Chiral iron complex catalyzed enantioselective oxidation of racemic benzoins†‡

Pandi Muthupandi, Santosh Kumar Alamsetti and Govindasamy Sekar*

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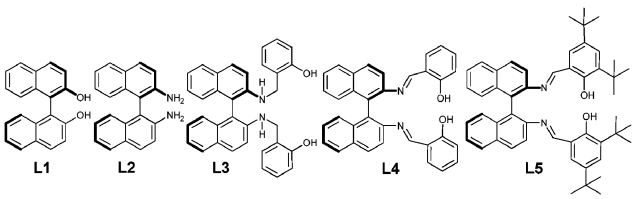
An efficient, economic and environmentally friendly enantioselective oxidation of racemic benzoins (α-hydroxy ketones) catalyzed by a chiral iron complex has been developed using molecular oxygen as a terminal oxidant with good selectivity and excellent enantiomeric excess.

Transition metal complexes play an important role in organic transformations as catalysts.[1] Particularly in the field of asymmetric synthesis, their role in chirality transfer is crucial.[2] However, many of these metal complexes are derived from heavy, rare and expensive metals. Among the chiral metal complexes, the environmentally benign biometals such as zinc, iron and copper have drawn more attention. Apart from being one of the most abundant metals on earth, iron is a non toxic, inexpensive and readily available metal. Thereby it becomes an ideal candidate for catalysis. During the last decades, iron catalysts were used as efficient catalysts for several organic reactions.[3] However, it is relatively under-represented compared to other transition metals such as Pd, Rh, Ru, Ir, Cu *etc*., especially in the field of enantioselective organic synthesis.[4]

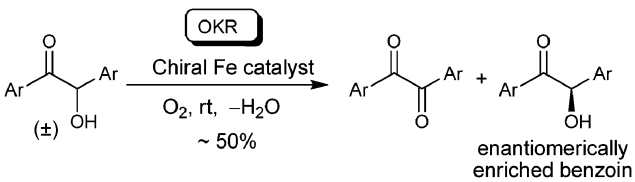


Enantiopure secondary alcohols are key intermediates in the field of asymmetric synthesis, pharmaceutical, agrochemical and fine chemical industries.[5] Although a plethora of methods to synthesize enantiopure alcohols exist, the non-enzymatic kinetic resolution route is particularly attractive and versatile.[6,7] Among the various kinetic resolution techniques, oxidative kinetic resolution offers extraordinary practical advantages such as the use of molecular oxygen as the sole stochiometric oxidant and the formation of water as the only by-product.

The pioneering work by Rychnovsky using a chiral nitroxyl catalyst[8] followed by independent reports of Stoltz[9] and Sigman[10] using a chiral palladium complex have contributed significantly to the field of oxidative kinetic resolution (OKR). Very recently, a chiral vanadium catalyst developed by Toste[11] for the resolution of racemic α-hydroxy esters, a chiral iridium catalyst developed by Ikariya,[12] a chiral manganese catalyst[13] and chiral ruthenium catalysts[14] have also added strength to the field of OKR of secondary alcohols.

As a part of our ongoing research towards the synthesis of enantiopure secondary alcohols by halogenating kinetic resolution using a stoichiometric chiral halogenating agent ((*R*)-BINAP/NCS)[15] and the first chiral copper complex (Galactose Oxidase model) catalyzed alcohol oxidation,[16] our quest is finding an efficient, easily available and environmentally friendly chiral metal catalyst for the synthesis of secondary alcohols through OKR under mild conditions where molecular oxygen will be used as sole oxidant (aerobic oxidation). In this communication for the first time we report our initial findings regarding chiral iron catalyzed oxidative kinetic resolution of racemic benzoins (α-hydroxy ketones) using molecular oxygen as the ultimate oxidant (Scheme 1).

