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Chiral cyclometalated iridium complexes for asymmetric reduction reactions†

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A series of chiral cyclometalated iridium complexes have been synthesised by cyclometalating chiral 2-aryl-oxazoline and imidazoline ligands with $[Cp^*IrCl_2]_2$. These iridacycles were studied for asymmetric transfer hydrogenation reactions with formic acid as the hydrogen source and were found to display various activities and enantioselectivities, with the most effective ones affording up to 63% ee in the asymmetric reductive amination of ketones and 77% ee in the reduction of pyridinium ions.

1. Introduction

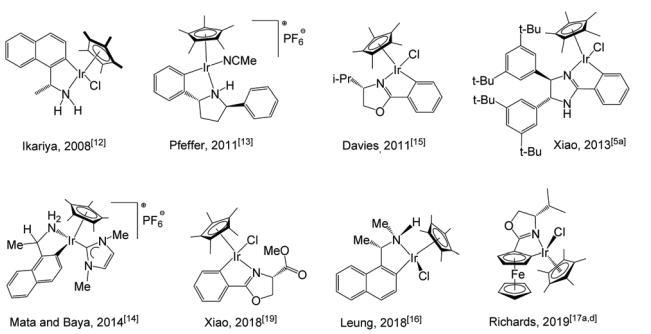
Cyclometalated Cp*-iridium complexes, or iridacycles, are easily accessible *via* base-assisted C–H activation. A number of such complexes have been documented both within our group[1] as well as by others with various applications.[2] Examples of their use as catalysts are seen in hydrogenation,[3] transfer hydrogenation,[4] dehydrogenation,[5] reductive amination,[6] alkylation,[7] hydrosilylation,[8] racemisation,[9] hydroamination[10] and aerobic oxidation.[11] However, most of these complexes are achiral, and the number of reported chiral iridacycles and their applications in asymmetric catalysis is much smaller.

Chiral iridacycle complexes have been sporadically reported over the past years. Selected examples are shown in Scheme 1. Ikariya *et al.* reported the use of chiral Cp*Ir(C–N) complexes[12] for asymmetric transfer hydrogenation (ATH) of acetophenone, yielding (*S*)-1-phenylethanol in over 90% yield with up to 66% ee. Pfeffer and de Vries *et al.* reported cyclometalated amino and imidazoline complexes;[13] the latter was used for ATH of acetophenone and *N*-phenyl-(1-phenylethylidene)amine, showing moderate to high yields with low enantioselectivities up to 19% ee.[13a] Baya *et al.* also reported the use of cyclometalated iridium complexes for ATH of ketones, affording low to moderate enantioselectivities (up to 58% ee).[14] Davies *et al.* synthesised iridacycles bearing a chiral oxazoline ligand.[15] Leung *et al.* carried out ATH of acetophenone with chiral iridacycles, providing up to 69% ee at −30 °C.[16] In recent years, the group of Richards have reported a series of planar chiral iridacycles bearing ferrocene-type ligands, although their application in asymmetric catalysis has rarely been seen.[17] More recently, novel chiral iridacycles have been reported by the groups of de la Torre, Sierra and Cramer.[18] Our group reported iridium complexes bearing N,O- and N,C-chelating oxazoline ligands for ATH of aromatic ketones; however, the cyclometalated N,C-complex was much less active and enantioselective (up to 7% ee) than the N,O-chelated complex (up to 99% ee).[19] In continuation of our study into iridacycles, we have synthesised a range of chiral iridium catalysts and examined their ability in direct asymmetric reductive amination (DARA) of ketones and reduction of pyridiniums *via* ATH. Reported herein is the results of these studies.

2. Results and discussion

2.1. Synthesis of chiral iridacycles

Base-promoted cyclometallation has been widely studied.[15,20] The reaction typically involves C–H bond activation of a chiral



Scheme 1 Examples of chiral iridacycles from the literature.

