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RuCl$_3$/CeCl$_3$/NaIO$_4$: A New Bimetallic Oxidation System for the Mild and Efficient Dihydroxylation of Unreactive Olefins

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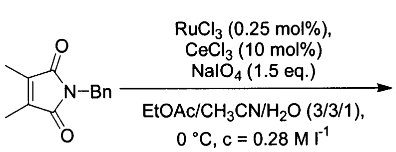
Received November 6, 2004



The catalytic dihydroxylation of olefins represents a unique synthetic tool for the generation of two C,O-bonds with defined relative configuration. Whereas OsO$_4$ has been established as a very general dihydroxylation catalyst within the past 30 years, the less expensive and toxic isoelectronic RuO$_4$ has found only limited use for this type of oxygen-transfer reaction. High catalyst loading and undesired side reactions were severe drawbacks in RuO$_4$-catalyzed oxidations of C,C-double bonds. Recently, we were able to improve the RuO$_4$-catalyzed dihydroxylation by addition of Brönsted acids to the reaction mixture. This protocol proved to be of general applicability, however, certain limitations were observed. To address these problematic functional groups a new Lewis acid accelerated oxidation was developed. The use of only 10 mol % of CeCl$_3$ allowed a further decrease in the catalyst concentration down to 0.25 mol % while broadening the scope of the reaction. Silyl ethers and nitrogen containing functional groups are now tolerated in this optimized protocol. Furthermore, competing scission reactions are supressed in the presence of Lewis acid allowing longer reaction times and the successful oxidation of electron-deficient tetrasubstituted double bonds that cannot be oxidized using known dihydroxylation protocols.

Transition-metal-catalyzed reactions are among the most powerful tools in modern organic synthesis. The success of this type of transformation is a direct consequence of the fruitful cooperation of organic and inorganic chemists.[1] Understanding the mode of action at the metal center as well as on the organic substrate is a fundamental prerequisite for the successful development of a broadly applicable catalytic system. Oxidation reactions are an important subdivision among transition metal-catalyzed transformations.[2] Although this type of reaction has been in the center of research for the past thirty years, the development of economically attractive and environmentally benign oxidation systems still remains a challenging problem in oxygen transfer chemistry. Hence, the main goal in this area is the use of a powerful, inexpensive and readily available catalyst and a stoichiometric reoxidant that is not hazardous and easy to handle.[3]

The osmium-catalyzed dihydroxylation of C,C-double bonds belongs to the most successful catalytic transformations developed so far. The early investigations of Criegee[4] on the chemistry of OsO$_4$ and Sharpless' subsequent studies on the effect of ligands and reoxidants on the course of the reaction[5] finally led to a broadly applicable asymmetric dihydroxylation for a variety of different olefins with predictable absolute configuration at the newly formed stereocenters. The use of OsO$_4$, however, has several drawbacks. It is very expensive, volatile, and toxic. Hence, the search for a less expensive and toxic albeit comparably selective oxidation catalyst is still of current interest. In 1994, Shing reported the dihydroxylation using catalytic amounts of RuO$_4$.[6] Due to the high reactivity of the catalyst, dihydroxylations using RuO$_4$ are usually less selective and accompanied by undesired fragmentation reactions. Furthermore, the high catalyst loading of 7 mol % is economically problematic. Recently we found that simple Brönsted acids are able to accelerate the rate of this reaction.[7] The new procedure allowed a decrease of the catalyst loading from the original 7 mol % down to only 0.5 mol % for the oxidation of a wide variety of olefins. However, the presence of protons led to problems with certain substrates due to protolytic side reactions. To avoid these undesired background reactions, we envisioned the use of Lewis acids as appropriate substitutes for Brönsted acids. Our investigations led to the discovery of an unprecedented bimetallic catalytic system of the bifunctional redox active Lewis acid CeCl$_3$ facilitating both the reoxidation and the subsequent hydrolysis of the resulting ruthenium(VIII) ester.

