



Quaternary Ammonium (Hypo)iodite Catalysis for Enantioselective Oxidative Cycloetherification Muhammet Uyanik *et al. Science* **328**, 1376 (2010); DOI: 10.1126/science.1188217

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Quaternary Ammonium (Hypo)iodite Catalysis for Enantioselective Oxidative Cycloetherification

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It is desirable to minimize the use of rare or toxic metals for oxidative reactions in the synthesis of pharmaceutical products. Hypervalent iodine compounds are environmentally benign alternatives, but their catalytic use, particularly for asymmetric transformations, has been quite limited. We report here an enantioselective oxidative cycloetherification of ketophenols to 2-acyl-2,3-dihydrobenzofuran derivatives, catalyzed by in situ—generated chiral quaternary ammonium (hypo)iodite salts, with hydrogen peroxide as an environmentally benign oxidant. The optically active 2-acyl 2,3-dihydrobenzofuran skeleton is a key structure in several biologically active compounds.

ver the past two decades, hypervalent iodine compounds have been increasingly explored as environmentally benign oxidation reagents in place of rare or toxic heavy metal oxidants (1, 2). However, their stoichiometric use has been limited because of potentially explosive shock-sensitivity and/or poor solubility in common organic solvents (1, 2). Thus, the development of hypervalent iodine-catalyzed reactions using more convenient stoichiometric co-oxidants is needed (3, 4). Harnessing chiral hypervalent iodine compounds for enantioselective oxidative coupling has proven a particular challenge in asymmetric catalysis. There are several examples of catalysis by in situ-generated chiral aryl- λ^3 - or aryl- λ^5 -iodane (5) with *meta*chloroperbenzoic acid (m-CPBA) as a co-oxidant (Fig. 1A, left) (6-9); these include Quideau et al.'s enantioselective hydroxylative dearomatization of phenols (6), Altermann et al.'s enantioselective α oxysulfonylation of ketones (7), and Dohi et al.'s and our independently reported enantioselective oxidative spirolactonizations of 1-napthol derivatives (8, 9). In contrast, no strong examples have emerged of asymmetric catalysis using chiral cations paired with inorganic iodine-derived oxoacids, such as hypoiodous acid [IOH, I(I)], iodous acid [O=IOH, I(III)], iodic acid [(O=)2IOH, I(V)], and periodic acid [(O=)₃IOH, I(VII)].

We report here an implementation of this strategy, using the atom-economical hydrogen peroxide as a mild stoichiometric oxidant to activate catalytic ion pairs of chiral quaternary ammonium iodide (Fig. 1A, right) (10, 11). Specifically, we targeted enantioselective oxidative cycloetherification of ketophenols to 2-acyl-2,3-dihydrobenzofuran derivatives, using a C_2 -symmetric chiral binaphthylbased quaternary ammonium (hypo)iodite catalyst generated in situ by reaction with hydrogen peroxide (Fig. 1B). The chiral 2-substituted 2,3dihydrobenzofuran skeleton is a key structure in several biologically active compounds of medicinal interest (12-19). Earlier preparations of optically active 2-alkenyl-2,3-dihydrobenzofuran derivatives have relied on transition metal catalysis (20-23).

The catalytic or stoichiometric oxidation of 3-(2-hydroxyphenyl)-1-phenylpropan-1-one (1) with phenyl- λ^3 -iodanes gave a complex mixture, and the desired (2,3-dihydrobenzofuran-2-yl) (phenyl)methanone (2) was not detected (Fig. 2A, entries 1 and 2). In sharp contrast, and to our delight, the oxidation of 1 with two equivalents of hydrogen peroxide [30 weight percent (wt %) in water] in the presence of 10 mole percent (mol %) of tetrabutylammonium iodide (Bu₄NI) in acetonitrile at room temperature gave 2 in 87% yield (Fig. 2A, entry 3) (24). Furthermore, the oxidation of 1 was much faster in diethyl ether (Et₂O), tetrahydrofuran (THF), or ethyl acetate (EtOAc) (Fig. 2A, entry 4, and table S1). Notably, the oxidation of 1 did not occur on substitution of tetrabutylammonium bromide or chloride for Bu₄NI. Excellent chemoselectivity was observed



Fig. 1. (**A**) (Left) Known in situ—generated aryl- λ^3 - or aryl- λ^5 -iodane catalysis. (Right) In situ—generated hypoiodite(I) or iodite(III) catalysis. (**B**) Design of inorganic iodide precatalyst paired with a chiral quaternary ammonium counter ion for the enantioselective oxidative cycloetherification of ketophenols to 2-acyl-2,3-dihydrobenzofuran derivatives. Ar, aryl; L, ligand; M⁺, metal or onium cation, R, alkyl or aryl group. Symbols (Ar and L) marked with asterisks represent chiral groups.

