Record Review

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THE CHEMICAL RECORD

Recent Development in the Synthesis and Catalytic Application of Iridacycles

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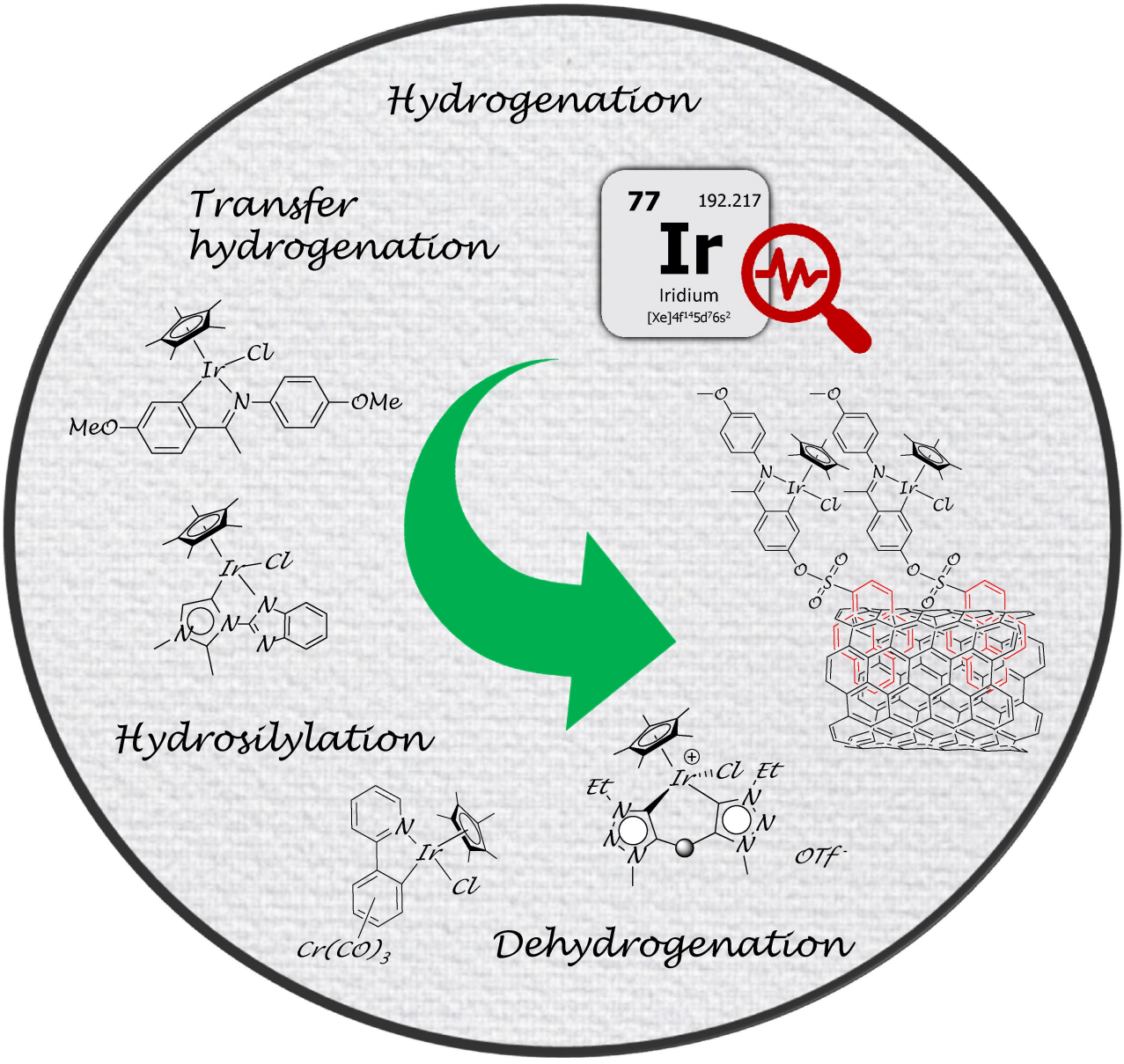

Abstract: Cyclometallated complexes are well-known and have found many applications. This article provides a short review on the progress made in the synthesis and application to catalysis of cyclometallated half-sandwich Cp*Ir(III) complexes (Cp*: pentamethylcyclopentadienyl) since 2017. Covered in the review are iridacycles featuring conventional C,N chelates and less common metallocene and carbene-derived C,N and C,C ligands. This is followed by an overview of the studies of their applications in catalysis ranging from asymmetric hydrogenation, transfer hydrogenation, hydrosilylation to dehydrogenation.

Keywords: cyclometallated complexes, iridacycles, hydrogenation, transfer hydrogenation, hydrosilylation, dehydrogenation

1. Introduction

The term "cyclometallation" was defined by Trofimenko[1] and this type of reactions has been known since the early 1960s. A lot of transition metals, such as Pd, Ru, Rh and Ir, have been studied for this reaction to provide metal complexes having chelating rings embedded with a metal–carbon bond.[2] The use of iridium in cyclometallation leads to iridacycles. Iridacycles have found applications in a diverse range of areas, such as medicine,[3–5] organic light emitting diodes[6] and bioimaging/sensing applications.[7] In particular, they are active as catalysts for various reactions, such as hydrogenation, transfer hydrogenation (TH), reductive amination, dehydrogenation, hydrosilylation, oxidation, racemisation, etc..[8]

Cyclometallation reactions mostly occur through C–H activation. The use of acetate in C–H activation provides facile access to cyclometallated complexes. Shaw and co-workers made the pioneering studies, showing that sodium acetate promotes cyclometallation reactions.[9] Later in 1998, Beck et al. performed an initial study of cycloiridation in the presence of sodium acetate, reacting 2-phenyl-4-R-5(4*H*)-oxazolones (R = Me, CH_2Ph, CHMeEt) with the iridium dimer $[IrCl_2Cp^*]_2$.[10] In 2003, Davies et al. reported cyclometallation through C–H activation of nitrogen donor ligands (amines, imines and oxazolines) with the dimers $[IrCl_2Cp^*]_2$, $[RhCl_2Cp^*]_2$, and $[RuCl_2(p\text{-cymene})]_2$ in the presence of NaOAc at room temperature.[11] More recently, Muller et al. isolated and crystallographically characterised phosphinine-Ir(III)/Rh(III) complexes via an unprecedented C–H activation of 2,4,6-triphenylphosphinine with $[MCl_2Cp^*]_2$ (M = Ir or Rh).[12] The role of acetate in C–H activation was established in subsequent studies, both computationally and experimentally, by Davies, Jones, Zheng and Muller.[13]

Although there are some early reports of cyclometallation with iridium,[14] the use of iridacycles in catalysis is later. Scheme 1 shows selected half-sandwich Cp*-iridacycles, with their applications in catalysis highlighted. For example, in 2007, Peris and Fernandez et al. first reported catalytic diboration of olefins with iridium complex **1**, giving organodiboranates with high conversions and chemoselectivities.[15] In 2008, Ikariya et al. reported asymmetric transfer hydrogenation (ATH) of acetophenone with chiral iridium complex **2**, giving (*S*)-1-phenylethanol in high yield (95%) and moderate ee (66%).[16] In 2009, de Vries, Feringa et al. reported the use of cationic half-sandwich iridacycles, such as complex **3**, as racemisation catalysts for chiral alcohols and amines.[17] In 2009, Eisenstein, Brudvig and Crabtree et al. reported Cp*Ir complexes **4** for catalytic water oxidation.[18] In 2011, Fujita and Yamaguchi et al. developed the α-hydroxypyridine-ligated Cp*Ir complex **5** for dehydrogenative oxidation of primary and secondary alcohols, yielding aldehydes and ketones, respectively.[19] In 2012, Morris et al. reported that complex **6** could catalyse the hydrogenation of acetophenone and benzophenone.[20] In the same year, Djukic et al. reported the catalytic activity of $Cr(CO)_3$-bound half-sandwich iridacycle **7** in tandem transformation of terminal alkynes into N-phenylamines, including hydroamination and hydrosilylation/protodesilylation reactions under mild conditions.[21] In 2014, Sarkar et al. reported that complex **8** catalyses TH of benzaldehyde to form benzylalcohol in isopropanol/KOH; but the TH of acetophenone was slower under the same conditions.[22] In 2010, our group reported a highly effective catalyst **9**, which enables transfer hydrogenative reductive amination of various carbonyl compounds.[23] In the following several years, we and others have found that iridacycles comprised of such simple imino ligands catalyse a number of interesting reactions. The progress made prior to 2017 has been summarised.[8] The aim of this minireview article is to show new iridacycles that have appeared and their applications

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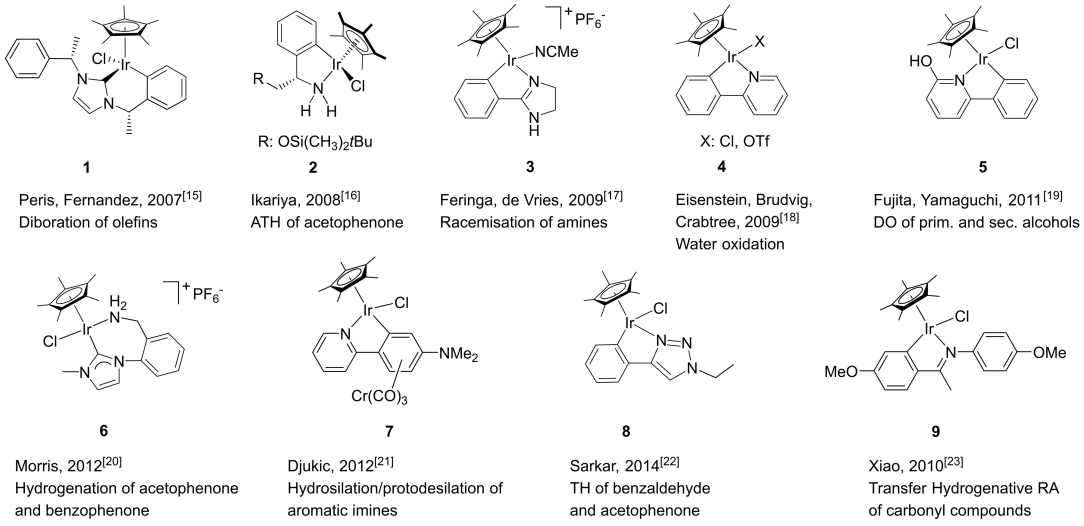
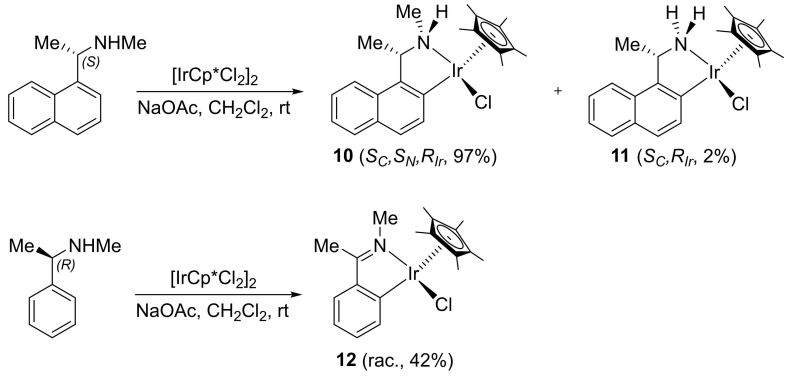
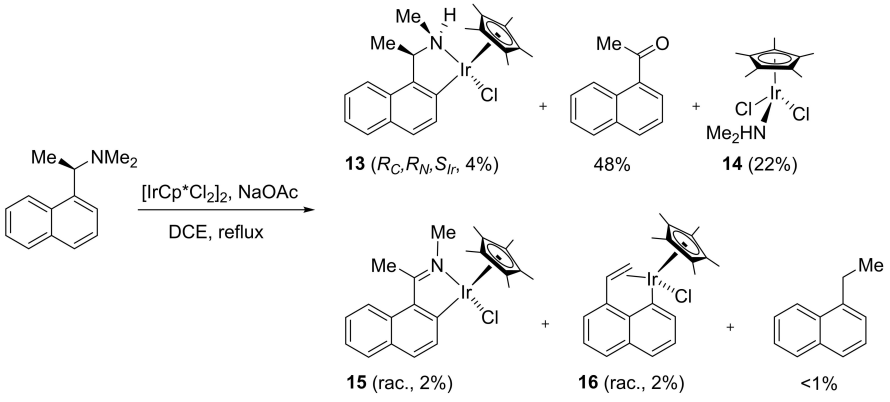


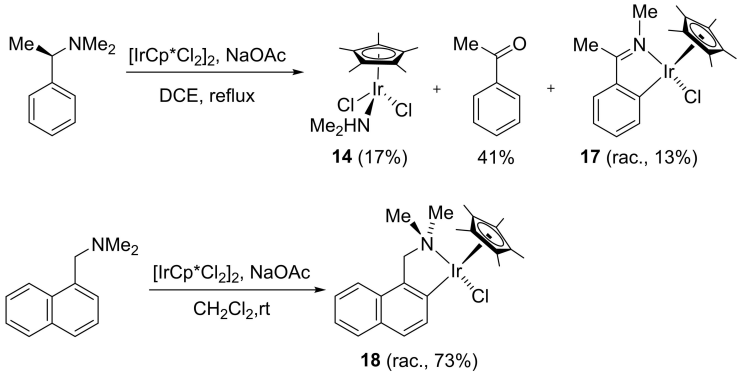
Scheme 1. Selected examples of Cp*-featuring iridacycles.



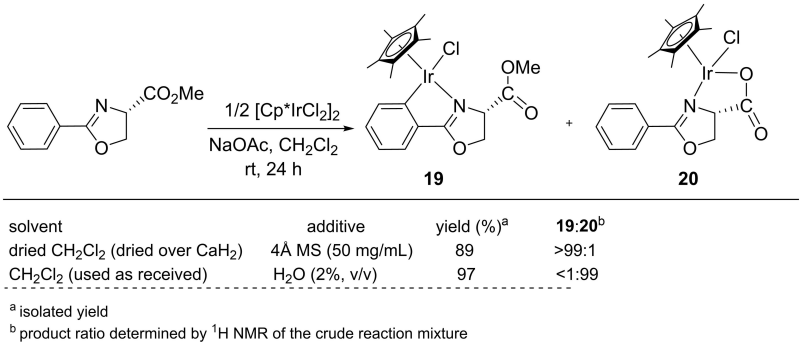
Scheme 2. Cycloiridation of chiral secondary amines with $[IrCp^*Cl_2]_2$.



Scheme 3. Cycloiridation of (*R*)-*N,N*-dimethyl-1-(1-naphthyl)ethylamine.