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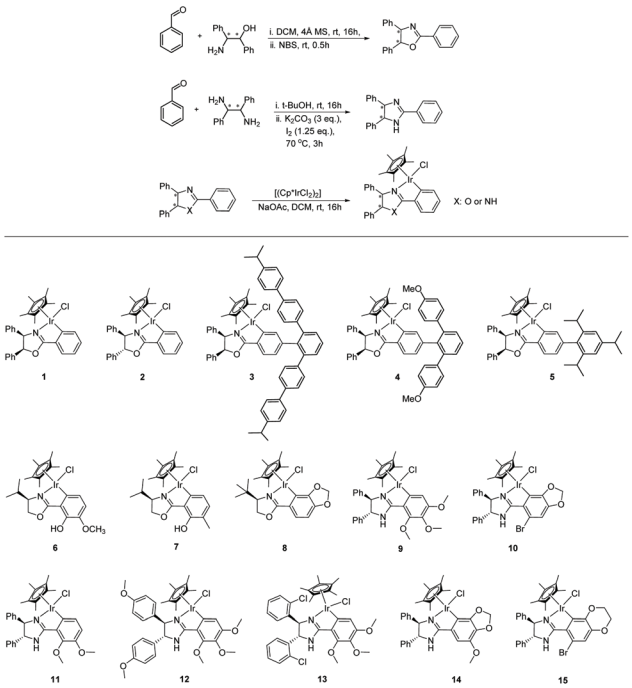


Scheme 2 Synthesis of oxazoline and imidazoline ligands and related chiral iridacycles.

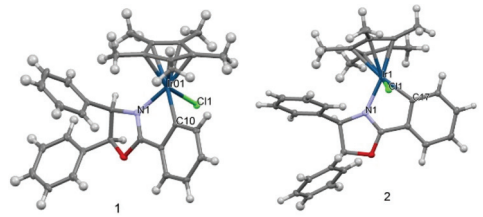


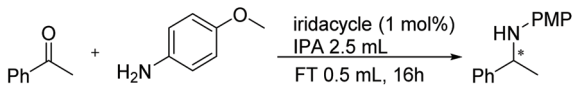
Fig. 1 Molecular structures of **1** and **2** determined by single crystal X-ray diffraction. For **1**: selected bond distances (Å): Ir1–Cl1 2.402(1), Ir1–N1 2.084(2), Ir1–C10 2.052(3). Selected bond angles (°): Cl1–Ir1–N1 85.1(1), Cl1–Ir1–C10 83.2(1), N1–Ir1–C10 77.4(2). For **2**: selected bond distances (Å): Ir1–Cl1 2.4056(6), Ir1–N1 2.101(2), Ir1–C17 2.062. Selected bond angles (°): Cl1–Ir1–N1 86.57(5), Cl1–Ir1–C17 84.18, N1–Ir1–C17 77.48(8).

ligand with an iridium precursor to form the cyclometalated structure. In 1998, Beck *et al.*[20b] reported iridacycles being produced from the reaction of $[Cp^*IrCl_2]_2$ with substituted 2-phenyl-4-*R*-5(4*H*)-oxazolones in the presence of NaOAc. In 2003, Davies[20c] carried out similar cyclometalation of nitrogen-containing ligands with $[Cp^*IrCl_2]_2$, $[Cp^*RhCl_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$, revealing the assisting role of the acetate. In most subsequent studies, a similar strategy has been deployed.

To access the chiral iridacycles in this study, a range of ligands consisting of chiral oxazoline and imidazoline motifs were prepared. These were easily accessible from the reaction between a benzaldehyde derivative and a chiral amino alcohol or diamine, using reported methods (Scheme 2).[21] The subsequent cyclometalation of the iridium precursor $[Cp^*IrCl_2]_2$ with the chiral oxazoline and imidazoline ligands generally occurred under mild conditions, affording the chiral iridacycles **1–15** (Scheme 2). However, more forcing conditions were required for some iridacycles, *e.g.* **4**, likely due to the increased steric hindrance in the ligands.

The formation of the iridacycles was confirmed by NMR and HRMS analysis and by X-ray diffraction in the case of complexes **1** and **2**. Chelation of the ligands onto iridium introduces chirality at the metal centre. However, the iridacycles are formed generally as a mixture of two diastereoisomers, presumably due to the small difference between their thermodynamic stability, as has been observed in analogous cases.[13,20c] For example, **1** and **2** exist as a 2 : 1 and 1 : 1 mixture, respectively, in chloroform. The X-Ray diffraction structures of **1** and **2** (Fig. 1) were obtained from single crystals by diffusing *n*-hexane into a dichloromethane solution of the complexes. As expected, piano-stool style geometries are observed for both complexes. The structure of **1**, which bears the *cis*- or (*S*,*R*)-oxazoline ligand, features a *S*-configured iridium centre in the solid state. In contrast, the iridium centre of **2**, which bears the *trans*- or (*R*,*R*)-oxazoline ligand, is *R*-configured. The bond distances involving the iridium show no notable difference between the two complexes except for a slightly longer Ir–N distance in **2** and are in the expected range. A CH/π interaction appears present between the methyl

