Recent Catalytic Applications of (Cyclopentadienone)iron Complexes

Luca Pignataro*[a] and Cesare Gennari*[a]

Abstract: (Cyclopentadienone)iron complexes (CICs) are attractive pre-catalysts due to their easy preparation and robustness, which are uncommon features in homogeneous iron catalysis. They represent a striking example of how deeply a non-innocent ligand may affect the catalytic properties of the metal. Swinging between the cyclopentadienone and the hydroxycyclopentadienyl form, the ligand induces iron to engage in H_2 heterolytic cleavage and transfer. The latter represents the basis for numerous applications of CICs in redox chemistry (multiple bond reduction, alcohol oxidation) and 'hydrogen borrowing' processes (e.g., alcohol amination) that have been reported over the last few years. Moreover, very recently catalytic applications of CICs in different types of reactivity (where again the non-innocent ligand plays a key role), have appeared in the literature. This minireview summarizes the advancements that have been made in the field of CICs and their catalytic applications in the period 2014-2019.

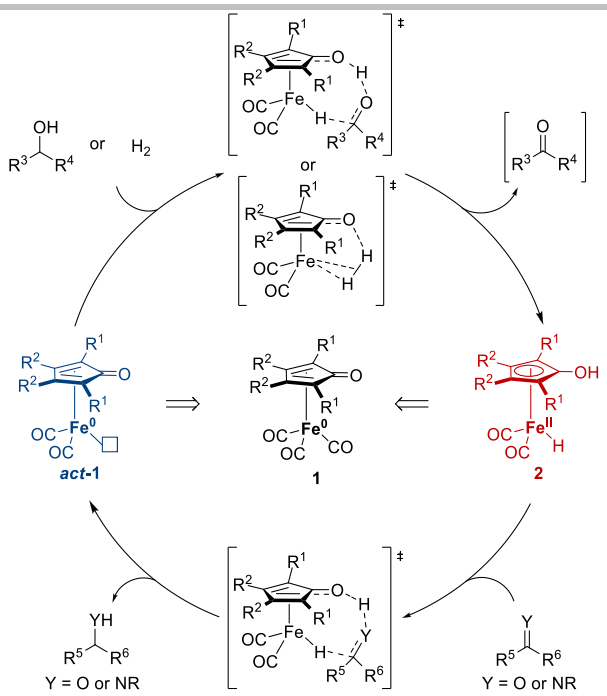
1. Introduction

For a long time, the application of iron in homogeneous catalysis was substantially neglected in favor of the "noble" metals (e.g., Ru, Rh, Ir, Pd, Au) and of other transition metals (e.g., Ni, Cu) that share some reactivity with them. This is quite surprising, considering that iron possesses several attractive features such as ready availability (2nd most abundant metal in the Earth's crust), low cost, scarce toxicity and a rich redox chemistry. The preference of iron complexes to undertake single electron transfer instead of two-electron processes is perhaps the main reason of this paradox, together with the analytical difficulty to carry out mechanistic investigations with this metal.[1] However, after the turn of XXI century, concerns about the sustainability of noble metals have stimulated the interest in the catalytic applications of 3d transition metals, and the number of publications on homogeneous Fe-catalysis has started growing exponentially.[1, 2] In this context, it soon became evident the importance of the ligand to harness the complex redox chemistry of iron and achieve the desired catalytic activity. In particular, use of the so-called "non-innocent" ligands – influencing the redox properties of the metal rather than being mere 'spectators' – emerged as an effective approach.[3] (Cyclopentadienone)iron complexes (CICs) **1** showcase this concept very well (Scheme 1): the ligand, swinging between the non-aromatic (***act*-1**) and the aromatic form (**2**), induces iron to engage in a bielectronic Fe^0/Fe^{II} catalytic cycle operating in hydrogen transfer (HT) reactions. Metal center and ligand cooperate to abstract H_2 from a donor (e.g. an alcohol, or H_2 itself) and to transfer it to a polar double bond (typically C=O or C=N). The active forms ***act*-1** and **2** may be easily accessed in situ from the parent CICs **1** by de-coordination of a CO ligand (Scheme 2 A)[4,5] and by Hieber base reaction (Scheme 2 B),[6,7] respectively. Unlike ***act*-1** and **2**, compounds **1** are stable complexes which can be even purified by flash column chromatography: besides the π-coordinated cyclopentadienone, three strong-field CO ligands are present, which enhance the d orbital splitting and stabilize a low-spin iron configuration. Alternatively, complexes ***act*-1** may also be generated by thermal dissociation of the isolated complexes **3** (Scheme 2 C), in which one of the CO groups has been replaced by a labile nitrile ligand.[4a,4c,8]

