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Communication

Dearomatization

Phase-Transfer-Catalyzed Oxaziridine-Mediated Hydroxylative Phenol and Naphthol Dearomatization

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Abstract: A new methodology for the dearomative *ortho*-hydroxylation of substituted phenolic substrates is reported. In the presence of a phase-transfer catalyst and a base, *N*-sulfonyloxaziridines react with phenols to give the corresponding 6-alkyl-6-hydroxycyclohexadienone products in moderate to good yields. The reaction proceeds in fair to good yields and excellent chemoselectivity for 2,6-disubstituted phenols, 1-naphthols, and 2-naphthols.

Introduction

Catalytic dearomatization reactions represent an ideal method to introduce molecular complexity by starting from cheap, readily accessible starting materials in a straightforward and highly efficient manner.[1] During the last decade, these dearomatization reactions have also been successfully used in the key step of the synthesis of highly functionalized polycyclic natural products.[2] Among these, hydroxylative phenol and naphthol dearomative strategies play a pivotal role in metabolite degradation[3] through the formation of the 6-hydroxy-2,4-cyclohexadienone moiety **1**,[4] which thus represents a key structural intermediate in the biomimetic total synthesis of natural products, including bacchopetiolone[5] (**2**), bisorbicillinol[6] (**3**), sclerotiorin[7] (**4**), and arianciamycinone[8] (**5**) (Figure 1).

The transformation of phenols and naphthols into the corresponding *ortho*-quinol products was investigated by using a variety of reagents including peracids,[9] $(PhSeO)_2O$,[10] hypervalent iodine compounds,[11] as well as (oxo)- or (peroxo)metal species either in a stoichiometric[12] or catalytic[13] amount. Unfortunately, these methodologies often exhibit low chemo- and regioselectivities due to side-reactions including competitive *para* oxidation,[11f,13b] overoxidation of alkene functions,[11d] α-ketol rearrangement[12,13a] or phenol homocoupling[11f,12] (Scheme 1).

New strategies for the synthesis of the 6-alkyl-6-hydroxy-2,4-cyclohexadienone moiety **1** from phenols or naphthols still represents a synthetic challenge. Since the first report of their preparation by Emmons in 1957,[14] oxaziridine heterocycles established itself as a class of organic aprotic oxidizing reagents mainly known for their ability to act as oxene transfer agents.[15]

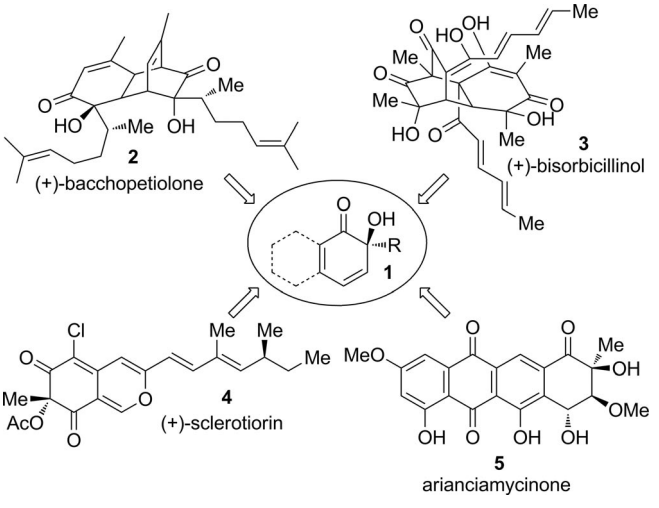
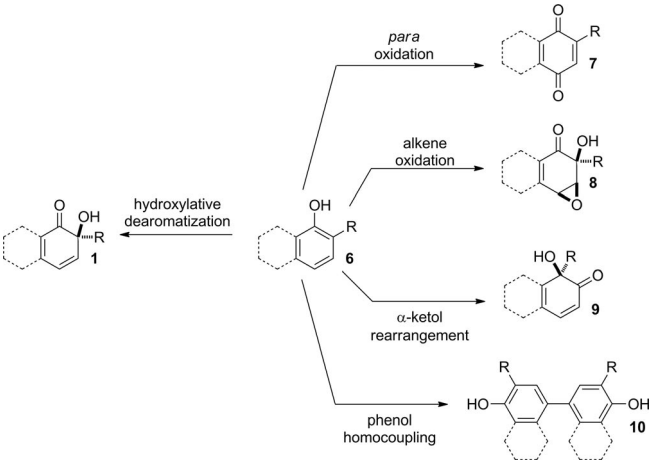


Figure 1. Selection of natural products resulting from the *ortho*-quinol intermediate **1**.