Table 1 Screening of iridacycles for DARA



Entry	İridacycle	Conv. (%)	ee (%)	Entry	İridacycle	Conv. (%)	ee (%)
1	**1**	68	23	9	**9**	78	56
2	**2**	83	14	**10**[a]	**9**	**92**	**56**
3	**3**	62	10	11	**10**	72	50
4	**4**	60	0	12	**11**	75	42
5	**5**	95	25	13	**12**	78	21
6	**6**	50	30	14	**13**	75	39
7	**7**	50	17	15	**14**	65	43
8	**8**	80	30	16	**15**	75	43

Reaction conditions: 0.5 mmol acetophenone, 0.6 mmol *p*-methoxy aniline, 1 mol% iridacycle, 2.5 mL anhydrous IPA, 0.5 mL FT, sealed in air, ambient temperature; PMP: *p*-methoxyphenyl. The product is of *R* configuration. [a] Optimization at 23 °C.

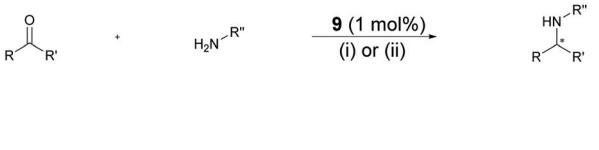
of the Cp* ring and the phenyl ring from the oxazoline. For example, in **1**, the distance between a Cp* hydrogen and the closest hydrogen on the phenyl ring is only 2.640 Å.

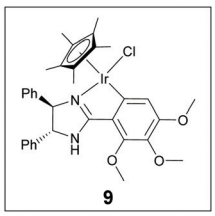
2.2. Asymmetric reductive amination of ketones

Chiral amines have received considerable attention in fine chemical and pharmaceutical applications.[22] DARA represents a convenient pathway for their synthesis and can be accomplished through metal-catalysed, organocatalytic or biocatalytic approaches, using a range of hydrogen sources.[22c,23] Among them, DARA reactions utilising hydrogen gas have been the most widely reported,[24] whilst ATH systems,[25] exploiting other hydrogen sources, have remained underdeveloped. DARA *via* transfer hydrogenation is, however, highly appealing, as it is likely to be easier and safer in operation than using hydrogen gas.

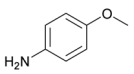
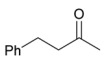
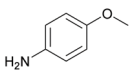
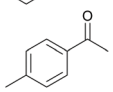
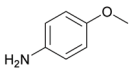
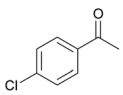
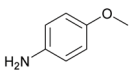
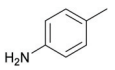
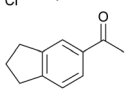
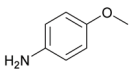
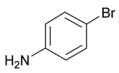
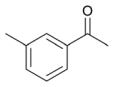
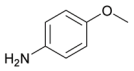
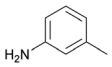
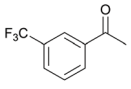
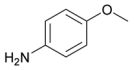
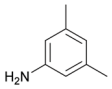
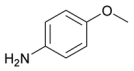
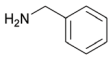
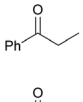
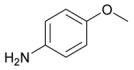
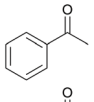
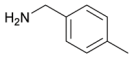
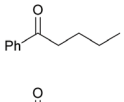
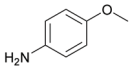
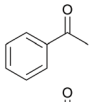
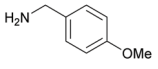
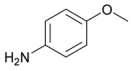
Iridacycles **1–15** were initially screened for the DARA of acetophenone with *p*-methoxyaniline in isopropanol (IPA), using formic acid as the hydrogen source in the form of formic acid-triethylamine azeotrope (FT) (Table 1). All the complexes showed good to high catalytic activities; however, the enantioselectivities varied considerably, ranging from 0 to 56% ee. There appears to be little correlation between the ee's and the ligand structure in general, partially due to the diversity of the ligand structures. Of those screened, complex **9**, a 3,4,5-trimethoxy imidazoline iridicycle, yielded the highest enantio-

Table 2 DARA of ketones with amines catalyzed by **9**[a]





