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Chiral aryl iodide catalysts for the enantioselective synthesis of *para*-quinols†

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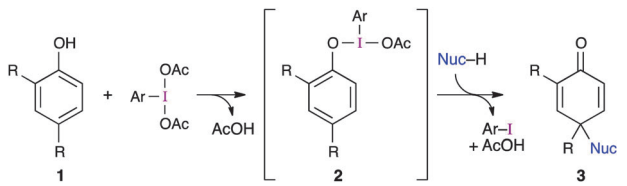
Kelly A. Volp and Andrew M. Harned*

Molecular modelling of an iodine(III) phenoxide was used as a starting point in the design of chiral aryl iodide catalysts for stereoselective oxidative dearomatization reactions. Using this approach, catalysts derived from 8-iodotetralone and tartaric acid were constructed and used to synthesize enantioenriched *para*-quinols from phenols.

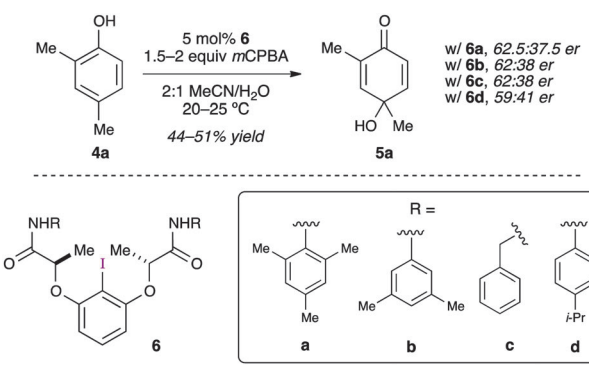
Recent years have seen great progress in the development of asymmetric hypervalent iodine reagents and catalysts for use in enantioselective oxidation reactions.[1] Although high levels of enantiocontrol (>90 : 10 er) can be achieved in oxidative lactonization reactions[2] and for dioxygenation[3] and amination[4] of olefins, analogous results in oxidative dearomatization reactions have been slow to develop.[5] Quideau[6] and Birman[7] have shown that chiral iodine catalysts can be used for the asymmetric ortho-hydroxylation of phenols.[8] A chiral iodine(v) intermediate is postulated to be the active oxidant in these reactions. Meanwhile, Kita[9] and Ishihara[10] have used chiral iodine(III) catalysts/reagents to perform asymmetric spirocyclizations of ortho-substituted naphthol derivatives. To the best of our knowledge, there have been no reports of using asymmetric hypervalent iodine reagents for the enantioselective construction of 2,5-cyclohexadienones (*e.g.*, **1** → **3**, Scheme 1), and a general solution to this problem remains elusive. Herein, we report our initial efforts aimed at designing a chiral aryl iodide catalyst capable of generating enantioenriched *para*-quinols.



Scheme 1 Iodine(III)-mediated oxidative dearomatization of phenols to access 2,5-cylohexadienones.

Our group's interest in using *para*-quinols as building blocks in organic synthesis[11] led us to consider the use of a chiral aryl iodide catalyst for their preparation. We began by investigating the use of the easily prepared and modifiable aryl iodide **6**,[10] developed by Ishihara, as a catalyst for the conversion of phenol **4a** into quinol **5a** (Scheme 2).[12] For simplicity, these reactions were only performed at ambient temperatures and were not optimized for yield. Promising levels of enantiocontrol were realized using catalytic amounts of **6a–d**, however, all of the catalysts resulted in approximately the same level of stereocontrol. Although these results were quite encouraging, further modifications to the catalyst structure did not improve the stereoselectivity. At this point we began to search for alternative catalyst architectures that might lead to improved selectivity.

The overall behavior of the reaction outlined in Scheme 1 is generally well understood.[12,13] However, the mechanism of the conversion of **1** into **3** is still unclear. This is due to the highly reactive nature of the intermediates in question. The first step is almost certainly a ligand exchange between phenol **1** and the iodine(III) carboxylate to form intermediate **2**. Much like the familiar S_N1/S_N2' continuum, the reductive decomposition of **2** likely involves a spectrum of reactivity.[9,10] On one end would be direct nucleophilic attack on the aromatic ring of the phenoxide



Scheme 2 Initial attempts at asymmetric oxidative dearomatization.

