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Unprecedented Halide Dependence on Catalytic Asymmetric Hydrogenation of 2-Aryl- and 2-Alkyl-Substituted Quinolinium Salts by Using Ir Complexes with Difluorphos and Halide Ligands

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Asymmetric hydrogenation by using chiral transition-metal complexes represents one of the cleanest and most environmentally benign processes available for producing optically pure organic compounds.[1] Currently, a wide variety of chiral compounds with outstanding levels of enantioselectivity has been synthesized by reduction of C=C,[1] C=O,[2,3] C=N,[4–6] and, more recently, heteroaromatics compounds.[7–18] Among heteroaromatics, 2-substituted quinolines have been targeted[9–18] because optically active 2-substituted-1,2,3,4-tetrahydroquinoline derivatives are key components of many bioactive natural products and drugs.[19] In contrast with the successful asymmetric hydrogenation of 2-alkyl-substituted quinolines catalyzed by chiral iridium complexes with an iodide source or iodine,[9–13] which dramatically enhances both catalytic activity and enantioselectivity,[5,9a] only limited success has been achieved in the catalytic hydrogenation of 2-aryl-substituted quinolines. So far, the only known examples used 2-phenylquinoline as a unique model substrate. The first example of catalytic hydrogenation of 2-phenylquinoline (72% *ee* (enantiomeric excess)), described by Zhou and co-workers,[9a] is based on an $[Ir(cod)Cl]_2$/MeO-biphep/I_2 (cod = 1,5-cyclooctadiene; MeO-biphep = 6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl) catalytic system that was recently improved to 80% *ee* with a moderate yield of 41% by using benzyl chloroformate as an activating agent, although this required an additional deprotection step on the resulting carbamate.[18] In recent years, only a few examples of the catalytic hydrogenation of 2-phenylquinoline have been reported with *ee* values up to 88%.[14] We describe herein a highly enantioselective hydrogenation of the HX salts (X = Cl, Br, and I) of various 2-aryl-substituted quinolines by using cationic dinuclear iridium complexes[6,17] with [(4,4′-bi-2,2-difluoro-1,3-benzodioxole)-5,5′-diyl]bis(diphenylphosphine) (difluorphos),[20] which demonstrates an unexpected halide effect in which iridium complexes with chloro and bromo ligands serve as better catalysts than an iodo–iridium complex. The present catalyst was also effective for the hydrogenation of 2-alkyl-substituted quinolinium salts, which shows the high versatility of this new catalyst system. Furthermore, this system was applied to a formal asymmetric synthesis of selective estrogen receptor modulator (SERM) 6-hydroxy-2-(4-hydroxyphenyl)-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-benzyl}-1,2,3,4-tetrahydroquinoline (**1**)[21] by asymmetric hydrogenation of the HCl salt of 6-methoxy-2-(4-methoxyphenyl)quinoline (**2**·Cl) as a key step.

We recently developed cationic dinuclear triply halogen-bridged iridium complexes $[\{Ir[(S)\text{-diphosphine}](H)\}_2(\mu\text{-}X)_3]X$ (**3**–**8**; X = Cl, Br, and I) (Figure 1), which were conveniently prepared by adding excess aqueous HX to a mixture of $[\{IrCl(coe)_2\}_2]$ (coe = cyclooctene) and the required chiral diphosphine ligand in toluene at room temperature.[6,22] Thus, we first examined the asymmetric hydrogenation of 2-phenylquinolinium salts **9**·X (X = Cl, Br, and I) promoted by Ir–binap complex (*S*)-**3**·X. Each reaction was conducted at 30 °C under hydrogen (30 bar) with 2 mol% of Ir complex in THF followed by a basic workup (Table 1, en-

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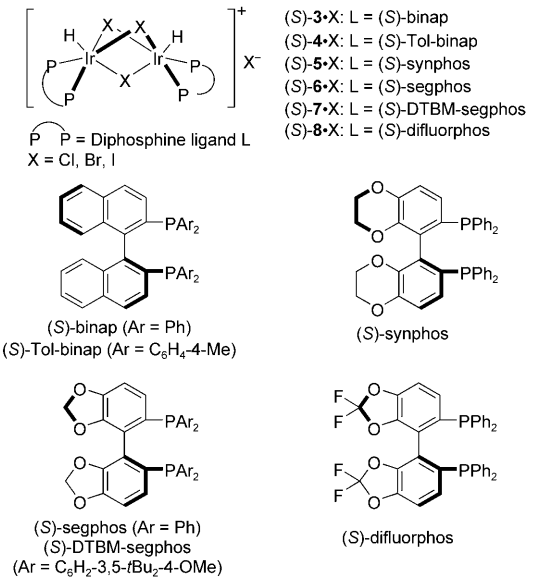
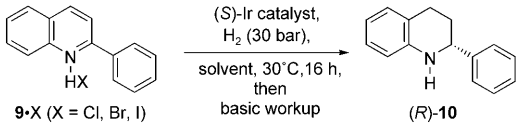


