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WO_3/70 % TBHP/Aqueous NaOH: An Efficient Catalytic Combination for the Selective Oxidation of Methylarenes and Alkyl Aryl Ketones to Benzoic Acids

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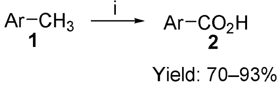
A new solvent-free, reusable catalytic combination consisting of WO_3/70 % TBHP/aqueous NaOH has been described for the direct oxidation of methylarenes and acetophenones to the corresponding benzoic acids in high yields. Alkylarenes are oxidized to the corresponding aromatic ketones or benzylic alcohols depending upon whether NaOH is used or not.

Introduction

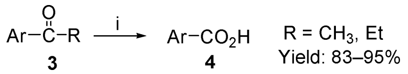
The oxidation of benzylic C–H bonds to the corresponding oxy-functionalized products constitutes one of the most fundamental transformations in organic synthesis.[1] In particular, the direct conversion of methylarenes to the corresponding benzoic acids assumes greater industrial importance, as such carbonyl derivatives are versatile building blocks in pharmaceutical and polymer industries.[2] A variety of oxometal oxidants[3] such as $KMnO_4$, $Na_2Cr_2O_7$, CrO_3, CeO_2, TiO_2, or $NaIO_4$ in stoichiometric amounts and $Co(OAc)_2$,[4] Cu–Fe,[5] ZnO,[6] $MnCO_3$[7] $AlBr_3$[8] $FeCl_3$,[9] and more recently Ni^{II}(TPA),[10] $RuCl_3$,[11] CuCl,[12] and Bi salts[13] in catalytic amounts have been employed for such oxidative processes. Among non-oxometal oxidants, urea hydrogen peroxide, HNO_3, HBr, and CBr_4–PPh_3 are commonly used.[14] However, stoichiometric use of metallic oxidants generally cause problems associated with either environmental pollution or difficult separation of the metal reagent from the products. The development of catalytic benzylic oxidative process with a readily available and inexpensive catalyst with no toxicity would be of considerable relevance for academia and industries. We wish to report herein tungsten(VI) oxide (WO_3)-catalyzed solvent-free oxidation of methylarenes or alkyl aryl ketones to the corresponding benzoic acids by using 70% *tert*-butyl hydroperoxide (TBHP) as oxidant in the presence of 40% NaOH as additive (Schemes 1 and 2).



$$\underset{\mathbf{1}}{Ar{-}CH_3} \xrightarrow{i} \underset{\mathbf{2}}{Ar{-}CO_2H}$$

Yield: 70–93%

Scheme 1. Reagents and conditions (i): (a) methylarene (3 mmol), WO_3 (20 mol-%), 70% TBHP (24 mmol), 40% NaOH (24 mmol), 80 °C, 10 h; (b) acidified with 6 N HCl.



$$\underset{\mathbf{3}}{Ar{-}\overset{O}{\overset{\|}{C}}{-}R} \xrightarrow{i} \underset{\mathbf{4}}{Ar{-}CO_2H} \quad R = CH_3, Et$$

Yield: 83–95%

Scheme 2. Reagents and conditions (i): (a) WO_3 (10 mol-%), 70% TBHP (12 mmol), 40% NaOH (12 mmol), 80 °C, 8 h; (b) acidified with 6 N HCl.

Results and Discussion

Oxidation of Methylarenes

Table 1 shows the results of WO_3-catalyzed oxidation of 4-bromotoluene as a model substrate to the corresponding 4-bromobenzoic acid with 70% TBHP as oxidant in the presence of NaOH as additive. Thus, when 70% TBHP (1 equiv.) and 40% NaOH (8 equiv.) was used, the corresponding 4-bromobenzoic acid was obtained only in 27% yield. A larger amount of TBHP (4 equiv.) resulted in an improved yield up to 36%. When the reaction was performed with an even larger concentration of TBHP (8 equiv.) and WO_3 (5 mol-%), 4-bromobenzoic acid was obtained in moderate yield (42%). Also, when the quantity of NaOH was reduced to 9 or 15 mmol, the product was obtained in 15 or 57% yield, respectively. Thus, optimal reaction conditions comprised WO_3 (20 mol-%), 70% TBHP (8 equiv.), and 40% NaOH (8 equiv.) as additive. This gave 4-bromobenzoic acid in 89% isolated yield. The use of other tungsten-based catalysts like Na_2WO_4 and H_2WO_4 gave poor yields of the product (<15%). Also, the reaction failed when H_2O_2 (aq. 30% or 50%) was used as the oxidant. Control experiments showed that, in the absence of NaOH, no reaction took place.