[a] Prof. Dr. L. Pignataro, Prof. Dr. Cesare Gennari
Università degli Studi di Milano, Dipartimento di Chimica
Via C. Golgi, 19 - 20133, Milan (Italy)
E-mail: luca.pignataro@unimi.it
cesare.gennari@unimi.it
Homepage: https://sites.unimi.it/gennarigroup/

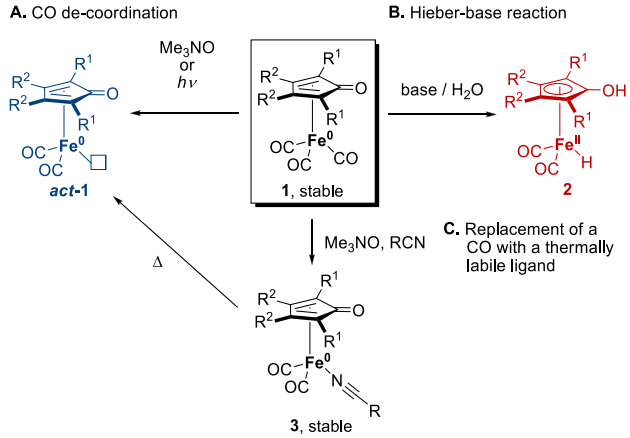
Luca Pignataro studied Industrial Chemistry at the University of Milan, where he graduated in 2003 and received his PhD in 2006 under the supervision of Prof. Franco Cozzi. In 2007 he joined the group of Prof. David Leigh at the University of Edinburgh (UK) as a post-doc, then he returned to Italy (2008) for post-doctoral experiences in the groups of Prof. Cesare Gennari (University of Milan) and Prof. Umberto Piarulli (University of Insubria). In 2012 he became a researcher at the University of Milan and in 2019 he was appointed associate professor. His main research interests include synthetic methodologies, homogeneous catalysis and medicinal chemistry.

Cesare Gennari graduated in Chemistry cum laude at the University of Milan in 1975. After becoming an assistant professor at the same University in the group of Prof. Carlo Scolastico (1978), he joined Prof. Clark Still's group at Columbia University (NY) as a research associate (1982-1983). In 1985 he became an associate professor and in 1994 a full professor of organic chemistry at the University of Milan. His awards include a NATO senior fellowship (1985), the Federchimica prize (1993), the Ziegler-Natta award and lecture (German & Italian Chemical Societies, 1997), the Ciamician medal (1986), the "Prize for research in synthetic organic chemistry" (2006), the Quilico (2013) and the Piria (2017) gold medals of the Italian Chemical Society. He is presently a member of the International Advisory Board of *EurJOC* and a *ChemPubSoc Europe* Fellow. His present research interests include the synthesis and biomedical applications of tumor-targeted drug conjugates, and the use of (cyclopentadienone)iron complexes as catalysts in hydrogen transfer reactions.



Scheme 1. Fe^0/Fe^{II} catalytic cycle operating in CIC-promoted hydrogen transfer (HT) reactions.

