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Indanol-based Chiral Organoiodine Catalyst for Enantioselective Hydrative Dearomatization

Takuya Hashimoto,*[a,b,c] Yuto Shimazaki,[a] Yamato Omatsu,[a] and Keiji Maruoka*[a,d]

Abstract: Rapid development in the last decade rendered chiral organoiodine(I/III) catalysis a reliable methodology in asymmetric catalysis. However, due to the severely limited numbers of effective organoiodine catalysts, many reactions are still practiced with low to modest enantioselectivities. We report herein a solution to this issue by the introduction of a pivotal indanol scaffold to the catalyst design. Our catalyst architecture exhibits the advantage of a high modularity and thereby expedites catalyst optimization. The catalyst was optimized for the challenging and highly sought-after hydrative dearomatization of 2-substituted phenols at the 4-position.

Organoiodine compounds exert a unique catalytic property based on its iodine(I/III) cycle in the presence of a stoichiometric amount of oxidant. This organoiodine catalysis has recently attracted considerable attention in synthetic organic chemistry as a way to implement oxidation reactions with low environmental impact.[1] The current emphasis on this area has been driven by emergence of effective chiral organoiodine catalysts which paved the way for highly enantioselective transformations (Fig. 1a).[2-5] These chiral catalysts have already found application in a variety of reactions by other researchers, giving enantioenriched products accessible only by the use of organoiodine catalysis.[6] However, chiral organoiodine catalyst which surpasses the selectivities achievable by these leading catalysts is virtually non-existent,[7] and many organoiodine-catalyzed reactions are still performed with unsatisfactory level of selectivities.[7,8] As a solution to overcome this limitation, we became interested to apply our chiral indanol scaffold, which demonstrated outstanding selectivities in our studies on a thiyl radical and a electrophilic selenium catalyst,[9] to design a new chiral organoiodine catalyst (Fig. 1b).[10]

As a proof of concept, we surmised that the enantiocontrol of the hydrative dearomatization of phenols at the *para*-position, to give *p*-quinols, would be particularly challenging and rewarding (Fig. 1c).[11-14] Such organoiodine(III)-mediated oxidative dearomatizations of phenols are a common strategy in natural product synthesis, practiced for more than two decades.[15,16] However, they are mostly conducted by the use of a stoichiometric amount of achiral reagent like $PhI(OAc)_2$. While chiral organoiodine-catalyzed hydrative dearomatization will certainly be the solution as presented by Harned and Muñiz,[13] the enantioselectivities remained poor to modest in both cases. It is assumed that the remote prochiral center, which is five bonds away from the organoiodine moiety, and the use of water as small nucleophile render the chirality transfer from the catalyst to the substrate difficult.[14]

Our study unveiled an indanol-based chiral organoiodine catalyst which performs the hydrative dearomatization of phenols to *p*-quinols in up to 84% ee. Taking advantage of our indanol scaffold, equipped with two hydroxy groups, the chiral structure was strategically diversified to expedite the optimization process. In a broader context of chiral organoiodine(I/III) catalysis, this report demonstrates the first chiral catalyst which achieves good enantioselectivities in an intermolecular dearomatization.[17]

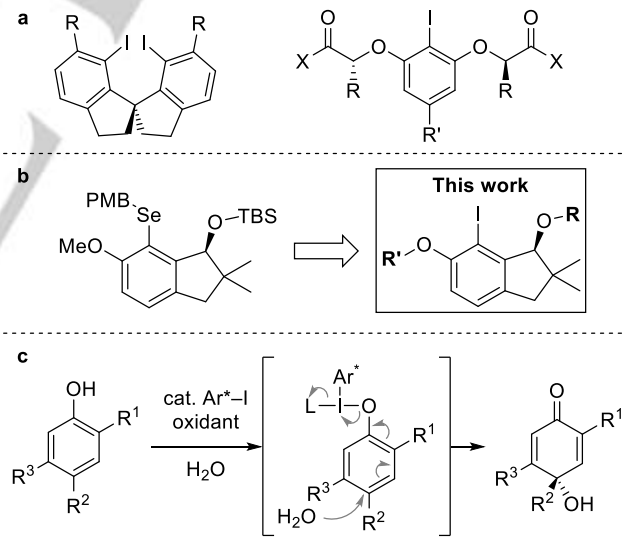

Figure 1. a) Representative chiral organoiodine catalysts, b) Indanol-based chiral organoiodine catalyst, c) para-Hydrative dearomatization of phenols.

Armed with a chromatography-free, scalable synthesis of enantiopure indanol **4**,[9a,18] we set up the synthesis of a indanol-based organoiodine catalyst library (Scheme 1). The hydroxy group-directed lithiation was carried out to install the iodo moiety at the 7-position, giving organoiodine **5**. By attaching different substituents to the hydroxy moiety this intermediate can be derivatized to a variety of chiral organoiodine catalysts **1**. Furthermore, compound **1** can be demethylated by treatment with a thiolate, allowing us to modify the phenol moiety of **6** and hence to fine tune the properties of organoiodine catalysts **2**.