Scheme 1. Chemo- and regioselectivity of the hydroxylative dearomatization reactions of phenols.

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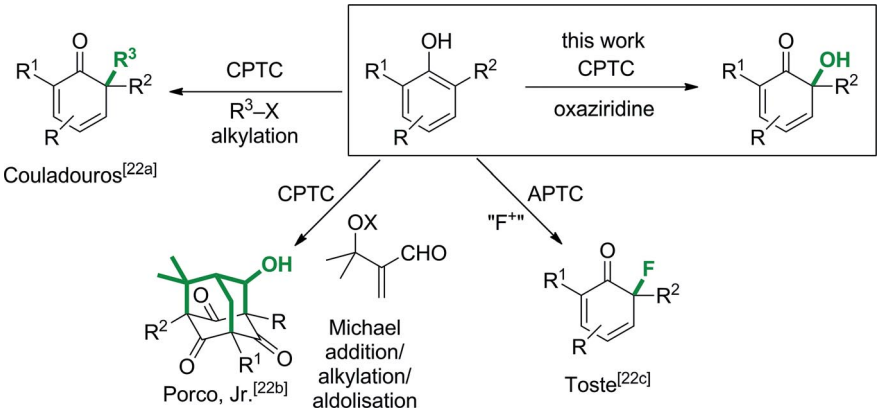
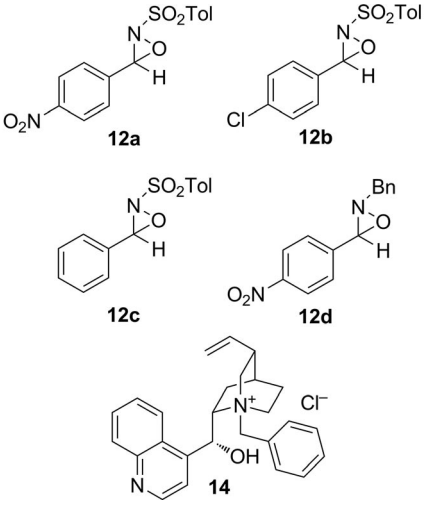


Scheme 2. Phase-transfer-catalyzed phenol dearomatization reactions.

They noticeably found applications in organomagnesium compound hydroxylation,[16] alkene epoxidation,[17] sulfide to sulfoxide oxidation,[18] amine to hydroxylamine oxidation,[19] but remain mostly known for enolate[20] or enol surrogates, such as silyl enol ethers,[21] to α-hydroxy ketone oxidations. Furthermore, recent reports[22] highlighted the possibility to obtain dearomatized 2,2-disubstituted cyclohexanone products from phenols under either cationic (CPTC) or anionic (APTC) phase-transfer catalysis in the presence of an adequate electrophile (Scheme 2). Taking these literature precedents into account, we decided to engage in a study dealing with the hydroxylative dearomatization of phenolic substrates under phase-transfer conditions in the presence of oxaziridines as electrophilic reagents.