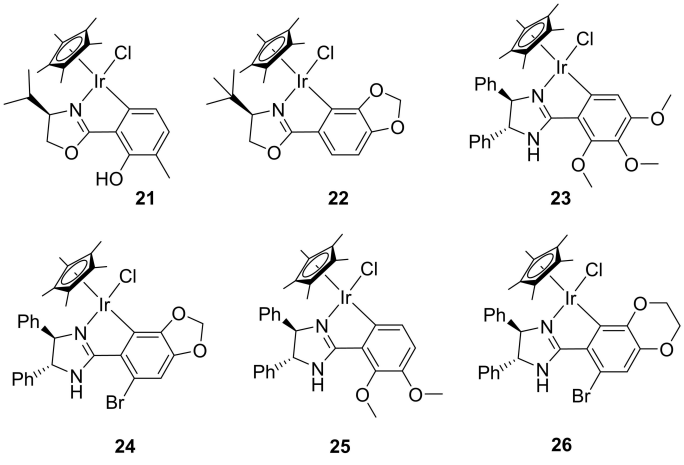
Scheme 4. Iridation of tertiary amines leading to racemic iridacycles.



solvent	additive	yield (%)[a]	19:20[b]
dried CH_2Cl_2 (dried over CaH_2)	4Å MS (50 mg/mL)	89	>99:1
CH_2Cl_2 (used as received)	H_2O (2%, v/v)	97	<1:99

[a] isolated yield
[b] product ratio determined by ^1H NMR of the crude reaction mixture

Scheme 5. Formation of N,C- and N,O-chelated iridium complexes.



Scheme 6. Chiral iridacycles bearing oxazoline and imidazoline ligands.

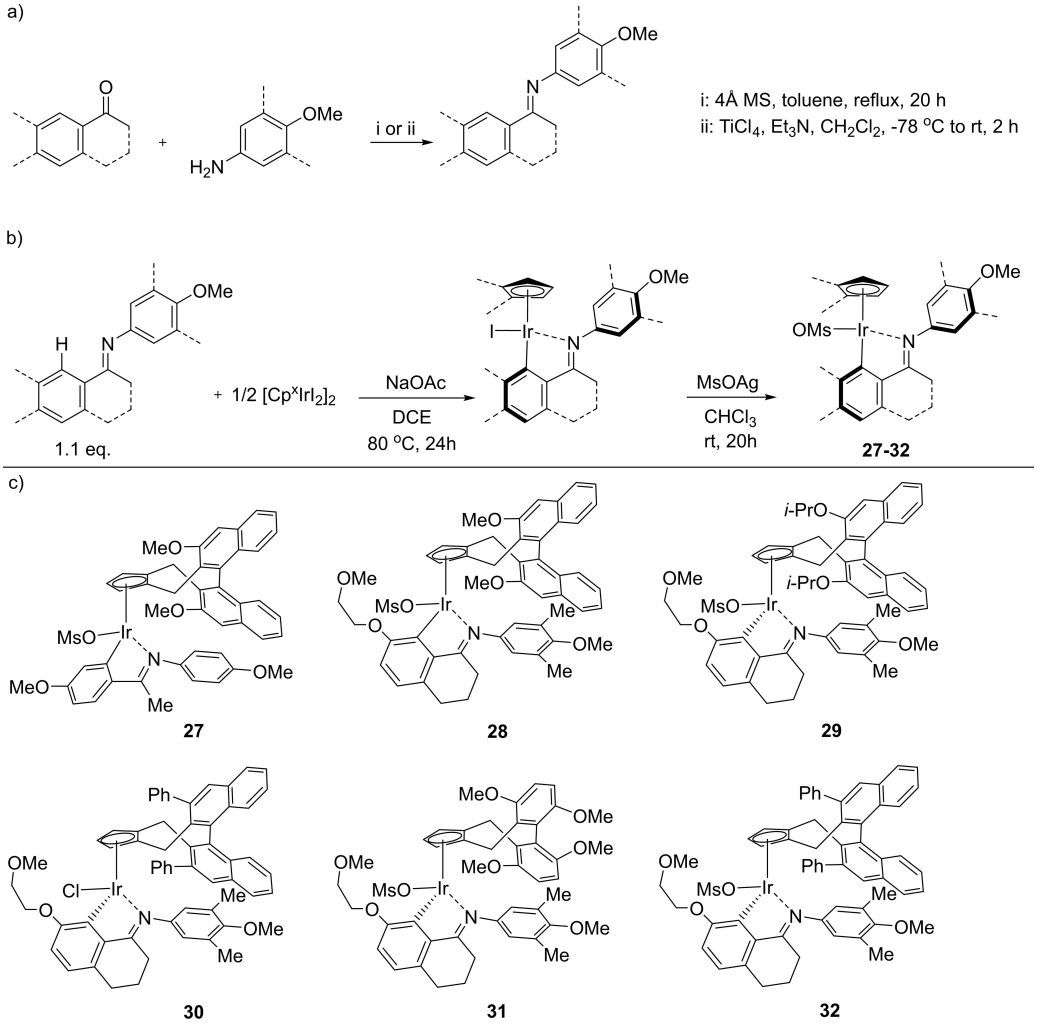
in catalysis since 2017. Earlier publications are mentioned where appropriate. The coverage is restricted to half-sandwich iridacycles, i. e. those bearing Cp* and related ligands.

2. Synthesis of Chiral Iridacycles

2.1. Conventional C,N Ligands

Aiming for asymmetric catalysis, a number of chiral iridacycles have been synthesised in the past a few years. In 2018, Leung et al. synthesised 1-naphthylalkylamine-based chiral iridacycles **10** and **11** by cycloiridation of the optically-active secondary amine ligand (*S*)-*N*-methyl-1-(naphthalen-1-yl)ethan-1-amine with $[IrCp^*Cl_2]_2$, with each iridacycle observed as only one stereoisomer (Scheme 2).[24] This observation is notable, because many Cp*-based iridacycles are mixtures of diastereomers upon cyclometallation. For example, whilst complex **10** has three stereogenic centres, only the isomer indicated was observed. This is believed to be due to a structurally locking mechanism. The demethylation product **11** was isolated as a by-product with a low yield; but it could be obtained from direct cyclometallation of the primary amine with a high yield of 90%. In comparison, the phenyl derivative gave the racemic imino-iridacycle **12** as the major product, with a moderate yield of 42% (Scheme 2).

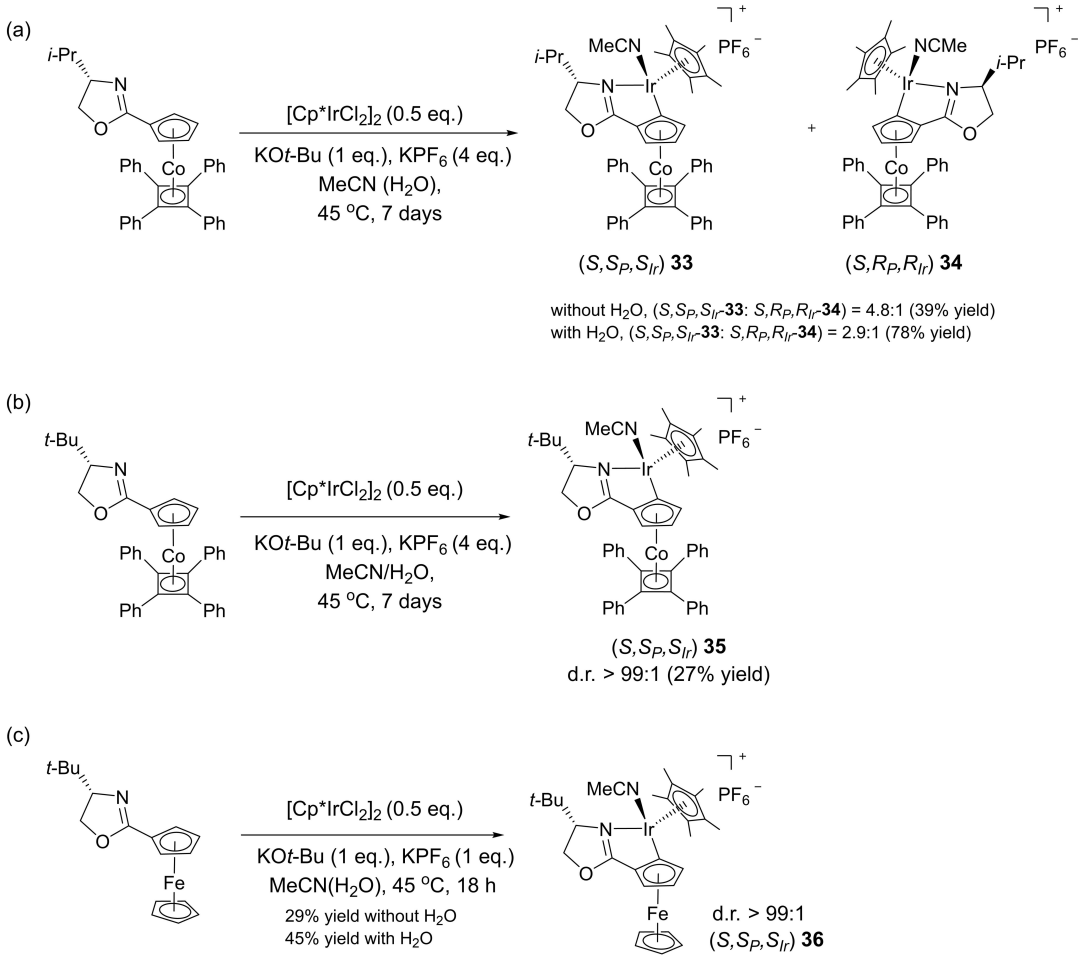
In the same year, the same group carried out the reaction of (*R*)-*N,N*-dimethyl-1-(1-naphthyl)ethylamine with $[IrCp^*Cl_2]_2$, employing sodium acetate in 1,2-dichloroethane



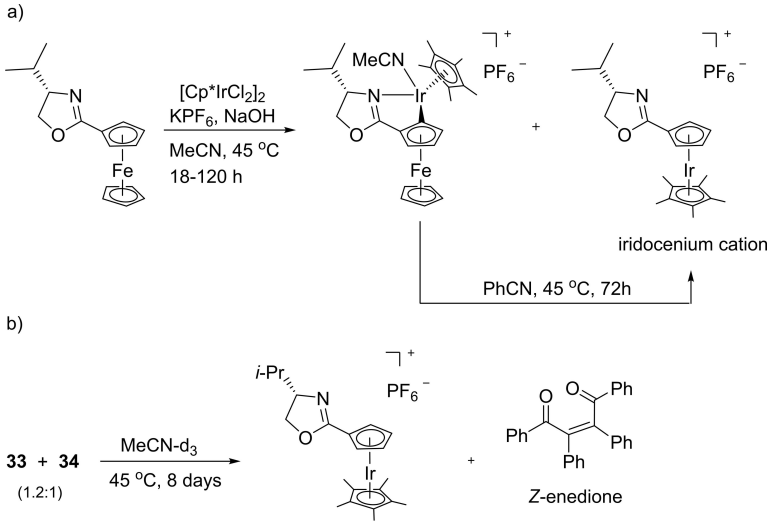
Scheme 7. Synthesis of chiral iridium(III) complexes bearing chiral Cp ligands.

(DCE) at reflux temperature, in order to gain more insight into the selectivity of cyclometallation.[25] This reaction generated six isolable products: cycloiridated complexes **13**, **15**, and **16**, dimethylamine coordinated complex **14** and organic molecules 1-acetonaphthone and 1-ethylnaphthalene, as shown in Scheme 3. It was suggested that the formation of **13**, **14** and 1-acetonaphthone could start from a β-hydride elimination-like process, **15** could be derived from **13** via a dehydrogenation procedure, and **16** could be formed from the dehydroamination of a complexed cyclic intermediate, hydrogenation of which could produce 1-ethylnaphthalene. To investigate the steric effect on the reaction pathway, the authors carried out cycloiridation of a phenyl derivative and an achiral naphthalene-based ligand, as shown in Scheme 4. The reaction of the phenyl ligand under the similar conditions gave complex **14**, acetophenone and racemic compound **17**, while the achiral naphthalene ligand provided the racemic compound **18**. These results indicate that steric effects in the coordination sphere favour a β-hydride elimination-like pathway, competing with *ortho*-metalation.

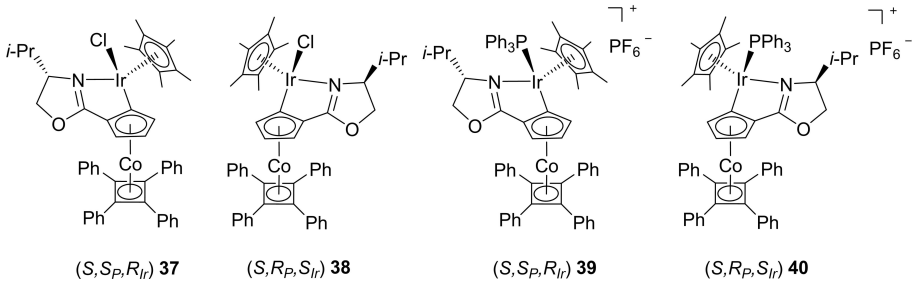
In 2018, we demonstrated the importance of reaction conditions on ligand coordination mode in attempted cyclometallation.[26] The reaction was carried out with $[IrCp^*Cl_2]_2$ and methyl (*S*)-2-phenyl-4,5-dihydrooxazole-4-carboxylate in the presence of anhydrous sodium acetate at room temperature, affording a mixture of two half-sandwich Cp*Ir(III) complexes, the expected N,C-chelated complex **19** and an "abnormal" N,O-chelated complex **20** (Scheme 5). Interestingly, a simple change in reaction conditions, such as water content (in the solvent) and additive, affected the ratio of these complexes in a dramatic way (up to $>99:1$ ratio for each complex). Each complex is air stable and appears as a mixture of two diastereomers.



Scheme 8. Iridacycles bearing cobalt oxazoline and ferrocenyloxazoline ligands.

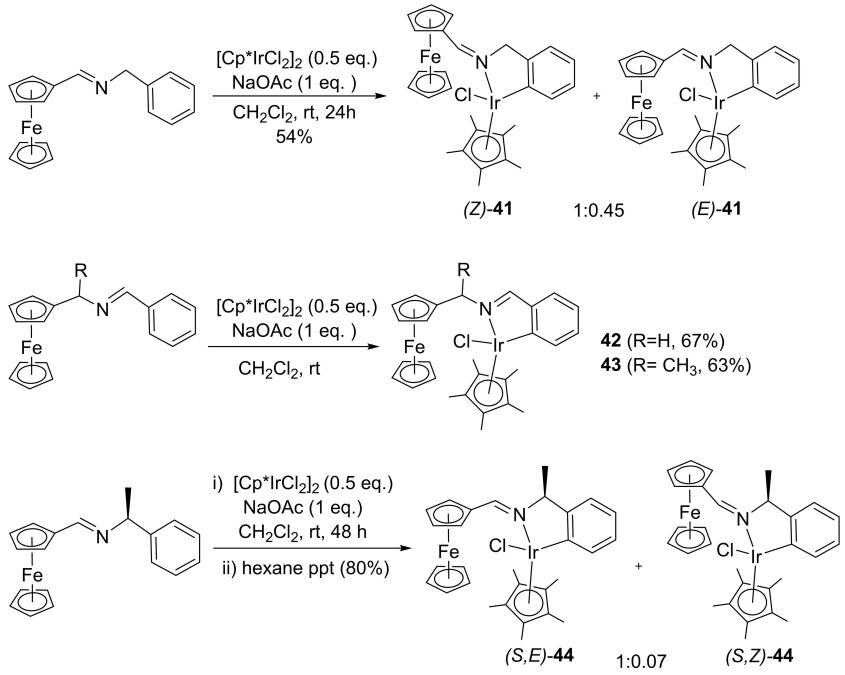


Scheme 9. Synthesis of cationic iridacycle and iridocenium cation (a) and transformation of **33** and **34** into iridocenium (b).