We have started our chiral iron catalyzed asymmetric oxidation with racemic benzoins because of their importance in the pharmaceutical industry[17] and also due to existing difficulties in synthesizing them in an enantiomerically pure form.[18] When simple (±)-benzoin was reacted with 5 mol% of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and 5 mol% of enantiopure (*R*)-BINOL **L1**–$Fe(OAc)_2$ complex in the presence of molecular oxygen at 60 °C, the oxidation took 31 h for 63% conversion (C)[19] and provided 59% of oxidized product benzil. In this asymmetric oxidation reaction, 30% of benzoin was recovered with 9% enantiomeric excess and selectivity $(s)^{20}$ = 1.2 at C = 63% (Table 1, entry 1). (*R*)-BINAM (1,1′-binaphthyl-2,2′-diamine) **L2**–$Fe(OAc)_2$ complex failed to give any selectivity (entry 2) and (*R*)-BINAM derived amino phenol **L3**–$Fe(OAc)_2$ complex provided the asymmetric oxidation with s = 2.9 at C = 30% (entry 3). The corresponding salen ligand[21] **L4**–$Fe(OAc)_2$ complex also provided similar selectivity s = 2.8 at C = 50% with improved *ee* (34%) for the recovered benzoin (entry 4). We thought of increasing the bulkiness of the salen ligand to enhance selectivity. As per our expectation, usage of



Scheme 1 Chiral iron catalyzed OKR of (±)-benzoins.

Department of Chemistry, Indian Institute of Technology Madras, Chennai, 600 036, India. E-mail: gsekar@iitm.ac.in; Fax: +91 44 2257 4202; Tel: +91 44 2257 4229
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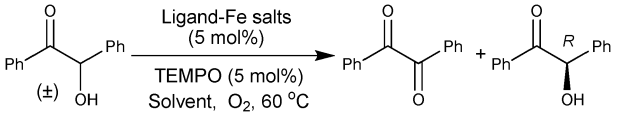
‡ Electronic supplementary information (ESI) available: Typical experimental procedure, spectral data, HPLC data, ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b904021h

Table 1 Effect of ligands, iron salts and solvents on OKR of (±)-benzoins



Entry	Ligand	Fe salt	Solvent	Time	C[a] (%)	% *ee* of benzoin[b]	*s*[c]
1	**L1**	$Fe(OAc)_2$	PhMe	31 h	63.0	9	1.2
2	**L2**	$Fe(OAc)_2$	PhMe	24 h	74.0	0	—
3	**L3**	$Fe(OAc)_2$	PhMe	8 d	30.0	18	2.9
4	**L4**	$Fe(OAc)_2$	PhMe	4 d	50.0	34	2.8
5	**L5**	$Fe(OAc)_2$	PhMe	3 d	68.0	87	6.0
6	**L5**	$FeCl_3$	PhMe	25 h	69.0	10	1.2
7	**L5**	$Fe(acac)_3$	PhMe	30 h	86.0	23	1.3
8	**L5**	$Fe(NO_3)_3{\cdot}9H_2O$	PhMe	3 d	60.0	7	1.1
9	**L5**	$Fe(OAc)_2$	EtOAc	8 d	52.5	26	2.1
10	**L5**	$Fe(OAc)_2$	$CHCl_3$	8 d	47.8	5	1.2
11	**L5**	$Fe(OAc)_2$	THF	33 h	85.7	4	1.0
12	**L5**	$Fe(OAc)_2$	Hexanes	21 h	70.0	91	6.5

[a] Conversion was determined by ^{1}H NMR analysis of crude reaction mixture. [b] % *ee* was determined by HPLC using a Daicel Chiralpak AS-H column. [c] $s = k_{rel}(k_{fast}/k_{slow}) = \ln[(1 - C)(1 - ee)]/\ln(1 - C)(1 + ee)$.