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Table 1. WO_3-catalyzed oxidation of 4-bromotoluene to 4-bromobenzoic acid.[a]

Entry	WO_3 [mol-%]	70% TBHP [mmol]	40% NaOH [mmol]	Yield[b] [%]
1	20	3	24	27
2	20	12	24	36
3	5	24	15	42
4	20	24	9	15
5	20	24	15	57
6	20	24	24	89

[a] (i) 4-Bromotoluene (3 mmol), WO_3, 70% TBHP, 40% NaOH, 80 °C, 10 h; (ii) acidified with 6 N HCl. [b] Isolated yield and product was characterized by m.p. and ^1H and ^{13}C NMR spectroscopy.

For understanding the scope and generality of this oxidation method, several methylarenes were subjected to oxidation under the optimized conditions, and the results are presented in Table 2. Alkylarenes with electron-withdrawing as well as electron-donating substituents underwent oxidation readily to produce the corresponding benzoic acids in excellent yields. It is noteworthy that for substrates with polymethyl groups, one of the methyl groups is selectively oxidized to give monocarboxylic acid (Table 2, Entries 4 and 9). However, α-picoline failed to undergo oxidation under the reaction conditions.

Table 2. WO_3-catalyzed oxidation of methylarenes to benzoic acids with 70% TBHP.[a]

Entry	$ArCH_3$ (**1**)	$ArCO_2H$ (**2**) Yield [%][b]
1	C_6H_5	85
2	$4\text{-}BrC_6H_4$	89
3	$4\text{-}ClC_6H_4$	84
4	$4\text{-}MeC_6H_4$	78
5	$2\text{-}MeC_6H_4$	71
6	$4\text{-}MeOC_6H_4$	85
7	$4\text{-}t\text{Bu}C_6H_4$	74
8	$4\text{-}NO_2C_6H_4$	93
9	$3,5\text{-}Me_2C_6H_3$	72
10	$2,3\text{-}Cl_2C_6H_3$	75
11	$2,4\text{-}Cl_2C_6H_3$	83
12	$3,4\text{-}Cl_2C_6H_3$	80
13	2-methylnaphthalene	70

[a] (i) Methylarene (3 mmol), WO_3 (20 mol-%), 70% TBHP (3 mL, 24 mmol), 40% NaOH (24 mmol), 80 °C, 10 h; (ii) acidified with 6 N HCl. [b] Isolated yields and products were characterized by m.p. and ^1H and ^{13}C NMR spectroscopy.

Oxidation of Aromatic Ketones

The catalytic oxidative cleavage of aryl methyl ketones to the corresponding benzoic acids is a potentially useful transformation in organic synthesis.[15] When we extended the present methodology to aryl ketones, we observed that the corresponding benzoic acids were formed in high yields, and the results are presented in Table 3. Thus, acetophenone underwent oxidative cleavage with WO_3 (10 mol-%) and 70% TBHP (4 equiv.) and 40% NaOH as additive to give benzoic acid in 89% yield. The reaction was found to be general with other acetophenones as well. When 4-methylacetophenone was subjected to oxidation, *p*-toluic acid was obtained selectively in 83% yield, whereas propiophenone gave benzoic acid in 95% yield (Table 3, Entry 3).