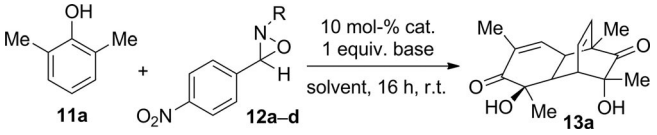


Results and Discussion

As a test experiment, the hydroxylation of 2,6-dimethylphenol (**11a**) was investigated in the presence of an oxaziridine **12** and a base by using a variety of conditions. Results are reported in Table 1. Treatment of the sodium phenolate of **11a** with oxaziridine **12a** in THF at room temperature provided the [4+2] cycloadduct of the α-hydroxycyclohexadienone **13a** in 8 % yield (Entry 1). The use of Na_2CO_3 alone as a base failed to provide any conversion, whereas its combination with an ammonium salt such as $BnEt_3NCl$, acting as a phase-transfer agent, gave 20 % yield (Entries 2 and 3). The use of an aqueous solution of NaOH resulted in only trace amounts of the oxidized product (Entry 5), but shifting to solid NaOH proved beneficial (Entry 4). The screening of different ammonium salts showed that benzylcinchonidinium chloride (**14**) exhibits the best catalytic activity (Entry 8 vs. Entries 4, 6, 7), whereas toluene turned out to be the best solvent for this transformation (Entries 12–14). The best yield was obtained at an optimal concentration in substrate of 1 M (see Entries 9, 10 for comparison). An increase of the oxaziridine/substrate ratio (Entry 11) or the use of other hydroxide salts (Entries 15, 16) had no beneficial effect on the yield. The screening of various oxidants showed that the 4-chlorophenyl-substituted *N*-sulfonyloxaziridine **12b** gave the best yield (Entry 17), whereas the use of the *N*-benzyloxaziridine **12d**, known to exhibit a weaker electrophilic character, did not lead to any conversion (Entry 19).

With the optimized conditions in hand, we examined the scope of the transformation (Scheme 3). The reaction proceeded in good yield for the *ortho*-dimethyl-substituted phenol substrates **11a**,**b**. A lower yield was observed for the very challenging derivative **11c**, which contains a bulky, electron-withdrawing chlorine atom in the *para* position. The molecular structure of this representative product **13c** was confirmed by X-ray crystallography and shows the *endo* selectivity previously demonstrated for **13a**[3a,23] (Figure 2). In the presence of bulkier substituents on the *ortho* positions, lower yields of the [4+2] tricycles **13d**–**f** were also observed. In the case of phenol **11f**, the product was obtained as a mixture of two different cycloadducts **13f** and **13f′** (16 % and 6 % yield, respectively). Whereas the formation of **13f** resulted from the *endo* [4+2] cyclodimerization of **1f**, the formation of **13f′** was the consequence of a Diels–Alder reaction between one molecule of **1f**, playing the role of the dienophile, and one molecule of **1f′**, playing the role of the diene. This observation seems to indicate that, with this system, phenol hydroxylation is controlled by the steric hindrance of the *ortho* positions. Finally, it should also be mentioned that no conversion was obtained for substrates with an unsubstituted *ortho* position such as **11g** or with 2,6-diphenylphenol (**11h**). Remarkably, for sterically congested substrates, the [4+2] cycloaddition reaction was not straightforward, and the intermediate 6-alkyl-6-hydroxy-2,4-cyclohexadienone **1** may

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxaziridine	Base	Cat.	Solvent	Yield of **13a**[b]
1	**12a**	NaH	–	THF	8 %
2	**12a**	Na_2CO_3	–	toluene	0 %
3	**12a**	Na_2CO_3	$BnEt_3NCl$	toluene	20 %
4	**12a**	NaOH	$BnEt_3NCl$	toluene	22 %
5[c]	**12a**	NaOH	$BnEt_3NCl$	toluene	4 %
6	**12a**	NaOH	Bu_4NCl	toluene	19 %
7	**12a**	NaOH	$Me(C_{10}H_{21})_3NCl$	toluene	36 %
8	**12a**	NaOH	**14**	toluene	56 % (54 %)
9[d]	**12a**	NaOH	**14**	toluene	45 %
10[e]	**12a**	NaOH	**14**	toluene	47 %
11[f]	**12a**	NaOH	**14**	toluene	46 %
12	**12a**	NaOH	**14**	CH_2Cl_2	44 %
13	**12a**	NaOH	**14**	iPr_2O	19 %
14	**12a**	NaOH	**14**	C_6H_{12}	7 %
15	**12a**	KOH	**14**	toluene	46 %
16	**12a**	CsOH	**14**	toluene	44 %
17	**12b**	NaOH	**14**	toluene	64 % (60 %)
18	**12c**	NaOH	**14**	toluene	59 %
19	**12d**	NaOH	**14**	toluene	0 %

[a] Conditions unless otherwise stated: substrate **11a** (0.2 mmol), base (0.2 mmol), oxaziridine **12a–d** (0.2 mmol) and catalyst (0.02 mmol) were added to toluene (2 mL), and the mixture was stirred at room temperature for 16 h. [b] Yields were determined by ^{1}H NMR spectroscopy by using fluorene as a standard. Isolated yields are given in parerntheses. [c] 1 mL of a 1 M solution of NaOH in water was used. [d] [**11a**] = 2 M. [e] [**11a**] = 0.4 M. [f] Ratio substrate **11a**/oxaziridine **12a** = 1:2.

