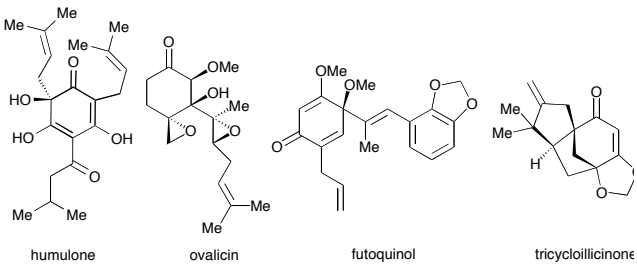
STEREOSELECTIVE OXIDATIVE DEAROMATIZATION REACTIONS

Reported by Sean Reed March 27, 2008

INTRODUCTION

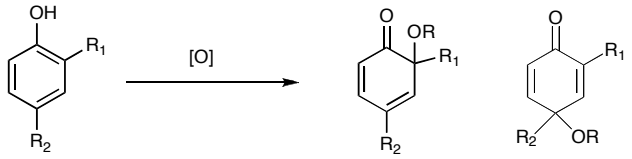
The cyclohexadienone building block has long been a highly useful, widely applicable intermediate in the synthesis of numerous biological and medicinally valuable natural products.[1] For instance, four such molecules are shown in **Figure 1**. The cyclohexadienone core can be generated in several different ways, the most common being an oxidation of a phenol substrate. This transformation falls into a general category of fascinating reactions deemed "dearomatizations", in which the stabilizing energy of an aromatic system is broken to afford a product with new chemical reactivity. This type of strategy can be very useful, given the large number of chemical transformations(ortho-lithiation, cross-coupling) that have been developed to functionalize aromatic rings; however, methodology to access these building blocks in enantiomerically pure form has only recently emerged. Efforts toward this end could enable the stereoselective synthesis of a wide range of natural products, using previously racemic routes.

Figure 1. Cyclohexadieneone natural products



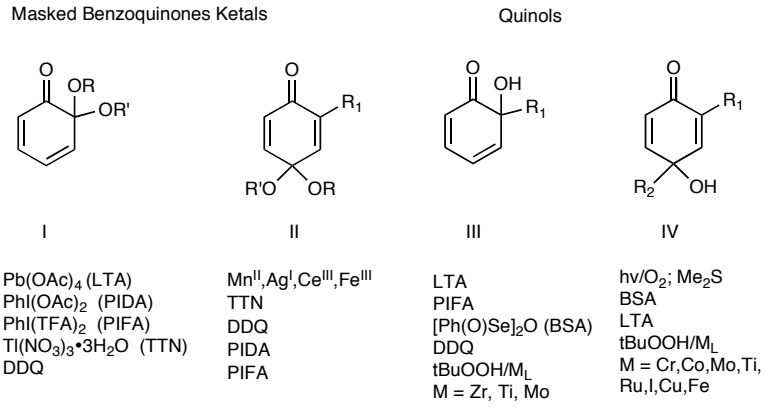
GENERAL TRANSFORMATION

Equation 1. General Transformation



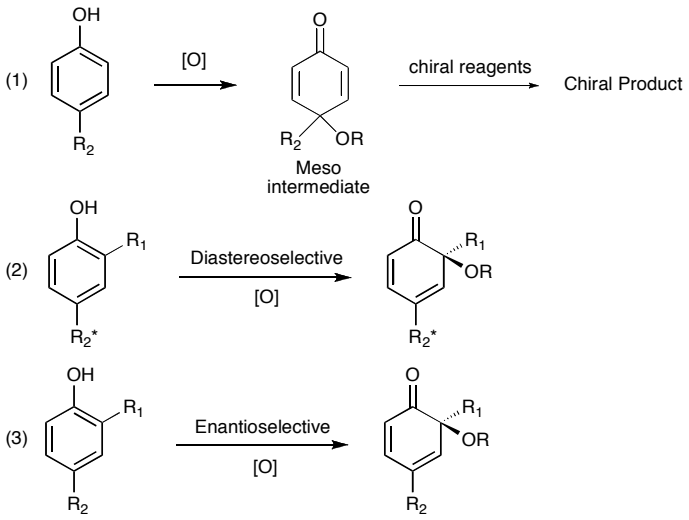
The general transformation for an oxidative dearomatization is shown in **Equation 1.** Depending on the nature of the substrate and oxidant,[2] a number of different structures can be generated, and several structural patterns have emerged. For instance, several types of oxidants such as $Pb(OAc)_4$ can instigate a directed oxidation to the ortho position.[3] Hypervalent iodine(III) reagents tend to functionalize at the para position through a two electron process, [4] although radicals are sometimes observed.[5]