Table 3. WO_3-catalyzed oxidative C–C bond cleavage of alkyl aryl ketones.[a]

Entry	Alkyl aryl ketones (**3**)	Benzoic acids (**4**)	Yield[b] [%]
1	acetophenone	benzoic acid	89
2	4-methylacetophenone	*p*-toluic acid	83
3	propiophenone	benzoic acid	95
4	4-bromoacetophenone	4-bromobenzoic acid	95
5	2,4-dichoroacetophenone	2,4-dichlorobenzoic acid	92
6	4-nitroacetophenone	4-nitrobenzoic acid	84
7	4-methoxyacetophenone	4-methoxybenzoic acid	85
8	4-fluoroacetophenone	4-fluorobenzoic acid	93
9	4-chloroacetophenone	4-chlorobenzoic acid	94

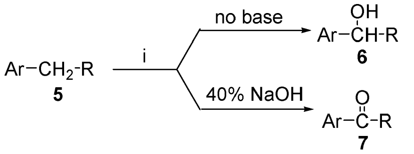
[a] (i) Alkyl aryl ketone (3 mmol), WO_3 (10 mol-%), 70% TBHP (1.5 mL, 12 mmol), 40% NaOH (12 mmol), 80 °C, 8 h; (ii) acidified with 6 N HCl. [b] Isolated yields and products were characterized by m.p. and ^1H and ^{13}C NMR spectroscopy.

Upon oxidation, acetophenones with both electron-withdrawing and electron-donating substituents gave the corresponding benzoic acids in high yields. The halo-substituted acetophenones also underwent facile oxidation to give the benzoic acids in high yields.

The workup procedure for both the methods generally involves acidification of the reaction mixture with ice-cold diluted HCl (6 N), followed by extraction of the product with ethyl acetate so that WO_3 is left dispersed in the aqueous layer. Concentration of the organic layer gave pure benzoic acid, whereas WO_3 in the aqueous layer was recovered by simple filtration. The recovered WO_3 was found to be effective for oxidation of toluene to benzoic acid (55%) although with reduced activity.

Oxidation of Alkylarenes

Interestingly, alkylarenes when subjected to oxidation with WO_3 (20 mol-%) and 70% TBHP (2 equiv.), *in the absence of base*, exhibited an unusual product selectivity (Scheme 3). For example, ethylbenzene on oxidation with the WO_3/TBHP combination gave either acetophenone **7** or benzylic secondary alcohol **6** in moderate yields (48 and 35%, respectively) depending upon whether NaOH was used or not; the remaining substance was unreacted ethylbenzene. Other alkyl arenes such as indane, tetraline, fluorene, and so on have exhibited similar behavior in terms of product selectivities as well as yields (Table 4). However, when 4-ethyltoluene was subjected to oxidation under the reaction conditions, in the absence of base, the corresponding 4′-methyl-1-phenylethanol was obtained selectively in 20% isolated yield.



Scheme 3. Reagents and conditions (i): (a) WO_3 (20 mol-%), alkyl arenes (3 mmol), 70% TBHP (6 mmol), 80 °C, 12 h.

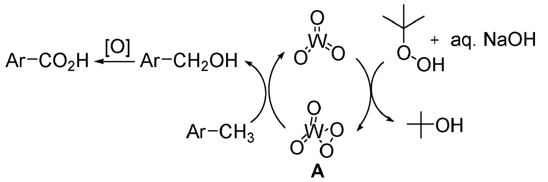
Table 4. The effect of base in WO_3-catalyzed benzylic C–H oxidation.[a]

Entry	Substrates **5**	Yield [%][b]	
		Alcohols **6**[c]	Ketones **7**[d]
1	ethylbenzene	35	48
2	4-bromoethylbenzene	35	40
3	indane	43	58
4	tetraline	40	51
5	fluorene	48	55

[a] Alkylarene (3 mmol), WO_3 (20 mol-%), 70% TBHP (6 mmol), 80 °C, 12 h. [b] Isolated yield and products were characterized by m.p. and ^1H and ^{13}C NMR spectroscopy. [c] No base was added. [d] 40% NaOH (0.6 mL) was used.