CICs were firstly reported in 1953 by Reppe and Vetter[9] and their structure was elucidated by Schrauzer in 1959,[10] but their potential for catalysis was then neglected for decades. Despite bearing strong similarity to the Shvo complex, whose activity in HT reactions was known since the 1980s,[11] the first catalytic applications of CICs were reported only in the late 2000s.



Scheme 2. In situ formation of the active complexes ***act*-1** and **2** from the stable pre-catalysts **1** and **3**.

In 2007, Casey and Guan published a seminal paper on ketone hydrogenation catalyzed by the (hydroxycyclopentadienyl)iron complex (HCIC) **2a** (Figure 1).[12] The latter compound, sensitive to air and light, had been originally prepared by Knölker and co-workers in 1999[13] starting from CIC **1a** (Figure 1), which was reported by the same group in 1992.[14]

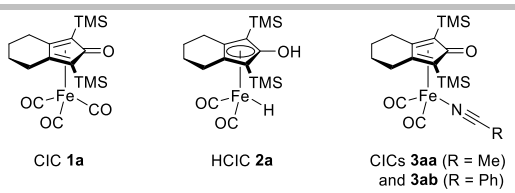


Figure 1. The 'Knölker's complexes' **1a** and **2a**, and the Funk's complexes **3aa** and **3ab**.

The studies of Casey and Guan established the mechanistic pattern outlined in Scheme 1 and triggered the interest of several research groups for the ambivalent reactivity of CIC/HCIC systems in HT reactions. A number of papers followed, in which the bench-stable CICs **1** were activated in situ (see Scheme 2), and were generally preferred to the sensitive isolated HCICs **2**.

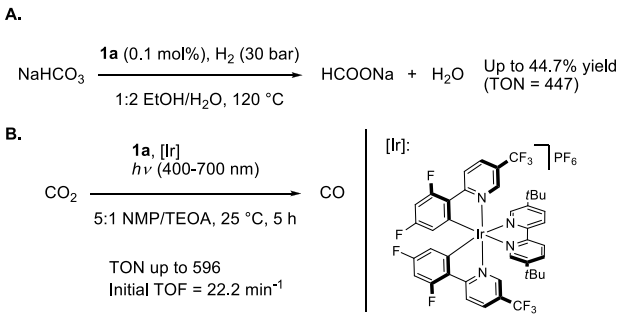
The catalytic applications of CICs/HCICs developed until the end of 2013 are nicely illustrated in an excellent review by Quintard and Rodriguez.[15] The present minireview has the purpose to summarize the most important applications of CICs published in the period 2014-2019, including the use of CICs in reactions not involving HT steps.

2. Applications in reactions involving HT steps

HT processes at large (i.e., covering both redox reactions and transformations not affecting the final oxidation state) represent by far the broadest application area of CICs, and a number of new reports have appeared in the literature since 2014.

2.1. Redox catalysis

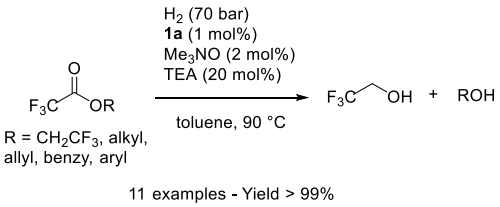
Redox processes – and reductions in particular – represented the first application of CICs/HCICs, and a number of advances in this field have been made in recent years. Using the Knölker's complex **1a** – which displayed higher catalytic activity than other screened CICs – Yang, Zhou and co-workers reported the catalytic hydrogenation (CH) of sodium bicarbonate to sodium formate (Scheme 3 A), proceeding with up to 44.7% yield at low catalyst loading (TON = 447).[16] The same transformation was also performed generating $NaHCO_3$ from CO_2 and NaOH before the hydrogenation step. In this reaction the catalyst activation seemingly took place by Hieber base reaction of pre-catalyst **1a** with the basic substrate.