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Fig. 2. (A) Oxidative cycloetherification of 1. Isolated yields of 2 are reported. Ts, *p*-toluenesulfonyl. (B) Enantioselective oxidative cycloetherification of 4a. Isolated yields of 2 are reported. ee was determined by chiral stationary-phase high-performance liquid chromatography (HPLC). Ph, phenyl; Pr, propyl; Bu, butyl; h, hours.



PhI (10 mol%), TsOH (10 mol%), m-CPBA (2 equiv), CH₃CN, rt to 50 °C 1 messv

2	PhI(OH)(OTs) <i>or</i> PhI(OAc) ₂ (2 equiv), CH ₃ CN, rt to 50 °C	messy

3 Bu₄N⁺ I⁻ (10 mol%), 30% H₂O₂ (2 equiv), CH₃CN, rt, 72 h 87

4 Bu₄N⁺ I⁻ (10 mol%), 30% H₂O₂ (2 equiv), THF, Et₂O or EtOAc, rt, 6 to 9 h 97 to 99

В	0			
	\sim Í	Ph N \downarrow \rangle + co-oxidant	pre-catalyst 3 (10 mol%)	
	OH	N_/	room temperature	0 Z
	4a	Z		5a
entry	3	co-oxidant	conditions	yield (%), ee (%)
1	3a	30% H ₂ O ₂ (2 equiv)	Toluene/H ₂ O (5:1, <i>v/v</i>), 24 h	54, 2
2	3b	30% H ₂ O ₂ (2 equiv)	Toluene/H ₂ O (5:1, <i>v/v</i>), 5 h	83, 7 (<i>ent</i>)
3	3c	30% H ₂ O ₂ (2 equiv)	Toluene/H ₂ O (5:1, <i>v/v</i>), 1 h	99, 76
4	3d	30% H ₂ O ₂ (2 equiv)	Toluene/H ₂ O (5:1, <i>v/v</i>), 1 h	99, 88
5	3e	30% H ₂ O ₂ (2 equiv)	Toluene/H ₂ O (5:1, <i>v/v</i>), 4 h	99, 42
6	3f	30% H ₂ O ₂ (2 equiv)	Toluene/H ₂ O (5:1, <i>v/v</i>), 1 h	99, 48
7	3d	30% H ₂ O ₂ (2 equiv)	Et ₂ O/H ₂ O (5:1, <i>v/v</i>), 1 h	99, 90
8	3d	30% H ₂ O ₂ (1.1 equiv)	Et ₂ O/H ₂ O (5:1, <i>v</i> / <i>v</i>), 4 h	99, 91 (99)*
9	3d	TBHP (2 equiv)	Et ₂ O, 4 h	99, 92

* After a single recrystallization from *i*-PrOH/EtOH (4:1, v/v).



under the present oxidation. We detected no phenol oxidation products, which are well known to form in reactions with aryl- λ^3 -iodanes (1–9).

To render the catalysis asymmetric, we examined N-spiro-type quaternary ammonium iodide precatalysts (3) bearing chiral 3,3'-disubstituted 1,1'-binaphthyl skeletons, analogous to Ooi and Maruoka's chiral phase-transfer catalysts (Fig. 2B) (25). As a result, we found that a 1-phenyl-1Himidazol-2-yl moiety (Z) at the 1-position of the substrates (4a) was effective for inducing high enantioselectivity (26) (Fig. 2B and table S3). The oxidation of 4a with two equivalents of hydrogen peroxide (30 wt % in water) in the presence of 10 mol % of 3a in mixed toluene/water solvent (5/1, v/v) gave 2a in 54% yield, but with very low enantioselectivity [2% enantiomeric excess (ee)] (Fig. 2B, entry 1). The substituents at the 3,3'-positions of the binaphthyl moiety were



Fig. 3. Conversion of 5a to (R)-ethyl ester 6. MeOTf, methyl trifluoromethanesulfonate; MS, molecular sieves; DBU, 1,8-diazobicyclo[5.4.0]undec-7-ene.