The search for an appropriate Lewis acid started with an intense screening of a variety of metal chlorides known to possess Lewis acidic properties and to be stable in the presence of water (Table 1).[8] Main group metal salts showed a remarkable effect on reaction rate and selectivity. Apparently, softer Lewis acids improve the conversion rate while maintaining the selectivity (entries

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[1] *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; Hegedus, L. S., Ed.; University Science Books: Sausalito, 1999.

[2] *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford University Press: Oxford, 2001; p 128.

[3] *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Ed.; Wiley-VCH: Weinheim, New York, 1998.

[4] (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75. (b) Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99.

[5] (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, Weinheim, 2000; p 357. (b) Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis*, 2nd.ed.; Ojima, I., Ed.; Wiley-VCH: New York, Weinheim, 2000; p 399.

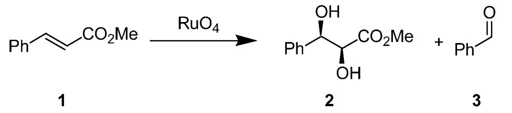
[6] (a) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem.* **1994**, *106*, 2408; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312. (b) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W. F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50.

[7] (a) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353. (b) Plietker, B.; Niggemann, M. *Org. Biomol. Chem.* **2004**, *2*, 1116.

[8] Different anions were screened in order to exclude a possible influence on the reaction course. Whereas bromide and iodide are oxidized under the dihydroxylation conditions, chlorides and fluorides are stable and have only a minor influence. Hydrogen sulfate, however, increases both selectivity and conversion rate. Unfortunately, attempts to combine the Lewis acid acceleration and the anion effect failed.

10.1021/jo048020x CCC: $30.25

TABLE 1. Lewis Acid Effect in RuO_4-Catalyzed Dihydroxylation



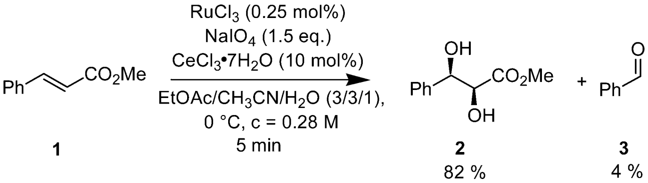
entry[a]	Lewis acid	**2/3**[b]	conversion[b] (%)
1		2.0:1.0	61
2	LiCl	1.0:1.7	32
3	NaCl	1.6:1.0	51
4	KCl	2.1:1.0	57
5	RbCl	2.5:1.0	67
6	$MgCl_2$	1.0:1.8	26
7	$CaCl_2$	1.7:1.0	71
8	$SrCl_2$	1.8:1.0	74
9	$FeCl_3$	1.8:1.0	98
10	$FeCl_2$	2.3:1.0	99
11	$CoCl_2$	1.3:1.0	70
12	$NiCl_2$	1.4:1.0	72
13	$CuCl_2$	1.2:1.0	66
14	$ZnCl_2$	2.2:1.0	97
15	$CeCl_3$	4.0:1.0	92

[a] All reactions were performed on a 2 mmol scale using 0.5 mol % $RuCl_3$ (as a 0.1 M stock solution in water), 20 mol % Lewis acid, and 1.5 equiv of $NaIO_4$ in a solvent mixture of $EtOAc/CH_3CN/H_2O$ (3 mL/3 mL/1 mL) at 0 °C and stopped after 3 min by addition of aq Na_2SO_3 solution. [b] Determined by GC integration using *n*-dodecane as internal standard.

5 and 8, Table 1). It is in line with these observations that transition-metal chlorides such as $FeCl_3$, $FeCl_2$. and $ZnCl_2$ led to full conversions after only 3 min. The selectivity, however, was not satisfying (entries 9, 10, and 14, Table 1). The use of lanthanides as Lewis acids has received growing attention within the past 10 years due to their unique ability to act as weak but efficient Lewis acids even in aqueous reaction systems.[9] Based upon the results obtained in the screening of main group and transition metal chlorides, we envisioned lanthanides to be suitable for both a rate acceleration and an improvement of the selectivity in dihydroxylations. Indeed, the use of $CeCl_3$ led to outstanding conversion rates and good diol: aldehyde ratios (entry 15, Table 1).

