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In Situ Electrophilic Activation of Hydrogen Peroxide for Catalytic Asymmetric α-Hydroxylation of 3-Substituted Oxindoles

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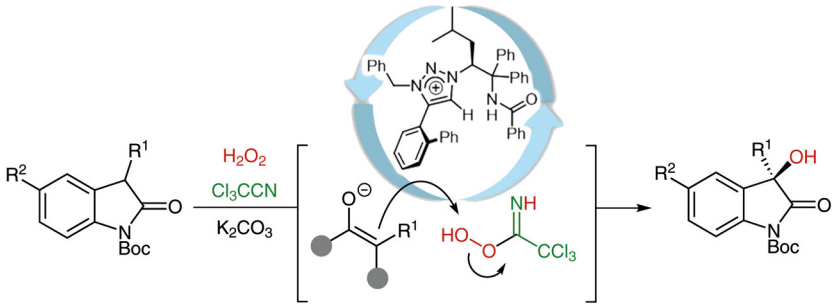

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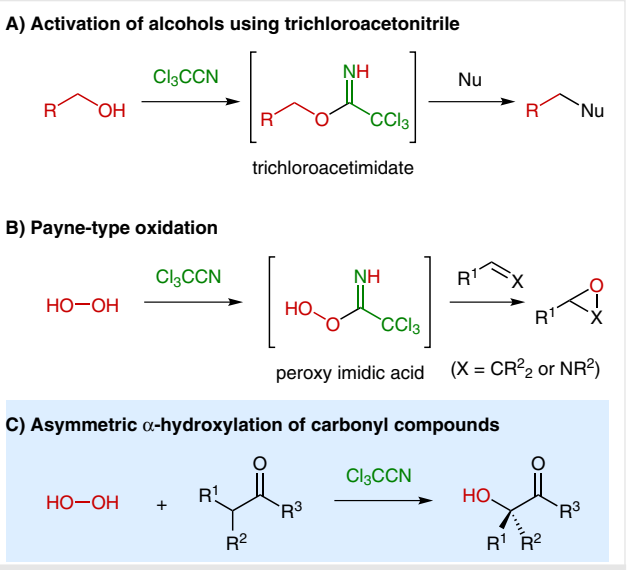
Abstract Peroxy trichloroacetimidic acid, in situ generated from aqueous hydrogen peroxide and trichloroacetonitrile, was found to act as a competent electrophilic oxygenating agent for the direct α-hydroxylation of oxindoles. The use of chiral 1,2,3-triazolium salt as a phase-transfer catalyst enabled rigorous absolute stereocontrol in the carbon–oxygen bond-forming reaction. The present study provides a new, yet practical method for straightforward access to optically active α-hydroxycarbonyl compounds.

Key words hydroxylation, carbonyl compound, hydrogen peroxide, imidic acid, oxindole, chiral ion pair, 1,2,3-triazolium ion

Conversion of the hydroxyl group into a better leaving group, such as acetoxy or sulfonyloxy, represents one of the most fundamental and versatile activation processes for implementing the subsequent bond-forming reactions. Facile generation of trichloroacetimidates from alcohols by the treatment with trichloroacetonitrile is a particularly unique example (Scheme 1 A),[1,2] which has been classically utilized for glycosylation reactions.[3] The trichloroacetimidate is a reactive electrophile, yet compatible with Brønsted acid or hydrogen-bond donor catalysis. The groundwork for this hydroxyl-group activation tactic was laid by Payne through the development of the epoxidation of alkenes by peroxy trichloroacetimidic acid, which was generated in situ from hydrogen peroxide and trichloroacetonitrile under basic conditions (Scheme 1 B).[4,5] The potential applicability of this mode of peroxy imidic acid generation to asymmetric catalysis was demonstrated by our group in the development of the enantioselective Payne-type oxidation of *N*-sulfonyl imines.[6] On the other hand, we recently established a catalytic system for the direct asymmetric α-amination of carbonyl compounds based on the activation of hydroxylamines with trichloroacetonitrile as an electrophilic amine source.[7] In conjunction with these studies, we became interested in the possibility of exploiting the reactivity of the peroxy imidic acid as an electrophilic oxygenating agent to directly install a hydroxyl group at the α-position of carbonyl compounds using hydrogen peroxide as a terminal oxidant (Scheme 1 C).