(S,S_P,R_{Ir}) **37** (S,R_P,S_{Ir}) **38** (S,S_P,R_{Ir}) **39** (S,R_P,S_{Ir}) **40**

Scheme 10. Chloride-ligated diastereoisomers and cationic isomers produced from iridacycles **33** and **34**.



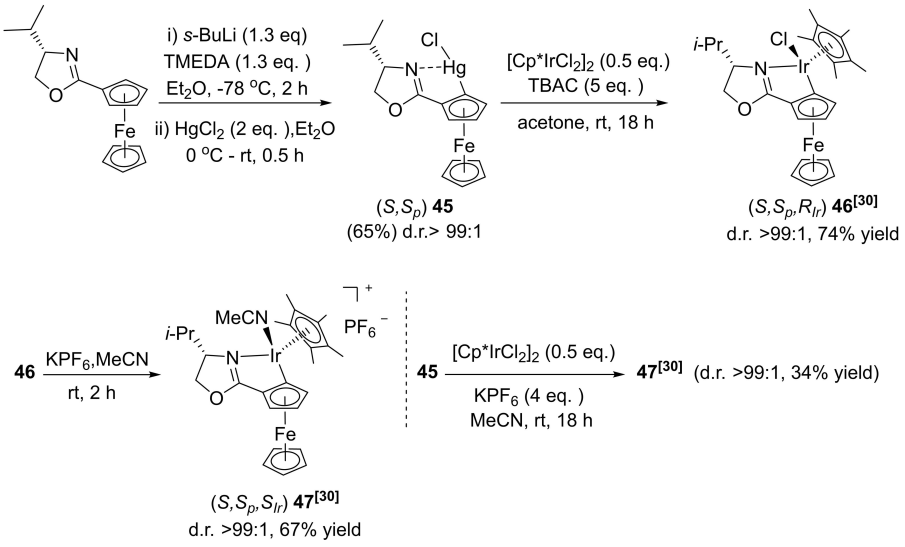
Scheme 11. Cycloiridation of ferrocenyl and phenyl-bearing imines.

We have recently reported a range of chiral iridacycles, obtained by cyclometalation of $[Cp^*IrCl_2]_2$ with chiral oxazoline and imidazoline ligands via C–H bond activation under generally mild reaction conditions.[27] These iridacycles appeared mostly as a mixture of two diastereoisomers, presumably due to the small difference between their thermodynamic stability. Some examples (**21**–**26**) are shown in Scheme 6.

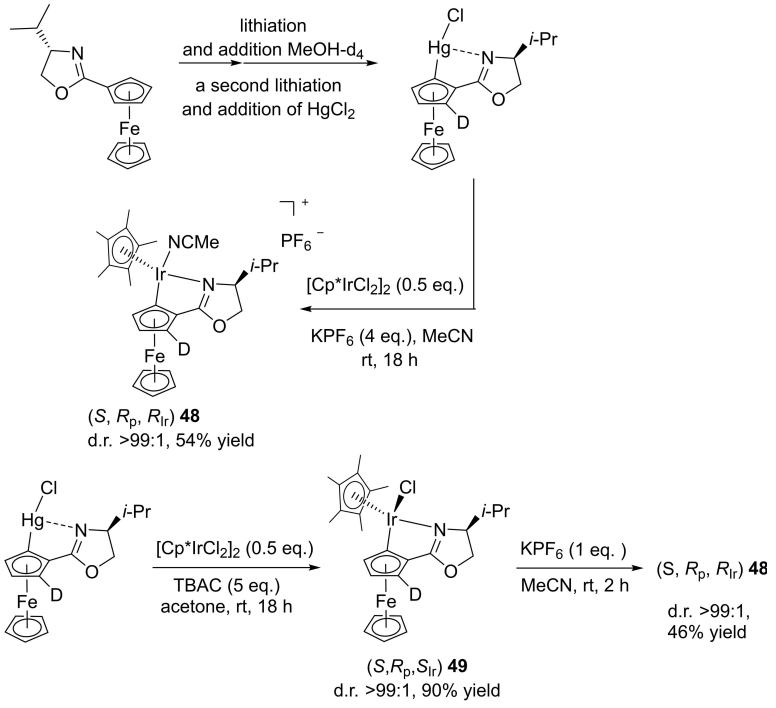
In 2020, Cramer et al. reported air and moisture-stable C,N-chelated Ir(III) complexes bearing a chiral cyclopentadienyl ligand.[28] The complexes were synthesised via a two-step sequence (Scheme 7). Some complexes are presented in Scheme 7c.

2.2. Metallocene-based Ligands

Ferrocene-featuring iridium complexes have long been known.[29] Among them, ferrocene-based planar chiral iridacycles was reported by Richards and co-workers in 2016.[30] The work was extended to planar chiral iridacycles featuring oxazoline-appended cobalt sandwich complexes in 2018.[31] Thus, diastereoselective cycloiridation of cobalt oxazoline and ferrocenyloxazoline gave iridacycles **33**–**36**, as shown in Scheme 8. The influence of base, water, time, and auxiliary at the oxazoline on the cycloiridation was studied. For example, when using *iso*-propyl (*i*-Pr) oxazoline, the selectivity of cycloiridation in the absence of water resulted in a higher selectivity (**33**:**34** = 4.8:1) with a lower yield (39%) than in the presence of water (**33**:**34** = 2.9:1 with 78% yield) (Scheme 8a). But with the *tert*-butyl (*t*-Bu) oxazoline, the

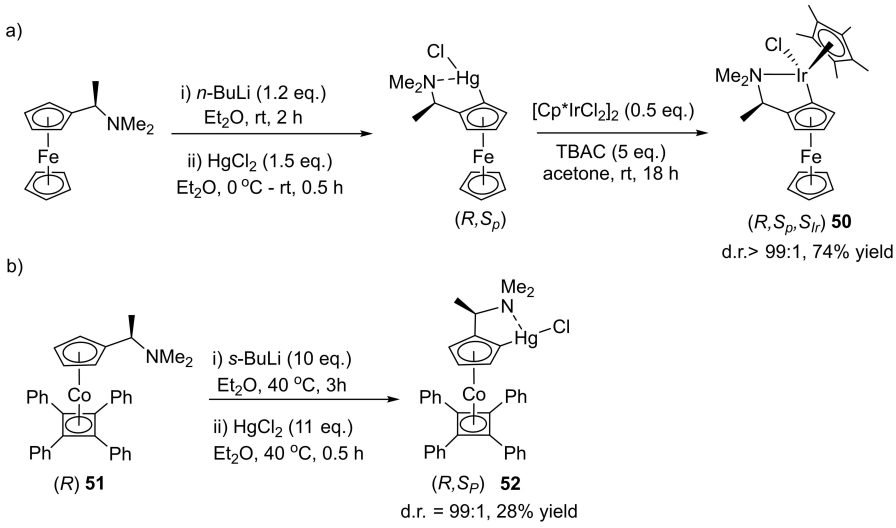


Scheme 12. Synthesis of iridacycles via transmetallation of mercurated ferrocenyl oxazoline.



Scheme 13. Synthesis of ferrocenyl iridacycles via transmetallation.

diastereoselectivity was not affected by the addition of water, and only the yield increased from 29 % to 45 % (Scheme 8c). Notably, the iridacycles **33** and **34** could be converted into an iridocenium cation in deuterated acetonitrile on heating at 45 °C. This iridocenium cation was obtained in their previous work in 2016[32] from a ferrocene-derived iridacycle, as shown in Scheme 9a. Also, stereospecific ligand exchange with chloride and triphenylphosphine at iridium was performed, providing neutral chloride-ligated diastereoisomers and cationic isomers (**37**, **38** and **39**, **40**), respectively, as shown in Scheme 10.



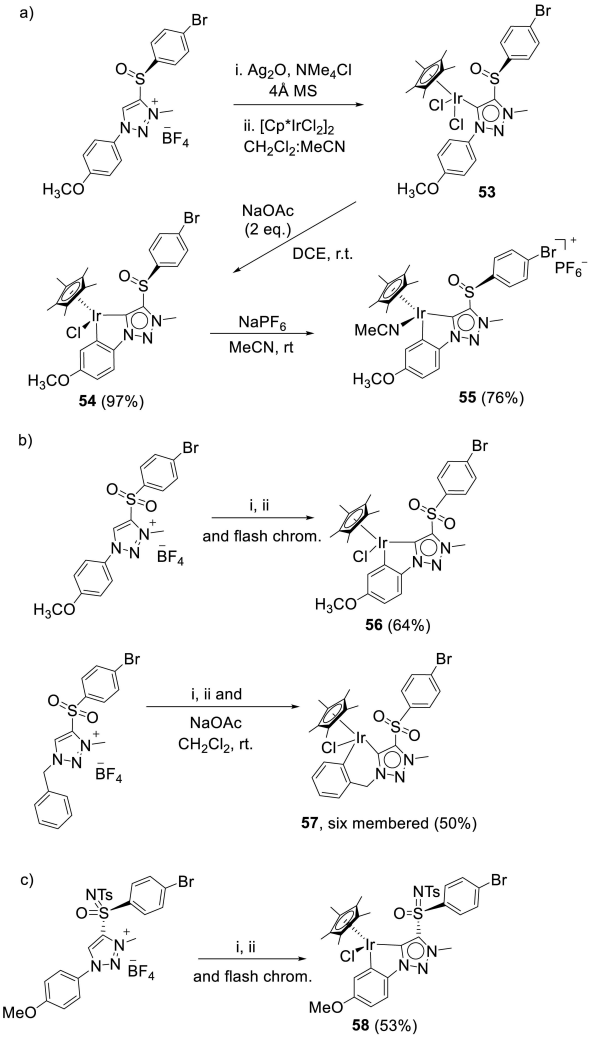
Scheme 14. Synthesis of iridacycle **50** from Ugi's amine (a) and of cobalt sandwich complex-based mercury derivative **52** (b).

In 2017, Richards et al. reported iridacycles via cycloiridation of ferrocenyl and phenyl-containing imines with $[Cp^*IrCl_2]_2$ in the presence of NaOAc in CH_2Cl_2 (Scheme 11).[33] They studied the *exo* vs. *endo* and phenyl vs. ferrocenyl selectivity arising from α or *ortho* C–H bond activation, observing, interestingly, that the iridacycles resulted from *ortho*-phenyl instead of α-ferrocenyl C–H activation. The complexes derived from FcCH=NCH(R)Ph (R = H, Me) were a mixture of *E* and *Z* imine diastereoisomers, and while the ligands FcCH(R)N=CHPh were *endo* selective, the FcCH=NCH(R)Ph were *exo* selective (Fc: ferrocenyl; Ph: phenyl).

More recently, Richards et al. reported the synthesis of ferrocene-based planar chiral iridacycles by using transmetallation as an alternative approach to cycloiridation (Scheme 12).[34] This has made possible previously unavailable iridacycles by direct introduction of iridium via C–H activation. In the presence of tetramethylethylenediamine (TMEDA) and *sec*-butyllithium (*s*-BuLi), diastereoselective lithiation of ferrocenyloxazoline followed by the addition of $HgCl_2$ resulted in mercury-substituted ferrocenyloxazoline **45** with d.r. > 99 : 1 (Scheme 12). In comparison, direct cyclomercuration of ferrocenyloxazoline by C–H activation resulted in a mixture of two mercury-substituted complexes (**45** and its S,R_p isomer) with a very low diastereoselectivity (d.r. = 1.1–1.3) (not shown in scheme). Then, transmetallation of **45** with the iridium dimer in the presence of tetrabutylammonium chloride (TBAC) in acetone resulted in iridacycle **46**[30] as only a single diastereoisomer (d.r. > 99 : 1). Transmetallation of **45** in the presence of KPF_6 in acetonitrile produced cationic complex **47**, affording again a single diastereoisomer (d.r. > 99 : 1), as shown in Scheme 12. Complex **47** was also produced via ligand exchange from **46** by using KPF_6 in acetonitrile with d.r. > 99 : 1. Mercuration of a cobalt sandwich analogue of ferrocenyloxazoline by the use of $Hg(OAc)_2$ led to a mixture of isomeric mercury complexes with d.r. = 2 : 1 (S,S_p and S,R_p). Transmetallation of this mixture with $[Cp^*IrCl_2]_2$ in the presence of KPF_6 in acetonitrile gave a 2 : 1 ratio of cationic iridacycles, but with a low yield (not shown in scheme). The group also synthesised deuterated ferrocenyloxazoline-derived iridacycles **49** and **48** with d.r. > 99 : 1 for each. Lithiation of ferrocenyloxazoline, followed by a sequence of addition of MeOD-d_4, second lithiation, mercuration and finally transmetallation with $[Cp^*IrCl_2]_2$, afforded **48** in the presence of KPF_6 and **49** in the presence of TBAC (Scheme 13). A similar approach was used to form the chiral iridacycle **50** (Scheme 14a) derived from Ugi's amine. The application of lithiation to **51**, a bulky cobalt sandwich complex analogous to Ugi's amine, followed by the addition of excess $HgCl_2$, led to **52** (Scheme 14b). However, transmetallation of **52** with $[Cp^*IrCl_2]_2$ was found unsuccessful.

2.3. Carbene-based Ligands

N-Heterocyclic carbenes (NHCs) provide another easy entry to cyclometallated complexes, those featuring a C,C-chelate ring. In 2017, Sierra and de la Torre et al. reported the application of 1,2,3-triazolylidine mesoionic carbenes (MIC) bearing enantiopure sulfoxide moieties to the synthesis of chiral cyclometallated Ir(III) and Rh(III) half-sandwich complexes (Scheme 15).[35] Treatment of the enantiopure sulfinyl triazolium salt with Ag_2O in the presence of NMe_4Cl and 4 Å MS, followed by transmetallation with $[Cp^*IrCl_2]_2$, gave the neutral Ir(III) complex **53**. On treatment of **53** in DCE with



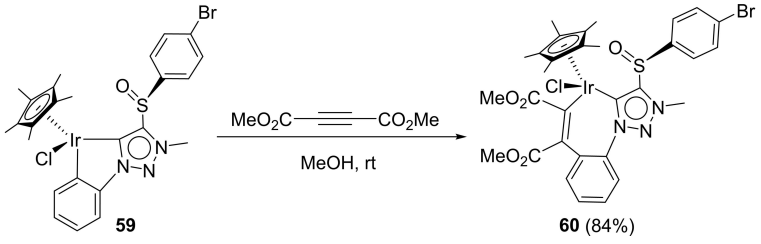
Scheme 15. Synthesis of iridacycles having sulfoxide (a), sulfone group (b) and sulfoximine groups (c).