Figure 1. Cationic dinuclear Ir^{III} complexes $[\{Ir[(S)\text{-diphosphine}](H)\}_2(\mu\text{-}X)_3]X$ (**3**–**8**) and chiral diphosphine ligands used as catalysts for asymmetric hydrogenation; binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, segphos = [(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis(diphenylphosphine) synphos = [2,2′,3,3′-tetrahydro(5,5′-bi-1,4-benzodioxin)-6,6′-diyl]bis(diphenylphosphine).

Table 1. Optimization of the hydrogenation conditions with 2-phenylquinolinium salts **9**•X.[a]



Entry	Catalyst	X	Solvent	Conv.[b] [%]	*ee*[c] [%]
1	(*S*)-**3**•Cl	Cl	THF	>95	72
2	(*S*)-**3**•Br	Br	THF	95	71
3	(*S*)-**3**•I	I	THF	76	14
4	(*S*)-**3**•Cl	Cl	toluene	66	72
5	(*S*)-**3**•Cl	Cl	CH_2Cl_2	64	69
6	(*S*)-**3**•Cl	Cl	dioxane	67	68
7	(*S*)-**3**•Cl	Cl	MeOH	44	39
8	(*S*)-**3**•Cl	Cl	dioxane/MeOH[d]	>95	73
9	(*S*)-**4**•Cl	Cl	dioxane/MeOH[d]	43	68
10	(*S*)-**5**•Cl	Cl	dioxane/MeOH[d]	62	78
11	(*S*)-**6**•Cl	Cl	dioxane/MeOH[d]	>95	79
12	(*S*)-**7**•Cl	Cl	dioxane/MeOH[d]	52	24
13	(*S*)-**8**•Cl	Cl	dioxane/MeOH[d]	38	91
14	(*S*)-**8**•Br	Br	dioxane/MeOH[d]	>95	91
15	(*S*)-**8**•I	I	dioxane/MeOH[d]	46	71
16	(*S*)-**8**•Br	Cl	dioxane/MeOH[d]	>95	91
17	(*S*)-**8**•Cl	Br	dioxane/MeOH[d]	30	84

[a] Reaction conditions: quinolinium salt (0.22 mmol), Ir complex (4.4 μmol), H_2 (30 bar), solvent (3 mL) at 30°C for 16 h. [b] Conversion of **9**•X was determined by ^1H NMR analysis. [c] The *ee* of **10** was determined by HPLC analysis. The absolute configuration of **10** was (*R*).[23] [d] The ratio of dioxane and MeOH was 9:1 (v/v).