After optimization, a further decrease in the catalyst and Lewis acid loading was achieved while increasing the overall substrate concentration by a factor of 2 (Scheme 1). Compared to Shing's original protocol (7 mol % $RuCl_3$, 1.5 equiv of $NaIO_4$, $c = 0.07$ M)[6] and the Brönsted acid-assisted protocol developed in our group (0.5 mol % of $RuCl_3$, 1.5 equiv of $NaIO_4$, $c = 0.14$ M),[7] the new $CeCl_3$-assisted procedure (0.25 mol % of $RuCl_3$, 1.5 equiv of $NaIO_4$, 10 mol % of $CeCl_3$, $c = 0.28$ M) represents a significant improvement in the dihydroxylation of olefins using RuO_4. Interestingly, minor amounts of scission products were only formed in the beginning of the reaction. However, the initial amount did not increase even at longer reaction times. Hence, the selectivity for the formation of diol **2** increases with ongoing conversion. This is an unusual and new behavior for oxidations employing $NaIO_4$ as a stoichiometric reoxidant. Thus, the observed selectivities are the highest obtained so far in RuO_4-catalyzed dihydroxylations. The optimized protocol is shown in Scheme 1.

SCHEME 1. $CeCl_3$-Accelerated RuO_4-Catalyzed Dihydroxylation



Having in hand the optimized conditions, we turned our interest to the dihydroxylation of olefins that proved to be problematic in the Brönsted acid accelerated dihydroxylation. We were pleased to find that the new $CeCl_3$-accelerated dihydroxylation proceeded particularly well in the oxidation of such olefins.[7b] The already mentioned phenomenon of a reduced formation of scission products at longer reaction times led to outstanding selectivities with the amount of fragmentation product usually being below 10%. Representative results are listed in Table 2.

Acid-labile silyl ethers or acetals are dihydroxylated in good yields (entries 2 and 3, Table 2) using the milder Lewis acidic conditions. Furthermore, cyclic olefins known to undergo a rapid fragmentation[7b] were dihydroxylated in excellent yield with only minor formation of scission products. Competing allylic oxidations were not observed in the dihydroxylation of electron-rich cyclohexene **10**. Diol **11** was observed as the only product (entry 4, Table 2). The competing acid-induced saponification of coumarin **12** or the corresponding diol **13** as observed upon longer reaction times in the presence of Brönsted acids is disfavored in the presence of $CeCl_3$. Diol **13** was isolated in almost quantitative yield (entry 5, Table 2). Importantly, amides (entry 7−9, Table 2) can be oxidized to give interesting building blocks in excellent yields with no formation of scission products.[10] The efficiency of this new protocol is underlined by the successful oxidation of electron-poor tetrasubstituted olefin **20**, which cannot be dihydroxylated with OsO_4 or RuO_4 under the standard conditions. In the presence of catalytic amounts of $CeCl_3$ however a clean reaction to the corresponding *vic*-diol **21** was observed (entry 9, Table 2). As can be seen from Table 2, the reaction times are longer compared to the dihydroxylations under RuO_4 catalysis published to date.[6,7] Although the RuO_4-catalyzed dihydroxylation reaction is slowed by catalytic amounts of $CeCl_3$, the undesired fragmentation pathway is almost inhibited thus allowing for a better control of the reaction course.