NaOAc, cyclometallation took place, affording iridacycle **54** (Scheme 15a). The five and six membered sulfone analogues **56** and **57** and sulfoximine analogue **58** were prepared in a similar fashion (Scheme 15b and 15c). The enantiopure cationic Ir(III) complexes, such as **55**, are easily accessible (Scheme 15a), and further, insertion of alkynes into the Ir–C bond was demonstrated, as seen in the conversion of **59** to **60** (Scheme 16). The process of MIC coordination and C–H aromatic activation was found effective and diastereoselective for the formation of enantiopure five-membered metallacycles, whilst the formation of six-membered analogues exhibited a considerably lower diastereoselectivity.

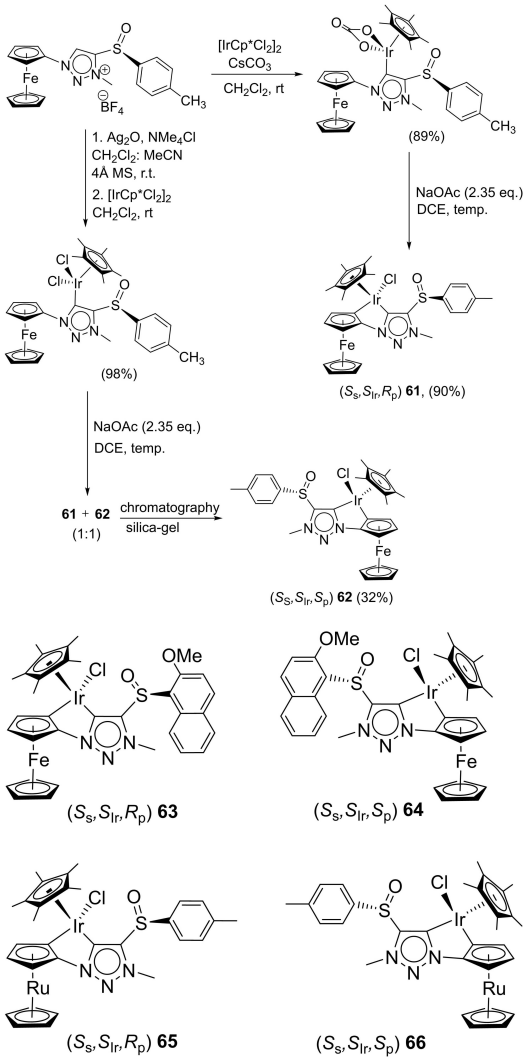
More recently, the same group reported planar chiral bimetallic ruthenocene or ferrocene-derived iridacycles incorporating sulfoxide-substituted mesoionic carbenes (Scheme 17).[36] These iridacycles contain three different types of chirality, sulfur-based point chirality, iridium-centred metal chirality and metallocene-imposed planar chirality. The reactions leading to the formation of complexes **61**–**66** are shown in Scheme 17. It was observed that whilst the sense of asymmetric induction at Ir(III) remained the same, the planar chirality depended on the nature of the ligands at the iridium centre (carbonate vs chloride). For instance, while **61** was isolated as a single isomer from the Ir-carbonate intermediate in a high yield, the dichloro-Ir yielded a mixture of diastereomeric **61** and **62**.

3. Asymmetric Reduction

Asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) have been extensively used to introduce chirality into prochiral molecules, such as enamines, imines, ketones, alkenes and unsaturated carboxylic acids. AH uses hydrogen gas as hydrogen donor while ATH commonly uses isopropanol and formic acid as hydrogen source. In comparison with AH where high pressure H_2 is often required, ATH is generally easier to operate, with no need for special equipment or measures. Both methods of reduction have found wide applications in the synthesis of fine chemicals, pharmaceuticals and agrochemicals. Iridium-catalysed AH or ATH reactions are well-known. The interested reader is referred to selected reviews[37] and articles.[38] However, the use of half-sandwich Cp* type iridacycle catalysts in these reactions is less explored.[39] Recent examples are presented below.



Scheme 16. Insertion of an alkyne into the Ir–C bond of an iridacycle.



Scheme 17. Synthesis of chiral ferrocene and ruthenocene-derived iridacycles.

In 2020, Cramer et al. reported an efficient AH of oximes with the iridacycle **32**, producing chiral hydroxylamines.[28] The reduction of oximes to chiral hydroxylamines is challenging due to the possible cleavage of the N–O bond leading to undesirable products. The iridium complex **32** in the presence of a strong acid serves as an efficient catalyst for this reduction without disturbing the N–O bond. The hydrogenation was carried out at room temperature, 1 mol% catalyst, 50 bar pressure in the presence of methanesulfonic acid (MsOH) giving high yields and high enantiomeric ratio (er) for various hydroxylamines, as shown in Scheme 18. A comparison of the analogous iridacycles **27**–**31** in the AH of an oxime is shown in Scheme 19.

Earlier, Leung et al. reported the use of iridacycles **10** and **11** for ATH of acetophenone (Scheme 20).[24] Both complexes provided high conversions (ca. 90 %) and modest ee (60 %) at −15 °C in 30 min. When the ATH reaction was performed with **10** at a lower temperature (-30 °C), the enantioselectivity was improved to 69 % ee.

We compared the N,C- and N,O-chelated Cp*Ir(III) complexes **19** and **20** for ATH of substituted acetophenones.[26] The N,O-chelated **20** exhibited much higher catalytic activity and enantioselectivity than the N,C-analogue **19**, with differing sense of asymmetric induction, as exemplified in Scheme 21. Thus, complex **20** was applied to ATH of various aromatic ketones, providing high enantioselectivities (90–99 % ee) as shown in Scheme 22. These results reveal that the chelation mode of a ligand can dramatically affect the outcome of ATH reactions. The suggested mechanism for ATH with **20** includes the formation of iridium-hydride and participation of isopropylammonium cation in the transition state of enantioselectivity-determining step. A hydrogen bonding network was suggested, which would be expected to lower the barrier of the diastereomeric transition state, enhancing the enantioselectivity of the hydride transfer.

In a related work, we examined the catalytic activity of a series of oxazoline and imidazoline-based iridacycles in direct asymmetric reductive amination (DARA) of acetophenone with *p*-methoxy aniline and in ATH of N-benzyl pyridinium bromide salts.[27] Among them, the 3,4,5-trimethoxy imidazoline-bearing iridacycle, complex **23**, was found the most effective catalyst for DARA. Applying **23** to DARA of a range of ketones with amines afforded chiral amines with high yields and moderate enantioselectivities in most cases. Some chiral amine products are presented in Scheme 23. The dioxole iridacycle, complex **24**, provided the best enantioselectivity (up to 77 % ee) for ATH of pyridiniums by using HCO_2H/Et_3N in isopropanol (Scheme 24).

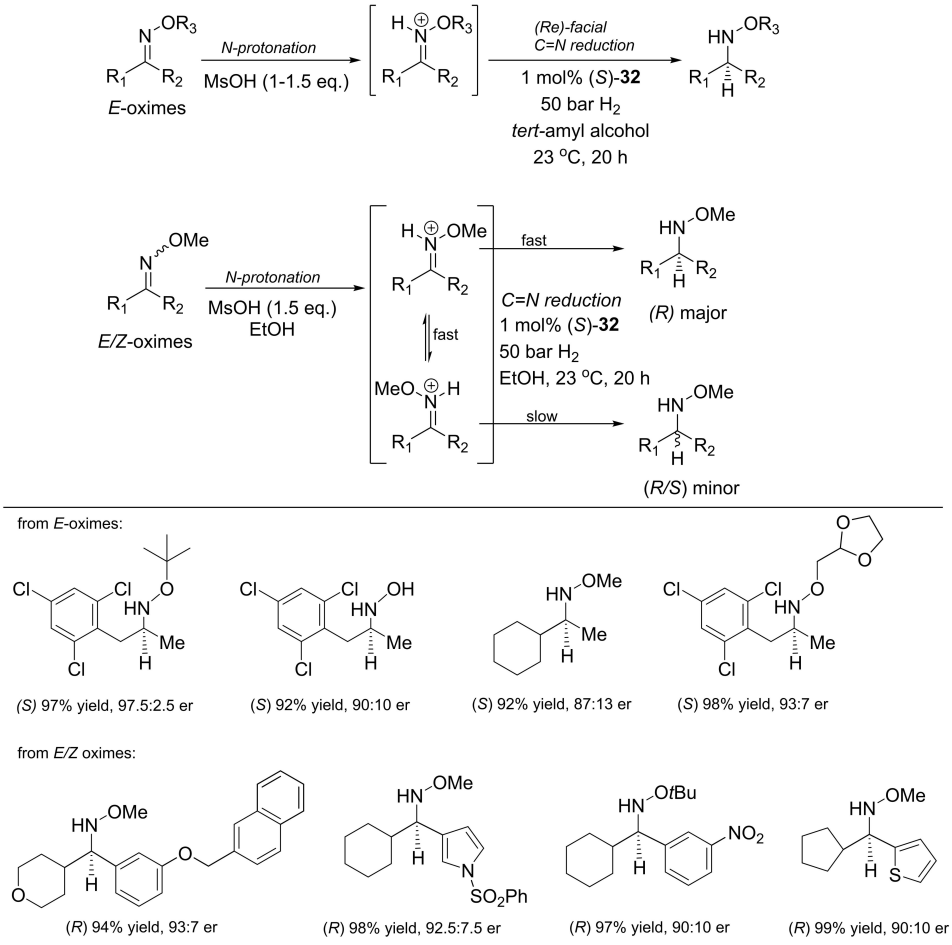
Iridacycle **49** was investigated as a catalyst for reductive amination of acetophenone with benzylamine. However, the catalyst showed no asymmetric induction (Scheme 25).[34]

More recently, Leung et al.[40] explored the iridacycle below, an isomer of **10**, for the catalytic asymmetric 1,2-dihydrophosphination of acrylonitrile, obtaining a remarkably high ee of 99 %. However, the conversion was low under the conditions employed even after three days of reaction (30 %), as shown in Scheme 26.

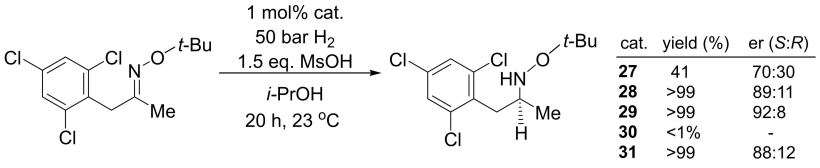
4. Achiral Reduction

4.1. Achiral Hydrogenation

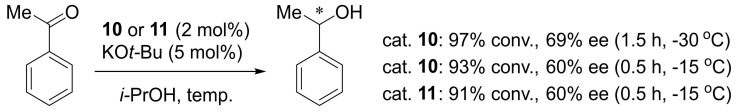
A great number of chiral but racemic iridacycles have been synthesized in the past, some of which have been explored for achiral hydrogenation with H_2. The recent results are summarized below. The Choudhury group reported an "abnormal NHC"-derived iridacycle[41] for atmospheric pres-



Scheme 18. AH of oximes with iridacycle **32**.

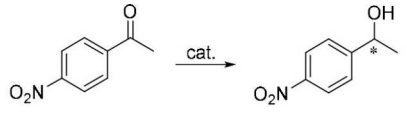


Scheme 19. Comparison of AH with iridium complexes **27**–**31**.



Scheme 20. ATH of acetophenone with iridacycles **10** and **11**.

sure hydrogenation of various aldehydes.[42] Based on their previous studies,[43,44] the free, basic imino-nitrogen from the benzimidazoleto moiety is prone to protonation and thus has the ability to capture the proton generated from heterolytic H_2 splitting. Additionally, the imidazole-5-ylidene moiety, an abnormal NHC with strong σ donor capacity, facilitates hydride transfer. The bifunctional iridium catalyst showed efficient, chemoselective hydrogenation of aldehydes in aque-

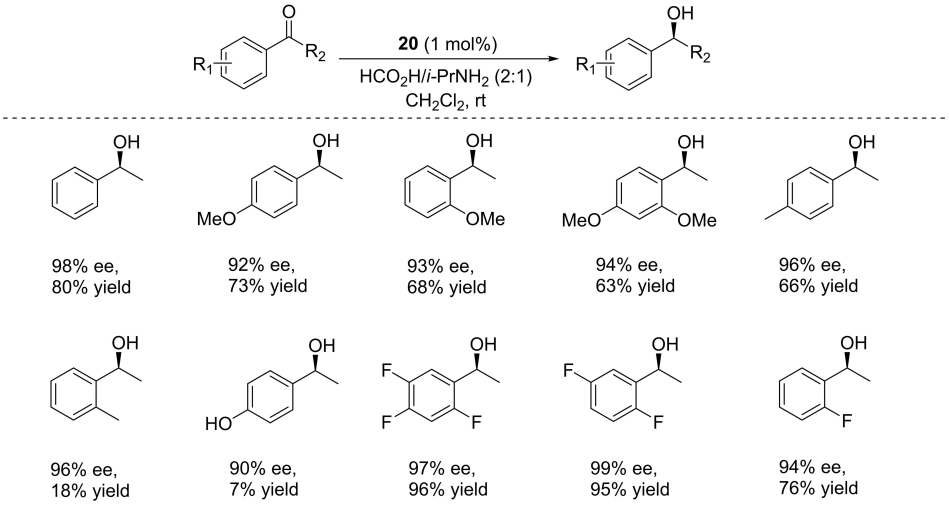


Cat.	Condition	Time (h)	Conv. (%)	ee (%)
19	HCO_2H/Et_3N (5/2), CH_2Cl_2, rt	15h	75	4 (*R*)
20	HCO_2H/Et_3N (5/2), CH_2Cl_2, rt	2h	100	73 (*S*)
19	HCO_2H/*i*-$PrNH_2$ (2:1), CH_2Cl_2, rt	3h	30	5 (*R*)
20	HCO_2H/*i*-$PrNH_2$ (2:1), CH_2Cl_2, rt	3h	100	93 (*S*)

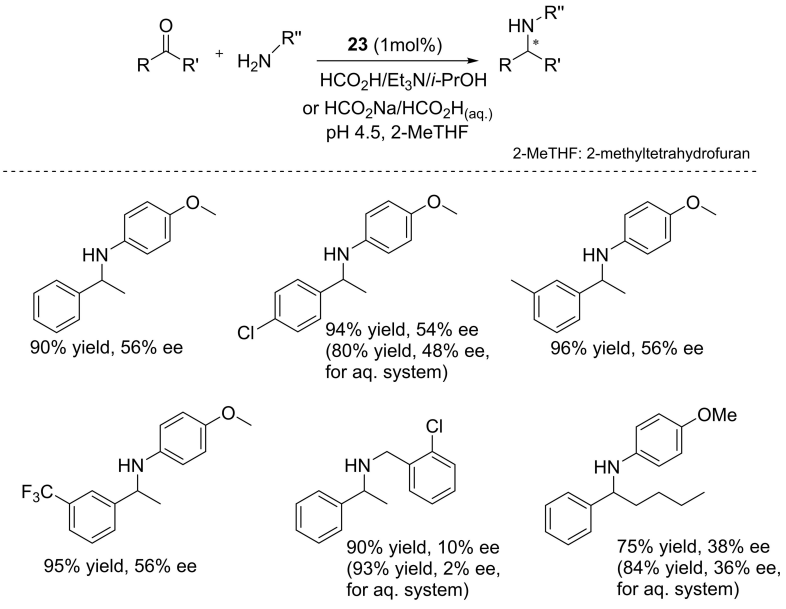
Scheme 21. Comparison of ATH of *p*-nitroacetophenone catalysed by **19** and **20**.

ous conditions. Mechanistic studies show a first-order rate dependence on the aldehyde during catalysis, suggesting a bimolecular reaction mechanism and the possibility of an outer-sphere hydride transfer pathway (Scheme 27).