be monitored by ^{1}H NMR spectroscopy or even isolated upon filtration.[24]

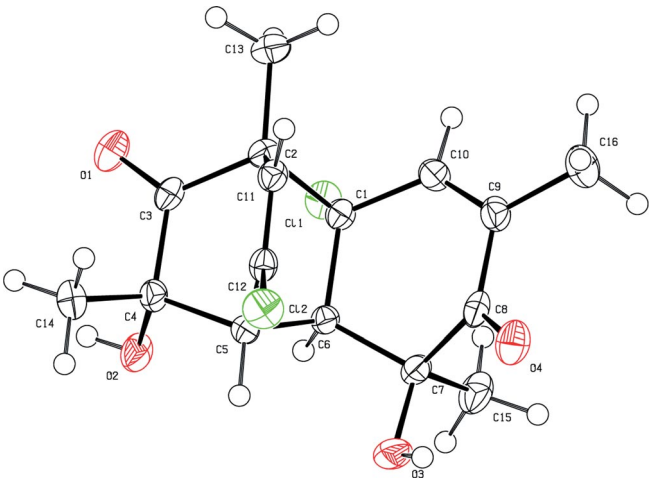
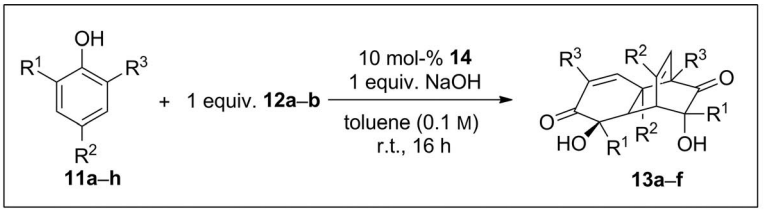
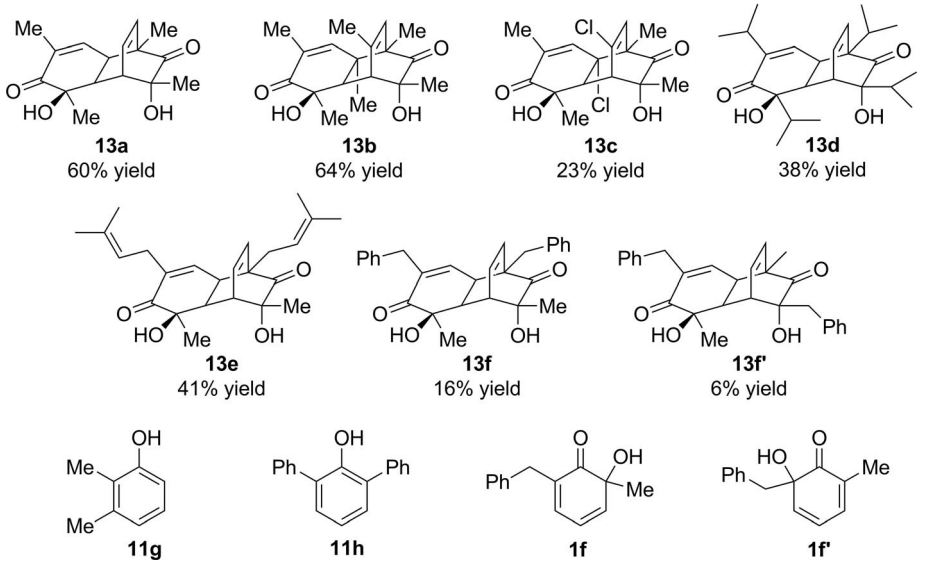


Figure 2. Structure of cyclodimer **13c** determined by X-ray crystallography. Only one enantiomer is represented.[25]

This strategy of oxidation was also successfully employed for the hydroxylative dearomatization of naphthols. In the case of 1-naphthols **15a–c**, the reaction proceeded with moderate yields to give – depending on the nature of the substituent in *ortho* position – either the expected 2-alkyl-2-hydroxynaphthalen-1-one **16** or the 1-alkyl-1-hydroxynaphthalen-2-one **17** resulting from the α-ketol rearrangement (Table 2). In the case of **15a** (R = Me), the hydroxylative dearomatization furnished