A correlation of the pH value and redox potential for the most powerful dihydroxylation systems (entries 9, 10, 14, and 15, Table 1) indicates the accelerating effect of iron salts most likely to be a direct consequence of the more acidic reaction medium. According to the Nernst equation, the oxidation potential of $NaIO_4$ is inversely proportional to the pH value of the solution.[11] This behavior is found for the zinc and iron chlorides (Figure

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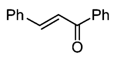
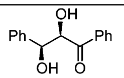
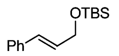
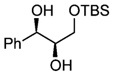
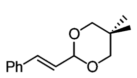
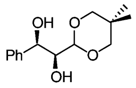
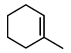
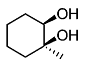
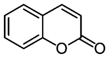
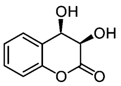
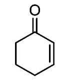
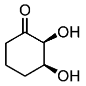
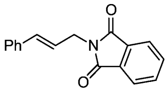
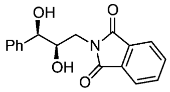
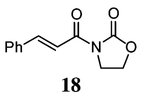
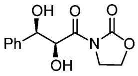
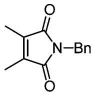
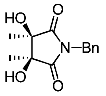
[9] *Topics in Organometallic Chemistry 2: Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer-Verlag: Berlin, Heidelberg, New York, 1999.

(10) We found amides to be problematic to dihydroxylate employing the original Upjohn-procedure (OsO_4 (cat.), NMO, acetone/water) or RuO_4 under Shingss or our Brönsted acid-accelerated conditions.

(11) The dependency of redox potential and pH value is reflected in the simplified Nernst equation:

$$E = E_0 - 0.059\text{pH}$$

TABLE 2. $CeCl_3$-Accelerated Dihydroxylation of Olefins

entry[a]	substrate	product	time [min]	yield [%][b,c]
1	 **4**	 **5**	20	68 (59)
2	 **6**	 **7**	8	81 (-)
3	 **8**	 **9**	8	87 (53)
4	 **10**	 **11**	10	82 (79)
5	 **12**	 **13**	10	93 (79)
6	 **14**	 **15**	10	83 (69)
7	 **16**	 **17**	10	91 (-)
8	 **18**	 **19**	15	86 (-)
9	 **20**	 **21**	10	89 (-)

[a] All reactions were performed on a 2 mmol scale using 0.25 mol % of $RuCl_3$ (as a 0.1 M solution in water), 10 mol % $CeCl_3 \cdot 7H_2O$, and 1.5 equiv of $NaIO_4$ at 0 °C in a solvent mixture of ethyl acetate/acetonitrile/water (3 mL/3 mL/1 mL). [b] Isolated yields. [c] Numbers in parentheses represent the yields obtained in the dihydroxylation in the presence of H_2SO_4.

1).[12] The redox potential of the $CeCl_3/NaIO_4$ system, however, indicates that the effect of $CeCl_3$ may not be a simple pH-driven effect as found for other acids.

The chemistry of periodate with various metal cations is literature known. A variety of transition metal salts form insoluble intensely colored periodato complexes.[13] The observation that a yellow precipitate is formed upon mixing $CeCl_3$ with $NaIO_4$ indicates an in situ oxidation toward Ce(IV) which is known to form insoluble yellow Ce(IV)−periodato complexes.[14] We envisioned these complexes to cause the increase in the redox potential at a lower pH value. Hence, $H[Ce(IO_6)]$ was prepared according to a literature procedure[14] and subjected to the dihydroxylation process. A reactivity study on the $CeCl_3/NaIO_4$ and the $H[Ce(IO_6)]/NaIO_4$ dihydroxylation system in the oxidation of methyl cinnamate **1** showed a dramatic rate acceleration and almost identical conversion rates for both cerium-assisted dihydroxylations compared to the reaction in the absence of any additive. However, the selectivity of the reaction in the presence of the preformed Ce(IV)−periodato complex was not satisfying (Table 3). The analysis of pH value and redox potential of the $CeCl_3/NaIO_4$ and the $H[Ce(IO_6)]/NaIO_4$ system indicated comparable potentials, the pH value, however, was different (Table 3).