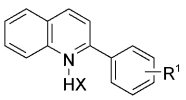
tries 1–3). This preliminary catalyst screening demonstrated that hydrogenation of HCl salt **9**•Cl catalyzed by (*S*)-**3**•Cl gave compound (*R*)-**10** in excellent conversion with a promising 72% *ee* (Table 1, entry 1). A comparable result was obtained when catalyst (*S*)-**3**•Br was used in combination with HBr salt **9**•Br (Table 1, entry 2; 95% conv., 71% *ee*), whereas catalyst (*S*)-**3**•I showed poor catalytic activity in terms of both conversion and selectivity with HI salt **9**•I (Table 1, entry 3; 76% conv., 14% *ee*). This surprising halogen dependence is in striking contrast to the previously reported finding that iodo–iridium complexes have superior catalytic activity and enantioselectivity for the asymmetric hydrogenation of imines[5] and 2-alkylquinolines.[8a] At this stage, we focused our attention on the effect of the solvent and the ligand. Screening of toluene, dichloromethane, dioxane, methanol, and a dioxane/methanol mixture as the hydrogenation solvent for the reaction of **9**•Cl with (*S*)-**3**•Cl indicated that the dioxane/methanol (9:1) mixture provided the best enantioselectivity and catalytic activity (Table 1, entry 8; >95% conv., 73% *ee*), whereas the catalytic activities and enantioselectivities conducted in dioxane (Table 1, entry 6; 67% conv., 68% *ee*) and methanol (Table 1, entry 7; 44% conv., 39% *ee*) were not as good. Despite the fact that reactions in THF and toluene produced (*R*)-**10** in the same enantioselectivity, we chose the dioxane/methanol (9:1) mixture to increase the solubility of **9**•Cl. For the chiral ligand, chloro dinuclear iridium complexes (*S*)-**4**–**8** (X = Cl) with different chiral diphosphine ligands were tested as catalysts for the hydrogenation of **9**•Cl (Table 1, entries 9–13). Among them, chloro complex (*S*)-**8**•Cl with the (*S*)-difluorphos ligand was the best in terms of enantioselectivity, producing 2-phenyl-1,2,3,4-tetrahydroquinoline (*R*)-**10** in 91% *ee* with 38% conversion (Table 1, entry 13). Pleasingly, we found that the corresponding bromo complex, (*S*)-**8**•Br, had better catalytic activity and the same enantioselectivity for HBr salt **9**•Br (Table 1, entry 14; >95% conv., 91% *ee*). Consistent with the results of binap catalysts, the asymmetric hydrogenation of HI salt **9**•I by using iodo complex (*S*)-**8**•I resulted in a lower conversion and enantioselectivity (Table 1, entry 15; 46% conv., 71% *ee*). Moreover, bromo complex (*S*)-**8**•Br catalyzed the reaction of HCl salt **9**•Cl (Table 1, entry 16) with the same catalytic activity and enantioselectivity as that of (*S*)-**8**•Br for **9**•Br (Table 1, entry 14). Interestingly, the opposite combination, chloro complex (*S*)-**8**•Cl and HBr salt **9**•Br (Table 1, entry 17) gave comparable results in terms of conversion to those obtained with (*S*)-**8**•Cl and HCl salt **9**•Cl (Table 1, entry 13). These results suggests that original halogen ligand X of iridium complex **9**•X remains in a catalytically active Ir^{III}•X complex and almost no halogen ligand exchange takes place even in the presence of excess amounts of a different halogen anion, which makes it possible to use less expensive and more readily accessible HCl salts as the substrate even for the reaction of (*S*)-**8**•Br. In contrast to the asymmetric hydrogenation of quinolinium salts, the asymmetric hydrogenation of 2-phenylquinoline by using the difluorphos catalysts (*S*)-**8**•X (X = Cl, Br, and I) gave (*R*)-**10** with lower enantioselectivities (83, 82, and 70% *ee*, respectively),[23] which indicates that the formation of quinolinium salts prior to the reduction of quinoline derivatives has synthetic merit in that it increases

enantioselectivity. DFT calculations with the B3LYP hybrid density functional theory of Ir–diphosphine complexes revealed dihedral angles (θ) of Ir–difluorphos (69.1°) < Ir–segphos (71.1°) < Ir–synphos (72.6°) < Ir–binap (73.6°).[23] As previously observed in ruthenium-promoted asymmetric hydrogenation by our group[20] and others,[24] ligands with narrower dihedral angles tend to provide higher enantioselectivities because the narrower θ should cause a higher ligand–substrate interaction and provide a better chiral discrimination of the catalyst.