Department of Chemistry, University of Minnesota, 207 Pleasant St SE, Minneapolis, MN 55455, USA. E-mail: harned@umn.edu; Fax: +1 612-626-7541; Tel: +1 612-625-1036

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(S_N2'-like). On the other end would be ionization to a highly reactive and short-lived[14] phenoxenium ion (S_N1-like).[15] Our initial results (Scheme 2), and those of Kita and Ishihara,[9,10] indicate that the approach of the nucleophile is being controlled no matter where on the S_N1/S_N2' continuum the dearomatization reaction of interest lies. In other words, these systems produce an iodine(III) phenolate that is capable of shielding one face of the substrate during direct nucleophilic attack and are able to shield one face of a rapidly trapped phenoxenium ion. We hypothesized that the three-dimensional structure of intermediate **2** could be used as a starting point for designing new aryl iodide catalysts with improved enantioselectivity.

In order to gather additional information about the structure of iodine(III) phenolates, DFT calculations were performed on structure **7** (Fig. 1). The calculations were carried out using Truhlar's M06-2X functionals[16] and a mixed basis set (6-31G** for C, H, O and SDD[17] for iodine.† The minimized structure (**7a**) was quite intriguing in that the phenolate ring had partially slipped beneath the phenyl ring of the iodane. We saw this as an opportunity to use this structural feature as a basis for the rational design of new chiral aryl iodides for use in enantioselective oxidative dearomatization reactions. Specifically, it was envisioned that asymmetry could be introduced using a tether bearing stereogenic centers to link one ortho position of the aryl iodide to the α-carbon of an iodine-bound carboxylate.

After investigating several alternative catalysts,† we identified tricyclic aryl iodide **8a** as a new lead structure. This structure was attractive for several reasons. The tetrahydronaphthalene moiety present in **8a** would limit the conformational freedom of the chiral information, while the two carboxylic acid groups could be used to introduce various H-bond donors (*e.g.*, amides) that might interact with the bound phenolate oxygen. Ishihara and co-workers have previously found H-bond donors to be beneficial when incorporated into chiral aryl iodide catalysts.[10] In the end, we found aryl iodide **8a** could be prepared easily† from L-(+)-dimethyl tartrate and 8-iodotetralone.[18]

Gratifyingly, the newly designed chiral aryl iodides were successful in providing enantioenriched *para*-quinols **5** (Table 1). Among the various amides that were tested, catalysts **8a–d** gave approximately the same level of selectivity. We were surprised to find that comparable selectivity was observed when a tertiary amide was incorporated into the catalyst (entry 2). This indicates that factors beyond simple hydrogen bonding are important when biasing the conformation of the presumed iodine(III) phenoxide. Catalysts **8f**, **8g**, and **8h** resulted in a higher yield of the quinol product (entries 6–9), but the enantioselectivity was not appreciably improved. One of the more intriguing results

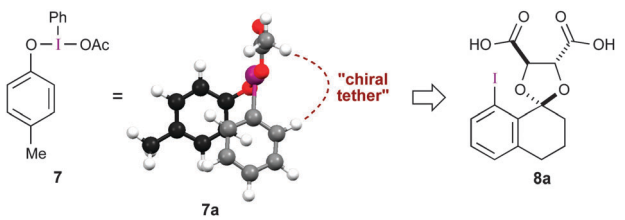
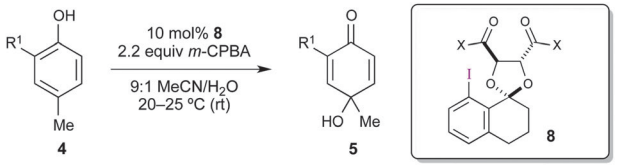
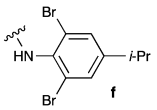
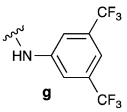
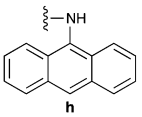
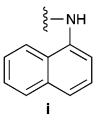


Fig. 1 Rational design of aryl iodide catalysts.

Table 1 Influence of catalyst structure[a]



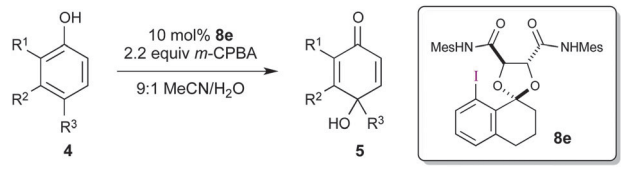
Entry	R^1 (**4** or **5**)	X (**8**)	Time (h)	Yield[c] (%)	er[d]
1[b]	Me (**a**)	OH (**a**)	1.5	36	60 : 40
2[b]	Me (**a**)	Morpholine (**b**)	1.5	33	59 : 41
3	Br (**b**)	NHPh (**c**)	16	48	60 : 40
4[b]	Br (**b**)	$NHCH_2Ph$ (**d**)	1.5	20	60 : 40
5[b]	Br (**b**)	NHMes (**e**)	0.3	45	65 : 35
6	Br (**b**)		16	80	63 : 37
7	TMS (**c**)		16	94	75 : 28
8	Br (**b**)		94	75	43 : 57
9	Br (**b**)		16	70	63 : 37
10	Br (**b**)		16	52	60 : 40