Scheme 3. Hydrogenation of bicarbonates promoted by CIC **1a** (A),[16] and photoreduction of CO_2 with triethanolamine (B).[17] NMP = *N*-methyl-2-pyrrolidone. TEOA = triethanolamine.

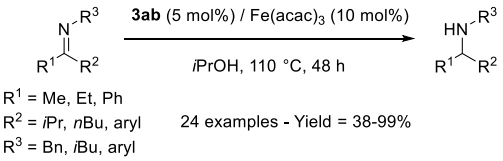
Later on, Beller and co-workers reported a methodology for the photochemical reduction of CO_2 promoted by CICs, visible light and an iridium complex as photosensitizer (Scheme 3 B).[17] Triethanolamine was used as electron/proton donor. Also in this case several CICs were tested, but **1a** gave the best result (TON up to 596 and initial TOF = 22.2 min^{-1}).

In 2016, our research group further extended the application scope of pre-catalyst **1a**, describing the first example of CIC-catalyzed hydrogenation of activated esters (Scheme 4).[18] Compared to the previously reported Fe-catalytic methods for ester reduction,[19] our method had the advantage of employing a readily available pre-catalyst instead of an expensive and air-sensitive pincer complex. However, the reaction scope in this case was limited to the highly activated trifluoroacetates.



Scheme 4. Hydrogenation of trifluoroacetate esters promoted by pre-catalyst **1a**.

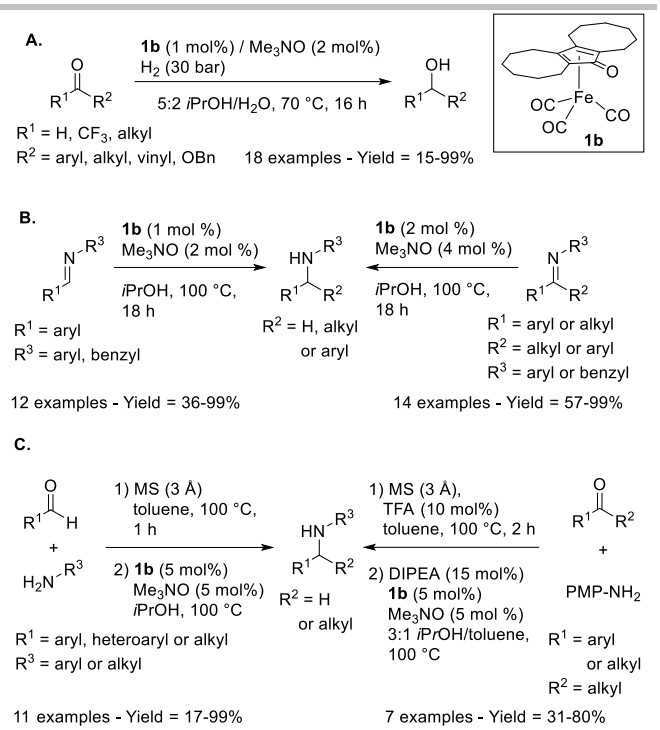
In 2016, Zhao and co-workers reported that both the HCIC **2a** and the thermally activable CIC **3ab** (Figure 1) can promote the catalytic transfer hydrogenation (CTH) of isolated ketimines with *i*PrOH in the presence of a Lewis acid co-catalyst [10 mol% $Fe(acac)_3$ under the optimized conditions].[20] The reaction scope covers a number of substrates deriving from both aliphatic and aromatic ketones (Scheme 5).



Scheme 5. Optimized conditions for ketimine transfer hydrogenation with *i*PrOH in the presence of a Lewis acid co-catalyst.

