38.4
6	1:5	5, 50	5, 50	78	46.8
7	1:10	5, 50	5, 50	73	59.9
8	1:10	5, 50	5, 60	83	66.4
9	1:20	5, rt	5, 60	88	80.1
10	**1:20**	**5, 50**	**5, 60**	**99**	**95.0 (93.0)**
11	1:20	5, rt	10, 60	99	92.7
12	1:20	5, 50	15, 60	99	86.0
13[d]	1:20	5, 50	5, 60	35	19.6

[a] Reagents: 1.00 M 2-methylallyl acetate in AcOH, 5 mol % $Pd(OAc)_2$ (0.05 M in AcOH), 1.2 equiv AcO_2H (solution of 35.5% AcO_2H, 6.5% hydrogen peroxide, 17% H_2O, 40% AcOH). [b] Wt/wt ratio of 35.5% AcO_2H solution/Ac_2O. [c] Conversion (%) and yield (%) were determined by GC/MSD analysis. The number in parentheses is the isolated yield. [d] No catalyst.

Recently, Jung et al. reported palladium-catalyzed diacetoxylation in the presence of peracetic acid and acetic anhydride.[9] Even though the reaction has the significant advantage of mild reaction conditions, the reaction had to be conducted slowly for higher selectivity and safety. We began our study by investigating the diacetoxylation in the microchemical system which was made of a commercial polytetrafluoroethylene (PTFE) tube (i.d.: 500 μm, length: 6 m); details are described in the Supporting Information. We regulated reaction parameters including temperature, reagents, and residence time; the results are summarized in Table 1. Because the commercially available peracetic acid solution (35.5%) always contains acetic acid (40%), hydrogen peroxide (6.5%), and water (17%) to stabilize the

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peracid, the region for the first reaction (A) was intended for the reaction of acetic anhydride with peracetic acid, hydrogen peroxide, and water. In the absence or lack of acetic acid anhydride, the reactions resulted in complicated mixtures. Wacker–Tsuji-type oxidation was dominant, which was detected by GC/MSD analysis (entries 1–8).[10] In the presence of increased amounts of acetic anhydride (35.5% AcO_2H solution/Ac_2O = 1/20), diacetoxylation became the exclusive reaction (entries 9 and 10). Even though the reactions in entries 10 and 11 showed similar results, it can be inferred from the result in entry 9 that the reaction pathway may be different. This indicates that hydrogen peroxide and water should be removed before beginning the palladium-catalyzed reaction. Yield was increased up to 95% because of the use of perfectly controlled conditions with a rapid mixing and homogeneous ratio of reagents and the avoidance of hot spots. Unlike batch reactions, which take several hours, diacetoxylation in the microchemical system was completed within 5 min when the temperature was increased to 60 °C. However, reaction temperature over 65 °C resulted in sharp self-decomposition of the oxidant and formation of oxygen bubbles, which resulted in a situation of gas bubbles and liquid slugs as in a droplet microreactor. The bubble formation disturbed the steady flow and resulted in an incomplete reaction. Entry 12 emphasized the need for optimized reaction conditions; the microchemical reaction should be regulated according to the stability of product.

To further explore the Pd-catalyzed diacetoxylation, we screened three alkenes including a nonconjucated alkene

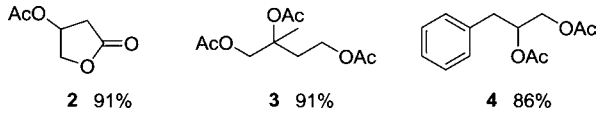
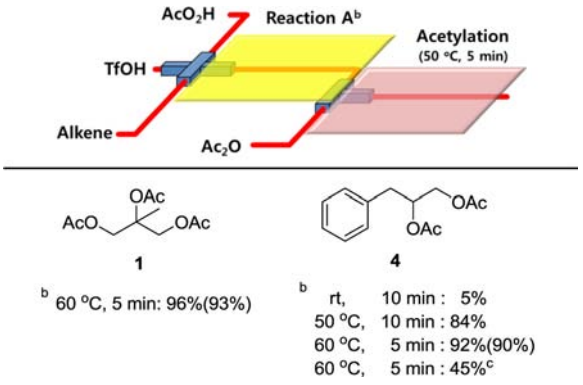


Figure 1. Products of the Pd-catalyzed diacetoxylation of alkenes. Reagents: 1.00 M alkene (in AcOH), 5 mol % of $Pd(OAc)_2$ (0.05 M in AcOH), 1.2 equiv of AcO_2H (solution of 35.5% AcO_2H, 6.5% hydrogen peroxide, 17% H_2O, 40% AcOH). Reaction conditions, see Table 1, entry 10.

and two terminal aliphatic alkenes (Scheme 2). Cyclization of but-3-enoic acid gave five-membered lactone **2** in 91% isolated yield. 3-Methylbut-3-enyl acetate and allylbenzene successfully generated compound **3** (91% isolated yield) and compound **4** (the slightly lower yield of 86%). All reactions were finished within a residence time of only 5 min.