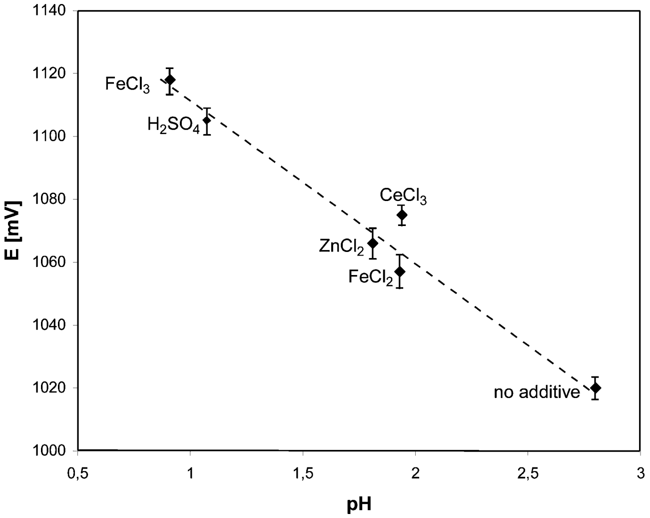


FIGURE 1. pH−*E* relation of a 0.25 M $NaIO_4$ solution in the presence of 20 mol % of additive at 6 °C. The potential and pH value were measured vs Ag/AgCl after addition of 0.25 mmol of additive to 5 mL of a 0.25 M aqueous solution of $NaIO_4$ at 6 °C. The data represent the average redox potentials out of five independent measurements with the given error.

TABLE 3. pH Value and Redox Potential of Reoxidation Systems

entry[a]	reoxidant	pH value	*E* (V)	**2/3**[b]
1	$NaIO_4$	2.8	1.020	1.0:1.0
2	$CeCl_3/NaIO_4$	1.94	1.075	10.2:1.0
3	$H[Ce(IO_6)]/NaIO_4$	2.61	1.071	4.6:1.0

[a] The potential and pH value were measured vs Ag/AgCl after addition of 0.25 mmol of Ce source to 5 mL of a 0.25 M aqueous solution of $NaIO_4$ at 6 °C. [b] The reactions were performed as indicated in Table 2. Ratios were determined by GC integration.

The addition of $CeCl_3$ to an aqueous solution of $NaIO_4$ induces a slight decrease in the pH value and an increase in the redox potential (entries 1 and 2, Table 3). The latter effect might be caused by the in-situ formed Ce(IV)-periodato complex, which upon addition to a $NaIO_4$ solution shows an almost identical oxidation potential albeit at a higher pH value (entry 3, Table 3). At the current state of research, however, it seems as if both effects account for the observed high reactivity and selectivity observed in the $CeCl_3$-assisted RuO_4-catalyzed dihydroxylation. The latter aspects need to be investi-

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[12] $FeCl_3$ reacts with water with concomitant release of HCl according to the equation:

$$FeCl_3 + 6\,H_2O \rightarrow [Fe(H_2O)_6]^{3+} + 3Cl^- \xrightarrow{pH<2} [Fe(OH)(H_2O)_5]^{2+} + 2Cl^- + HCl$$

[13] For a review see: (a) Siebert, H. *Fortschritte Chem. Forsch.* **1967**, *8*, 470. (b) Dratovsky, M.; Pacesova, L. *Russ. Chem. Rev.* **1968**, 243. (c) Levason, W. *Coord. Chem. Rev.* **1997**, *161*, 22.

[14] (a) Alimarin, I. P.; Pusdrenkowa, I. W.; Schiryajewa, O. A. *Nachr. Moskauer University Ser. II Chem.* **1962**, *17*, 61. (b) Levason, W.; Oldroyd, R. D. *Polyhedron* **1996**, *15*, 409. (c) Griffith, W. P.; Moreea, R. G. H.; Nogueira, H. I. S. *Polyhedron* **1996**, *15*, 3493.

gated in detail in order to get a deeper understanding on the interplay between $CeCl_3$, $NaIO_4$, pH value, and redox potential in the dihydroxylations. Hence, future work will focus on these interesting results. However, to the best of our knowledge this is the first successful application of cerium-periodato complexes in organometallic catalysis. The high oxidation potential and good selectivity of these unexplored reagents might also be beneficial in other oxygen transfer reaction employing stoichiometric amounts of $NaIO_4$.