9

Entry	Ketone	Amine	Yield[d] (%)	ee[e] (%)	Entry	Ketone	Amine	Yield[d] (%)	ee[e] (%)
1			90	56	11			97 97[b]	0 5[b]
2			95	50	12			37 82[c]	53 48[c]
3			94 80[b]	54 48[b]	13			37 84[c]	55 53[c]
4			80	54	14			8 42[c]	52 54[c]
5			96	56	15			47	53
6			95	56	16			50 65[c]	62 60[c]
7			88	34	17			80 97[c]	16 10[c]
8			88	63	18			66 94[c]	14 16[c]
9			75 84[c]	38 36[c]	19			77 93[c]	17 22[c]
10			38 76[c]	63 59[c]	20			90 93[c]	10 2[c]

[a] Reaction conditions (unless otherwise stated) (i): 0.5 mmol ketone, 0.6 mmol amine, 1 mol% **9**, 2.5 ml anhydrous IPA, 0.5 mL FT, sealed in air, 16 h. We assume the products to be of the same configuration, *i.e. R.* [b] Reaction conditions (ii): 0.5 mmol ketone, 0.6 mmol amine, 1 mol% **9**, 3 mL HCO_2Na/HCO_2H pH 4.5, 0.3 mL 2-MeTHF, sealed in air, 8 h. [c] The same reaction condition with [b] but 16 h. [d] Yield of isolated product. [e] Determined by HPLC.

selectivity (56% ee) for the DARA (Table 1, entry 9). Therefore, **9** was subjected to a range of different solvents, additives, hydride sources and temperatures to determine the optimal conditions (ESI, Table S1†). Finally, it was determined that using the FT in IPA at 20–25 °C would provide the best conversion and enantioselectivity (Table 1, entry 10).

Subsequently, a range of ketones and amines were investigated to determine whether the iridacycle **9** could be exploited for DARA. As can be seen from Table 2, whilst **9** catalysed efficient reductive amination, affording the amine products generally in high yields, the enantioselectivities were only moderate in most cases. More specifically, utilising *p*-methoxyaniline as the amine source, the *para*- and *meta*-substituted acetophenones provided very high yields and moderate enantioselectivities (Table 2, entries 2–6). However, an *ortho*-substituted ketone displayed a lower enantioselectivity (Table 2, entry 7), indicating that the *ortho* substituent interferes with the enantioselectivity-determining step. Changing R′ to an ethyl or a phenyl group led to enhanced selectivity (Table 2, entries 8 and 10); however, lengthening the alkyl group resulted in a lower selectivity (Table 2, entry 9), demonstrating a limit to the functionalisation that can be tolerated in this position. The reaction with an alkyl ketone afforded a very high yield (97%), but racemic amine (Table 2, entry 11). In the case of other aniline derivatives coupling with acetophenone, the yields decreased significantly (Table 2, entries 12–16), indicating that the electron donating methoxy group on the amine is crucial, probably assisting in the imine formation. With the more nucleophilic benzylamines (Table 2, entries 17–20), the yields were high; but the enantioselectivity was disappointingly low, presumably as a result of reduced steric rigidity in the imine intermediate.

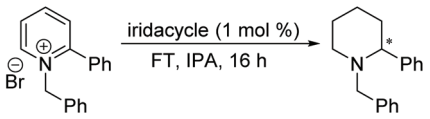
Aiming to improve the yield and enantioselectivity, the impact of aqueous conditions was also investigated, utilising $NaCO_2H/HCO_2H_{(aq.)}$ at pH 4.5 as a hydrogen source for DARA, with 2-methyltetrahydrofuran (2-MeTHF) as a co-solvent. Under such conditions, some of the yields were improved; however, the enantioselectivities showed little change (Table 2, entries 3, 9–14, 16). In particular, benzylamines afforded higher yields but still low enantioselectivities (Table 2, entries 17–20).

2.3. ATH of pyridinium salts

Chiral piperidines are valuable building blocks for natural products and synthetic bioactive molecules. Asymmetric hydrogenation of pyridines can be used to obtain chiral piperidines.[26] However, these reactions are generally difficult to carry out, due to the coordination ability and the resonance stability of the pyridines. To overcome these challenges, pyridines can be activated, in the form of pyridinium salts or auxiliary-substituted pyridines.[26b,27] Whilst transfer hydrogenation of pyridines has been reported,[4a,28] very little has been reported for ATH of pyridines. In 2007 Rueping *et al.* developed the first organocatalytic ATH system, utilising a Brønsted acid to activate the substrate and induce chirality.[29] With the chiral iridacycles in hand, we also examined their potential for ATH of pyridinium salts.