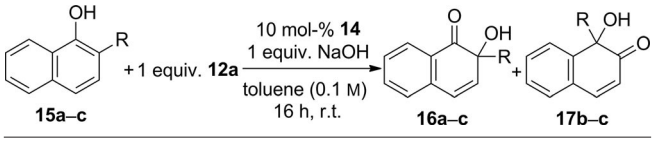


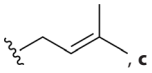


Scheme 3. Scope of the phase-transfer-catalyzed phenol hydroxylative dearomatization reaction.

exclusively the 1-naphthalenone **16a** in 55 % yield (Entry 1), whereas for **15b** (R = Et), a mixture of **16b**/**17b** in a 83:17 ratio was formed (Entry 2). In the case of the substrate **15c** bearing a prenyl substituent, a reversal of selectivity was observed. The hydroxylation reaction delivered a mixture of **16c**/**17c** in a 24:76 ratio with a modest 11 % yield (Entry 3).

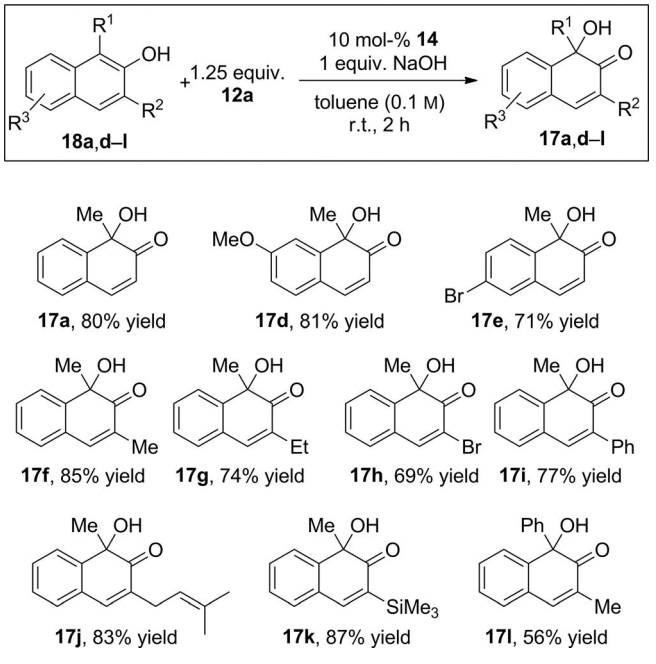
Table 2. 1-Naphthol phase-transfer-catalyzed hydroxylative dearomatization reaction.[a]



Entry	R	Yield[b]	**16**/**17** ratio
1	Me, **a**	55 %	100:0
2	Et, **b**	61 %	83:17
3	 **c**	11 %	24:76

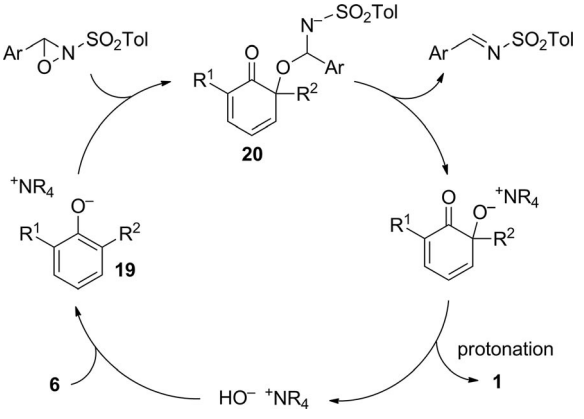
[a] Conditions unless otherwise stated: substrate **15a**–**c** (0.2 mmol), NaOH (0.2 mmol), oxaziridine **12a** (0.2 mmol) and catalyst **14** (0.02 mmol) were added to toluene (2 mL), and the mixture was stirred at room temperature for 16 h. [b] Isolated yields.