In 2015, Fu and co-workers reported the synthesis of γ-valerolactone by CTH of ethyl levulinate using *i*PrOH and catalyst **2a**.[21] More recently, De Wildeman and co-workers described the synthesis of the same product by CH of levulinic acid promoted by the Funk's complex **3aa**.[22]

Besides the advancements that have been made in recent years employing the Knölker's complexes (**1a**, **2a**) or their thermally activable derivatives ('Funk's complexes' such as **3aa** and **3ab**), attempts were also made to improve the catalytic activity of CICs by modifying the cyclopentadienone ligand's substitution. In 2017, our research group reported a cyclooctene-derived CIC (**1b**, Scheme 6) displaying higher catalytic activity compared to **1a** in the CH of C=O bonds.[23] Several ketones, aldehydes and a trifluoroacetate ester were reduced in high yield. In the CH of acetophenone, pre-catalyst **1b** showed a TON of 620, ca. five times higher than that obtained with **1a**.



Scheme 6. The highly active CIC **1b**, developed by our research group, and its applications in the CH of carbonyl compounds (A),[23] in the CTH of imines (B), and in the reductive amination of carbonyl compounds (C).[25] DIPEA = *N*,*N*-diisopropylethylamine.

A comparison of the kinetics of acetophenone CH promoted by **1a** and **1b** (Figure 2) shows that, while both reactions initially follow a pseudo-first order profile, after about 20 min the **1a**-catalyzed reaction remarkably slows down, reaching completion at reduced rate. This behavior is seemingly due to progressive catalyst degradation, which does not occur in the case of **1b**, possibly due to the bulky cyclooctane fused rings that prevent complex dimerization.[24]

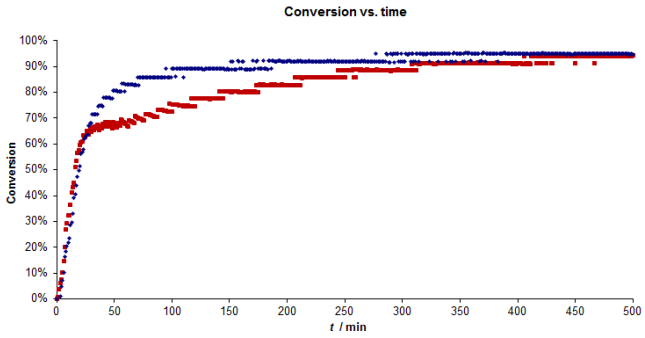
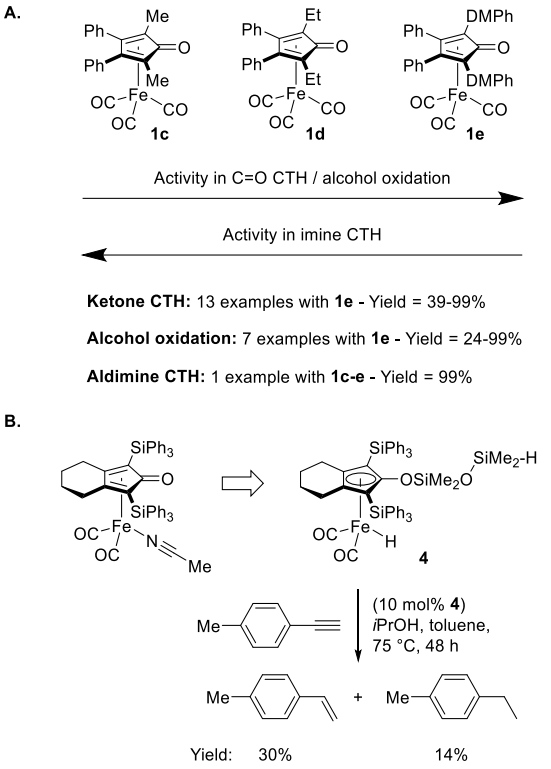


Figure 2. Kinetics of acetophenone CH promoted by pre-catalyst **1a** (■) and **1b** (♦) activated with Me_3NO. Reproduced from ref.[23]

Our group later developed a methodology for the Fe-catalyzed CTH of C=N bonds with *i*PrOH based on pre-catalyst **1b** (Scheme 6 B).[25] Thanks to the high activity of **1b**, non-activated aldimines and ketimines could be reduced by *i*PrOH without need of any co-catalyst (indispensable in the case of **1a**).[20] A one-pot protocol for the reductive amination of aldehydes and ketones was also developed (Scheme 6 C), which provided access to the amine products without need to isolate the imine intermediates.