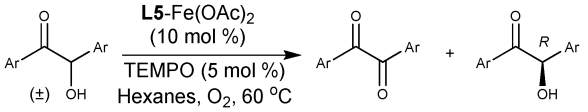
highly sterically hindered salen ligand **L5** with $Fe(OAc)_2$ as catalyst increased the enantiomeric excess of recovered benzoin to 87% and the selectivity was enhanced two-fold (s = 6 at C = 68%, entry 5).

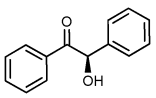
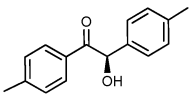
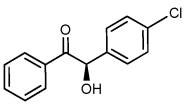
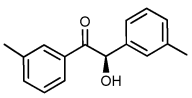
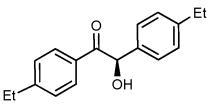
Replacing $Fe(OAc)_2$ with other iron salts such as $FeCl_3$, $Fe(acac)_3$ or $Fe(NO_3)_3{\cdot}9H_2O$ reduced the selectivity drastically to 1.1–1.3 (Table 1, entries 5–8). Screening a wide range of solvents showed that the enantioselectivity (s) of the OKR of (±)-benzoin is highly dependent on the solvent employed (Table 1, entries 5 and 9–12). Although we have not yet been able to correlate enantioselectivity with any single solvent parameter, it is clear that hexane is the solvent of choice as it gave the highest selectivity s = 6.5 with 91% *ee* for recovered benzoin (entry 12).

Then we examined the effect of ratio of ligand **L5** and $Fe(OAc)_2$ in OKR of (±)-benzoin and the results are summarized in Table 2 (entries 1–4). Among the several combinations, 10 mol% of ligand **L5** and 10 mol% of $Fe(OAc)_2$ gave a maximum of 7.2 selectivity at C = 76% with 98% *ee* for the recovered alcohols (entry 4). Reducing the reaction temperature from 60 °C reduces the selectivity of the OKR (entry 4 *vs.* 5 and 6). Asymmetric oxidation without TEMPO took more time and the selectivity also reduced to 6.5 with reduced % *ee* of the recovered benzoin (entry 7). When the oxidation was carried out only with TEMPO and without iron complex it gave only a trace amount of oxidized product benzil and the unreacted benzoin was recovered quantitatively from which we inferred that there was no background reaction merely due to TEMPO.

To probe the scope of the chiral iron catalyst, a wide range of racemic benzoins were oxidized under optimized reaction conditions and the results obtained are summarized in Table 2.§ The asymmetric oxidation of (±)-*m*-methylbenzoin proceeded to 65% conversion after 41 h, providing

Table 2 OKR of (±)-benzoins catalyzed by chiral iron complex



				Recovered benzoins		
Entry	Benzoins	Time/h	C (%)[a]	Yield (%)[b]	*ee* (%)[c]	*s*
1		27	79	20 (96)	82	3.4[d]
2		27	73.0	24 (93)	84	4.5[e]
3		21	70.0	26 (91)	91	6.5[f]
4		**25**	**76.0**	**21 (94)**	**98**	**7.2**
5		64	59.3	33 (89)	60	3.8[g]
6		44	73.4	24 (93)	70	3.2[h]
7		50	56.0	42 (95)	68	6.5[i]
8		29	66.0	32 (95)	90	7.7
9		32	67.0	31 (97)	94	8.8
10		41	65.0	33 (96)	95	10.6
11		52	72.0	26 (96)	94	6.7

[a] Conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of enantiomerically enriched benzoins; numbers in parentheses are the combined yield of recovered benzoin and benzyl. [c] The % *ee* was determined by HPLC using a Daicel Chiralpak AS-H column. [d] 2.5 mol% of $Fe(OAc)_2$, 2.5 mol% of **L5** used. [e] 2.5 mol% of $Fe(OAc)_2$, 5 mol% of **L5** used. [f] 5 mol% of $Fe(OAc)_2$, 5 mol% of **L5** used. [g] Reaction at 40 °C. [h] Reaction at 50 °C. [i] Without TEMPO.