Figure 2. Product classes and common oxidants



In general, many active oxidizing species are electrophilic in nature, and target electron-rich sp^2 C-H bonds. A list of common oxidants and their use towards the four general structure classes is listed in **Figure 2**. In pursuit of a stereoselective reaction for this transformation, three main strategies could be imagined (**Figure 3)**. First, a p-substituted phenol could be oxidized to the p-quinol, followed by a desymmetrization reaction that would lead to a chiral product.

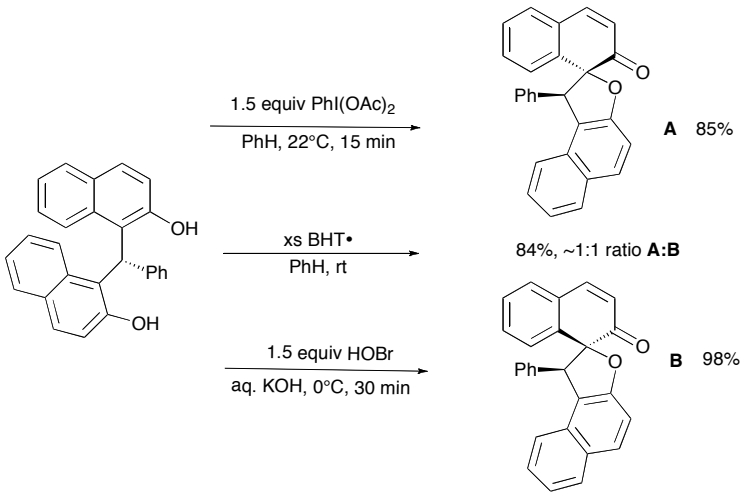
Figure 3. Stereoselective oxidative dearomatization strategies



Although this reaction is formally a stereoselective dearomatization reaction with several promising examples,[6] this report will instead focus on reactions where the new C-O bond is formed stereoselectively. The second strategy involves tethering a group that would force the oxidant to discriminate between the two faces of the aryl ring, which would constitute a diastereoselective oxidation. The third strategy, notably the most challenging, entails a direct oxidation of one of the two enantiotopic faces of the phenol to generate an enantiomerically enriched product. Although all four cyclohexadienone structural types have been used in natural product syntheses, this report will primarily focus on quinols, due to the inherent difficulty of generating them stereoselectively.

