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Relay Catalysis: Manganese(III) Phosphate Catalyzed Asymmetric Addition of β-Dicarbonyls to *ortho*-Quinone Methides Generated by Catalytic Aerobic Oxidation

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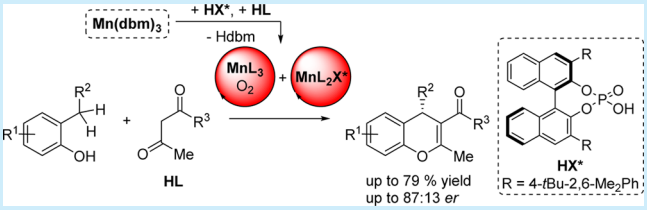
Supporting Information

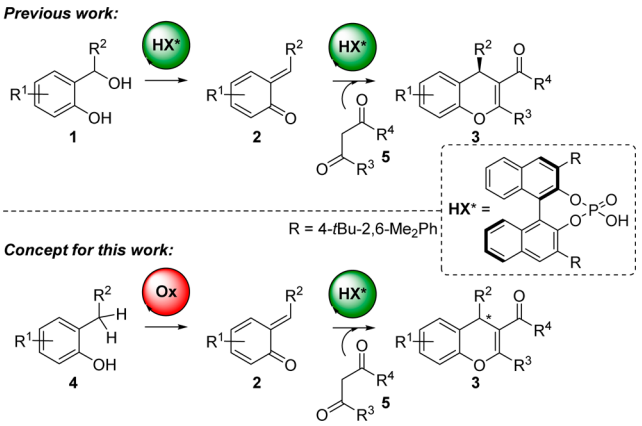
ABSTRACT: The combination of an *in situ* formed MnL_3 complex (HL = Hacac or $R(C{=}O)CH_2CO_2R$) and a chiral phosphoric acid HX* allows for a fully catalytic, asymmetric synthesis of 4*H*-chromenes starting from 2-alkyl-substituted phenols. The aerobic oxidation toward a transient *ortho*-quinone methide was efficiently catalyzed by a manganese(III) species MnL_3 while the ensuing Michael addition of β-dicarbonyl compounds proved to be catalyzed by a chiral manganese phosphate MnL_2X^*.



Although *ortho*-quinone methides (*o*-QMs) have been known since 1907[1] and have been shown to play an important role in many biological processes, they have only recently come into focus as viable intermediates in synthetic organic chemistry.[2] Featuring a highly reactive 1-oxabutadiene system they have been employed in [4 + 2]-cycloadditions, Michael additions, and 6π-electrocyclizations. In recent years a broad variety of asymmetric processes have been developed to fully exploit their synthetic potential.[3] In general, *o*-QMs can be formed *in situ* by various procedures, e.g. by thermolysis,[4] photolysis,[5] tautomerization,[6] oxidation,[7] and acid- or base-mediated[3c] transformations. Out of this potpourri of methods, the oxidative approach occupies a special role because it is the only way to obtain stable and isolable *o*-QMs.[8] Accordingly, they have proved to be a valuable testing ground for the diversification of *o*-QMs through catalytic, enantioselective ensuing transformations. One-pot procedures combining the oxidative generation of an *o*-QM and subsequent functionalization, especially in a catalytic and asymmetric fashion, have only been reported in select cases, but typically require super-stoichiometric quantities of a metal-based oxidant.[9]

In recent years our group has developed a number of Brønsted acid catalyzed processes for the highly enantioselective synthesis of nitrogen and oxygen heterocycles from *in situ* generated *o*-QMs.[10] For the latter, we started from *ortho*-hydroxy benzhydryl alcohols **1**, which were easily dehydrated with chiral BINOL-based phosphoric acid HX*[11] to form *o*-QMs of structure **2**, and we reacted them with various π-nucleophiles. For example, the reaction with β-diketones **5** furnished 4*H*-chromenes **3** with excellent enantioselectivity (Scheme 1).[10a] The chiral phosphoric acid triggered the dehydration toward the *o*-QM intermediate **2** and controlled the enantioselective Michael addition of the β-diketone **5** at the same time.

Scheme 1. Design Plan



However, some very electron-rich *ortho*-hydroxy benzhydryl alcohols **1** decomposed rapidly before a productive reaction could occur. We reasoned that an oxidative approach starting from more stable 2-alkyl-substituted phenols **4** could significantly expand the substrate scope of the Michael addition (Scheme 1).

