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Diastereo-recognizable reaction between Cr(VI) reagents and tertiary α-hydroxy epoxide

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Abstract—Chromium(VI) reagents containing pyridine derivatives were found to be able to oxidize diastereo-recognizably tertiary α-hydroxy epoxides to form carbonyl compounds. The correlation of structure–selectivity of this reaction was discussed, and the diastereo-recognizability proved to be dependent largely upon the substitution patterns of the pyridine moiety. © 2001 Elsevier Science Ltd. All rights reserved.

In connection with our investigation of the diastereoselective reactions of tertiary α-hydroxy epoxides with Lewis acids, we have reported in a previous paper the diastereoselective reductive rearrangement mediated by $Al(i\text{-}OPr)_3$.[1] Recently we have found that these kinds of epoxides could undergo an interesting diastereo-recognizable oxidation with PCC (pyridinium chlorochromate) and its improved reagents,[2] in which one of the diastereoisomer pairs could react selectively to form different kinds of carbonyl compounds, and the other was recovered with purity of up to 96% d.e. Further research also led to another interesting observation that this stereoselectivity is dependent, to a great extent, upon the substitution of the pyridine moiety of PCC. Although the oxidation with PCC has long been one of the most popular and practically useful methods for the preparation of aldehyde and ketone since Corey's report in 1975,[3] no chemists reported its stereoselectivity[4] and the origin of this property. In this paper we would like to present our research results regarding this subject.

The tertiary α-hydroxy epoxides we examined were prepared as diastereoisomeric pairs from the corresponding tertiary allylic alcohols by epoxidation with *m*-CPBA or $^t BuO_2H/VO(acac)_2$,[5,6] and their structures and stereochemistry were determined by 1 and 2 D NMR spectroscopy. These pairs were hard to resolve even by HPLC, and yet we were not able to prepare the optically pure epoxides by the Sharpless epoxidation. Therefore, the oxidation experimentals were run in a typical procedure with 1.5 equiv. PCC in CH_2Cl_2 solution, and the results were listed in Table 1,[3b] in which the data in column 3 represented the time at which the oxidation reaction achieved its optimum diastereoselectivity indicated in column 4. It could be seen that entries 1–8 in general showed good diastereo-recongnizable reactivity to PCC oxidation. Further examination of these examples revealed some more detailed information about the relationship between structure and reactivity and diastereoselectivity. For example, entries 1–5 had the same distribution of hydroxyl and epoxy groups, and displayed similar results: all the isomers **1b**–**5b** with *cis*-substitution of epoxy and sterically hindering C_4–Me were oxidized selectively by PCC, but those (**1a**–**5a**) with *trans*-substitution were recovered as enriched mixtures in high yields. The epoxides in entries 6–7 had another kind of similar substitution form of hydroxyl and epoxy, and showed reverse diastereo-recognizability, i.e. the epoxides **6a** and **7a** with the *trans*-substitution of epoxy and C_4–Me were more reactive than the *cis*-substituted **6b** and **7b**, respectively. However, the diastereoselectivity (46/54, entry 7) and the recovery yield of the enriched mixture (25%, entry 6) were poor. This fact possibly resulted from the presence of the very large hindering group at the tertiary carbon bearing hydroxyl. Entry 8 belonged to the third forms of structures, which had the conformationally fixed hydroxyl closer to the C_4–Me and the epoxy farther away from it. Thus we could see that the isomer **8b** with epoxy and hydroxyl being in the same direction were more reactive than the isomer **8a**.

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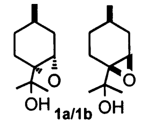
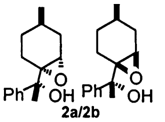
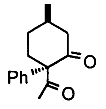
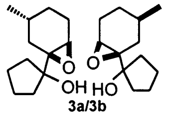
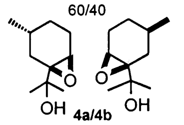
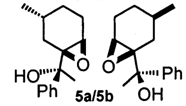
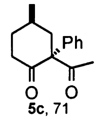
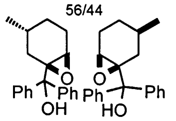
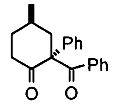
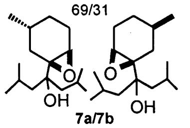
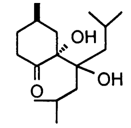
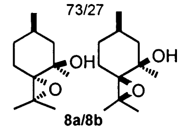
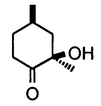
Table 1. Diastereo–recognizable reaction between α-hydroxy epoxides and PCC[a–d]

Entry	Substrate **a/b**, ratio	Reaction time	Recovered **a/b** ratio, yield(%)	Product yield(%)
1	 **1a/1b** 61/39	5h	96/4, 53	—
2	 **2a/2b** 63/37	4.5h	92/8, 42	 **2c**, 84
3	 **3a/3b** 60/40	5h	96/4, 54	—
4	 **4a/4b** 61/39	10h	96/4, 55	—
5	 **5a/5b** 56/44	25h	83/17, 40	 **5c**, 71
6	 **6a/6b** 69/31	25h	2/98, 25	 **6c**, 98
7	 **7a/7b** 73/27	50h	46/54, 45	 **7c**, 75
8	 **8a/8b** 47/53	24h	91/9, 45	 **8c**, 55

[a] Structures of all compounds were determined with ^1H and ^{13}C NMR. MS and isomer ratios were measured with ^1H NMR and/or GC.

[b] '—' Represented complicated mixture unidentified.

[c] The yield in column 4 referred to the ratios of recovered **a**+**b** to starting **a**+**b** , and those in column 5 represented the ratios to the single starting isomer.