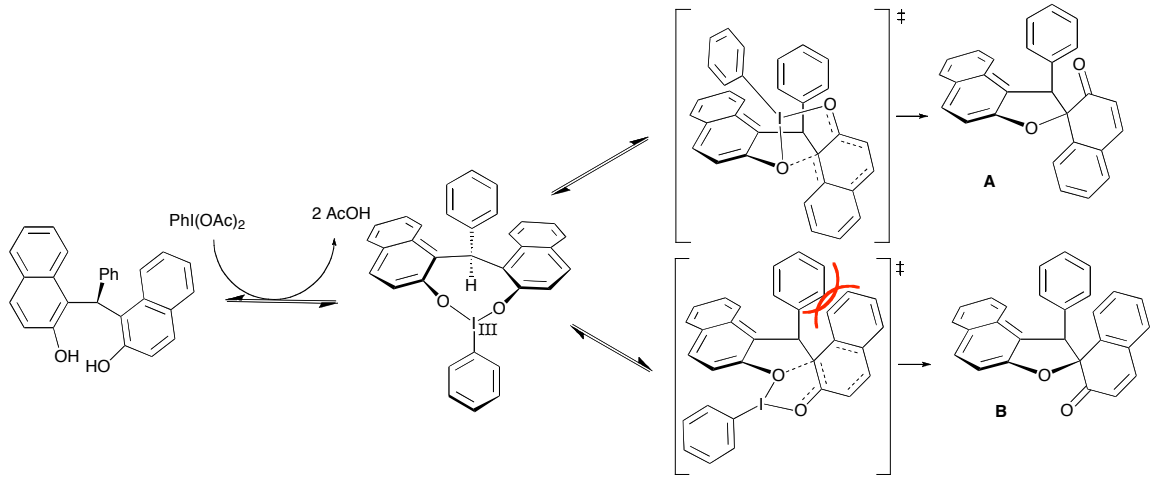
DIASTEREOSELECTIVE EXAMPLES

Figure 4. Diastereomeric control by oxidant choice



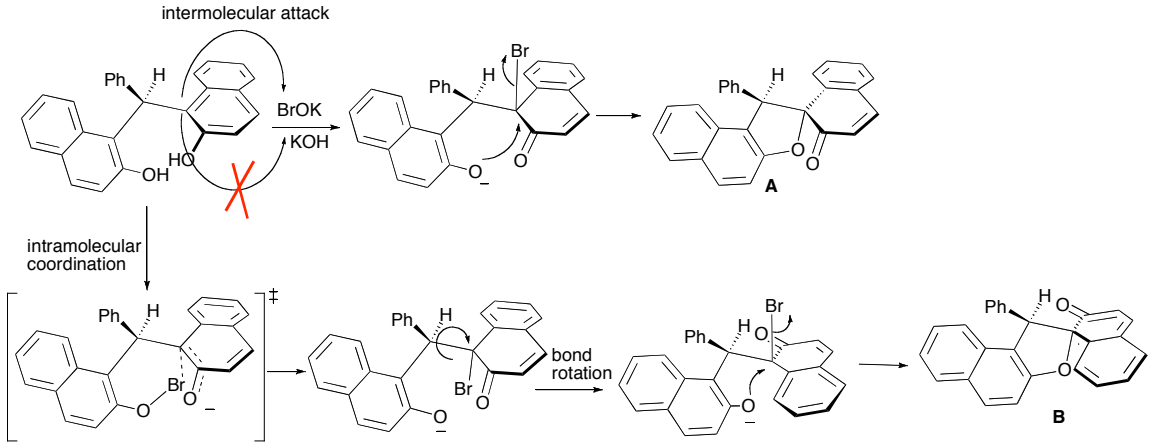
One of the earlier reports on the diastereoselectivity of phenol oxidations was by Dean and coworkers,[7] during the oxidation of a binaphthyl substrate (**Figure 4).** Exposure of the starting material to either $PhI(OAc)_2$ or HOBr oxidants generated different diastereomers. A change in mechanism was proposed for the reversal of diastereoselectivity; both oxidants bind to the substrate through the phenols before functionalizing. In the iodine case, intramolecular attack by phenol generates the product **A** (**Figure 5**); using KOBr, substitution with bromine precedes an S_N2 attack of phenol, causing inversion of the stereocenter (**Figure 6**). A phenolic radical mechanism was discounted on the absence of any selectivity when the starting material was subjected to a BHT radical oxidant (**Figure 4**).