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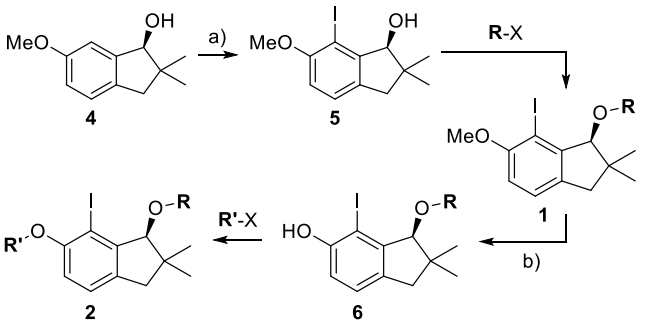


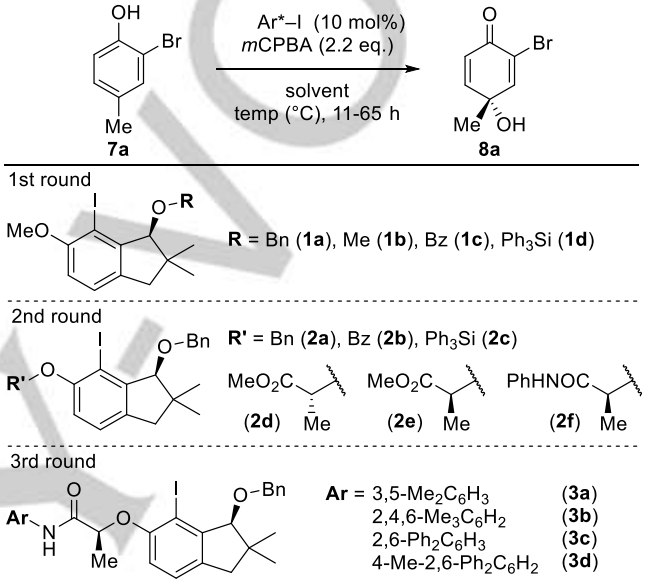
Scheme 1. Modular synthesis of indanol-based chiral organoiodine catalysts. a) BuLi, ether, rt, then I_2, THF, –78 °C, 47% yield (87% brsm); b) *t*-$C_{12}H_{25}SH$, NaH, DMF, 130 °C, 86% yield (R = benzyl).

By the use of this strategy, we could diversify the indanol scaffold **5** rapidly and created a library containing more than 80 chiral organoiodine catalysts, with which the hydrative dearomatization was optimized (Table 1). 2-Bromo-4-methylphenol **7a** was chosen as model substrate with respect to the synthetic utility of the bromo moiety for further functionalization and the poor selectivities achieved in previous studies (around 40% ee).[13] Taking the aforementioned derivatization strategy for the catalyst into account, we split the catalyst optimization into three consecutive rounds. The first round of optimization was commenced with organoiodines **1**, synthesized by the attachment of alkyl, aryl, acyl and silyl groups on the C1-alcohol moiety of indanol **5**. In the initial screening, benzyl substitution stood out with which the dearomatized product could be obtained with 50% ee (entries 1-4). At this stage, solvents and reaction conditions were examined, revealing the use of a 2:1 mixture of acetone/H_2O at 10 °C as optimal to give **8a** with 59% ee (entries 5-7). Encouraged by the observed enantioselectivity, comparable to the highest reported selectivity,[13] we further screened other C1-alcohol functionalities for catalyst **1** in expectation to attain a higher selectivity. However, even after thorough investigations, the ee remained in the range of 40-60% in all cases (see Supporting Information).

We then turned our attention to the second round of the catalyst optimization using C1-benzyloxy **6** (Scheme 1, R = benzyl) as template. This time, the phenolic OH group at the 6-position was modified. After screening of achiral substituents which ended in vain (entries 8-10, see also SI), we turned our focus to a chiral lactate moiety introduced by Fujita *et al.* in their development of chiral organoiodine(III) reagents.[19] Examination of both enantiomers of methyl lactate revealed that one isomer (**2d**) lowered the ee by 18% and the other (**2e**) improved the ee by 11% (entries 12 and 13). It is of note that the chirality of the lactate is crucial as catalysts bearing achiral glycolate (CH_2CO_2Me) or 2-methyllactate (CMe_2CO_2Me) had no effect on the selectivity, respectively (see, SI). Further improvement of the enantioselectivity was observed by the incorporation of N-phenyl lactamide as the supporting chiral entity (**2f**, entry 13).[5]