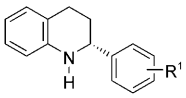
With the optimized reaction conditions and Ir–difluorphos complexes (*S*)-**8**·Cl and (*S*)-**8**·Br in hand, a range of 2-arylquinolinium salts was reduced to the corresponding tetrahydroquinolines in high chemical yield and good-to-excellent enantiomeric excess. The HCl and/or HBr salts of various *para*-, *meta*-, and *ortho*-substituted phenyl derivatives of quinolinium salts **11**–**18** were used as substrates, and representative results are given in Table 2.[23] *para*-Substituted quinolinium salts **11**–**14** were consistently hydrogenated to give the corresponding tetrahydroquinolines (*R*)-**19**–**22** with 95–88% *ee*. In a similar way, the hydrogenation of *meta*-substituted derivatives **15** and **16** gave (*R*)-**23** (90% *ee*) and (*R*)-**24** (82% *ee*), respectively. *ortho*-Substituted derivatives (*R*)-**17** and (*R*)-**18** resulted in lower enantioselectivities (Table 2, entries 7 and 8) compared with the corresponding *meta*- and *para*-substituted derivatives. Bulkiness due to the *ortho*-Me and *ortho*-OMe substituents reduced their enantioselectivities. This experimental evidence for a nonchelating mechanism, as opposed to chelation of the substrates to the metal center in most of the successful asymmetric hydrogenations or hydrogen-transfer reactions of the functionalized ketones and related substrates,[2a,f,g,3,24,25] suggests that coordinatively unsaturated species with the empirical formula of Ir(chelate diphosphine)(H)X_2, derived from the dinuclear complexes, are pentacoordinated and the iminium moiety of the substrates coordinates in a η^2 fashion to the vacant site, as observed for the iridium–binap–P–N system that catalyzed a highly enantioselective asymmetric hydrogenation of simple ketones.[26] To our delight, the present catalyst system was also highly effective for the reaction of 2-alkyl-substituted quinolinium salts **27**–**29** (Table 2, entries 9–11). The reaction of the HBr salt of 2-methylquinoline, **27**·Br, proceeded with higher enantioselectivity (Table 2, entry 9, 94% *ee*) than our original conditions (2-methylquinoline, [Ir{(*S*)-difluorophos}(H)(O_2CMe)]/HBr, 90% *ee*),[17] which again shows advantage of using the quinolinium salt. Substrates with ethyl (Table 2, entry 10) and isopropyl (Table 2, entry 11) substituents were also hydrogenated with the same efficiency to (*S*)-**31** and (*R*)-**32** with *ee* values up to 95%.

These results prompted us to reduce substrate **2**·Cl using Ir-difluorphos (*S*)-**8**·Br as a key step for synthesizing optically active **1** (Scheme 1).[21] The catalytic hydrogenation of the

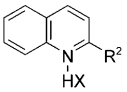
Table 2. Asymmetric hydrogenation of 2-arylquinolinium salts **11**–**18** and 2-alkylquinolinium salts **27**-**29** catalyzed by Ir-difluorphos complexes (*S*)-**8**·Cl or (*S*)-**8**·Br.[a]



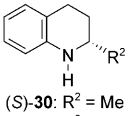
11·X: R^1 = 4-OMe
12·X: R^1 = 4-Me
13·X: R^1 = 4-*i*Pr
14·X: R^1 = 4-CF_3
15·X: R^1 = 3-OMe
16·X: R^1 = 3-Me
17·X: R^1 = 2-OMe
18·X: R^1 = 2-Me



(*R*)-**19**: R^1 = 4-OMe
(*R*)-**20**: R^1 = 4-Me
(*R*)-**21**: R^1 = 4-*i*Pr
(*R*)-**22**: R^1 = 4-CF_3
(*R*)-**23**: R^1 = 3-OMe
(*R*)-**24**: R^1 = 3-Me
(*R*)-**25**: R^1 = 2-OMe
(*R*)-**26**: R^1 = 2-Me



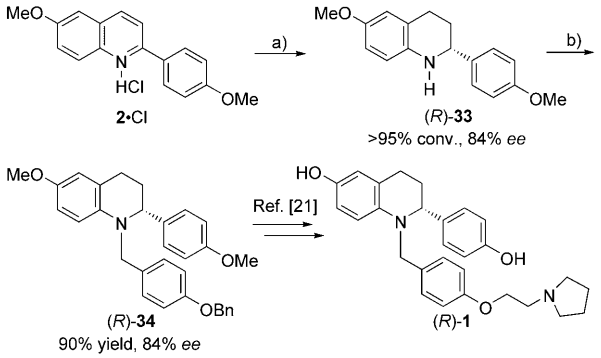
27·X: R^2 = Me
28·X: R^2 = Et
29·X: R^2 = *i*Pr



(*S*)-**30**: R^2 = Me
(*S*)-**31**: R^2 = Et
(*R*)-**32**: R^2 = *i*Pr

Entry	Substrate	Catalyst	Product[b]	*ee*[c] [%], abs. config.
1	**11**·Br	(*S*)-**8**·Br	**19**[d]	95, (*R*)
2	**12**·Cl	(*S*)-**8**·Cl	**20**	90, (*R*)
3	**13**·Cl	(*S*)-**8**·Cl	**21**	89, (*R*)
4	**14**·Cl	(*S*)-**8**·Cl	**22**	88, (*R*)
5	**15**·Cl	(*S*)-**8**·Cl	**23**	90, (*R*)
6	**16**·Cl	(*S*)-**8**·Cl	**24**	82, (*R*)
7	**17**·Cl	(*S*)-**8**·Cl	**25**	62, (*R*)
8	**18**·Br	(*S*)-**8**·Br	**26**	86, (*R*)
9	**27**·Br	(*S*)-**8**·Br	**30**[d]	94, (*S*)
10	**28**·Cl	(*S*)-**8**·Cl	**31**[d]	93, (*S*)
11	**29**·Cl	(*S*)-**8**·Cl	**32**[d]	95, (*R*)