We also investigated the hydroxylative dearomatization of 2-naphthol substrates (Scheme 4). The reaction was compatible with a large range of substituents, affording the products in good yields (ranging from 56 to 87 %). Substrates bearing a single substituent in position 1 (**18a**,**d**,**e**) gave clean conversion, and no product resulting from the hydroxylation in position 3 could be detected. The reaction was also amenable to substrates possessing a disubstitution in positions 1 and 3. Alkyl, aryl and allyl groups as well as a bromine atom were all tolerated (products **17f**–**j**). The hydroxylation also took place cleanly with a naphthol bearing a silyl substituent in position 3 to deliver the hydroxylated product **17k** in excellent yield and selectivity. Finally, in the case of 2-naphthols, we have also shown that it was possible to observe the hydroxylation at a position bearing a phenyl substituent in position 1; the 1-hydroxy-1-phenylnaphthalen-2-one **17l** was isolated in 56 % yield.



Scheme 4. Hydroxylative dearomatization of 2-naphthols **18** mediated by *N*-sulfonyloxaziridines.

The postulated mechanism involves the initial formation of the phenolate anion **19** upon phase transfer of the hydroxide anion in the presence of the ammonium salt, followed by a reaction with the oxaziridine to give transiently the intermediate **20**, in analogy with what has been proposed for the α-hydroxylation of ketones[26] (Scheme 5). Liberation of the imine furnishes the anion of **1** that is released after protonation.



Scheme 5. Postulated mechanism of the hydroxylative dearomatization of phenols.

Conclusions

We have developed a new methodology for the hydroxylative dearomatization of phenols and naphthols furnishing the corresponding *ortho*-quinol building blocks in moderate to good yields. This method exhibits a large substrate scope in the case of the 2-naphthols. Phenolate and naphtholate anions, generated under phase-transfer conditions, react with *N*-sulfonyloxaziridines to give the hydroxylated products at room temperature in toluene. This methodology holds promise for the development of an enantioselective version of the hydroxylative dearomatization of phenols and naphthols in the presence of a chiral phase-transfer catalyst.[27] Studies toward this goal are currently underway in our laboratory and will be reported in due course.

Acknowledgments

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Keywords: Phenols · Naphthols · Dearomatization · Phase-transfer catalysis · Oxidation