Mechanism

The catalytic cycle for the oxidative process is shown in Scheme 4. In the case of methylarenes and aryl ketones, it was observed that no oxidation took place in the absence of base. However, upon the addition of NaOH, WO_3 became homogeneous and readily reacted with TBHP to produce a metal peroxo species, **A**; the evidence for its formation came from its typical IR absorption bands at 495, 640, and 950 cm^{-1}.[16] The metal peroxo species **A** then probably undergoes C–H insertion at benzylic C–H bond of alkylarenes to give the benzylic alcohols. Although none of the benzylic alcohols were isolated during the oxidative process, its formation as an intermediate has been suggested, as 4-nitrobenzyl alcohol when subjected to oxidation [WO_3 (20 mol-%), 70% TBHP (8 molar equiv.), no base] gave 4-nitrobenzoic acid (57%). For aryl ketones, it is established[17] that formation of α-hydroxyacetophenones followed by its facile oxidative cleavage gave benzoic acids.



Scheme 4. Plausible mechanism for WO_3-catalyzed benzylic C–H oxidation of methylarenes.

Conclusions

We have developed a new catalytic method consisting of WO_3/TBHP/NaOH for the oxidation of methyl arenes and alkyl aryl ketones to the corresponding benzoic acids in high yields. Oxidation of alkylarenes to the corresponding secondary alcohols or ketones is dependent upon whether we use alkali or not. In the present protocol benzoic acids were isolated in pure form without the need for column chromatographic purification.

Experimental Section

Typical Procedure for Oxidation of Methylarenes: To a mixture of toluene (3 mmol), WO_3 (20 mol-%), and TBHP (70%, 24 mmol) was added NaOH (40% in water, 24 mmol, 2.4 mL). The reaction mixture was then heated at 80 °C (using oil bath) for 10 h, cooled to room temperature, and acidified by using ice-cold HCl (6 N). The mixture was extracted with ethyl acetate (3 × 40 mL), and the combined organic phase was washed with saturated brine solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give pure benzoic acid. Yield: 85%.

General Procedure for Oxidation Aryl alkyl Ketones: To a mixture of aryl alkyl ketone (3 mmol), WO_3 (10 mol-%), and TBHP (70%, 12 mmol) was added NaOH (40% in water, 12 mmol, 1.2 mL). The reaction mixture was then heated at 80 °C (using oil bath) for 8 h, cooled to room temperature, and acidified by using ice-cold HCl (6 N). It was extracted with ethyl acetate (3 × 40 mL), and the combined organic phase was washed with saturated brine solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give pure benzoic acid.

General Procedure for Oxidation of Alkylarenes: To a mixture of alkylarenes (3 mmol) and WO_3 (20 mol-%), was added TBHP (70%, 6 mmol). The reaction mixture was then heated at 80 °C (using oil bath) for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (3 × 20 mL), and the combined organic phase was washed with saturated brine solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography packed with silica gel (*n*-hexane/ethyl acetate, 9:1) to afford pure secondary benzylic alcohol.

Procedure for Oxidation of Alkylarenes to Benzylic Secondary Ketones: Alkylarenes were subjected to oxidation as mentioned above with NaOH (40% in water, 0.6 mL, 6 mmol with respect to substrate) to give benzylic secondary ketones.

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[1] a) D. Dyker (Ed.), *Handbook of C–H Transformations*, Wiley-VCH, Weinheim, **2005**; b) R. A. Sheldon, J. K. Kochi in *Metal-Catalyzed Oxidation of Organic Compounds*, Academic Press, New York, **1981**; c) S. D. Burke, R. L. Danheiser, *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agent*, Wiley, Chichester, U. K. **1999**; d) G. A. Olah, D. G. Parker, N. Yoneda, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 909–931; e) J. Eames, M. Watkinson, *Angew. Chem. Int. Ed.* **2001**, *40*, 3567–3571; f) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; g) Y. Ishii, S. Sakaguchi, T. Iwahama, *Adv. Synth. Catal.* **2001**, *343*, 393–427; h) T. Hirabayashi, S. Sakaguchi, Y. Ishii, *Angew. Chem. Int. Ed.* **2004**, *43*, 1120–1123.