In summary, a new $CeCl_3/NaIO_4$ reoxidation system was developed for RuO_4-catalyzed diyhdroxylation. This new protocol possesses several advantages compared to the previously published Brönsted acid-accelerated dihydroxylation. Due to the milder conditions, protolytic side reactions of the starting material are not observed. Furthermore, the moderate pH value might account for the result that neither a RuO_4-catalyzed nor a $NaIO_4$-induced glycol cleavage of the final product becomes a serious side reaction. These background processes, however, are known to be particularly problematic in RuO_4-catalyzed oxidations of C,C-double bonds at longer reaction times. Hence, by disfavoring undesired reaction pathways, the oxidation of unreactive tetrasubstituted olefins was possible by a simple prolongation of the reaction time. In addition, this new protocol allows a further reduction in the catalyst concentration down to only 0.25 mol % $RuCl_3$. Thus, the new bimetallic oxidation system of $RuCl_3/CeCl_3/NaIO_4$ represents an improved protocol for the preparation of racemic *syn*-diols from unreactive or acid sensitive olefins in good to excellent yields. Further studies toward the development of an asymmetric version of this reaction and an environmentally friendly reoxidation process are currently under investigation in our laboratories.

Experimental Section

General Procedure for the Dihydroxylation. In a 50-mL round-bottomed flask equipped with magnetic stirring bar and overpressure valve were stirred $NaIO_4$ (642 mg, 3 mmol) and $CeCl_3{\cdot}7H_2O$ (74.6 mg. 0.2 mmol, 10 mol %) in 0.9 mL of H_2O and gently heated until a bright yellow suspension was formed. After cooling to 0 °C, ethyl acetate (2.5 mL) and acetonitrile (3 mL) were added, and the suspension was stirred for 2 min. A 0.1 M aqueous solution of $RuCl_3$ (50 μL, 0.01 mmol) was added, and the mixture was stirred for 2 min. A solution of the olefin (2 mmol) in ethyl acetate (0.5 mL) was added in one portio,n and the resulting slurry was stirred until all starting material was consumed. Solid Na_2SO_4 (1 g) was added followed by ethyl acetate (6 mL). The solid was filtered off, and the filter cake was washed several times with ethyl acetate. The filtrate was washed with satd Na_2SO_3 solution (3 mL), and the organic layer was dried over Na_2SO_4 and concentrated in a vacuum. The crude product was purified by flash chromatography.

(3*R,4*S**)-1-Benzyl-3,4-dihydroxy-3,4-dimethylpyrrolidine-2,5-dione (15):** (443 mg, 1.78 mmol, 89%); white solid; mp 89 °C; R_f 0.12 (1:1 pentane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 5H), 4.61 (s, 2H), 4.23 (s, 2H), 1.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 136.5, 130.2, 129.6, 129.4, 76.9, 43.7, 20.1; IR (KBr) ν 3450 (s), 2991 (w), 1703 (s), 1404 (m), 1343 (m), 1134 (s), 1070 (m), 699 (s). Anal. Calcd for $C_{13}H_{15}NO_4$ (249.26): C, 62.64; H, 6.07. Found: C, 62.65; H, 6.08.

Acknowledgment. We thank Prof. Dr. N. Krause for generous support. B.P. thanks the Fonds der Chemischen Industrie (Liebig fellowship), the Otto-Röhm-Gedächtnisstiftung, and the Deutsche Forschungsgemeinschaft (Emmy–Noether fellowship). Further financial support by the Fonds zur Förderung des wissenschaftlichen Nachwuchses im Fachbereich Chemie der Universität Dortmund is gratefully acknowledged.

Supporting Information Available: Copies of ^{1}H NMR spectra and spectral data for all diols. This material is available free of charge via the Internet at http://pubs.acs.org.

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