Figure 5. Proposed oxidation mechanism using iodobenzenediacetate



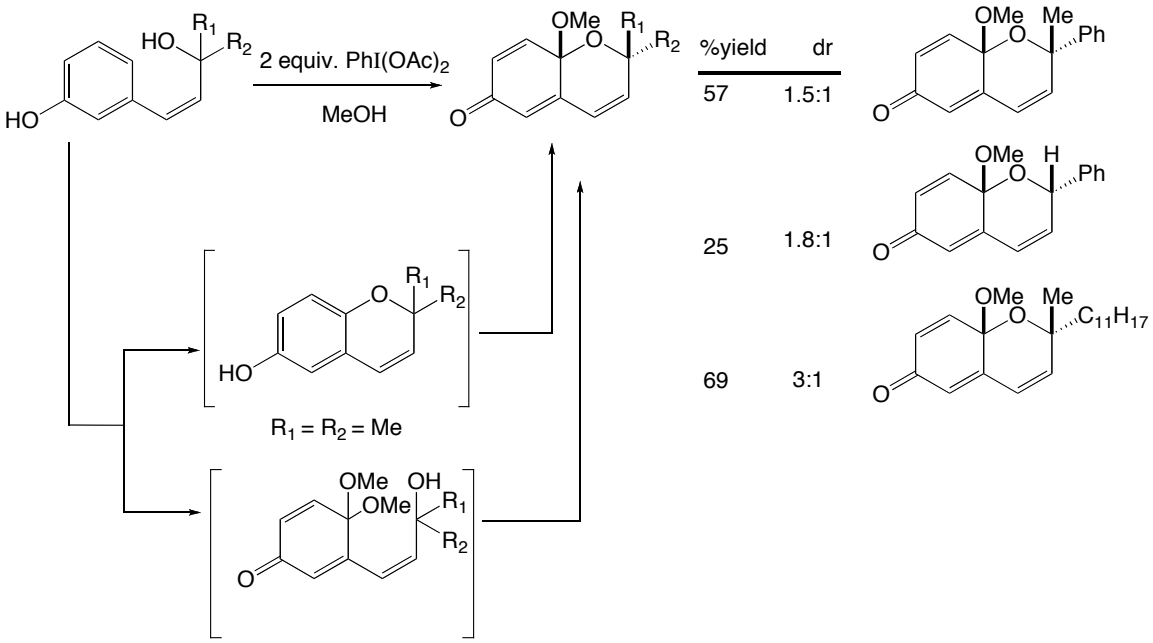
Pelter & Ward explored the double oxidation of *m*-substituted phenols with $PhI(OAc)_2$ in MeOH to generate ketals (**Scheme 1**).[8] It was observed that the larger R group was found to be trans to the methoxy group in the product. Although a pre-formed substrate containing the benzopyran generated the product when exposed to 1 equiv. of $PhI(OAc)_2$, it is unclear which oxidation occurs first (intermolecular or intramolecular).

Figure 6. Proposed mechanism using potassium hypobromite



The corresponding dimethyl ketal could not be independently prepared for testing as a possible intermediate. Rigidity of the tether was found to be required for the intramolecular reaction; substrates with the double bond epoxidized were also competent. These basic examples set the stage for chiral auxiliary-based methods that would be used for the synthesis of natural products.

Scheme 1. Diastereoselectivity effects during chromenone synthesis

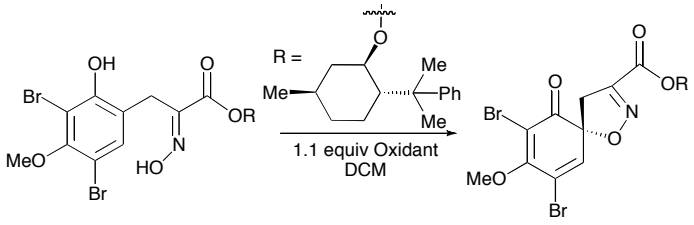


CHIRAL AUXILLARY-BASED STRATEGIES

The first example of a chiral auxiliary used specifically to influence the oxidation step was reported by Hoshino and coworkers.[9] A 9-phenylmenthyl ester linkage, when combined with

camphorsulfonic acid and iodosylbenzene was found to induce useful diastereoselectivity for the substrate shown in **Figure 7.**

Figure 7. Chiral auxiliary approach

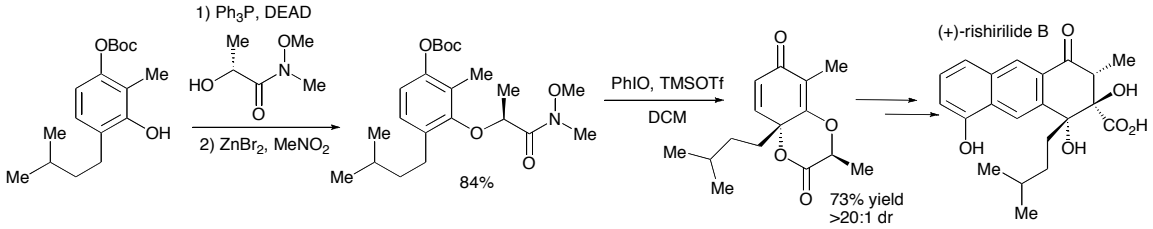


Oxidant	Yield (%)	d.r.
$PhI(OAc)_2$	31	1.5:1
$PhI(O_2CCF_3)_2$	88	5:1
PhIO/(+)-CSA	70	10:1
PhIO/(-)-CSA	87	10:1

The active oxidizing species is likely a [hydroxy((10-camphorsulfonyl)oxy)iodo)] benzene,[10] and there appeared to be a matched/mismatched combination of chiral auxiliary/chiral catalyst with respect to yield only (not dr).