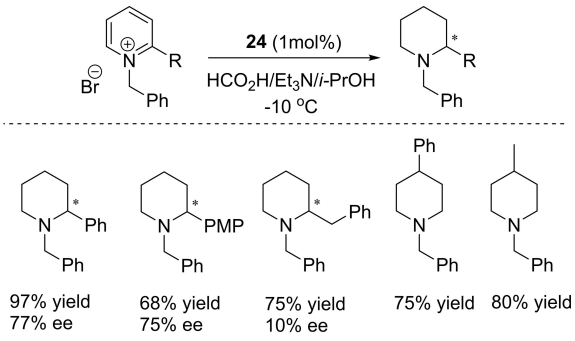
Later, Choudhury et al. reported a bifunctional iridium complex bearing an uracil-abnormal NHC ligand, which undergoes acid/base switchable hydrogenation catalysis.[45] Inspired by nature, chemists have long been interested in the development of catalysts whose activity could be influenced by external chemical or physical stimuli, such as light, pH, metal ion coordination and mechanical forces.[46] In this work, the



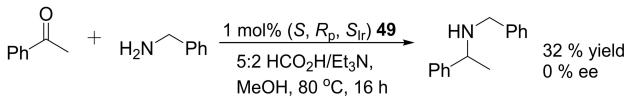
Scheme 22. ATH of various aromatic ketones with complex **20**.



Scheme 23. DARA of ketones with amines catalysed by complex **23**.



Scheme 24. ATH of selected pyridinium salts with complex **24**.

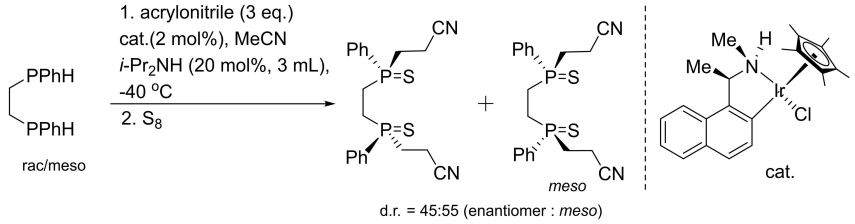


Scheme 25. Iridacycle **49** catalysed reductive amination.

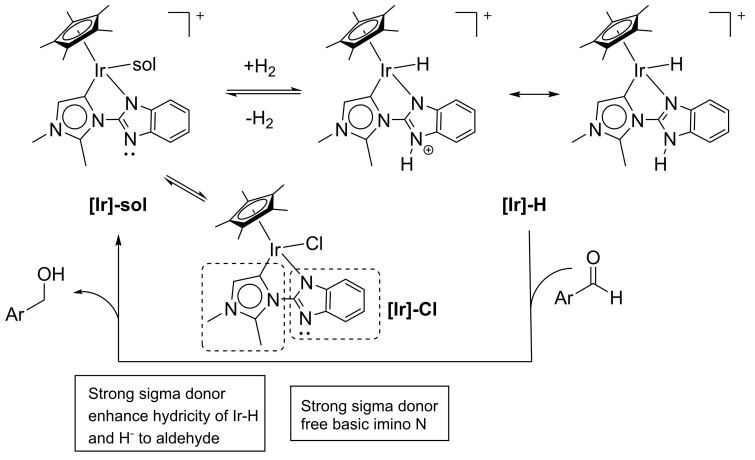
Ir–NHC catalyst showed high activity in hydrogenation of quinoxalines under atmospheric H_2 pressure. The catalysis was found to be switched off by addition of K_2CO_3 and switched on again by acid. The uracilate moiety may undergo lactam-lactim tautomerization, thus favouring heterolytic H_2 activation. Based on in situ NMR studies, a mechanism was proposed as shown in Scheme 28. The coordinatively saturated Ir–H intermediate is prone to transfer the hydride to quinoxaline assisted by the adjacent protic O–H functionality. In the presence of a base, no protic O–H is available, making quinoxaline hard to accept the hydride. The addition of acid restores the acidic hydroxy group, activating the substrate while facilitating hydride and proton transfer.[47,48]

In 2018, Deng et al. reported benzothiazole-derived iridacycles for hydrogenation of imines and quinolines.[49] The air-stable C,N-chelated iridium complexes were prepared via C–H activation of benzothiazole ligands with $[Cp^*IrCl_2]_2$; no C,S-chelated product obtained. Various imines and quinolines were hydrogenated in high yields (Scheme 29). In the presence of AgOTf, the yields were significantly improved.

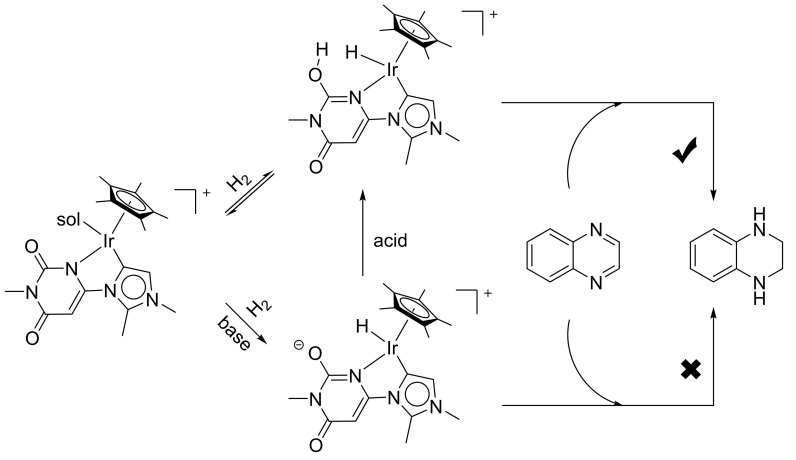
In 2019, Hartwig et al. reported a linear-selective hydroaminomethylation of α-olefines with a dual-catalytic system (Scheme 30).[50] The transformation comprised two steps, hydroformylation catalysed with a rhodium–diphosphine complex followed by reductive amination enabled with an iridacycle (**68**), which we reported earlier.[51] The latter step was conducted under transfer hydrogenation conditions, however, using sodium formate as



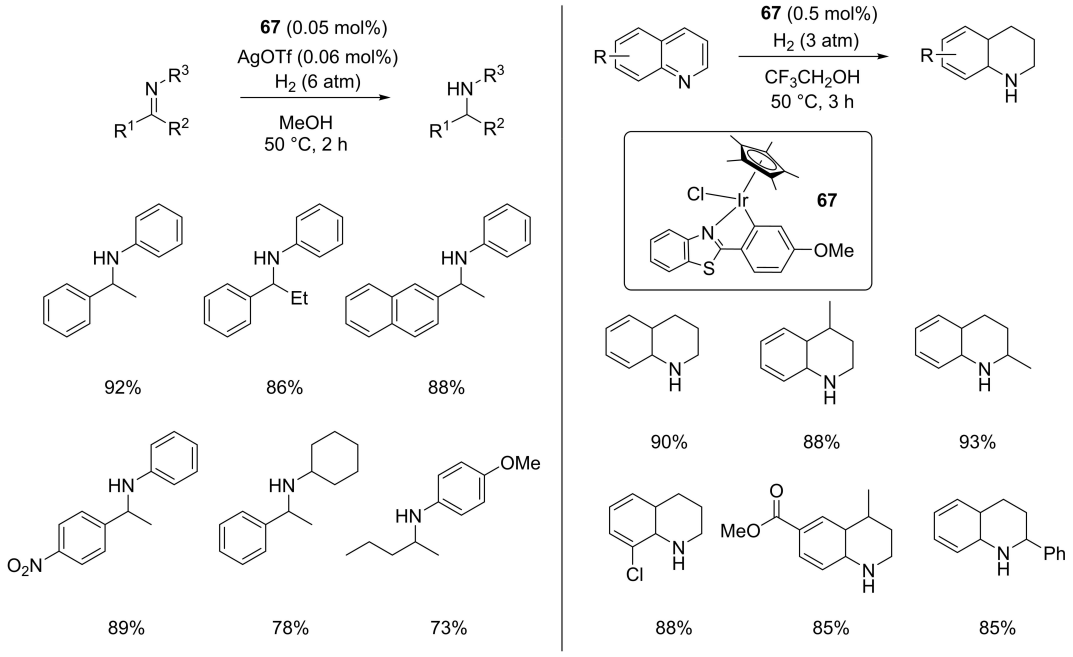
Scheme 26. Asymmetric 1,2-dihydrophosphination of acrylonitrile with an iridacycle.



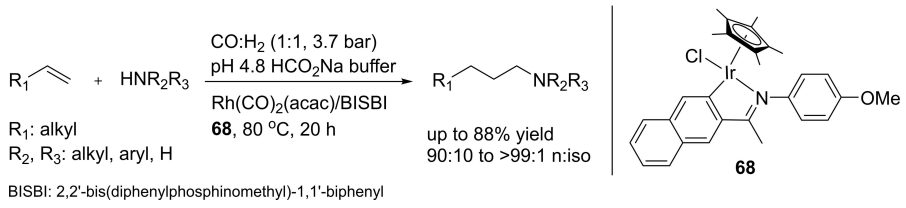
Scheme 27. Plausible reaction mechanism involving outer-sphere hydride transfer.



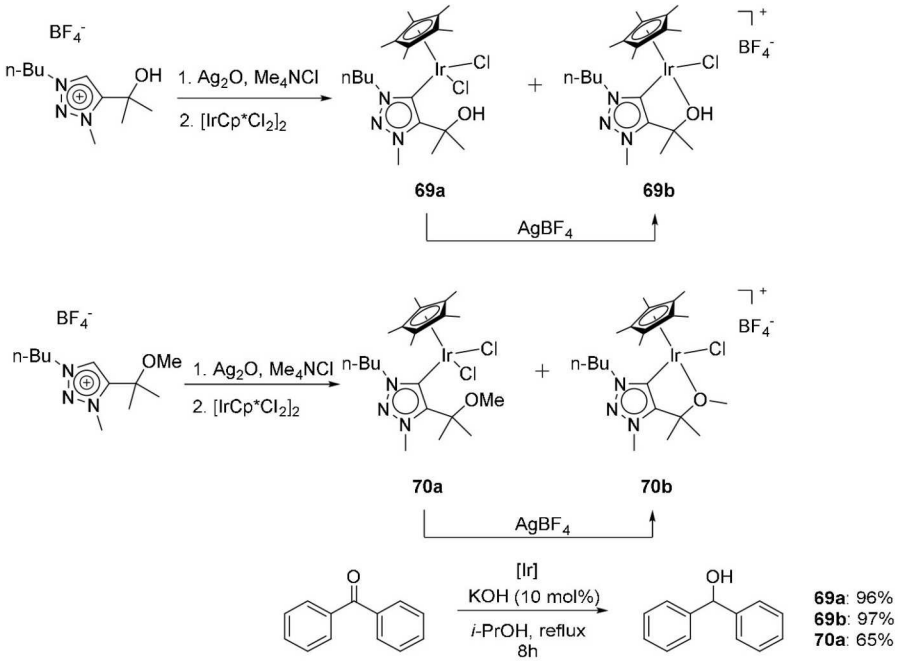
Scheme 28. Proposed reaction mechanism for switchable hydrogenation of quinoxaline.



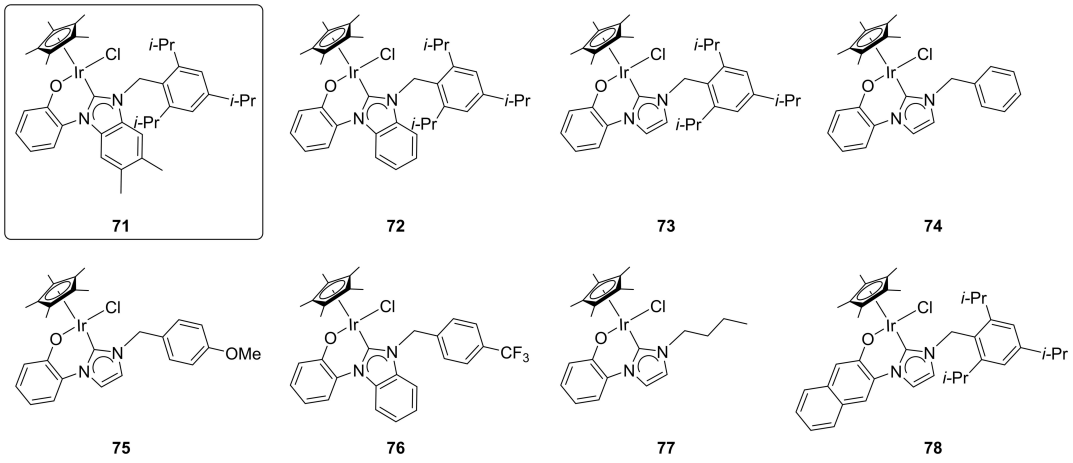
Scheme 29. Selected examples of iridacycle-catalysed hydrogenation of imines and quinolines.



Scheme 30. Linear-selective hydroaminomethylation of α-olefins catalysed by two metal complexes.



Scheme 31. Synthesis and application in TH of iridium complexes with triazolylidene ligands.

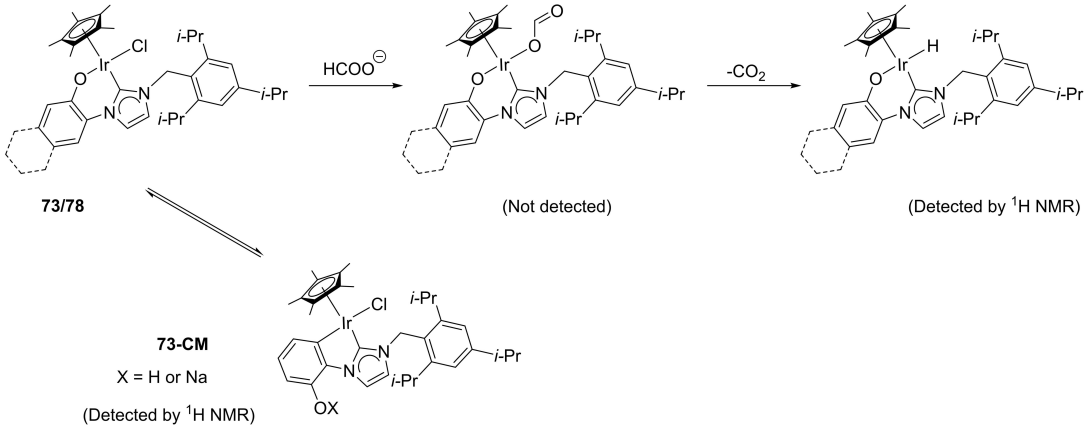


Scheme 32. NHC–Ir complexes bearing *O*-aryloxide moieties.