Scheme 1 Transformations based on the activation of hydroxyl group with trichloroacetonitrile

Asymmetric α-hydroxylation of carbonyls is an efficient and straightforward method to access chiral tertiary α-hydroxycarbonyl compounds, which constitute structural components of many biologically active organic molecules and serve as versatile synthetic intermediates.[8] There have been various successful examples that relied on the combined use of effective catalysts and appropriate oxygenating

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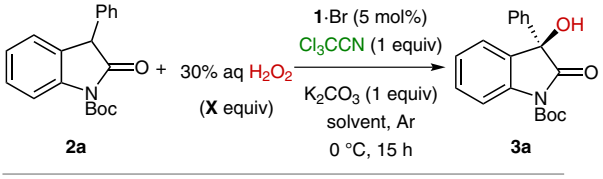
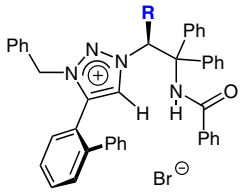
reagents such as alkyl hydroperoxide,[9] dimethyldioxirane,[10] oxaziridine,[11] nitrosoarene,[12] and molecular oxygen.[13] However, reliable catalytic systems that can use abundant and safe-to-handle hydrogen peroxide as an oxidant are extremely scarce because of its low electrophilicity.[14] Here, as our solution to this problem, we report the development of a highly enantioselective direct α-hydroxylation of 3-substituted oxindoles under the catalysis of chiral 1,2,3-triazolium salts.[15]

We initially attempted the reaction of *N*-Boc-3-phenyloxindole (**2a**) with excess 30% aqueous solution of hydrogen peroxide (20 equiv) in the presence of trichloroacetonitrile (1.0 equiv), potassium carbonate (1.0 equiv), and a catalytic quantity of L-alanine-derived chiral 1,2,3-triazolium bromide **1a**·Br (5 mol%) in toluene at 0 °C under argon atmosphere (Table 1, entry 1). The carbon–oxygen bond formation proceeded smoothly, and the desired α-hydroxyoxindole **3a** was obtained with moderate enantioselectivity. It should be noted that no oxidation products were detected in the absence of trichloroacetonitrile and substrate **2a** was recovered quantitatively (Table 1, entry 2). This observation emphasizes the critical importance of the combination of hydrogen peroxide and trichloroacetonitrile in promoting direct α-hydroxylation. For improving the stereoselectivity, we evaluated the effect of the catalyst structure, specifically that of the aliphatic substituent (*R*) on the stereogenic center of amino acid origin, and identified the L-leucine-derived triazolium salt **1c**·Br as an optimal catalyst (Table 1, entry 4). Subsequent screening of the solvents revealed the significant influence on the reactivity and selectivity profiles (Table 1, entries 6–9). In particular, diethyl ether proved to be the solvent of choice, making it feasible to attain high reaction efficiency and enantioselectivity (Table 1, entry 7). An additional insight gained from a control experiment was that the present hydroxylation could occur in the absence of the triazolium catalyst to give the racemic prod-

Table 1 Optimization of Reaction Conditions[a]



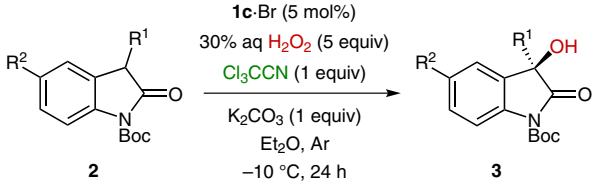


1a·Br (**R** = Me)
1b·Br (**R** = CH_2Ph)
1c·Br (**R** = CH_2*i*-Pr)
1d·Br (**R** = *n*-Pr)

Entry	**1**	Solvent	H_2O_2 (X equiv)	Yield (%)[b]	ee (%)[c]
1	**1a**	toluene	20	65	65
2[d]	**1a**	toluene	20	0	–
3	**1b**	toluene	20	77	79
4	**1c**	toluene	20	66	83
5	**1d**	toluene	20	82	79
6	**1c**	CH_2Cl_2	20	49	61
7	**1c**	Et_2O	20	80	90
8	**1c**	THF	20	10	24
9	**1c**	EtOAc	20	54	75
10	**1c**	Et_2O	5	83	92
11	**1c**	Et_2O	2	57	92
12[e]	**1c**	Et_2O	5	97	94

[a] Unless otherwise noted, reaction was conducted with **2a** (0.1 mmol), 30% aq solution of H_2O_2, Cl_3CCN (1 equiv), K_2CO_3 (1 equiv), and **1**·Br (5 mol%) in solvent (1 mL) at 0 °C for 15 h under Ar.
[b] Isolated yield.
[c] Determined by HPLC with chiral column.
[d] Without Cl_3CCN.
[e] Reaction was performed at –10 °C for 24 h.

Table 2 Scope of Oxindoles[a]



Entry	R^1	R^2	**3**	Yield (%)[b]	ee (%)[c]
1	4-MeC_6H_4	H	**3b**	86	93
2	4-$MeOC_6H_4$	H	**3c**	80	92
3	4-FC_6H_4	H	**3d**	81	93
4	3-MeC_6H_4	H	**3e**	89	90
5	3-$MeOC_6H_4$	H	**3f**	90	93
6	1-Naph	H	**3g**	67	92
7	2-Naph	H	**3h**	93	90
8	Et	H	**3i**	58	94
9	*n*-Bu	H	**3j**	71	89
10	*c*-$HexCH_2$	H	**3k**	87	94
11	CH_2=$CHCH_2$	H	**3l**	96	95
12	Bn	H	**3m**	97	97
13	4-$MeOC_6H_4CH_2$	H	**3n**	96	94
14	4-$FC_6H_4CH_2$	H	**3o**	89	98
15	Ph	Me	**3p**	90	94
16	Ph	MeO	**3q**	89	94
17	Ph	F	**3r**	71	90

[a] Reaction was conducted with **2** (0.1 mmol), 30% aq solution of H_2O_2 (5 equiv), Cl_3CCN (1 equiv), K_2CO_3 (1 equiv), and **1c**·Br (5 mol%) in Et_2O (1 mL) at –10 °C for 24 h under Ar.
[b] Isolated yield.
[c] Determined by HPLC with chiral column.