crucial for increasing not only the enantioselectivity but also the chemical yield of 5a (Fig. 2B, entries 1 to 4). Ammonium cations bearing bulky and electron-deficient substituents $\{Ar = 3, 5 [3,5-(CF_3)_2C_6H_3]C_6H_3$ at the 3,3'-positions gave the best results (1 hour, 99% yield, 88% ee) (Fig. 2B, entry 4). The use of mono(1,1'-binaphthyl-2,2'-dimethyl)ammonium iodides such as 3e and **3f** in place of bis(1,1'-binaphthyl-2,2'-dimethyl) ammonium iodide (3c) gave moderate enantioselectivities (Fig. 2B, entries 5 and 6 versus entry 3). Notably, moderate-to-high enantioselectivities were observed, regardless of the polarity of the solvent (table S3). In particular, 5a was obtained in 99% yield with 90% ee in mixed diethyl ether/ water solvent (5/1, v/v) (Fig. 2B, entry 7). 1.1 equivalent of hydrogen peroxide was suitable as a cooxidant for quantitative conversion (Fig. 2B, entry 8). Importantly, nearly enantiomerically pure **5a** was obtained after a single recrystallization (99% ee) (Fig. 2B, entry 8). When anhydrous *tert*-butylhydroperoxide (TBHP) was used as a co-oxidant in place of aqueous hydrogen peroxide, **5a** was obtained with higher enantioselectivity (92% ee) in diethyl ether (Fig. 2B, entry 9).

The **5** products are very useful chiral intermediates for further synthetic elaboration (*26*). For instance, **5a** was transformed efficiently into the known (*R*)-ethyl ester (**6**) (*12*, *27*), which is a synthetic intermediate for natural products such





Method A: 30% H₂O₂, Et₂O/H₂O (5:1, v/v); Method B: TBHP, Et₂O

Entry	Product	5	Method, time (h)	Yield (%)	ee (%)
1	F 0	5b	A , 2	99	93
2		5c	A , 2	99	91
3	F ₃ CO	5d	A , 2	99	91
4	MeO	5e	A 15	84	85
5		5e	B , 4	99	91
6	BnO	5f	A 2	08	80
7		5f	B , 6.5	99	92
	∽ U Z OMe				
8		5g	A , 2	26	70
9	MeO	5g	B *, 0.5	99	85
	Me				
10	Me	5h	A , 2	99	90
11		5i	A , 2.5	99	89
12	<i>t</i> -BuMe ₂ SiO	5j	A , 1.5	78	87
13		5k ‡	A , 3	99	96
14†		5k ‡	B , 17	99	96

*Reaction was performed in toluene instead of Et₂O. †The reaction was performed with 2 mmol of **5k** with 4 mmol of TBHP in the presence of 1 mol % of **3d**. ‡Absolute configuration of **5k** was determined by transformation into the known (R)-methyl ketone (*24*). as tremetone (12, 22), fomannoxin (28), and anodendroic acid (Fig. 3) (28).

To explore the generality and scope of the present enantioselective oxidative cyclization, we prepared and examined several ketophenol derivatives (4) as substrates under optimized conditions (Table 1). The oxidation of 4-substituted phenol derivatives 4b to 4f bearing electrondonating or electron-withdrawing groups gave the corresponding dihydrofuran derivatives 5b to 5f in excellent yields with high enantioselectivities (91 to 93% ee) (Table 1, entries 1 to 7). In most cases, we observed high enantioselectivities using method A or B, though method B offered substantially higher yield and ee in the case of the 3,5-dimethoxy-substituted phenol derivative 4g (Table 1, entries 8 and 9). The 2-alkenyl-derivative of compound 5g is a synthetic intermediate for natural products such as entremirol and ent-remiridol (29). The reaction was effective for the 2-napthol derivative 4i (Table 1, entry 11), as well as for penta-substituted phenol derivative 4j (Table 1, entry 12). Oxidation of 2methyl-substituted substrate 4k gave a product (5k) bearing a tetrasubstituted stereogenic center in 96% ee (Table 1, entry 13). The precatalyst loading of 3d could be reduced to 1 mol % without affecting the chemical yield and enantioselectivity (Table 1, entry 14). Compound 5k and its analogs would potentially offer a different route to biologically active targets, such as peroxisome proliferator-activated receptor α agonists (15).

To understand the reaction pathway, we conducted several control experiments directed toward identifying an active hypervalent iodine species (table S4). No oxidation of 1 occurred in the presence of stoichiometric amounts of tetrabutylammonium iodate(V) or periodate(VII). Thus, the iodate(V) and periodate(VII) active species were ruled out. Additionally, the stoichiometric oxidation of 1 with N-iodosuccinimide or molecular iodine (I₂) gave a complex mixture, and desired product 2 was not detected. Notably, no iodinated products were detected, even in the oxidation of electronrich phenol 4h under our catalytic conditions (Table 1, entries 8 and 9). In contrast, the oxidation of 1 with I₂ in the presence of two equivalents of tetrabutylammonium hydroxide ([Bu₄N]⁺[OH]⁻) gave desired product 2 in 91% yield (30, 31). This result suggests that in situ-generated tetrabutylammonium hypoiodite $\{[Bu_4N]^+[IO]^-, I(I)\}$ may be an active oxidant species for 1. However, [Bu₄N]⁺[IO]⁻ may also disproportionate to tetrabutylammonium iodite $\{[Bu_4N]^+[IO_2]^-, I(III)\}$ and Bu₄NI under our reaction conditions, implying that $[Bu_4N]^+[IO_2]^-$ is another potential actual oxidant species. Thus, we propose a catalytic cycle involving chiral quaternary ammonium hypoiodite ($[R_4N]^+[IO]^-$) or iodite ($[R_4N]^+[IO_2]^-$), which should be generated in situ from ammonium iodide (R₄NI) and a co-oxidant (Fig. 1A, right).