[a] All reactions were performed on a 0.17 mmol scale. [b] 2 : 1 MeCN–H_2O was used. [c] All yields are following purification using silica gel chromatography. [d] Determined by chiral HPLC (see ESI).

was with catalyst **8g** (entry 8), where a reversal of selectivity was observed in comparison to the other catalysts. Taken as a whole, these results show that the identity of the amide has some influence on the enantioselectivity, but this is a rather minor "fine tuning" of the selectivity inherent to the structure of catalyst **8**. In the end, we felt that the mesityl amide **8e** (entry 5) offered the most favourable combination of yield and selectivity; therefore, this catalyst was chosen for further studies.[19] It should be noted that a solvent screen revealed that 9 : 1 MeCN–H_2O was the best solvent mixture.†

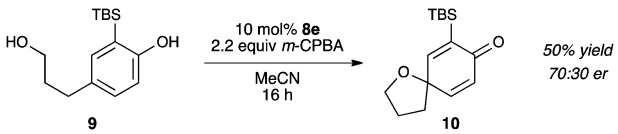
Having identified a viable catalyst, the substrate scope was investigated using catalyst **8e** and various substituted phenols (Table 2). Overall, the enantioselectivity was moderate and ranged from 63 : 37 to 80 : 20 er. In general, an approximately 10% (relative) increase in selectivity was observed when the temperature was lowered to 0 °C, however, this often came at the expense of yield. Increasing the size of the ortho substituent had a generally positive effect on selectivity (**4a–4c**, **4g**), but negative effects were seen when larger para substituents were present (**4i** and **4j**). Substrate **4e** shows that an ortho substituent is required to achieve effective enantiofacial discrimination. However, substrate **4f** demonstrates that a meta substituent is tolerated as long as an ortho substituent is also present. Our recent synthesis of sorbicillatone A[11b] demonstrates the utility of quinol **5f** along with the synthetic potential of an asymmetric

Table 2 Influence of substrate structure[a]



Cmpd	R^1	R^2	R^3	Temp (°C)	Time (h)	Yield[b] (%)	er[c]
a	Me	H	Me	25	16	52	64 : 36
b	Br	H	Me	0	3	21[d]	69 : 31
b	Br	H	Me	25	16	52	65 : 35
c	TMS	H	Me	0	7	58[e]	80 : 20
c	TMS	H	Me	25	16	79	75 : 25
d	Cl	H	Me	25	16	65	65 : 35
e	H	Me	Me	0	0.5	23[d]	53 : 47
e	H	Me	Me	25	16	43	50 : 50
f	Me	OMe	Me	0	1	20[d]	69 : 31
g	TBS	H	Me	0	16	64	77 : 23
g	TBS	H	Me	25	16	48	71 : 29
h	TIPS	H	Me	0	16	56	64 : 36
i	TMS	H	i-Pr	25	16	53	67 : 33
j	TBS	H	i-Pr	25	16	41	63 : 37

[a] All reactions were performed on a 0.17 mmol scale. [b] All yields are following purification using silica gel chromatography. [c] Determined by chiral HPLC (see ESI). [d] 2 : 1 MeCN–H_2O was used. [e] Repeating this experiment using catalyst **6a** instead of **8e** gave the *para*-quinol in 57% yield and 63 : 37 er.



Scheme 3 Asymmetric spirocyclization with catalyst **8e**.

synthesis of *para*-quinols. The highest enantioselectivity (80 : 20 er) was observed with substrate **4c**.

In order to form the enantioenriched *para*-quinols, the chiral catalyst must control the approach of a relatively small, external nucleophile (*i.e.*, H_2O).[20] The stereoselective delivery of such a nucleophile is further complicated by the aforementioned mechanistic uncertainties associated with this reaction. With this in mind, we wanted to evaluate the ability of catalyst **8e** to control the approach of other nucleophiles. To this end, the spirocyclization of phenol **9** was attempted (Scheme 3). Gratifyingly, spirocycle **10** was produced with a level of stereoselectivity (70 : 30 er) that was consistent with those reported in Table 2.[21]

In summary, we have shown that computational methods can be used to gain insight into the structure of short-lived hypervalent iodine intermediates and that the results of this modelling can serve as a basis for the design of chiral aryl iodine catalysts. More importantly, we have shown, for the first time, that chiral aryl iodide catalysts can be used for the enantioselective synthesis of 2,5-cyclohexadienones. Our results indicate that this is a tractable problem, but new catalyst architectures are needed in order to achieve high selectivity. We are continuing our efforts in this area and will report our results in due course.

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