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uct (data not shown). We assumed that this competitive background pathway could be suppressed by reducing the amount of hydrogen peroxide. Indeed, the use of five equivalents of hydrogen peroxide enabled higher enantiocontrol without notable rate retardation (Table 1, entry 10). Finally, lowering the temperature to –10 °C with prolonged reaction time resulted in an almost quantitative formation of **3a** with a satisfactory level of enantiomeric purity (Table 1, entry 12).

The scope of **1c**·Br-catalyzed asymmetric direct α-hydroxylation of 3-substituted oxindoles **2** was explored under the optimized conditions, and the representative results are summarized in Table 2.[16] Generally, 5 mol% of **1c**·Br was sufficient to control the hydroxylation of a range of *N*-Boc oxindoles, giving rise to the corresponding chiral hydroxyoxindoles **3** with uniformly high enantioselectivity. With respect to 3-aryl oxindoles, this protocol tolerated the incorporation of both electron-donating and electron-withdrawing substituents (Table 2, entries 1–5). The reaction with 3-(1-naphthyl)oxindole showed slightly lower conversion (Table 2, entry 6), whereas the product was isolated in excellent yield in the oxidation of **2** having 2-naphthyl substituent (Table 2, entry 7). 3-Alkyl oxindoles also appeared to be suitable nucleophiles, and a similar degree of reactivity and selectivity was observed (Table 2, entries 8–14). Moreover, this catalytic system well accommodated differently 5-substituted 3-phenyloxindoles (Table 2, entries 15–17).

In conclusion, we have developed a catalytic enantioselective α-hydroxylation of 3-substituted oxindoles using aqueous hydrogen peroxide as a terminal oxidant. The judicious use of trichloroacetonitrile and the chiral 1,2,3-triazolium salt for the electrophilic activation of hydrogen peroxide and the stereocontrol of carbon–oxygen bond formation, respectively, allows for the direct asymmetric transfer of hydroxyl group into the α-position of carbonyls. We believe that this operationally simple, yet powerful method will be further applied to the development of synthetically valuable asymmetric hydroxylation reactions.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1558958.

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(16) In the present system, the *N*-Boc group on the oxindole nitrogen seemed crucial for achieving high efficiency and enantioselectivity. For instance, attempted reaction of *N*-4-methoxyphenyl 3-phenyloxindole under identical conditions described in Table 2 afforded the corresponding α-hydroxyoxindole in moderate yield with low enantioselectivity (45% yield, 28% ee).
(17) **Representative Procedure for Catalytic Asymmetric α-Hydroxylation of Oxindoles**
A solution of **1c**·Br (3.76 mg, 0.005 mmol), oxindole **2a** (30.9 mg, 0.10 mmol), and K_2CO_3 (13.8 mg, 0.10 mmol) in Et_2O (1.0 mL) was degassed by alternating vacuum evacuation/argon backfill. Then, the resulting mixture was cooled to –10 °C. To this solution were successively added a 30% aq solution of H_2O_2 (50 µL, 0.50 mmol) and trichloroacetonitirile (10 µL, 0.10 mmol), and the mixture was stirred for 24 h. The reaction was quenched with a sat. aq solution of NH_4Cl, and the extractive workup was performed with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel (hexane–$CHCl_3$ = 3:1 as eluent) to afford **3a** (31.5 mg, 0.097 mmol, 97% yield, 94% ee).
Compound **3a**: $[\alpha]_D^{23}$ = +45.6 (*c* = 3.0, $CHCl_3$) for 94% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (1 H, d, *J* = 8.2 Hz), 7.40 (1 H, td, *J* = 8.0, 1.2 Hz), 7.36–7.29 (6 H, m), 7.20 (1 H, t, *J* = 7.8 Hz), 3.42 (1 H, s), 1.63 (9 H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.0, 149.2, 139.9, 139.8, 130.3, 128.8, 128.7, 125.7, 125.4, 125.2, 115.6, 85.0, 77.8, 28.2, one peak for aromatic carbon was not found probably due to overlapping. IR (film): 3456, 3001, 2978, 1788, 1609, 1479, 1342, 1285, 1146, 908, 719 cm^{-1}. HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{19}NO_4Na^+$ [M + Na]$^+$: 348.1206; found: 348.1206. HPLC (ID3, hexane–*i*-PrOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm): *t* = 15.8 min (major isomer); 17.5 min (minor isomer).

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