The last optimization round was focused on the amide N-substituent of organoiodines **3** (entries 14-17). Consistent with Ishihara's report,[5b] attachment of 2,6-disubstituted anilines further improved the selectivity to more than 80% ee (entries 15-17). By fixing the catalyst to **3c**, the reaction conditions were fine-tuned, resulting in the use of butanone/H_2O solvent system at 0 °C (entry 18). Under these conditions, *p*-quinol **8a** was obtained in 54% yield and 82% ee. It is noted that no racemization of the product was observed in the reaction and the absolute configuration of **8a** was confirmed by X-ray crystallographic analysis.[20]

Table 1. Catalyst optimization.[a]



entry	Ar*I	solvent	°C	% yield[b]	% ee[c]
1	**1a**	acetone/H_2O = 9/1	rt	49	50
2	**1b**		rt	36	37
3	**1c**		rt	3	32
4	**1d**		rt	51	4
5	**1d**	CH_3CN/H_2O = 9/1	rt	31	30
6	**1d**	DMF/H_2O = 9/1	rt	5	68
7	**1a**	acetone/H_2O = 2/1	10	73	59
8	**2a**		10	63	57
9	**2b**		10	10	37
10	**2c**		10	46	52
11	**2d**		10	66	41
12	**2e**		10	68	70
13	**2f**		10	49	73
14	**3a**		10	55	74
15	**3b**		10	65	77
16	**3c**		10	46	81
17	**3d**		10	55	75
18[d]	**3c**	butanone/H_2O = 2/1	0	54[e]	82

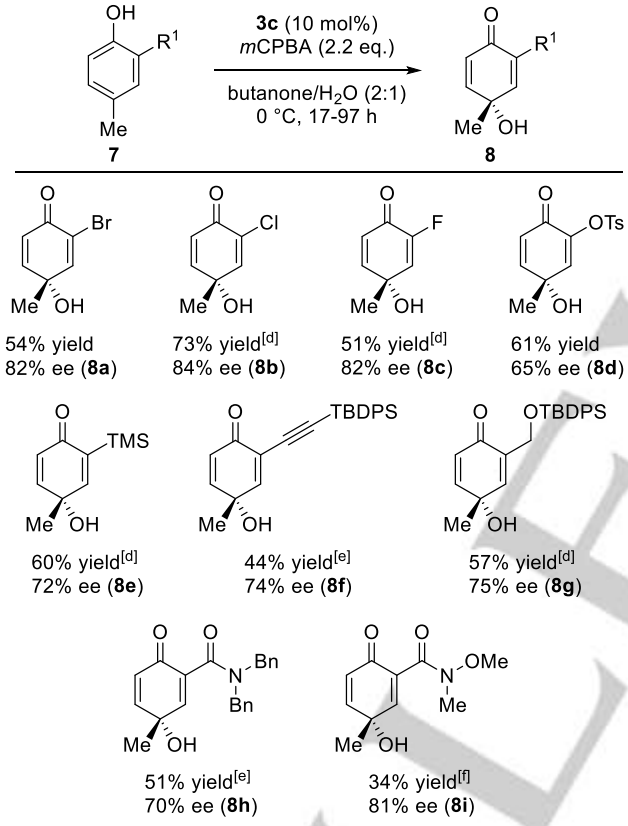
[a] Reaction conditions: **7a** (0.165 mmol), mCPBA (0.363 mmol), and Ar*–I (0.017 mmol) in solvent (1 mL). [b] NMR yield. [c] Ee determined by chiral HPLC analysis. [d] Performed on 0.1 mmol scale. [e] Isolated yield.

With the optimized catalyst and reaction conditions in hand, we then examined the substrate scope, initially focusing on the 2-substituent of phenols (Table 2). The optimized reaction conditions were applicable to 2-chloro-4-methylphenol with the same level of enantioselectivity (**8b**). Interestingly, the enantioselectivity was maintained even with 2-fluoro-4-methylphenol (**8c**), implying that the catalyst recognizes the electronic bias of the phenol ring. In these two cases, catalyst **3d**,

bearing a N-4-methyl-(2,6-diphenyl)phenyl group, gave a slightly higher ee. As for hetero-functionalities, a tosyloxy group was tolerated albeit with lower enantioselectivity (**8d**). 2-TMS substrate was converted to *p*-quinol **8e** with 72% ee.

Our focus then shifted to different carbon-substituents attached to the phenol ring. It was revealed that *p*-quinols **8f**-**h** bearing a alkynyl, siloxymethyl or amide functionality were obtained with 70-81% ee by conducting the reaction in either acetonitrile/H_2O or butanone/H_2O. The use of 5-methylsalicylate (**7**, $R^1 = CO_2Me$) resulted in an over-oxidation of the product by *m*CPBA (data not shown). The Weinreb amide, a useful synthetic handle, could be also incorporated into *p*-quinol **8i** with good enantioselectivity, although the reaction yield still needs to be improved.