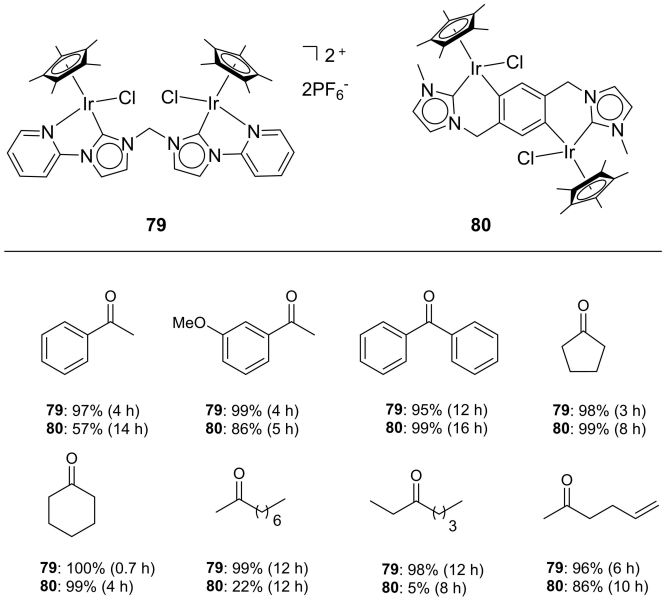
reducing agent. Notably, the iridacycle **68** was not poisoned by carbon monoxide. Aromatic, heteroaromatic, and aliphatic amines were obtained with high yields (up to 88%) and regioselectivities (90:10 to >99:1 *n*:*iso* ratios).

4.2. Achiral Transfer Hydrogenation

TH has attracted enormous attention due to its simple and safe operation compared to direct hydrogenation using molecular H_2.[52] Previously, our group reported iridacycle-catalysed TH of carbonyl compounds in water at optimal pH values.[51,53] In 2017, the Albrecht group reported synthesis of *O*-functionalised triazolylidene Ir(III) complexes (Scheme 31).[54] The activity of the iridium complexes **69–70** was examined in TH of a model substrate benzophenone with isopropanol as hydrogen source. **69a** and **69b** showed similar catalytic performance based on time-dependent conversion profiles, suggesting identical catalytically active species involved in the TH. Higher conversions were observed with the complexes bearing the hydroxy than ether functionality (**70a**),



Scheme 33. Formation of iridacycles and iridium hydrides from *O*-aryloxide NHC iridium complexes.

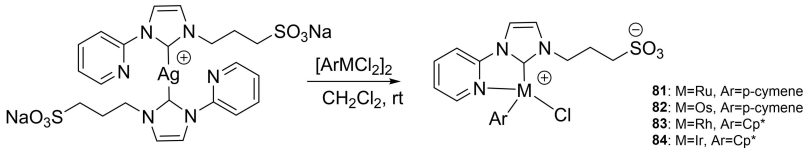


Scheme 34. TH of ketones with iridium complexes **79** and **80**.

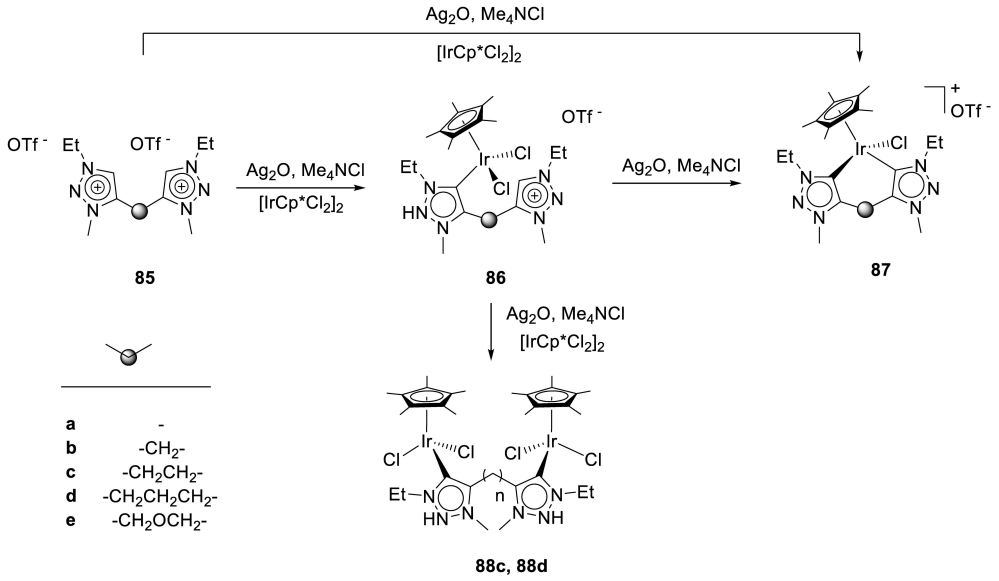
indicating the importance of hydroxy group in the formation of the C,O-cheated **70b**.[55]

NHC-bearing transition metal complexes have been successfully applied to numerous catalytic TH reactions.[56–70] In 2015, Gulcemal et al. reported a new phenoxide chelated Cp*Ir(NHC)complex for TH reductive amination under aqueous conditions.[71] As was shown before,[72] the catalytic activity was found highly affected by the structure of iridium complexes. Based on these studies, the Gulcemal group synthesized a set of new *O*-aryloxide chelated NHC–Ir complexes, which gave high yields for reductive amination of various carbonyls in water.[73] Scheme 32 shows the previously reported Ir–NHC complex **71** and modified variants **72**–**78**. The complex **73** with an imidazole moiety gave better conversions than the benzimidazole complex **72**. Further modifications revealed that complex **78**, where the phenyl ring is replaced by a naphthyl moiety, showed the highest catalytic activity. According to ^{1}H NMR, the higher activity of the *O*-naphthyl-based catalyst **78** than the *O*-phenoxide analogue **73** could be attributed to the faster formation of iridium hydride with the former during catalysis. Interestingly, the formation of the cyclometallated product **73-CM**, which was detected by ^{1}H NMR, slowed the metal hydride formation (Scheme 33).

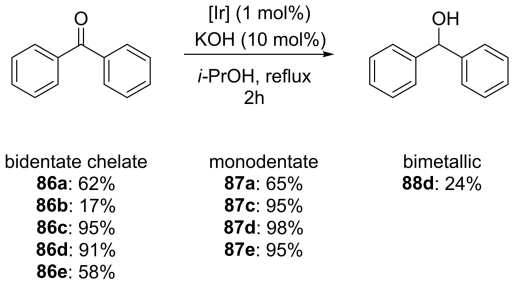
Most of the NHC–metal complexes are mononuclear.[74,75] The Graiff group developed binuclear iridium–NHC complexes, which showed good activities in the TH of ketones.[76] In these iridium complexes, a dicarbene ligand coordinates to two iridium centres in a bridging manner. The complexes **79** and **80** catalysed TH of various ketones in the presence of isopropanol and NaO*i*–Pr (Scheme 34). Interestingly, whilst complex **79** showed high activity for alkyl, aryl and cyclic



Scheme 35. Synthesis of water-soluble metal–NHC complexes.



Scheme 36. Synthesis of mono- and bi-metallic iridium complexes with ditriazolylidene ligands.

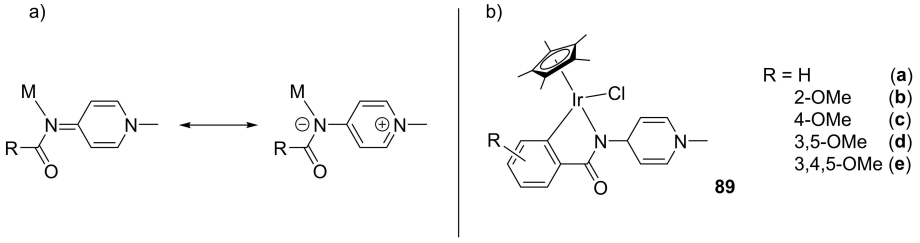


Scheme 37. Effects of linkers in ditriazolylidene ligands on TH of benzophenone.

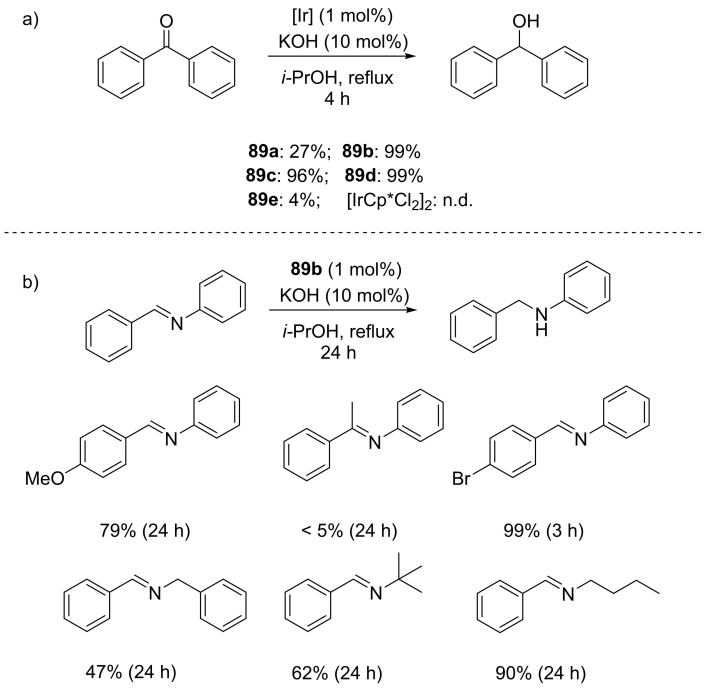
ketones, the iridacycle **80** was significantly less active for alkyl ketones.

By introducing highly hydrophilic substituents, the Kuhn group reported novel water-soluble metal–NHC catalysts.[77] The air-stable metal complexes were synthesized via trans-metallation from sulfonated Ag–NHC (Scheme 35). The catalytic TH of acetophenone with these water-soluble complexes was tested in HCO_2H/HCO_2Na at 80 °C. The rhodium complex **83** was shown to hydrogenate the substrate, affording 96% yield in 10 min. Ruthenium **81** and iridium **84** took 7 h to reach 87% and 92% yields, respectively, whilst the osmium complex **82** afforded only 3% yield in 7 h.

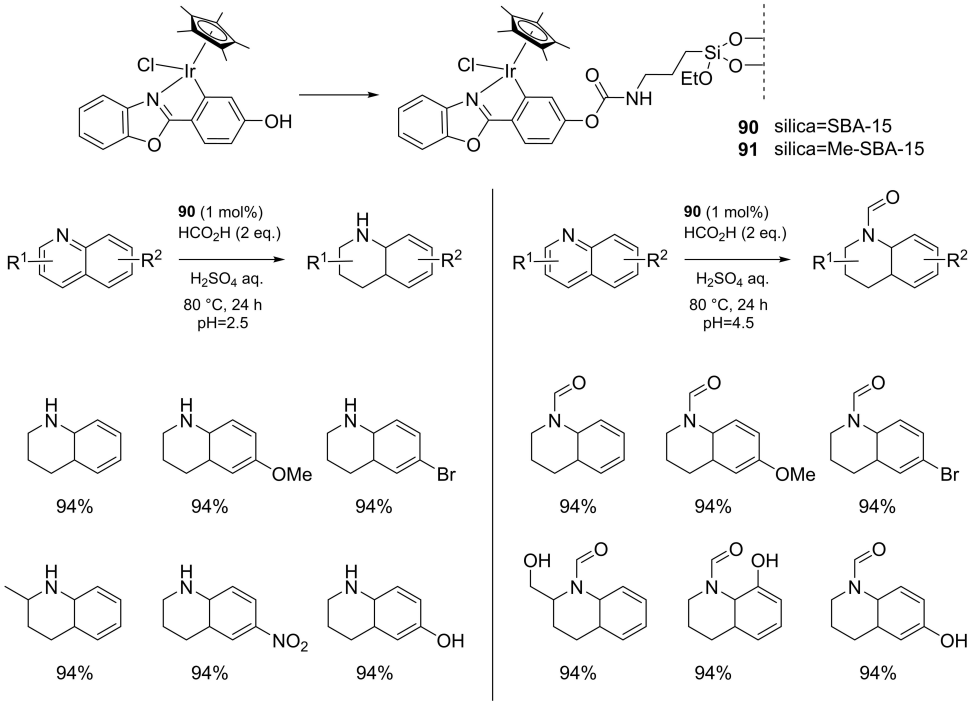
In 2017, the Albrecht group reported a series of ditriazolylidene–iridacycle complexes containing alkyl or ether linkers with different lengths, and studied the effect of the linkers on the catalytic performance in TH.[78] Scheme 36 shows the synthesis of mono- and bi-metallic iridium complexes with the ditriazolylidene ligands. The monocarbene Ir(III) complex **86** was formed when 1 equivalent of Ag_2O was used, while the bidentate–NHC complex **87** could be synthesised with additional Ag_2O. In the presence of the iridium dimer and Ag_2O, the bimetallic complexes **88** was formed from **86**. These complexes were examined as catalyst precursors in the TH of benzophenone using isopropanol as hydrogen donor. As shown in Scheme 37, there appears to be



Scheme 38. (a) Resonance structures of PYA; (b) Cp*Ir–PYA complexes synthesised.



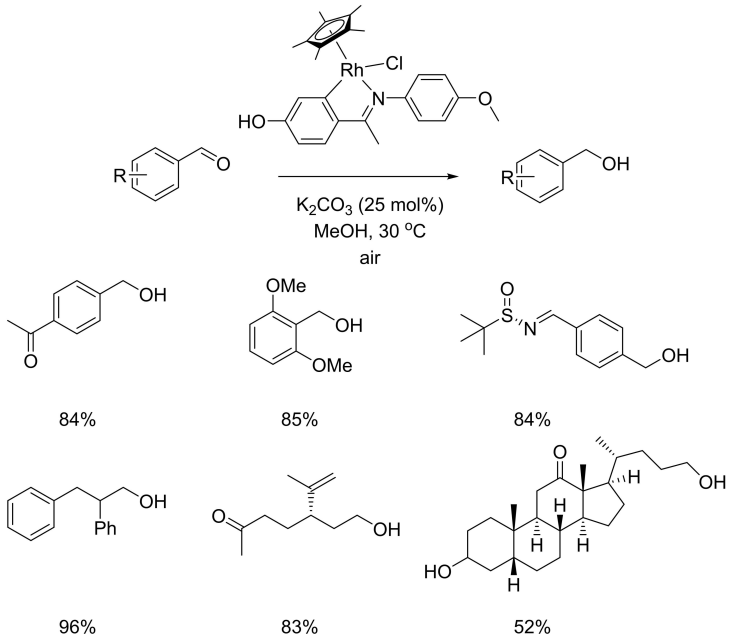
Scheme 39. TH of benzophenone and imines with Cp*Ir–PYA complexes.