[a] Reaction conditions: substrate (0.22 mmol), Ir complex (4.4 μmol), H_2 (30 bar), 1,4-dioxane/MeOH (3 mL; 9:1 v/v) at 30°C for 16 h. [b] Conversions of substrates **12**–**18** were determined by ^{1}H NMR analysis (over 95%). [c] The *ee* values of the products were determined by HPLC analysis.[23] [d] Conversions of **11**·Br, **27**·Br, **28**·Br, and **29**·Br were 65, 81, 81, and 84%, respectively.



Scheme 1. Formal asymmetric synthesis of bioactive compound **1**. Reagents and conditions: a) (*S*)-**8**·Br (2 mol%), dioxane/MeOH (7:3 v/v), 40°C, H_2 (30 bar), 30 h, then basic workup; b) 1-(benzyloxy)-4-(chloromethyl)benzene, BuLi, THF, −78°C, 18 h.

HCl salt **2**·Cl and following basic workup gave 6-methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolinium salt (*R*)-**33** (>95% conv., 84% *ee*). Alkylation of the nitrogen atom by the reaction of BuLi and 1-(benzyloxy)-4-(chloromethyl)-benzene in THF gave (*R*)-**34** without loss of enantiomeric purity (90% yield, 84% *ee*). The synthetic route from (*R*)-**34** to (*R*)-**1** was reported by Wallace et al.[21] Thus, the

formal asymmetric synthesis of bioactive compound (*R*)-**1** was accomplished.

In conclusion, we have developed the first highly enantioselective hydrogenation of 2-arylquinolinium salts by using cationic dinuclear iridium(III) halide complexes with difluorphos and some atropisomeric chiral diphosphine ligands as catalyst precursors. The resulting *ee* values of up to 95% are much better than those of the reduction of the corresponding 2-arylquinolines.[23,27] Moreover, this new catalyst system also successfully converted 2-alkylquinolinium salts to the corresponding tetrahydroquinolines with excellent enantioselectivities (up to 95% *ee*). A notable feature of this catalysis is the unexpected superiority of chloro– and bromo–iridium catalysts over the corresponding iodo–iridium catalyst, which is opposite to the halide effect. As an application of our new catalyst system, we demonstrated an efficient access to the optically active 6-hydroxy-2-(4-hydroxyphenyl)-1-(4-(2-(pyrrolidin-1-yl)ethoxy)-benzyl)-1,2,3,4-tetrahydroquinoline (**1**).

Experimental Section

General procedure for the Ir-catalyzed asymmetric hydrogenation of 2-arylquinolinium salts: 2-phenylquinolinium HBr salt **9**·Br (63.4 mg, 0.22 mmol) and Ir–difluorphos complex (*S*)-**8**·Br (9.2 mg, 4.4 μmol, 2 mol%) were placed in a glass tube and 1,4-dioxane/MeOH (9:1 v/v, 3 mL) was added under argon. The reaction mixture was then stirred under 30 bar of H_2 at 30°C for 16 h. After removal of H_2 and treatment with aqueous NaOH (2 M), the reaction mixture was extracted with ether and the organic layer was concentrated. The conversions were determined by ^{1}H NMR spectroscopic analysis of the crude product. The enantiomeric excesses of the products were determined by HPLC analysis of the crude product (Chiralcel OD-H, eluent: hexane/*i*PrOH (90:10), detector: 254 nm, flow rate: 1 mL min^{-1}, (*S*)-(−) t_R = 9.5 min, (*R*)-(+) t_R = 11.0 min). The crude product was purified by using silica gel column chromatography with hexane/EtOAc (9:1) as the eluent to quantitatively give (*R*)-2-phenyl-1,2,3,4-tetrahydroquinoline (*R*)-**10** (91% *ee*) as a colorless oil.

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Keywords: asymmetric synthesis · enantioselectivity · hydrogenation · iridium · quinolines

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