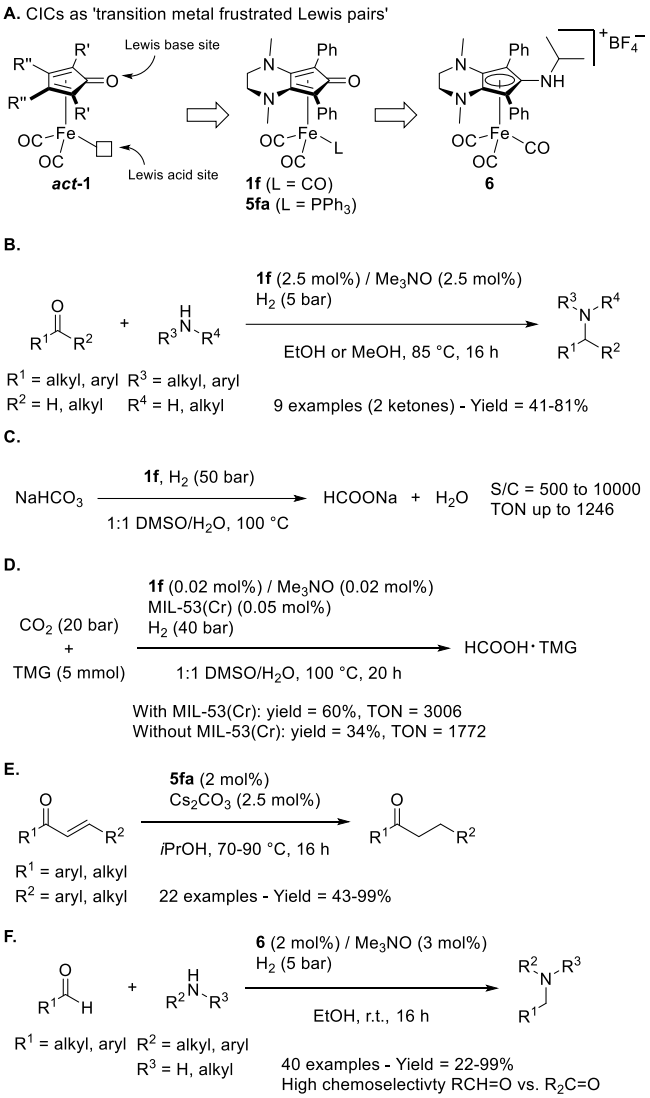
In 2018, Funk and co-workers published a study on the CICs possessing no rings fused to the cyclopentadienone,[24a] which have received less attention than bi- or tricyclic systems such as **1a-b**. Three new monocyclic CICs (**1c-e**, Scheme 7) were synthesized and tested in ketone CTH, alcohol oxidation and aldimine reduction, showing in all cases higher activity than the Knölker's complex **1a**.



Scheme 7. Monocyclic CICs **1c-e**, recently reported by Funk and co-workers, and their catalytic activity in HT reactions (A).[24] The (siloxyctclopentadienyl)iron complex developed by Nakazawa and its use in *p*-tolylacetylene CTH (B).[26] DMPh = 3,5-dimethylphenyl.

In 2014, Nakazawa and co-workers reported the transformation of a Funk-type complex into a (siloxycyclopentadienyl)iron complex (**4**) displaying totally different reactivity compared to CICs/HCICs (Scheme 7 B).[26] Indeed, complex **4** was found inert towards polar multiple bonds (e.g. aldehydes and ketones), promoting the CTH of *p*-tolylacetylene instead. Unfortunately, the catalytic activity displayed by complex **4** was modest and a mixture of alkene and alkane product was obtained.