[d] The product **2c** was formed during the expanded reaction period (10 h) from **2a**.

We were not clear about the exact stereocontrolling mechanism at this stage because the oxidation process for Cr(VI) reagents was generally complicated and substrate dependent,[4] but we felt that the presence of hydroxy in substrate was essential for activation of this oxidation because the simple epoxide was inert to PCC.[2,7] After all, however, the extent to which the diastereoselectivity of the oxidation reaction could reach would be largely dependent on the structure differentiation between two diastereoisomers of α-hydroxy epoxides, and occasionally could be tuned lightly by the experiment scale and the equivalents of PCC employed.

As for the chemo-selectivity of this oxidation, there were two major classes of products formed, depending upon the specified substrate structure. The first was the 1,3-diones (entries 2, 5 and 6), which was synthetically valuable due to the presence of stereoselective quaternary carbon. The structures of these 1,3-diones were confirmed by the PCC oxidation of the corresponding 1,3-diols obtained by other Lewis acid-mediated rearrangement.[1] The second was produced through the ring open-oxidation of epoxy (entry 7) or oxidative-fragmentation of C–C bonds, including that of C_1–C_2 (entry 8) or more complicated fragments (entries 1, 3 and 4).

Our further investigation goes to the original probe of the diastero-reconizability. Our initial consideration was based on the hypothesis that there would exist some steric restriction of pyridinium ion on PCC oxidation, though it was usually regarded as the ionic property. Thus the modified reagents PICC, LCC and ACC

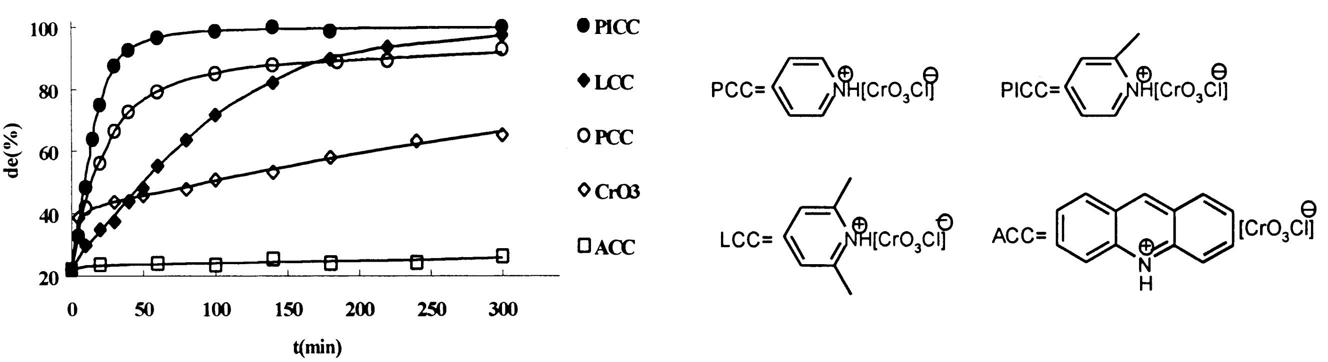
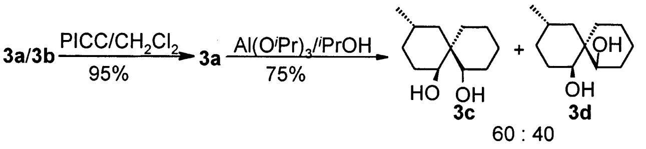


Figure 1. Diastereoselectivity of the oxidation of **1a**/**1b** with Cr(VI) reagents: (a) typical procedure:[3b] 0.47 mmol **1a**/**1b**, 15 ml CH_2Cl_2, 0.71 mmol Cr(VI) reagents and room temperature; (b) the d.e. values of **1a** (measured with GC) and the isolated yields of **1a**+**1b** for a 5 h reaction were as follows: PICC, d.e. 99, 52%; LCC, d.e. 97, 52%; PCC: d.e. 92, 53%; CrO_3, d.e. 65, 60%; ACC, d.e. 26, 96%.



Scheme 1.

were prepared from picoline, 2,6-lutidine and acridine, respectively,[8] and then subjected to the parallel oxidation experiment using **1a**/**1b** as substrates and CrO_3 as a control. The d.e. values of **1a** were measured with GC during the reaction and diagramed as showed in Fig. 1. It was interesting to note that both PICC and LCC displayed higher diastereoselectivity than PCC, with PICC being the best because it reached its optimum selectivity in the shortest time. However, ACC appeared to be inactive and the unreacted substrate **1a**/**1b** (62/38) was recovered in 96%, possibly because of the big acridine part, and/or some unknown electronic effects. We guessed the same result for other examples in Table 1 would be obtained if the suitable oxidant became available.

As an application example, the important chiral ligands **3c**/**3d**, have been successfully synthesized through the efficient oxidation–purification with PICC from **3a**/**3b** (Scheme 1),[9] which were hard to resolve even on HPLC. This work will be described in more detail in another paper.

In conclusion, here reported was an interesting diastereo-recognizable oxidation between Cr(VI) reagents and tertiary α-hydroxy epoxide, which were both a synthetic method of quaternary-carbon-contained 1,3-diones and the preparation procedure of diastereoisomerically pure tertiary α-hydroxy epoxides. More importantly, the observation that this stereoselectivity was dependent upon the substitution of the pyridine moiety of PCC implied the more extensive selectivity (including regio- and stereo-selectivity) in the oxidation of primary and secondary hydroxyls with PCC, which is under investigating in our group.

Acknowledgements

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