Table 2. 4-Methylphenols substrate scope.

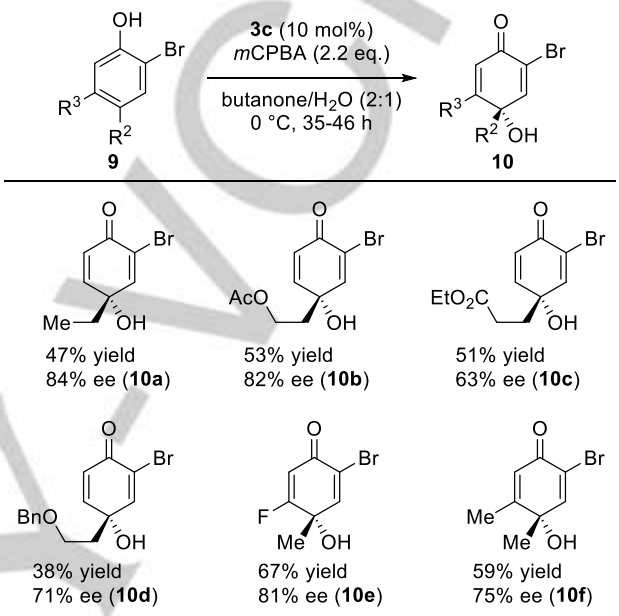


[a] Reaction conditions: **7** (0.10 mmol), *m*CPBA (0.22 mmol), and **3c** (0.01 mmol) in butanone/H_2O (2/1, 0.6 mL). [b] Isolated yield. [c] Ee determined by chiral HPLC analysis. [d] Performed with **3d** (0.01 mmol). [e] Performed in CH_3CN/H_2O (2/1, 1.0 mL). [f] Performed in $CH_3CN/CHCl_3/H_2O$ (7/1/2, 1.0 mL).

As the next step, we turned our attention to the 4-alkyl substituent of 2-bromophenols **9** (Table 3). An ethyl group instead of a methyl group at the 4-position had no negative effect on the enantioselectivity (**10a**). To examine the pendant functional group tolerance, we then examined substrates bearing acyl, ester, and ether moieties at the end of the alkyl chain. While these functionalities were tolerated, the reactions gave a variable level of enantioselectivities (**10b**-**10d**).

Finally, 4,5-disubstituted 2-bromophenols were briefly examined, using 5-fluoro and 5-methyl substituted phenols. In both cases, the enantioselectivities were unaffected by the additional substituent, giving **10e** and **10f** in good yields and enantioselectivities. It is expected that subsequent debromination of these products would give access to 3,4-disubstituted *p*-quinols which are valuable intermediates in natural product synthesis,[15c,d,f,h] but still hard to synthesize with state-of-the-art asymmetric catalysis.[13a,21]

Table 3. 2-Bromophenols substrate scope.



[a] Reaction conditions: **9** (0.10 mmol), *m*CPBA (0.22 mmol), and **3c** (0.01 mmol) in butanone/H_2O (2/1, 0.6 mL). [b] Isolated yield. [c] Ee determined by chiral HPLC analysis.

In conclusion, we developed the first chiral organoiodine catalyst which performs the intermolecular hydrative dearomatization of phenols to give *p*-quinols with good enantioselectivities. The key to success was the use of a readily available enantiopure indanol scaffold, allowing for rapid catalyst evolution and the creation of a library containing more than 80 organoiodine catalysts. With respect to the fact that selectivities of many organoiodine-catalyzed reactions still lag behind today's standards in asymmetric catalysis, our approach will find a way to provide a solution to this flourishing field.

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Keywords: asymmetric catalysis • iodine • dearomatization

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[21] The dearomatization of 3,4-dimethylphenol under the optimized reaction conditions gave the corresponding *p*-quinol in 20% yield and 2% ee.

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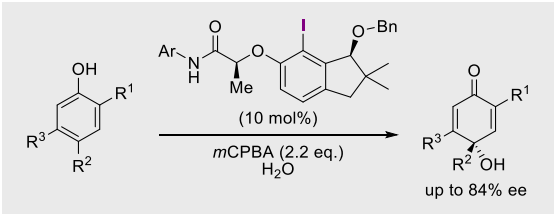

Takuya Hashimoto, Yuto Shimazaki, Yamato Omatsu, and Keiji Maruoka**

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Indanol-based Chiral Organoiodine Catalyst for Enantioselective Hydrative Dearomatization

We report herein the introduction of a pivotal indanol scaffold to a new chiral organoiodine catalyst design. Our catalyst architecture exhibits the advantage of a high modularity and thereby expedites catalyst optimization. The catalyst was optimized for the challenging and highly sought-after *para*-hydrative dearomatization of phenols, achieving up to 84% ee.