[1] a) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Angew. Chem.* **2012**, *124*, 12834; b) Q. Ding, R. Fan, *Synthesis* **2013**, *45*, 1; c) Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.* **2014**, *12*, 4807.
[2] S. P. Roche, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068; *Angew. Chem.* **2011**, *123*, 4154.
[3] a) H. Kneifel, C. Poszich-Buscher, S. Rittich, E. Breitmaier, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 202; *Angew. Chem.* **1991**, *103*, 189; b) A. Al Fahad, A. Abood, K. M. Fisch, A. Osipow, J. Davison, M. Avramovic, C. P. Butts, J. Piel, T. J. Simpson, R. J. Cox, *Chem. Sci.* **2014**, *5*, 523.
[4] D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004**, *104*, 1383.
[5] C. Zdero, F. Bohlmann, H. M. Niemeyer, *Phytochemistry* **1991**, *30*, 1597.
[6] N. Abe, T. Murata, A. Hirota, *Biosci. Biotechnol. Biochem.* **1998**, *62*, 661.
[7] T. McCurtin, J. Reilly, *Nature* **1940**, *146*, 335.
[8] W. Keller-Schierlein, J. Sauerbier, U. Vogler, H. Zähner, *Helv. Chim. Acta* **1970**, *53*, 779.
[9] a) J. D. McClure, *J. Org. Chem.* **1963**, *28*, 69; b) D. R. H. Barton, A. Fekih, X. Lusinchi, *Bull. Soc. Chim. Fr.* **1988**, 681.
[10] D. H. R. Barton, S. V. Ley, P. D. Magnus, M. N. Rosenfeld, *J. Chem. Soc. Perkin Trans. 1* **1977**, 567.
[11] a) D. Adler, J. Dahlen, G. Westin, *Acta Chem. Scand.* **1960**, *14*, 1580; b) D. Magdziak, A. A. Rodriguez, R. W. Van de Water, T. R. R. Pettus, *Org. Lett.* **2002**, *4*, 285; c) N. Lebrasseur, J. Gagnepain, A. Ozanne-Beaudenon, J.-M. Léger, S. Quideau, *J. Org. Chem.* **2007**, *72*, 6280; d) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem. Int. Ed.* **2009**, *48*, 4605; *Angew. Chem.* **2009**, *121*, 4675; e) J. K. Boppisetti, V. B. Birman, *Org. Lett.* **2009**, *11*, 1221; f) C. Bosset, R. Coffinier, P. A. Peixoto, M. El Assal, K. Miqueu, J.-M. Sotiropoulos, L. Pouységu, S. Quideau, *Angew. Chem. Int. Ed.* **2014**, *53*, 9860; *Angew. Chem.* **2014**, *126*, 10018; g) F. Berthiol, *Synthesis* **2015**, *47*, 587; h) M. Bergner, D. C. Duquette, L. Chio, B. M. Stoltz, *Org. Lett.* **2015**, *17*, 3008.
[12] S. Dong, J. Zhu, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2008**, *130*, 2738.
[13] a) K. Krohn, K. Brüggmann, D. Döring, P. G. Jones, *Chem. Ber.* **1992**, *125*, 2439; b) W. Adam, W. A. Herrmann, J. Lin, C. R. Saha-Möller, *J. Org. Chem.* **1994**, *59*, 8281; c) K. Krohn, *Synthesis* **1997**, 1115; d) K. Krohn, G. Zimmermann, *J. Org. Chem.* **1998**, *63*, 4140.
[14] W. D. Emmons, *J. Am. Chem. Soc.* **1957**, *79*, 5739.
[15] a) F. A. Davis, A. C. Sheppard, *Tetrahedron* **1989**, *45*, 5703; b) F. A. Davis, B.-C. Chen, *Chem. Rev.* **1992**, *92*, 919; c) K. S. Williamson, D. J. Michaelis, T. P. Yoon, *Chem. Rev.* **2014**, *114*, 8016; d) Y. Zhu, Q. Wang, R. G. Cornwall, Y. Shi, *Chem. Rev.* **2014**, *114*, 8199.
[16] F. A. Davis, P. A. Mancinelli, K. Balasubramanian, U. K. Nadir, *J. Am. Chem. Soc.* **1979**, *101*, 1044.
[17] F. A. Davis, N. F. Abdul-Malik, S. B. Awad, M. E. Harakal, *Tetrahedron Lett.* **1981**, *22*, 917.
[18] F. A. Davis, S. G. Lal, *J. Org. Chem.* **1988**, *53*, 5004.
[19] F. A. Davis, O. D. Stringer, J. Billmers, *Tetrahedron Lett.* **1983**, *24*, 1213.
[20] For the historical example introducing the α-hydroxylation of carbonyl compounds by using Li or K enolates and oxaziridines, see: a) F. A. Davis, L. C. Vishwakarma, J. M. Billmers, *J. Org. Chem.* **1984**, *49*, 3241. For an early example of the direct hydroxylation reaction of 1,3-dicarbonyl substrates involving oxaziridines and catalytically generated enolate intermediates, see: P. Y. Toullec, C. Bonaccorsi, A. Mezzetti, A. Togni, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5810.
[21] F. A. Davis, A. C. Sheppard, *J. Org. Chem.* **1987**, *52*, 954.
[22] a) E. A. Couladouros, M. Dakanali, K. D. Demadis, V. P. Vidali, *Org. Lett.* **2009**, *11*, 4430; b) J. Qi, A. B. Beeler, Q. Zhang, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2010**, *132*, 13642; c) R. J. Phipps, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 1268.
[23] For a discussion of the factors governing the regio- and stereoselectivity of the Diels–Alder reaction involving the cyclohexadienone intermediate **1**, see: J. Gagnepain, R. Méreau, D. Dejugnac, J.-M. Léger, F. Castet, D. Deffieux, L. Pouységu, S. Quideau, *Tetrahedron* **2007**, *63*, 6493.
[24] For example, in the case of the oxidation of phenol **11b**, **1b** appears as the main product after 15 min of reaction.
[25] CCDC 1436224 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[26] F. A. Davis, A. C. Sheppard, B.-C. Chen, M. S. Haque, *J. Am. Chem. Soc.* **1990**, *112*, 6679.
[27] In the presence of 20 mol-% of **14** at 5 °C in toluene, phenol **11a** reacts with oxaziridine **12a** to give the cycloadduct **13a** with 56 % yield and 12 % *ee*.

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