[2] a) L. S. Vondervoort, S. Bouttemy, F. Heu, K. Weissenböck, P. L. Alsters, *Eur. J. Org. Chem.* **2003**, 578–586; b) T. Maki, Y.

Suzuki in *Ullmann's Encyclopedia of Industrial Chemistry* (Ed.: W. Gerhartz), 5th ed., VCH, **1985**, vol. A3, p. 555; c) J. Opgrande, E. E. Brown, M. Hesser, J. Andrews, in *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed., Wiley, New York, **2004**, vol. 3, p. 625–635; d) P. Benz, R. Muntwyler, R. Wohlgemuth, *J. Chem. Technol. Biotechnol.* **2007**, *82*, 1087–1098; e) G. W. Parshall, S. D. Ittel, *Homogeneous Catalysis*, Wiley, New York, **1992**.

[3] a) K. B. Wiberg in *Oxidation in Organic Chemistry*, Academic Press, New York, **1965**, Part A, p. 69; b) G. Cainelli, G. Cardillo in *Chromium Oxidations in Organic Chemistry*, Springer, New York, **1984**, p. 23; c) D. J. Sam, H. E. Simmons, *J. Am. Chem. Soc.* **1972**, *94*, 4024–4025; d) L. Friedman, D. L. Fishel, H. Shechter, *J. Org. Chem.* **1965**, *30*, 1453–1457; e) J. Muzart, *Tetrahedron Lett.* **1986**, *27*, 3139–3142; f) J. Muzart, *Tetrahedron Lett.* **1987**, *28*, 2131–2132; g) S. Yamazaki, *Org. Lett.* **1999**, *1*, 2129–2132; h) D. Worsley, A. Mills, K. Smith, M. G. Hutchings, *J. Chem. Soc., Chem. Commun.* **1995**, 1119–1120; i) E. Baciocchi, G. C. Rosato, C. Rol, G. V. Sebastiani, *Tetrahedron Lett.* **1992**, *33*, 5437–5440; j) T. M. Shaikh, L. Emmanuvel, A. Sudalai, *J. Org. Chem.* **2006**, *71*, 5043–5046; k) Q. Z. Shi, J. G. Wang, K. Cai, *Synth. Commun.* **1999**, *29*, 1177–1181; l) W. S. Trahanovsky, L. B. Young, *J. Org. Chem.* **1966**, *31*, 2033–2035; m) R. H. Reitsema, N. L. Allphin, *J. Org. Chem.* **1962**, *27*, 27–28; n) D. G. Lee, U. A. Spitzer, *J. Org. Chem.* **1969**, *34*, 1493–1495; o) O. Kamm, A. O. Matthews, *Org. Synth. Coll. Vol. 1* **1941**, 392–393.

[4] a) E. Modica, G. Bombieri, D. Colombo, N. Marchini, F. Ronchetti, A. Scala, L. Toma, *Eur. J. Org. Chem.* **2003**, *15*, 2964–2971; b) R. A. Sheldon, I. W. C. E. Arends, *Adv. Synth. Catal.* **2004**, *346*, 1051–1071 and references cited therein; c) B. Saha, J. H. Espenson, *J. Mol. Catal. A* **2005**, *241*, 33–38; d) A. Gizli, G. Aytimur, E. Alpay, S. Atalay, *Chem. Eng. Technol.* **2008**, *31*, 409–416; e) T. W. Bastock, J. H. Clark, K. Martin, B. W. Trenbirth, *Green Chem.* **2002**, *4*, 615–617; f) N. Hirai, N. Sawatari, N. Nakamura, S. Sakaguch, Y. Ishii, *J. Org. Chem.* **2003**, *68*, 6587–6590; g) F. Yang, J. Sun, R. Zheng, W. Qui, J. Tang, M. He, *Tetrahedron* **2004**, *60*, 1225–1228.

[5] F. Wang, J. Xu, X. Li, J. Gao, L. Zhou, R. Ohnishi, *Adv. Synth. Catal.* **2005**, *347*, 1987–1992.

[6] M. Gupta, S. Paul, R. Gupta, A. Loupy, *Tetrahedron Lett.* **2005**, *46*, 4957–4960.