Herein, we report the successful execution of this strategy which features a relay catalysis approach with two different, *in situ* generated metal catalysts and establishes a catalytic oxidative access to *o*-QMs using oxygen as a cheap terminal oxidant.

Our investigation commenced with the model reaction of 2-(4-methoxybenzyl)-sesamol (**4a**) and 1,3-cyclohexanedione (**5a**) as substrates in the presence of the chiral phosphoric acid HX* which was previously identified as the most selective

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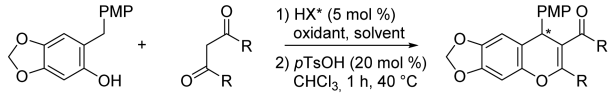
Org. Lett. XXXX, XXX, XXX−XXX

chiral catalyst for the conjugate addition of β-diketones.[10a] The examination of known oxidants for the *in situ* synthesis of *o*-QMs proved disappointing (Table 1). Whereas DDQ and

Table 1. Screening of Oxidants[a]



entry	oxidant (equiv)	5	solvent	yield (%)[b]	er[c]
1[d,e]	DDQ (2.2)	**5a**	CH_2Cl_2	17	92:8
2[e]	Ag_2O (1.5)	**5a**	$CHCl_3$	19	82:18
3	MnO_2 (5.0)	**5a**	PhMe	37	54:46
4	$K_3[Fe(CN)_6]$ (2.2)	**5a**	PhMe	0	–
5	$Mn(acac)_3$ (2.2)	–	$CHCl_3$	50	57:43
6	$Mn(acac)_3$ (2.2)	**5b**	$CHCl_3$	68	69:31
7	$Mn(acac)_3$ (0.1), O_2	**5b**	$CHCl_3$	81	85:15
8	$Mn(hfacac)_3$ (0.1), O_2	**5b**	$CHCl_3$	0	–
9	$Mn(dpm)_3$ (0.1), O_2	**5b**	$CHCl_3$	76	78:22
10	$Mn(dbm)_3$ (0.1), O_2	**5b**	$CHCl_3$	80	86:14

[a]Reaction conditions: sesamol **4a** (0.15 mmol, 1.0 equiv), nucleophiles **5a/b** (1.5 equiv), catalyst HX* (5 mol %), oxidant, 1.2 mL of solvent, 12–36 h, rt. [b]Isolated yield. [c]Determined by chiral HPLC. [d]40 °C. [e]4*H*-Chromene **3aa** was directly obtained after step 1. PMP = *para*-methoxyphenyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Hacac = acetylacetone, Hdpm = dipivaloylmethane, Hhfacac = hexafluoroacetylacetone, Hdbm = dibenzoylmethane.

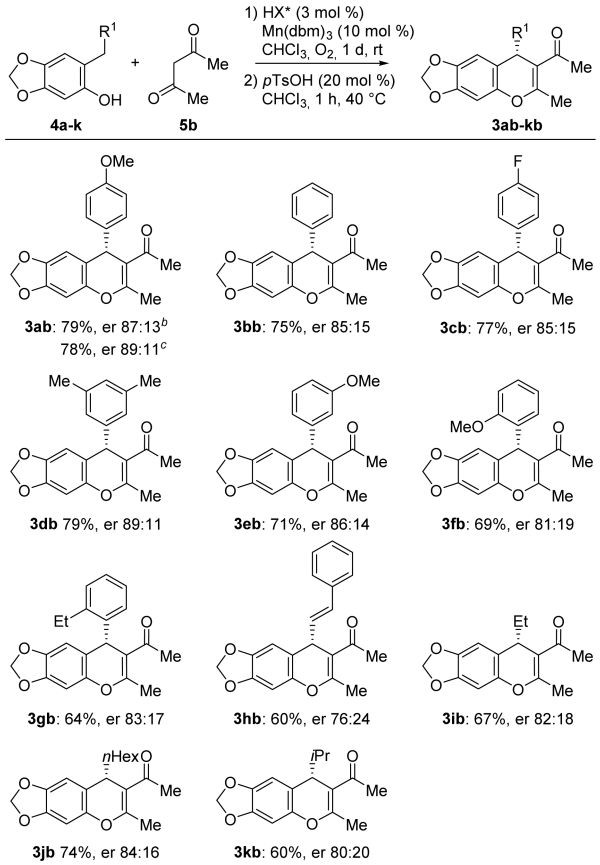
Ag_2O gave rise to the desired product **3aa** with good enantioselectivity, the yields were low in both cases (entries 1 and 2). MnO_2 proved to be more effective in terms of yield; however, a significant loss of asymmetric induction was observed (entry 3). No reaction was noticed with $K_3[Fe(CN)_6]$ as oxidant (entry 4). In all four cases a heterogeneous reaction medium was generated, and we speculated that a soluble oxidant might improve the efficacy of this transformation.