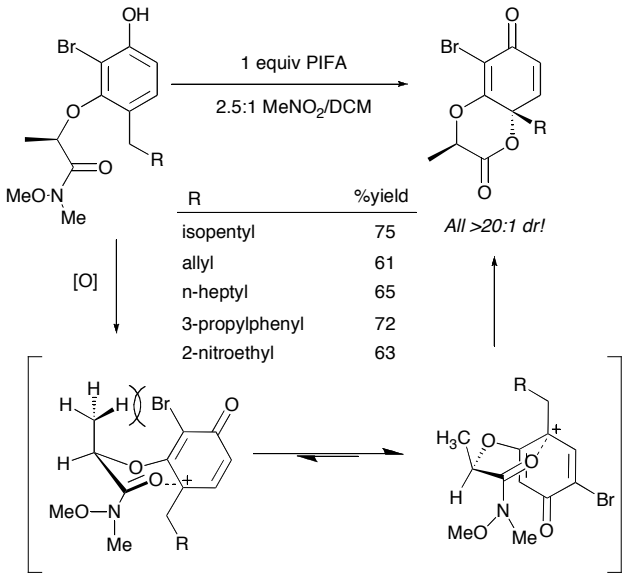
However, a widely applicable system would not be available until Pettus and coworkers harnessed lactic amides for the synthesis of (+)-rishirilide B[11] (**Equation 2)**. The auxiliary was easily removed by treatment with $Me_2AlNHNMe_2$.

Equation 2. Synthesis of (+)-rishirilide B



By stabilizing the intermediate cation with a Weinreb amide appendage, diastereoselectivities of >20:1 could be achieved for a wide variety of substrates[12] **(Figure 8)**.

Figure 8. Lactic amide chiral auxiliary



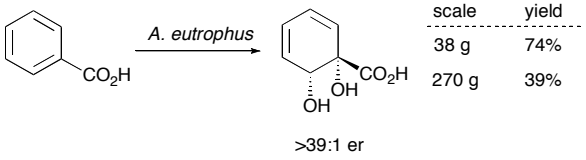
R	%yield
isopentyl	75
allyl	61
n-heptyl	65
3-propylphenyl	72
2-nitroethyl	63

With the goal of developing a general, enantioselective variant of these reactions, the catalyst is an obvious place to start. Although many chiral Pb(IV) complexes have been characterized, their performance in enantioselective transformations has been poor. This has been primarily traced back to rapid exchange for achiral ligands in the reaction mixture, leading to a racemic catalyst.[13] Chiral iodine(III) reagents have not been able to effect an enantioselective oxidative dearomatization; this could possibly be

due to the phenoxenium intermediate that distances chiral information from the site of oxidation,[14] although chiral I(III) reagents have had success in other processes.[15]

ENANTIOSELECTIVE EXAMPLES

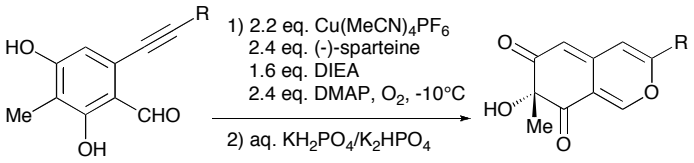
Equation 3. Oxidation with *A. Eutrophus*



scale	yield
38 g	74%
270 g	39%

A biological, enantioselective, oxidative dearomatization was reported by Breitmaier, although the identity of the organism responsible was not reported.[16] Many examples of enzymatic dihydroxylations have been discovered that build useful arene products.[17] Subsequently, Meyers and coworkers discovered that *Alcaligenes Eutrophus* could dearomatize benzoic acid to the corresponding diol, with >39:1 e.r. [18] (**Equation 3).** Porco & coworkers had previously developed a Au(III) catalyzed cycloisomerization reaction using o-alkynylbenzaldehydes that was designed to access members of the azaphilone natural product family.[19] Seeking to develop a tyrosinase enzyme mimic,[20] the Porco group screened a number of diamine ligands in the presence of O_2 and Cu(I).[21] Employing (-)-sparteine, a range of azaphilones could be accessed in up to 99:1 er, and 64-84% yield (after a phosphate buffer promoted cyclization[22]), demonstrating the first example of an enantioselective oxidative dearomatization (**Figure 9).** UV-studies at low temperature revealed absorbance maximums at 333 & 426 nm, indicating a bis(μ-oxo) dimeric structure.