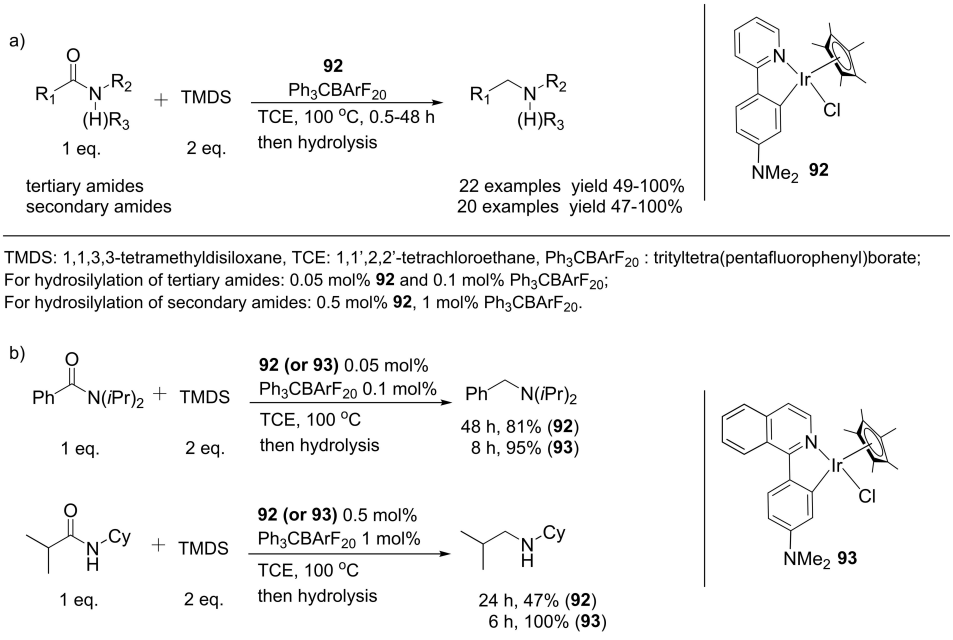
Scheme 40. TH of quinolines with immobilised iridacycles.

a correlation between the catalytic activity and linker, with the longer linker giving rise to faster TH.

The Albrecht group also reported a set of interesting iridium complexes decorated with aryl-substituted pyridylide-

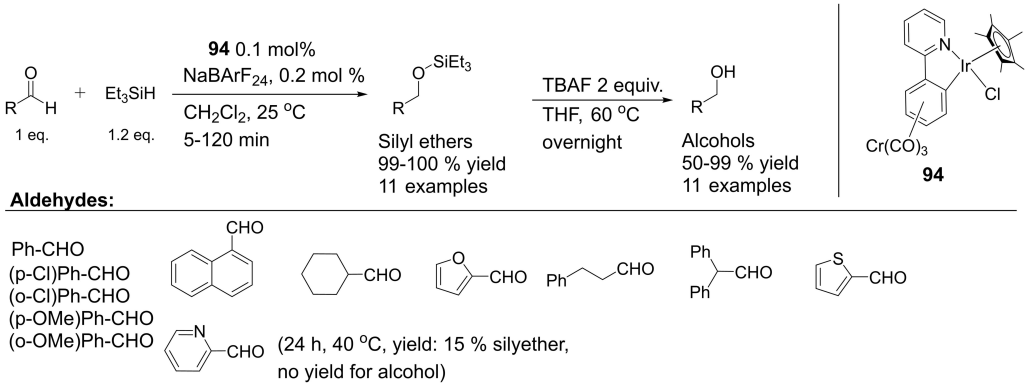


Scheme 41. Rhodacycle-catalysed TH of aldehydes with methanol at ambient conditions.

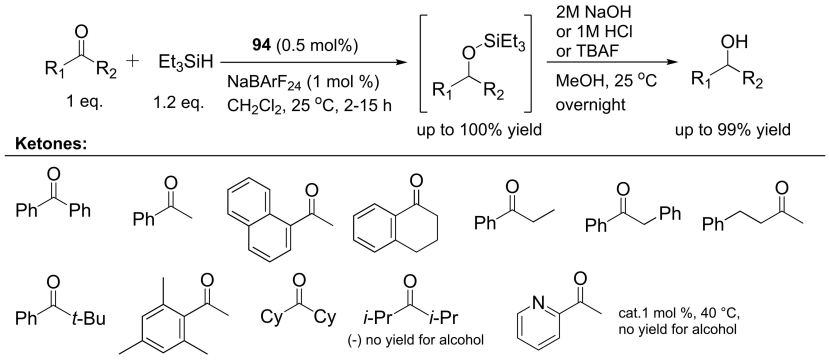


Scheme 42. a) Hydrosilylation of amides catalysed by **92** and b) comparison of **93** with **92** for hydrosilylation of amides.

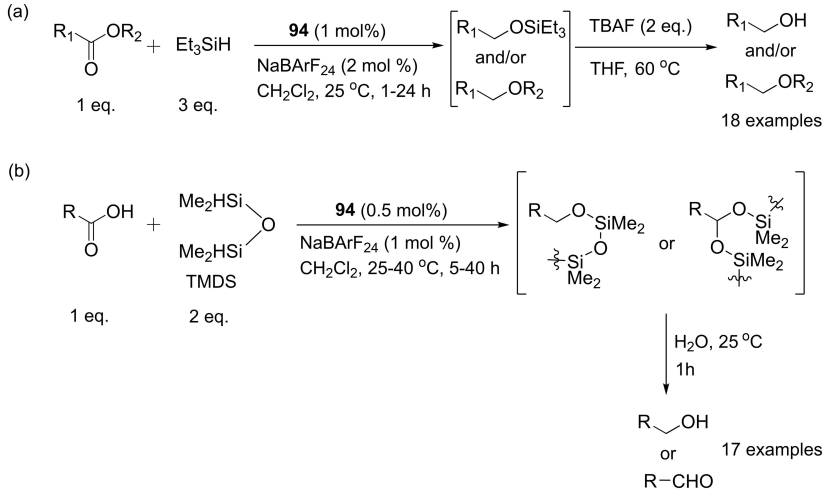
neamide (PYA) ligands.[79] PYAs have an electronically flexible nitrogen donor that can act as a π-acidic imine or as a π-basic pyridinium amide when coordinated to a metal (Scheme 38a). The simple synthetic procedures for PYAs allow for easy modification of their electronic and steric properties, which could be harnessed to improve the catalytic activity. Air-stable iridium complexes **89** were isolated from the reaction of $[IrCp^*Cl_2]_2$ with the corresponding ligands (Scheme 38b). In the catalytic TH of benzophenone, higher conversions were achieved with the PYA iridacycles compared with $[IrCp^*Cl_2]_2$, and the PYA ligands exerted a considerable effect on the TH activity, with high activity observed when electron-donating



Scheme 43. Hydrosilylation of aldehydes catalysed by iridacycle **94**.

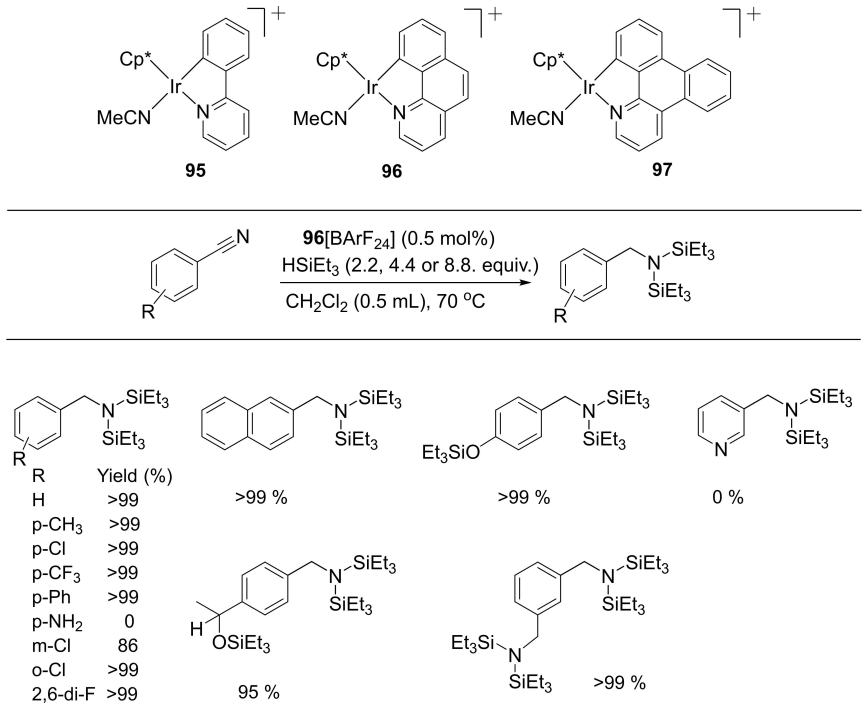


Scheme 44. Hydrosilylation of ketones into alcohols with iridacycle **94**.

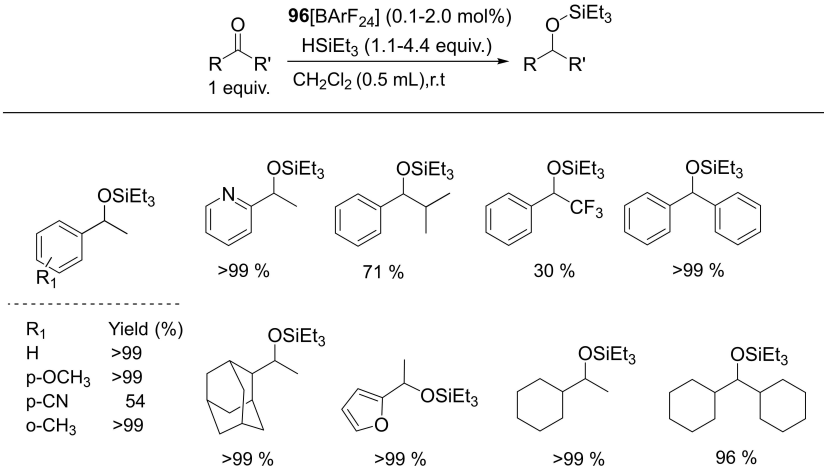


Scheme 45. Hydrosilylation of esters (a) and carboxylic acids (b) with iridacycle **94**.

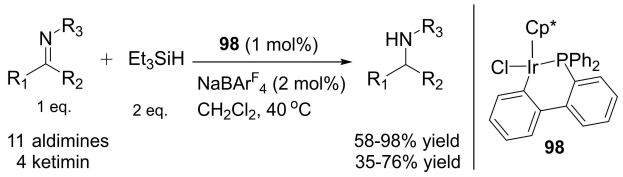
methoxy groups were appropriately introduced (**89 b,c,d**) (Scheme 39). The authors attributed the low activity of **89 e** to the shielding of iridium coordination site caused by excessive substitution of the arene group.[80] The complex **89 d** was used as the optimal catalyst for TH of various ketones, including ketones with pyridyl moieties.[56] Imines were investigated as substrates under similar conditions with **89 b** as catalyst (Scheme 39). Electron-withdrawing substituents on the sub-



Scheme 46. Cationic iridacycles and double hydrosilylation of arylnitriles catalysed by **96**.



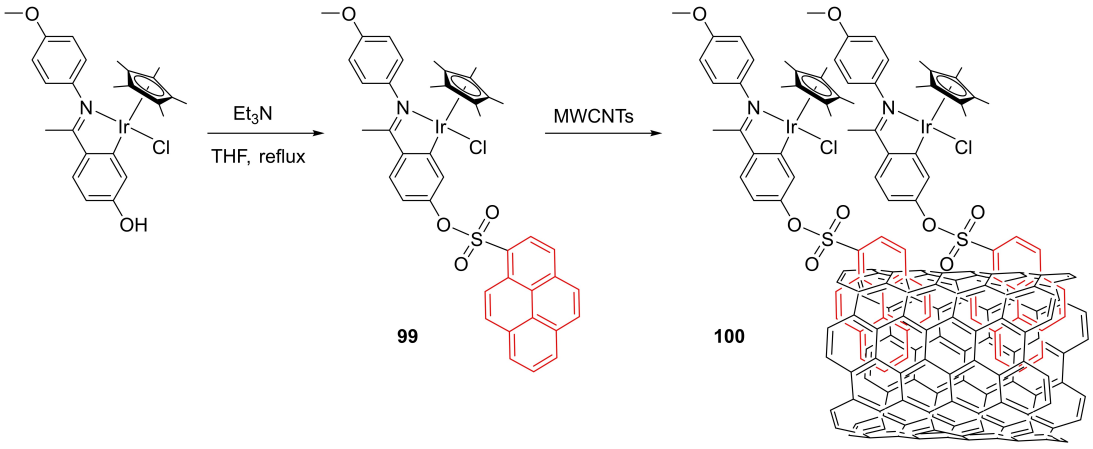
Scheme 47. Hydrosilylation of ketones catalysed **96**.



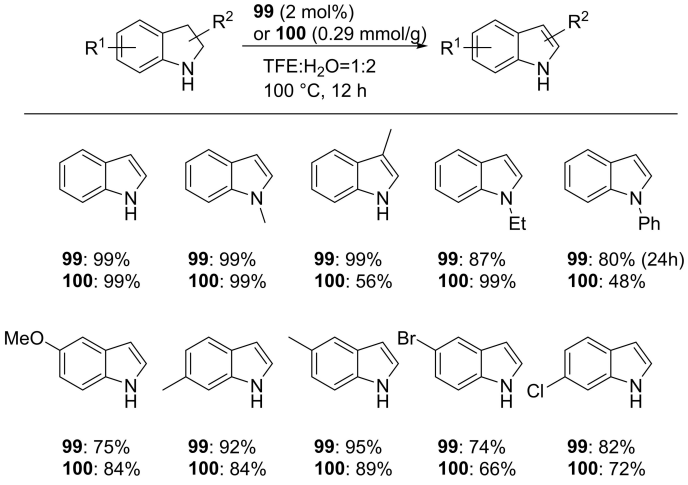
Scheme 48. Hydrosilylation of imines catalysed by iridacycle **98**.

strates facilitate the TH, whilst electron-donating groups decelerate the process, showing the same trend as for ketones.

TH is an attractive method to access tetrahydroquinolines, valuable building blocks for pharmaceutical synthesis.[81] The Fujita group[82] and ours[83] reported work on homogeneous TH of quinolines using $[IrCp^*Cl_2]_2$ and iridacycles, respectively. In 2017, Hou et al. developed mesoporous silica (SBA-15) supported iridium catalysts for selective TH of quinolines in water.[84] Two immobilized catalysts, **90** and **91**, were



Scheme 49. Synthesis of iridacycle **99** and immobilised variant **100**.