Hence, we concentrated on $Mn(acac)_3$ as oxidant which upon reduction to $Mn(acac)_2$ would also liberate 1 equiv of acetylacetone (**5b**) as the nucleophile for the subsequent Michael addition. To our delight, the desired product **3ab** was isolated in 50% yield using 2.2 equiv of this complex (entry 5).[11] The addition of another 1.5 equiv of acetylacetone (**5b**) to the reaction mixture further increased the overall yield to 68% (entry 6).[13] At this point we hypothesized that an interference of the manganese complex with the phosphoric acid might be causing the observed erosion of enantioselectivity compared to the reaction with DDQ as oxidant. Indeed, reducing the amount of $Mn(acac)_3$ to 10 mol % and using oxygen as the terminal oxidant not only increased the yield and enantiomeric excess of 4*H*-chromene **3ab** but also altered the overall process to a catalytic protocol (entry 7).

As a final parameter the nature of the β-dicarbonyl ligand of the oxidation catalyst was optimized. To ensure that this reaction was not limited to acetylacetone (**5b**) as a nucleophile, several manganese precatalysts were tested. These complexes were decorated with dummy ligands which should not react with the *o*-QM itself due to either electronic (entry 8) or steric factors (entries 9 and 10), but could be replaced by the nucleophile (e.g., **5b**) to generate the active catalyst. It turned out that the use of $Mn(dbm)_3$ (Hdbm = dibenzoylmethane) as a precatalyst perfectly matched our expectations and gave identical results as in the $Mn(acac)_3$-catalyzed reaction (compare entries 7 and 10).

After the identification of $Mn(dbm)_3/O_2$ as a superior catalytic system for the oxidative generation of *o*-QMs, we revisited all other reaction parameters (solvent, temperature, concentration, equivalents of nucleophile, phosphoric acid catalyst) and screened several additives (see Supporting Information). As a result, the optical purity of product **3ab** could be slightly improved by reducing the amount of chiral phosphoric acid HX* to 3 mol % and by diluting the reaction mixture (Scheme 2). The robustness of this method was

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: sesamols **4a–k** (0.15 mmol, 1.0 equiv), acetylacetone (**5b**) (1.5 equiv), catalyst HX* (3.0 mol %), $Mn(dbm)_3$ (10 mol %), 2.4 mL of $CHCl_3$, 24 h, rt; isolated yields after column chromatography; er determined by chiral HPLC. [b]Absolute configuration was determined by comparison with our previous results;[10a] see Table 2. [c]1 mmol scale, air as oxidant.

documented by running the reaction in an open flask on a 1 mmol scale and using air as the oxidant. Both the yield and the enantiomeric excess of **3ab** remained constant under these conditions (Scheme 2).

With these optimized reaction conditions in hand, the process could easily be applied to a variety of 2-benzyl-substituted sesamols **4a–g**. Electron-donating and -withdrawing substituents in the *para*-position as well as methoxy- and alkyl-substituents in the *meta*- and *ortho*-positions of the benzyl substituent were well tolerated, and the products **3ab–gb** were isolated in good yields and optical purities. Interestingly, 2-alkyl-substituted sesamols **4i–k** could also be converted to the

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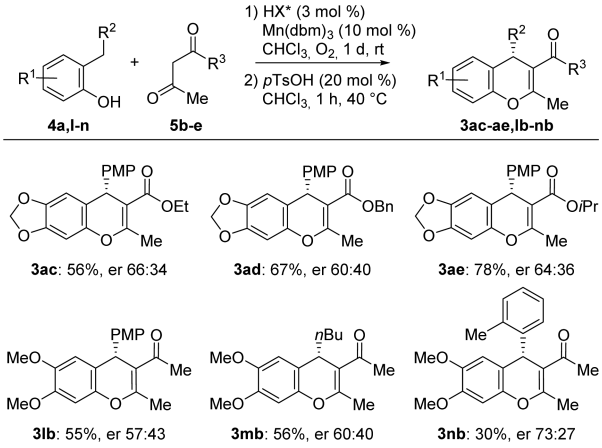
Org. Lett. XXXX, XXX, XXX–XXX

corresponding 4*H*-chromenes **3ib–kb** without affecting the overall outcome of the reaction.