Figure 9. Synthesis of azaphilones



R =	Yield (%)	e.r.
Me	84	99:1
1-cyclohexenyl	71	49:1
Phenyl	64	39:1
-$(CH_2)_4$OBn	68	66:1
-$(CH_2)CO_2$Et	72	66:1

This system was also applied by the Porco group towards the synthesis of bicyclo[2.2.2]octenones,[23] another common natural product motif. The reaction converts substituted phenols into the corresponding alpha-hydroxy cyclohexadienones, which undergo spontaneous [4+2] homodimerization. (**Figure 10**.) The authors observed a strong solvent effect (large conversion increase in THF), which was consistent with a μ-η^2:η^2-peroxodicopper(II)/(-)-sparteine complex, instead of the bis(μ-oxo)dicopper(III) complex, although UV-VIS studies in support of this hypothesis have yet to be published.[24]

When both ortho and para positions are substituted, the cyclohexadienone is proposed to undergo an alpha-ketol rearrangement. (**Figure 11)** This change in mechanism can be attributed to a very slow

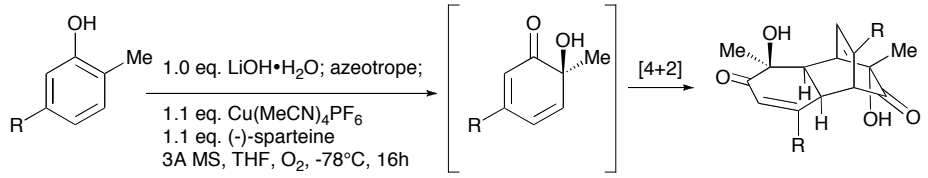
homodimerization due to steric hinderance of the initially formed cyclohexadienone, with a rearrangement being competitive for R = tBu.

Although unisolated due to stability reasons, this new cyclohexadienone could be successfully dimerized by gentle heating at 50°C for 40 min. The optimized conditions were used to synthesize (+)-aquaticol, as a single diastereomer in five steps from (+)-cuparene.

CONCLUSION

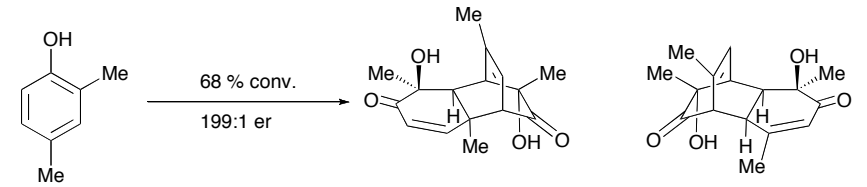
Oxidative dearomatization is a highly useful tool for the generation of quinols, with many methodologies designed to control regioselectivity. The potential of an asymmetric method to control the enantioselectivity of the reaction would be of great synthetic use, as many racemic synthesis could be adapted to give enantiomerically pure products.

Figure 10. Bicyclo[2.2.2]octenones

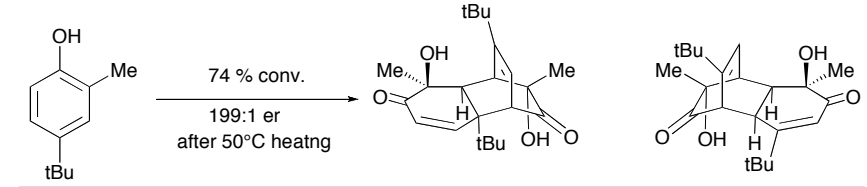


R =	Yield (%)	Conversion (%)	er
iPr	83	96	>199:1
Me	40	60	99:1
tBu	82	89	199:1
MeO	52	65	199:1

Figure 11. Alternative alpha-ketol rearrangement products



Yield (%)	25	7



Yield (%)	-	51

Although diastereoselective variants using chiral auxiliaries have shown promise towards making oxidative dearomatization a powerful process, recent advances employing biomimetic Cu/diamine catalysts have made the largest advances in stereocontrol. Current limitations of this system include stoichiometric amounts of catalyst, and the substitution pattern on the aromatic ring. Despite these shortcomings, this method will no doubt inspire future systems[25,26] that can take on this challenging problem.