(*R*)-*m*-methylbenzoin in 33% isolated yield and 95% *ee* with 10.6 selectivity (Table 2, entry 10). Importantly, benzoin derivatives bearing an electron-donating group at *para*-(entries 8 and 11) and *meta*-positions (entry 10) and electron-withdrawing constituents at *para*-positions are well tolerated (entry 9). All the benzoins were oxidized at 60 °C itself and we recovered the unreacted benzoins with good selectivity (s = 6.7–10.6) and excellent enantiomeric excess (90–98% *ee*). In all the examples, the (*S*)-enantiomers of racemate benzoins were oxidized to corresponding benzils and the slow reacting (*R*)-enantiomers were recovered in highly enantiomerically enriched form.[22] Enantiomeric excess (% *ee*) of recovered benzoins were determined by HPLC on a chiral stationary phase (see ESI for full details‡).

In summary, we have developed an efficient, economic and environmentally friendly asymmetric oxidative reaction catalyzed by chiral iron complex using molecular oxygen as the stoichiometric oxidant. To the best of our knowledge, this is the first report in the literature for chiral iron catalyzed

oxidative kinetic resolution of secondary alcohols. The mild reaction conditions of the catalytic system provide access to a wide range of benzoins (α-hydroxy ketones) in good selectivity (s = 6.7–10.6) and excellent enantiomeric excess (90–98% *ee*). This method is very versatile in that the sole by-product accompanying the oxidation process is water, making our system more eco-friendly and green as well. Efforts are currently underway to provide a detailed mechanistic insight into the catalytic cycle to expand the scope and synthetic utility of the enantioselective oxidation.

Notes and references

§ *Typical experimental procedure for OKR:* A mixture of **L5** (35.8 mg, 0.05 mmol) and iron(II)acetate (8.7 mg, 0.05 mmol) in 8 mL of hexanes was taken in a reaction tube and stirred at room temperature for 10 min, then TEMPO (3.9 mg, 0.025 mmol) was added to the reaction mixture. After stirring for 5 min, benzoin (106 mg, 0.5 mmol) was added and then the reaction mixture was stirred under an O_2 atmosphere (using an O_2 balloon) at 60 °C for 25 h. The reaction mixture was concentrated and the resulting residue was purified by silica gel column chromatography (eluents: hexanes–ethyl acetate) to give the benzil (77 mg, yield 73%) and recovered benzoin (22 mg, yield 21%). *Benzoin:* R_f 0.23 (hexanes–ethyl acetate, 90 : 10 v/v); $[\alpha]^{D}_{25}$ = −76.0 (c = 1 in acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.93 (m, 2H), 7.48–7.53 (m, 1H), 7.23–7.41 (m, 7H), 5.95 (d, J = 6 Hz, 1H), 4.55 (d, J = 6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 139.2, 134.0, 133.7, 129.3, 129.2, 128.8, 128.7, 127.9, 76.4; IR (neat) 3418, 1679, 1261, 1068 cm^{-1}; HRMS (m/z): $[MNa]^+$ calcd for $C_{14}H_{12}O_2Na_1$, 235.0735; found, 235.0727. The enantiomeric excess (% *ee*) was determined to be 98% by HPLC using a Daicel ChiralPAK AS-H column (15% *i*-PrOH–hexanes, 1 mL min^{-1}, 220 nm): t_R (major, 13.250 min), t_R (minor, 8.500 min). *Benzil:* R_f 0.43 (hexanes–ethyl acetate, 90 : 10 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–8.01 (m, 4H), 7.63–7.69 (m, 2H), 7.49–7.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 135.0, 133.3, 130.1, 129.2; IR (neat): 3064, 1656 cm^{-1}; HRMS (m/z): $[MNa]^+$ calcd for $C_{14}H_{10}O_2Na_1$, 233.0578; found, 233.0585.

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20 The selectivity factor (s) was determined using the equation $s = k_{rel}(k_{fast}/k_{slow}) = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion. See ESI for full details‡.

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