The catalytic protocol using $Mn(dbm)_3/O_2$ for the generation of the *o*-QMs is not only limited to acetylacetone (**5b**) as a nucleophile. Several *β*-ketoesters **5c–e** could be submitted to the reaction as well. Yields remained good, but the enantioselectivity decreased significantly (Scheme 3). Further-

Scheme 3. Substrate Scope[a]



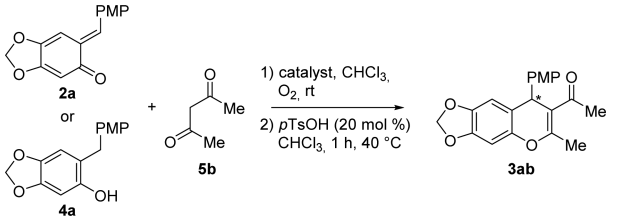
[a]Reaction conditions: phenols **4a,l–n** (0.15 mmol, 1.0 equiv), nucleophiles **5b–e** (1.5 equiv), catalyst HX* (3.0 mol %), $Mn(dbm)_3$ (10 mol %), 2.4 mL of $CHCl_3$, 24 h, rt; isolated yields after column chromatography; er determined by chiral HPLC. PMP = *para*-methoxyphenyl.

more, no product was formed using 1,3-cyclohexanedione (**5a**) as the nucleophile. Phenols with 3,4-methoxy substituents instead of the 3,4-dioxolane ring were tolerated as substrates as well but furnished 4*H*-chromenes **3lb–nb** in moderate yields and rather low enantioselectivity (Scheme 3).

In order to gain a deeper understanding of the reaction mechanism we performed several control experiments. First, we tackled the obvious question of whether the Michael addition of the nucleophile to the *o*-QM was catalyzed by the phosphoric acid itself or rather by a manganese phosphate complex (Table 2). Indeed, when the stable *o*-QM **2a** was treated with acetylacetone (**5b**) in the presence of phosphoric acid HX*, product **3ab** was obtained, but with an inverted absolute configuration compared to the same reaction with $Mn(acac)_3$ (entries 1 and 2). This switch in enantioselectivity has been observed before and occurs when metal phosphates act as catalysts instead of the corresponding chiral phosphoric acid.[14] The conclusion that $Mn(acac)_2X^*$ was in fact the active catalyst for the Michael addition was further supported by using $Mn(acac)_2X^*$ as a separately prepared chiral catalyst which provided product **3ab** with comparable selectivity (entry 3).[15] In addition, it could be shown that $Mn(acac)_3$ (generated from $Mn(dbm)_3$ and acetylacetone (**5b**)) was also capable of catalyzing the examined Michael addition (entry 4).

Next, the overall process starting from sesamol **4a** as a substrate was examined. No differences were observed when phosphoric acid HX* was replaced by the aforementioned manganese phosphate complex as a chiral catalyst (compare entries 5 and 6). Interestingly, employing solely $Mn(acac)_2X^*$ in the presence of acetylacetone (**5b**) did not catalyze the desired transformation and starting material **4a** was completely reisolated which indicated that the manganese phosphate

Table 2. Control Experiments[a]



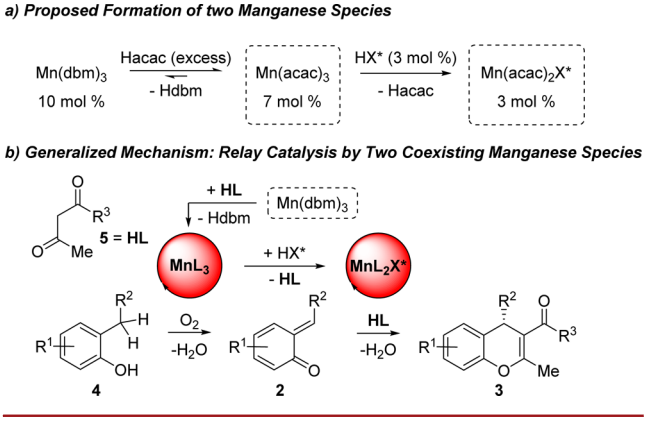
entry	2/4a	catalyst	*t* (h)	yield (%)[b]	er[c]
1	**2a**	HX*[d]	4	91	8:92
2	**2a**	$Mn(acac)_3$[e] + HX*[d]	24	82	75:25
3	**2a**	$Mn(acac)_2X^*$[d]	4	97(95[h])	73:27
4	**2a**	$Mn(dbm)_3$[d]	4	94	50:50
5	**4a**	$Mn(dbm)_3$[e] + HX*[f]	24	79	87:13
6	**4a**	$Mn(dbm)_3$[g] + $Mn(acac)_2X^*$[f]	24	80	87:13
7	**4a**	$Mn(acac)_2X^*$[f]	24	0	–
8	**4a**	$Mn(acac)_2$[e] + HX*[d]	24	77	81:19