Scheme 50. Dehydrogenation of indolines with iridacycle **99** and immobilised **100**.

prepared by connecting an iridacycle to SBA-15 and a trimethylsilylated variant (Me–SBA-15) with 3-(triethoxysilyl)-propyl-isocyanate as a linker. The catalyst showed high activities in TH of quinolines with formic acid as hydrogen source in water (pH = 2.5). *N*-Formyltetrahydroquinolines could be synthesized in a one-pot, two-step process by simply adjusting the pH value to 4.5 (Scheme 40). The silica-supported catalyst **90** could be separated by centrifugation and reused in the reductive transformation of quinolines without significant decrease in yield.

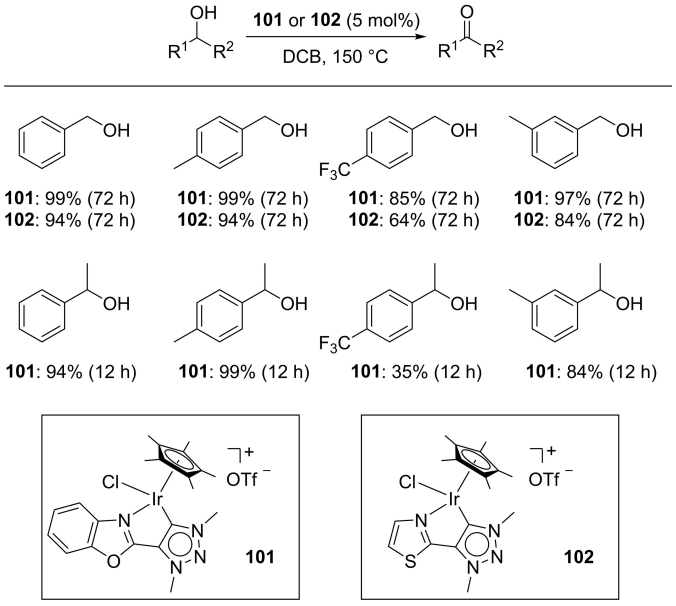
In recent years, our group have studied a series of simple iridacycles such as **9**, revealing their high catalytic efficiency in the TH of carbonyl compounds, with formic acid as the hydrogen source.[8a,53] Notably, the analogous rhodacycles are active in methanol dehydrogenation even at room temperature, allowing for TH reactions with methanol as the hydrogen source. For example, a wide range of aromatic and aliphatic aldehydes were reduced to the corresponding alcohols with methanol as both the hydrogen source and solvent near room temperature (Scheme 41).[85,86]

4.3. Achiral Hydrosilylation

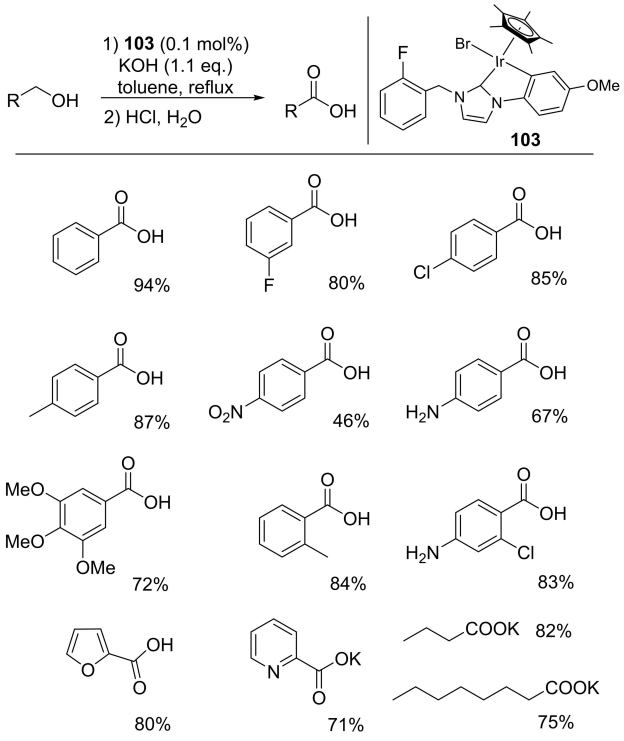
Iridacycle-catalysed hydrosilylation reactions of imines, esters and amides or *O*-dehydrosilylation of alcohols were reported by the groups of Agbossou-Niedercorn, Michon and Djukic.[21,87] In 2017, Agbossou-Niedercorn and Michon et al.[88] described iridacycle **92** as pre-catalyst for the hydrosilylation of tertiary and secondary amides at low catalyst loadings (Scheme 42). They found that the activity of **92** can be improved through ligand modification, by changing the chelating 2-phenylpyridine ligand to a 1-phenylisoquinoline one (**93**). When **93** was applied to hydrosilylation of challenging amides, the related amines were obtained with higher yields in a shorter time.

The same group also reported an interesting Ir(III) metallacycle **94** as catalyst for hydrosilylation of various ketones and aldehydes in the presence of sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate ($NaBArF_{24}$) under mild conditions (Scheme 43–44).[89] This complex was also able to catalyse selectively the reduction of esters and carboxylic acids (Scheme 45), resulting in, depending on the substrate, either alcohols/ethers or alcohols/aldehydes, respectively. The authors proposed an ionic hydrosilylation pathway, which starts from metathesis of the pre-catalyst **94** with $NaBArF_{24}$ to form a cationic complex.

In 2017, Djukic et al. reported cationic iridacycles **95**–**97**, which catalyse hydrosilylation of nitriles and carbonyls (Scheme 46 and Scheme 47).[90] For example, iridacycle **96** was shown to catalyse double hydrosilylation of a wide variety of aryl nitriles. These nitriles were converted into the correspond-



Scheme 51. Bass-free dehydrogenation of alcohols with iridacycles **101** and **102**.



Scheme 52. Acceptorless dehydrogenation of alcohols to acids with **103**.

ing *N,N*-disilylamines with good yields (86–99%), except for 4-aminobenzonitrile or 3-cyanopyridine, as shown in Scheme 46. Complex **96** (with the counter anion $BArF_{24}$) was also explored for hydrosilylation of a series of ketones and aldehydes at room temperature without the need for any additives. Examples of ketones reduction are seen in Scheme 47.

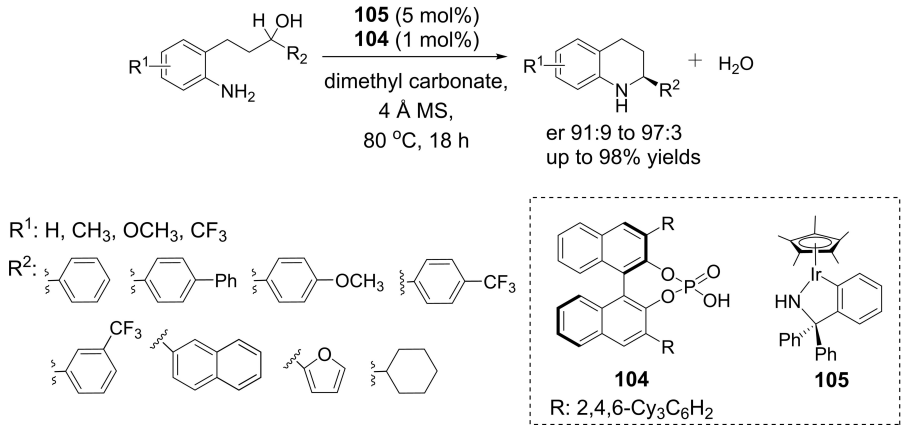
In 2018, Zhu et al. reported phosphine-containing five-, six- and eight-membered cycloiridated complexes, including their insertion reactions with aromatic alkynes.[91] The iridacycles were screened for their catalytic activities in the hydrosilylation of *N*-benzylideneaniline, the most active being the six-membered iridacycle **98**. The complex was applied to the hydrosilylation of various aldimines and ketimines, affording the corresponding amines in 35–98% yields (Scheme 48).

5. Dehydrogenation

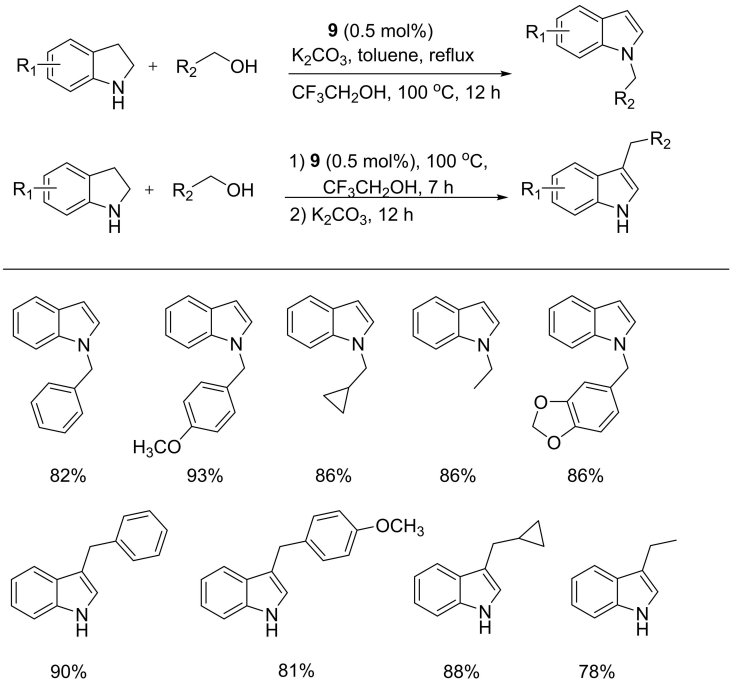
Catalytic dehydrogenation (CDH) has attracted much attention from the viewpoint of sustainable and green chemistry, avoiding the use of stoichiometric oxidants.[92,93] In 2013, we reported a versatile iridacycle for acceptorless CDH of benzofused *N*-heterocycles with high activity.[94] Later, this cyclometallated Ir complex was immobilized onto multiwalled carbon nanotubes (MWCNTs) via π-π stacking interactions, aimed at recycling of the catalyst (Scheme 49).[95] The iridacycle was modified with a pyrene substituent and then immobilized onto MWCNTs. The similar conjugated π systems in pyrene and MWCNTs led to effective π-π stacking. Addition of water into the THF solution of iridacycle **99** decreases its solubility, promoting the π-π interaction because of the hydrophobicity of **99**. The activity of the immobilized Ir catalyst **100** was investigated in CDH of indolines in aqueous conditions and was shown to be comparable with that of the homogeneous precursor (Scheme 50).

Since TH often involves the dehydrogenation of the hydrogen donor isopropanol, it is not surprising that cyclometallated iridium complexes have been explored for catalytic dehydrogenation of alcohols, although many methodologies are available for the oxidation of alcohols.[96–100] Dieguez et al. reported iridacycle-catalysed acceptorless oxidation of alcohols with liberation of hydrogen gas.[101] In their study, the iridium catalysts bearing benzoxazole (**101**) and thiazole (**102**) moieties show a higher activity than catalysts with a pendant ether group (Scheme 51). Generally, the conversion is substrate dependent, higher for secondary alcohols than for primary in 1,2-dichlorobenzene (DCB). It is noted that the common iridium precursor compound, $[Cp^*IrCl_2]_2$, is active in CDH of alcohols, as showed by Yamaguchi, Fujita and co-workers earlier.[102]

With the help of noble metal catalysts, aldehydes and ketones are easily obtained by CDH of alcohols.[103–109] However, the direct dehydrogenation of alcohols to carboxylic



Scheme 53. Asymmetric cyclization of amino alcohols catalysed by an iridacycle and a chiral phosphoric acid.



Scheme 54. Dehydrogenative alkylation of indolines with alcohols catalysed by **9**.

acids without using an oxidant has been less reported. Since the first report by the Milstein group in 2013 using a ruthenium PNP pincer complex,[110] several Ru–phosphine[111–115] and NHC complexes[116–118] have been described. However, there remain problems of high catalyst loading, low turnover numbers, and/or long reaction time. Very recently, the Das group reported an iridium(III)–NHC complex which catalyses efficient acceptorless dehydrogenation of alcohols to carboxylic acids.[119] Under a low metal loading of 0.1 mol%, a wide range of alcohols (aromatic and aliphatic) were converted to the corresponding carboxylic acids in high yields (Scheme 52). The acids may be formed via a pathway involving dehydrogenation to aldehydes followed by a base-induced Cannizzaro reaction. Notably, this iridium complex could be recycled at least three times without losing its activity under the conditions employed.

In 2017, Zhao and co-workers reported the first highly enantioselective synthesis of 2-substituted 1,2,3,4-tetrahydroquinolines through the borrowing hydrogen methodology.[120] The dehydrogenation and hydrogenation were effected by a racemic iridacycle, with the asymmetric induction in the hydrogenation step brought about by a chiral phosphoric acid,

as shown in Scheme 53. Similar chiral induction had been demonstrated earlier.[121–123]

In 2015, the iridacycle **9** was shown to catalyse alkylation of amines with high yields.[124] Later in 2017, Wang and co-workers reported that the same iridacycle catalyses dehydrogenative coupling of indolines with alcohols.[125] Interestingly, N- and C3-alkylation could be effected selectively by simply varying the sequence of base addition (Scheme 54). Mechanistic studies suggest a borrowing hydrogen-dehydrogenation process and a dehydrogenation-borrowing hydrogen process for the N-alkylation and C3-alkylation reactions, respectively. The iridacycle was believed to play multiple roles in the reaction, catalysing the dehydrogenation of both amines and alcohols as well as the subsequent coupling reactions.

6. Conclusions

The past several years has witnessed the reporting of a number of iridacycle complexes. Apart from the more conventional C,N-chelated iridacycles, metallocene-based C,N ligands have been introduced, affording novel ferrocenyl and closely related iridacycles. NHCs directed C–H activation has also been explored to form C,C-chelated iridacycles. A great deal of effort has been made in generating enantiomerically pure iridacycles, achieving various degrees of control of chirality at iridium. Most of these iridacycles have been examined in reactions such as hydrogenation, transfer hydrogenation, hydrosilylation, or dehydrogenation, with some displaying high versatility and high activity. However, with few exceptions, asymmetric reduction with chiral iridacycles remains challenging in terms of acceptable enantioselectivity. This stems at least partly from the difficulty in controlling the absolute configuration of the iridium centre.

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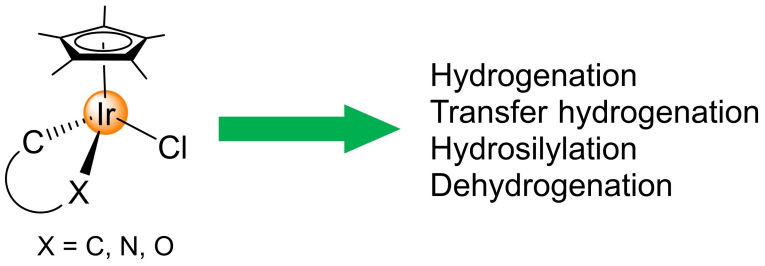

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Recent Development in the Synthesis and Catalytic Application of Iridacycles

A review is given of iridacycles featuring conventional C,N chelates and less common metallocene and carbene-derived C,N and C,C ligands, and their applications as catalysts in hydrogenation, transfer hydrogenation, hydrosilylation and dehydrogenation reactions.