The iridacycles were first examined for ATH of *N*-benzyl-2-phenylpyridinium bromide salt, using FT in IPA, as shown Table 3. It appears that the oxazoline-containing iridacycles

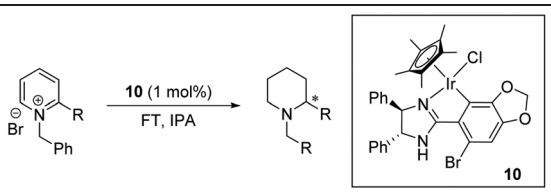
Table 3 Screening iridacycles for ATH of pyridinium salt

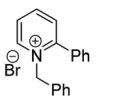
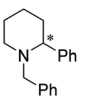
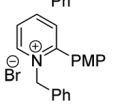
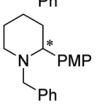
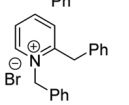
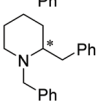
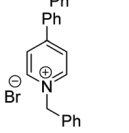
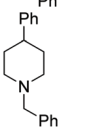
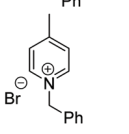
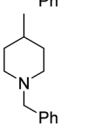


Entry	Iridacycle	ee (%)	Entry	Iridacycle	ee %
1	**3**	20	8	**10**	51
2	**4**	10	9[a]	**10**	77(97)[b]
3	**5**	15	10	**11**	33
4	**6**	6	11	**12**	24
5	**7**	34	12	**13**	20
6	**8**	25	13	**14**	46
7	**9**	44	14	**15**	38

Reaction conditions: 0.5 mmol pyridinium salt, 1 mol% Ir cat, 2.5 mL anhydrous IPA, 0.5 mL FT, sealed, ambient temperature. Enantiomeric excess determined by chiral HPLC. [a] Reaction conducted at −10 °C. [b] Isolated yield in parentheses.

Table 4 ATH of selected pyridinium salts with **10**[a]



Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)
1			97	77
2			68	75
3			75	10
4			75	
5			80	

[a] Reaction conditions: 0.5 mmol pyridinium salt, 1 mol% **10**, 5 mL anhydrous IPA, 1 mL FT, −10 °C, sealed, 16 h. [b] Yield of isolated product. [c] Determined by HPLC; configuration unknown. PMP: *p*-methoxyphenyl.

(Table 3, entries 1–6,) generally exhibited a low enantioselectivity (up to 34% ee). Among the imidazoline ligands, the previously used **9** provided 44% ee, and the best enantioselectivity was achieved with the dioxoleiridacycle **10**, which afforded 51% ee (Table 3, entry 8). Using **10** as catalyst at a lower temperature of −10 °C, the selectivity was increased and the piperidine was isolated in 97% yield with an ee of 77% (Table 3, entry 9)

Under the conditions identified, we examined the ATH of a range of pyridinium salts. Selected examples are shown in Table 4.‡ As can be seen, the iridacycle **10** is active for the substituted pyridinium salts, affording the corresponding piperidines in high yields. However, the enantioselectivity varied considerably, from 77% ee for the 2-aryl substituted substrates to 10% ee for the less sterically hindered 2-benzyl substituted one (Table 4, entries 1–3).

3. Conclusions

Chiral iridacycles can be easily accessed *via* cyclometalation reaction of $[Cp^*IrCl_2]_2$ with a ligand that undergoes C–H activation and such complexes could serve as catalysts for asymmetric reactions. In this study, we have synthesised a wide range of chiral iridacycles and examined their potential application in DARA *via* transfer hydrogenation. Among the iridacycles, the 3,4,5-trimethoxy imidazoline-bearing **9** proved to be the most effective, affording moderate enantioselectivities in the DARA of acetophenones with aniline derivatives. The iridacycles are also active in catalysing the ATH of pyridiniums, albeit with only good ee's in the case of 2-aryl substituted substrates. Research within our group continues to develop chiral iridacycles, aiming for better enantioselective catalysts.

Conflicts of interest

There are no conflicts to declare.

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‡The enantioselectivity of the other products could not be determined due to the lack of chiral HPLC columns at the time.

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