[a]Reaction conditions: substrate **2a**/**4a** (0.15 mmol, 1.0 equiv), acetylacetone (**5b**) (1.5 equiv), catalyst, 2.4 mL of $CHCl_3$, O_2, rt. [b]Isolated yield. [c]Determined by chiral HPLC. [d]5 mol %. [e]10 mol %. [f]3 mol %. [g]7 mol %. [h]Under argon atmosphere. PMP = *para*-methoxyphenyl.

complex did not catalyze the initial oxidation (entry 7). Finally, it was shown that the catalytic process could be initiated from $Mn(acac)_2$ by aerobic oxidation (entry 8).

Based on these mechanistic investigations, we draw the following picture of the process in solution (Scheme 4): First,

Scheme 4. Mechanistic Considerations



the ligands of the manganese precatalyst $Mn(dbm)_3$ are replaced by acetylacetone (**5b**). 30% of the so formed $Mn(acac)_3$ further reacts irreversibly with the phosphoric acid HX* to give rise to the mixed manganese phosphate complex $Mn(acac)_2X^*$. This complex acts as an effective chiral catalyst for the Michael addition of acetylacetone (**5b**) toward the *o*-QM **2a** but is not capable of phenol oxidation and *o*-QM formation. For this task, the remaining $Mn(acac)_3$ is required, and the oxidation catalyst is regenerated by oxygen as the terminal oxidant.

In general, the nature of the oxidation as well as Michael addition catalyst (MnL_3 and MnL_2X^*) depends on the structure of the applied nucleophile (**5**) because the *β*-dicarbonyl compound also functions as a ligand for the manganese complexes. This could explain the differences observed when *β*-ketoesters **5c–e** are used as reaction partners

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Org. Lett. XXXX, XXX, XXX–XXX

instead of acetylacetone (**5b**). Additionally, 1,3-cyclohexanedione (**5a**) is not able to act as a bidentate ligand due to its cyclic structure and neither the active oxidation catalyst nor the manganese phosphate are formed, eventually resulting in no product formation.

In conclusion, we have developed a novel protocol to synthesize electron-rich 4*H*-chromenes **3** using a relay catalysis strategy. The approach comprises a catalytic, aerobic oxidation of 2-alkylphenols **4** toward a transient *o*-QM **2** which was trapped subsequently in a catalytic Michael addition with *β*-dicarbonyl **5**. These two central steps were catalyzed by two coexisting manganese complexes which were generated *in situ* from the precatalyst $Mn(dbm)_3$ in the presence of a phosphoric acid HX* and an excess of the *β*-dicarbonyl **5**. A species of the generalized structure MnL_3 appeared to be the oxidation catalyst whereas the manganese phosphate complex MnL_2X* controlled the enantioselective Michael addition. The reaction was found to be very sensitive to structural changes within the phenolic substrate and the *β*-dicarbonyl compound. Studies to further elucidate the exact oxidation mechanism and expand the substrate scope are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02185.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Fries, K. *Justus Liebigs Ann. Chem.* **1907**, *339*, 350−356.

(2) Reviews: (a) Van de Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367−5405. (b) Amouri, H.; Le Bras, J. *Acc. Chem. Res.* **2002**, *35*, 501−510. (c) Ferreira, S. B.; da Silva, F. d. C.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. *J. Heterocycl. Chem.* **2009**, *46*, 1080−1097. (d) Willis, N. J.; Bray, C. D. *Chem. - Eur. J.* **2012**, *18*, 9160−9173. (e) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655−3664.

(3) Reviews: (a) Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210−9215. (b) Caruana, L.; Fochi, M.; Bernardi, L. *Molecules* **2015**, *20*, 11733−11764. (c) Wang, Z.; Sun, J. *Synthesis* **2015**, *47*, 3629−3644. (d) Jaworski, A. A.; Scheidt, K. A. *J. Org. Chem.* **2016**, *81*, 10145−10153.

(4) (a) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169−3171. (b) Sugimoto, H.; Nakamura, S.; Ohwada, T. *J. Org. Chem.* **2007**, *72*, 10088−10095. (c) Spence, J. T. J.; George, J. H. *Org. Lett.* **2013**, *15*, 3891−3893.