These results highlight the substantial scope of chiral salt catalysis using inorganic iodinederived oxoacids in place of aryliodane or transition metal catalysts.

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Regulation of Body Temperature by Some Mesozoic Marine Reptiles

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What the body temperature and thermoregulation processes of extinct vertebrates were are central questions for understanding their ecology and evolution. The thermophysiologic status of the great marine reptiles is still unknown, even though some studies have suggested that thermoregulation may have contributed to their exceptional evolutionary success as apex predators of Mesozoic aquatic ecosystems. We tested the thermal status of ichthyosaurs, plesiosaurs, and mosasaurs by comparing the oxygen isotope compositions of their tooth phosphate to those of coexisting fish. Data distribution reveals that these large marine reptiles were able to maintain a constant and high body temperature in oceanic environments ranging from tropical to cold temperate. Their estimated body temperatures, in the range from $35^{\circ} \pm 2^{\circ}$ C to $39^{\circ} \pm 2^{\circ}$ C, suggest high metabolic rates required for predation and fast swimming over large distances offshore.

The metabolic status of extinct vertebrates is a key to understand their feeding strategy, which was critical for satisfying their daily energy requirements, as well as their potential to exploit cold environments. Phylogeny and ecology most likely had a large influence on the thermophysiology of past vertebrates. High metabolic rates mean the need to access large amounts of high-quality food, which may be satisfied by adopting predatory behavior, as shared by many carnivorous mammals, except scavengers. Endothermy is the ability to generate and retain enough heat to elevate body temperature to a high but stable level, whereas homeothermy is the maintenance of a constant body temperature in different thermal environments (1, 2). Such internal production of heat is not restricted to mammals and birds. Heat generation can have several origins: digestive organs in mammals and birds (1) or muscles in endothermic lamniform sharks (3). Paladino et al. (4) proposed that some marine reptiles such as leatherback turtles display endothermy instead of inertial homeothermy, thus helping them to feed in cold waters. However, Lutcavage et al. (5) showed that the studied gravid female specimens raised their metabolic rates because of egg laying, thus biasing the evaluation of their true metabolic status. Most biologists agree that full or incomplete en-

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dothermy arose several times during species evolution and developed independently in several lineages. For example, partial endothermy is known in sharks, tunas, and even in some insects and flowers (6–8). The origin and spreading of endothermy are still a matter of great debate (9–11); its oldest occurrence could be as early as the Permian, with the appearance and radiation of the Synapsida. Among archosaurs, mass homeothermy or even endothermy have been proposed for dinosaurs (12) and pterosaurs (13) and suggested for the ancestors of crocodilians, because of the existence of a four-chambered heart, which modern crocodiles share with mammals and birds (11).

Large marine reptiles, including ichthyosaurs, plesiosaurs, and mosasaurs, inhabited the oceans from the Triassic to the Cretaceous. They represent three different lineages that became secondarily adapted to a marine mode of life. Ichthyosaurs evolved from basal neodiapsid reptiles, with the most obvious aquatic adaptations: a dolphin-like streamlined body without a neck, paddles, and a fish-like tail. Plesiosaurs are derived diapsids, which belong to the Sauropterygia, the sister group of the Lepidosauria (lizards and snakes). They are highly adapted for submarine locomotion, with powerful paddle-like limbs and heavily reinforced limb girdles. Motani (14) already discussed the possibility that plesiosaurs could not have had a typical reptilian physiology, thus indicating high metabolic activity. Mosasaurs constitute a family of Late Cretaceous varanoid anguimorphs highly adapted to marine life; they are derived lepidosaurs with an elongate body, deep tail, and paddle-like limbs (15). Both tooth morphology and the stomach contents of these three groups of marine reptiles indicate predatory behavior. Their anatomy could afford high cruising speeds and a basal metabolic rate similar to that of modern tunas (16). Moreover, the bone structure of adult

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