REFERENCES

(1) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem Rev.* **2004**, *104,* 1383.
(2) Rappoport, Z.; *The Chemistry of Phenols.* **2003,** John Wiley & Sons, England.
(3) a) Harrison, M. J.; Norman, R. O. C. *J. Chem. Soc. C* **1970,** 728. b) Greenland, H.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1986,** *39,* 2067. c) Pausacker, K. H.; Cordner, J. P. *J. Chem. Soc.* **1953,** 102.
(4) a) Pelter, A.; Elgendy, S. *Tett. Lett.* **1988,** *29*(6), 677. b) Pelter, A.; Elgendy, S. *J. Chem. Soc. Perkin Trans. 1* **1993,** 1891. c) Pausacker, K. H.; Cordner, J. P. *J. Chem. Soc.* **1953,** 107.
(5) Kita, Y.; Takada, T.; Tohma, H. *Pure & Appl. Chem.* **1996,** *68*(3), 627.
(6) a) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008,** *130,* 404. b) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc*. **2002**, *124*(2), 184. c) Hayashi, T.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005,** *127,* 16028. d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006,** *128,* 2552.
(7) Bennett, D. J. Dean, F. M.; Herbin, G. A.; Matkin, D. A.; Price, A. W. Robinson, M. L. *J. Chem. Soc. Perk. Trans. 1* **1980,** 1986.
(8) Pelter, A.; Hussain, A.; Smith, G.; Ward, R. S. *Tetrahedron,* **1997,** *53*(11), 3879.
(9) Murakata, M.; Yamada, K.; Hoshino, O. *J. Chem. Soc., Chem. Comm.* **1994,** 443.
(10) a) Hatzigrigoriou, E.; Varvoglis, A.; Bakola-Christianopoulou, M.; *J. Org. Chem.* **1990,** *55,* 315. b) Ray, D. G. III; Koser, G. F. *J. Am. Chem. Soc.* **1990,** *112,* 5672.
(11) Mejorado, L. H.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2006,** *128*, 15625.
(12) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*(10), 1535.
(13) Moloney, M. G.; Paul, D. R.; Prottey, S. C.; Thompson, R. M.; Wright, E. *J. Organometallic Chem.* **1997,** *534,* 195.
(14) Kürti, L; Herczegh, P.; Visy, J.; Simonyi, M.; Antus, S.; Pelter, A. *J. Chem. Soc. Perk. Trans.* **1999,** 379.
(15) a) Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999,** *121,* 9233. b) Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007,** *4*, 538. c) Ladziata, U.; Carlson, J.; Zhdankin, V. V. *Tett. Lett.* **2006,** *47*, 6301.
(16) Kneifel, H.; Poszich-Buscher, C.; Rittich, S.; Breitmaier, E. *Angew. Chem. Int. Ed.* **1991,** *30(2),* 202.
(17) Johnson, R. A. *Organic Reactions* **2004,** *63,* 117.
(18) Myers, A. G.; Siegel, D. R.; Buzard, D. J.; Charest, M. G. *Org Lett.* **2001,** *3*(18), 2923.
(19) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004,** *43,* 1239.
(20) a) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104,* 1047. b) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004,** *104,* 1013. c) Solomon, E. I.; Sundaram, U. M.; Machonkin, T. E. *Chem. Rev.* **1996,** *96,* 2563. d) Kitajima, N.; Fujisawa, K.; Moro-oka, Y. *J. Am. Chem. Soc.* **1989,** *111*, 8975.
(21) Zhu, J.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005,** *127,* 9342.
(22) Alvaro, M.; Garcia, H.; Iborra, S.; Miranda, A.; Primo, J. *Tetrahedron*, **1987,** *43(1)*, 148.
(23) Dong, S.; Zhu, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2008,** *130*(9), 2738.
(24) Hatcher, L. Q.; Karlin, K. D. *J. Biol. Inorg. Chem.* **2004,** *9*, 669.
(25) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A.-M.; Miqueu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008,** *47*(19), 3552.
(26) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008,** *47*(20), 3787.