[7] a) J. Gao, X. Tong, X. Li, H. Miao, J. Xu, *J. Chem. Technol. Biotechnol.* **2007**, *82*, 620–625; b) X. Li, J. Xu, F. Wang, J. Gao, L. Zhou, G. Yang, *Catal. Lett.* **2006**, *108*, 137–140; c) N. H. Lee, J. C. Byun, T.-H. Oh, *Bull. Korean Chem. Soc.* **2005**, *26*, 454–456.

[8] K. Nemoto, H. Yoshida, Y. Suzuki, N. Morohashi, T. Hattori, *Chem. Lett.* **2006**, *35*, 820–821.

[9] a) M. Nakanish, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 861–864; b) S. S. Kim, S. K. Sar, P. Tamrakar, *Bull. Korean Chem. Soc.* **2002**, *23*, 937–938.

[10] T. Nagataki, Y. Tachi, S. Itoh, *Chem. Commun.* **2006**, 4016–4018.

[11] a) Y. Sasson, G. D. Zappi, R. Neumann, *J. Org. Chem.* **1986**, *51*, 2880–2883; b) Y. Sasson, A. E.-A. Quntar, A. Zoran, *Chem. Commun.* **1998**, 73–74; c) S. I. Murahashi, Y. Oda, T. Naota, T. Kuwabara, *Tetrahedron Lett.* **1993**, *34*, 1299–1302.

[12] J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

[13] Y. Bonvin, E. Callens, I. Larrosa, D. A. Henderson, J. Oldham, A. J. Burton, A. G. M. Barrett, *Org. Lett.* **2005**, *7*, 4549–4552.

[14] a) S. Paul, P. Nanda, R. Gupta, *Synlett* **2004**, 531–533; b) S.-I. Hirashama, A. Itoh, *Synthesis* **2006**, 1757–1759; c) T. Sugai, A. Itoh, *Tetrahedron Lett.* **2007**, *48*, 9096–9099; d) B. Srinivasan, S. B. Chandalia, *Indian J. Technol.* **1971**, *9*, 274–275.

[15] a) A. Sudalai, S. Gurunath, *Synlett* **1999**, 559–560; b) S. Kajigaeshi, T. Nakagawa, N. Nagasaki, S. Fujisaki, *Synthesis* **1985**, 674–675; c) R. C. Fuson, B. A. Bull, *Chem. Rev.* **1934**, *15*, 275–309; d) T. V. Bukharkina, N. G. Digurov, S. B. Mil′ko, A. B. Shelud′ko, *Org. Process Res. Dev.* **1999**, *3*, 404–408; e) T. Shinozuka, A. Nakao, K. Saito, S. Naito, *Chem. Lett.* **2006**, *35*, 1090–1091; f) H.-R. Bjørsvik, J. A. V. Merinero, L. Liguori, *Tetrahedron Lett.* **2004**, *45*, 8615–8620; g) H.-R. Bjørsvik, L. Liguori, F. Minisci, *Org. Process Res. Dev.* **2001**, *5*, 136–140; h) A. Gokhale, P. Schiess, *Helv. Chim. Acta* **1998**, *81*, 251–267; i) S. W. Ashford, K. C. Grega, *J. Org. Chem.* **2001**, *66*, 1523–1524; j) Y. Nakatani, Y. Koizumi, R. Yamasaki, S. Saito, *Org. Lett.* **2008**, *10*, 2067–2070.

[16] a) Y. Lu, H. Yin, H. Wu, H. Liu, T. Jian, Y. Wada, *Catal. Commun.* **2006**, *7*, 832–838; b) R. Vijayalakshmi, M. Jayachandran, C. Sanjeeviraja, *Curr. Appl. Phys.* **2003**, *3*, 171–175; c) for C-H insertion, see: L. Farrugia, M. L. H. Green, *J. Chem. Soc., Chem. Commun.* **1975**, 416–417.

[17] a) See ref.[15a]; b) Y. Ogata, Y. Sawaki, M. Shiroyama, *J. Org. Chem.* **1977**, *42*, 4061–4066.

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