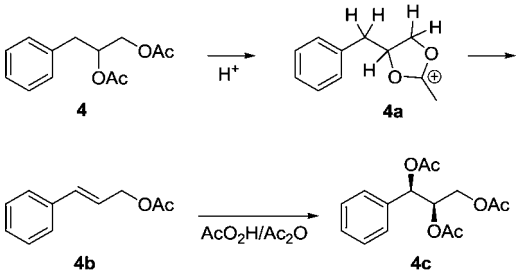
Trifluoromethanesulfonic acid (TfOH)-catalyzed diacetoxylation reported by Gade et al. is a metal-free, clean, and cheap method.[12] We used their method to perform microchemical reactions using the system applied in the

Scheme 2. TfOH-Catalyzed Diacetoxylation of Alkenes[a]



[a] Reagents: 1.00 M alkene in AcOH, 1 mol % of TfOH (0.05 M in AcOH), 2.5 equiv of AcO_2H (solution of 35.5% AcO_2H, 6.5% hydrogen peroxide, 17% H_2O, 40% AcOH). [b] Yields (%) were determined by GC/MSD analysis. The numbers in parentheses are the isolated yields. [c] 20 min in acetylation; main side products were triacetates.

Scheme 3. Plausible Pathway in Transformation of Product **4**



Pd-catalyzed reaction (Scheme 3). Two reactions were finished within only 5 min, when the temperature was increased to 60 °C. 2-Methylallyl acetate successfully generated compound **1** (96% isolated yield); allylbenzene was efficiently converted to product **4** (90% isolated yield). However, further transformation of product **4** into triacetates were significant at the elevated temperature, it may include dehydroacetoxylation and second diacetoxylation (Figure 1).

Diacetoxylation by peracetic acid generated in situ from much cheaper and stable hydrogen peroxide[4b] was achieved using the system shown in Scheme 4. 2-Methylallyl acetate and 3-methylbut-3-enyl acetate successfully generated compounds **1** and **3**, respectively (94% and 92% yields). The method was also very efficient in the oxidative lactonization; but-3-enoic acid and pent-4-enoic acid were perfectly transformed to five-membered lactones **2** and **5**, respectively (92% and 97% yields). Allylbenzene was converted to product **4** with slightly lowered 89% yield (side product **4c**, 4% yield; see the Supporting Information); propen-2-ylbenzene was transformed to product **7** with 90% yield. Internal alkenes gave only syn addition product **6** and **8** in 93% and 89% yields, respectively (side product **8b**, 6% yield; see the Supporting Information), which were

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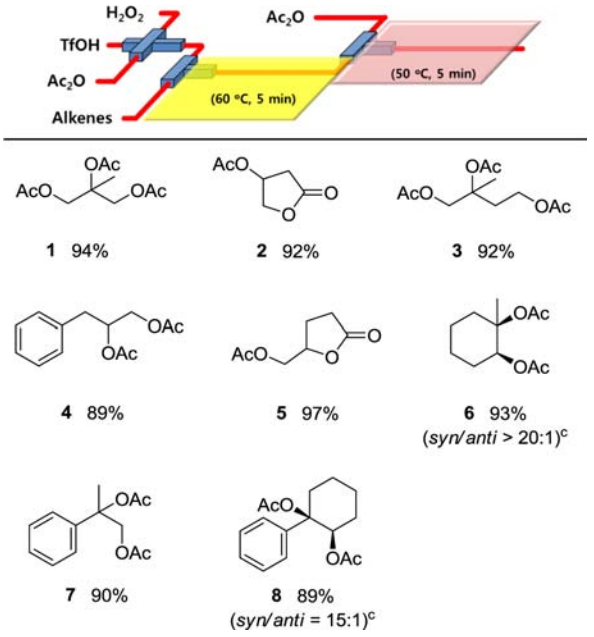
Scheme 4. TfOH-Catalyzed Diacetoxylation by Peracetic Acid Generated in Situ[a]



[a] Reagents: 1.00 M alkene in AcOH, 1 mol % of TfOH (0.05 M in AcOH), 2.5 equiv of H_2O_2 (50 wt % in H_2O). Yields (%) were determined by GC/MSD analysis. [b] The diastereomeric ratios were determined by ^{1}H NMR analysis.

determined by ^{1}H NMR analysis. All reactions were completed within only 5 min residence time. Herein, catalyst TfOH might perform multiple roles in peracetic acid formation, vicinal difunctioanlization, and/or ring-opening of epoxide, as well as acetylation of the hydroxyl group.[12] Because of the many-sided functions of TfOH, the system was significantly simplified, and might be useful in industrial applications. However, the TfOH carried out unexpected catalytic function in dehydroacetoxylation and rearrangement, it should be considered to minimize the decomposition of desired products. The daily output of microreactor with reaction volume of 1.178 mL (0.25 mm $\times$0.25 mm $\times$ $\pi \times$ 6 m) was calurated. Compound **8** of 4.12 g (14.9 mmol) was generated through the continuous running of 3 h, the obtainable product from the 1.178 mL volume was 32.96 g in one day. We also tested the reaction of a hypervalent iodine species ($PhI(OAc)_2$) in the presence of peroxide; the result was not impressive.[11]

In conclusion, we have described three types of microchemical reactions conducted using clean and cheap hydrogen peroxide and peracetic acid. The diacetoxylation reactions of alkenes were very fast, safe, and highly selective without rearrangement of diaceotoxylated products. Overall, our processes provide convenient and practical methods that we believe can be used not only for laboratory-scale synthesis, but on the industrial scale as well. Currently, another diacetoxylations involving heterogeneous catalysts and catalyst-free conditions are underway and will be reported in due course.

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Supporting Information Available. Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.