(5) (a) Chen, Y.; Steinmetz, M. G. *J. Org. Chem.* **2006**, *71*, 6053−6060. (b) Arumugam, S.; Popik, V. V. *J. Org. Chem.* **2010**, *75*, 7338−7346.

(6) Lumb, J.-P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865−5868.

(7) (a) Cardillo, G.; Cricchio, R.; Merlini, L. *Tetrahedron* **1968**, *24*, 4825−4831. (b) Cardillo, G.; Cricchio, R.; Merlini, L. *Tetrahedron Lett.* **1969**, *10*, 907−908. (c) Cook, C. D.; Butler, L. C. *J. Org. Chem.* **1969**, *34*, 227−229. (d) Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 715−719. (e) Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 3666−3670. (f) Iyer, M. R.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1662−1664. (g) Rosenau, T.; Stanger, A. *Tetrahedron Lett.* **2005**, *46*, 7845−7848. (h) Liao, D.; Li, H.; Lei, X. *Org. Lett.* **2012**, *14*, 18−21. (i) Osipov, D.; Osyanin, V.; Klimochkin, Y. *Synlett* **2012**, *23*, 917−919. (j) Marteau, C.; Guitard, R.; Penverne, C.; Favier, D.; Nardello-Rataj, V.; Aubry, J.-M. *Food Chem.* **2016**, *196*, 418−427.

(8) (a) Jurd, L. *Tetrahedron* **1977**, *33*, 163−168. (b) Setiabudi, F.; Boldt, P. *Justus Liebigs Ann. Chem.* **1985**, *1985*, 1272−1279. (c) Angle, S. R.; Yang, W. *J. Am. Chem. Soc.* **1990**, *112*, 4524−4528. (d) Laatsch, H.; Ernst, B. P. *Justus Liebigs Ann. Chem.* **1992**, *1992*, 1245−1250. (e) Angle, S. R.; Rainier, J. D.; Woytowicz, C. *J. Org. Chem.* **1997**, *62*, 5884−5892. (f) Bishop, L. M.; Winkler, M.; Houk, K. N.; Bergman, R. G.; Trauner, D. *Chem. - Eur. J.* **2008**, *14*, 5405−5408.

(9) (a) Wu, B.; Chen, M.-W.; Ye, Z.-S.; Yu, C.-B.; Zhou, Y.-G. *Adv. Synth. Catal.* **2014**, *356*, 383−387. (b) Wu, B.; Gao, X.; Yan, Z.; Chen, M.-W.; Zhou, Y.-G. *Org. Lett.* **2015**, *17*, 6134−6137. (c) Wong, Y. F.; Wang, Z.; Hong, W.-X.; Sun, J. *Tetrahedron* **2016**, *72*, 2748−2751. A single iron-catalyzed aerobic oxidation of 1-methyl-2-naphthols to *o*-QMs has been reported; see: (d) Oguma, T.; Katsuki, T. *Chem. Commun.* **2014**, *50*, 5053−5056.

(10) (a) El-Sepelgy, O.; Haseloff, S.; Alamsetti, S. K.; Schneider, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 7923−7927. (b) Saha, S.; Schneider, C. *Chem. - Eur. J.* **2015**, *21*, 2348−2352. (c) Saha, S.; Alamsetti, S. K.; Schneider, C. *Chem. Commun.* **2015**, *51*, 1461−1464. (d) Saha, S.; Schneider, C. *Org. Lett.* **2015**, *17*, 648−651. (e) Alamsetti, S. K.; Spanka, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2392−2396. (f) Kretzschmar, M.; Hodik, T.; Schneider, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 9788−9792. (g) Hodik, T.; Schneider, C. *Org. Biomol. Chem.* **2017**, *15*, 3706−3716.

(11) Selected reviews: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744−5758. (b) Terada, M. *Chem. Commun.* **2008**, 4097−4112. (c) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262−5276. (d) Terada, M. *Synthesis* **2010**, *2010*, 1929−1982. (e) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2009**, *291*, 395−456. (f) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539−4549. (g) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047−9153.

(12) 31% of a byproduct resulting from cleavage of the C-2/C-3 bond prior to elimination were also isolated.

(13) Other transition metal *β*-dicarbonyl complexes were not effective (see Supporting Information).

(14) Hatano, H.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823−3826.

(15) Preparation of manganese phosphate according to: Liao, S.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 628−631.

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