In 2015, Poater, Renaud and co-workers reported the new CIC **1f** (Scheme 8 A) and its application in CH-based processes.[27] The catalyst design is based on the view of the activated CICs ***act*-1** as 'transition metal frustrated Lewis pairs',[28] in which the cyclopentadienone acts as base and the iron center as acid site. In agreement with the authors' expectation, the increase of electron density in the cyclopentadienone ligand due to the two amino substituents led to an improved catalytic activity of CIC **1f** compared to the Knölker's complex **1a** in the CH-based reductive amination of carbonyl compounds (Scheme 8 B). From the DFT-calculated reaction energy profile with **1a** and **1f** it emerged that, with the latter pre-catalyst, the TS of the rate-determining H_2 splitting step (see Scheme 1) is 3.4 kcal mol^{-1} lower in energy. Moreover, imine reduction by the active species **2f** (Scheme 1) was found exothermic, whereas the same step promoted by **2a** is endothermic.[27] CIC **1f** was also tested in the CH of sodium bicarbonate to sodium formate (Scheme 8 C), showing remarkable activity (TON up to 1246 with S/C = 10000). In a recent paper,[29] the use of pre-catalyst **1f** has been also extended to the CH of CO_2 in the presence of a base (1,1,3,3-tetramethylguanidine in the optimized conditions, Scheme 8 D). Remarkably, it was found that performing the reaction in the presence of a catalytic amount of the chromium-based MOF MIL-53(Cr) leads to a two-fold increase of the catalytic activity.

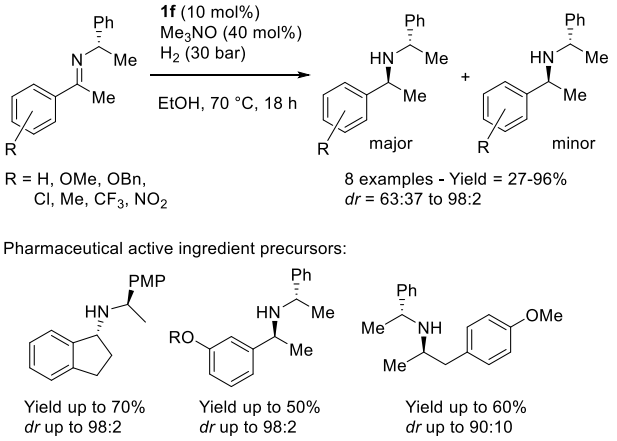


Scheme 8. The electron-rich Fe-complexes developed by Poater, Renaud and co-workers (A), and their use in CH-based reductive amination (B[27] and F[32]), in the CH of $NaHCO_3$ (C)[27] / CO_2 (D),[29] and in the chemoselective reduction of α,β-unsaturated ketones (E).[31] TMG = 1,1,3,3-tetramethylguanidine.

Using pre-catalyst **5fa** – a modified version of **1f** in which one CO is replaced by PPh_3[30] – Poater, Renaud and co-workers also developed an effective and general protocol for the chemoselective 1,4-reduction of α,β-unsaturated ketones by CTH with *i*PrOH (Scheme 8 E).[31] Use of cesium bases was found crucial to achieve the desired reaction, which gave good results also with several natural products. Very recently, the same research group brought further the concept of increasing the ligand's electron density, replacing the ketone functionality of complex **1f** with an amino group and so obtaining the cationic (aminocyclopentadienyl)iron complex **6** (Scheme 8 A).[32] As

expected, the latter pre-catalyst was found even more active than the CIC **1f**, promoting the CH-based reductive amination of aldehydes at room temperature (Scheme 8 F). Remarkably, under such mild conditions the reaction occurred with perfect chemoselectivity, leaving other functional groups, such as ketones and esters, unaffected. Very recently, Renaud and co-workers reported the synthesis of two water-soluble CICs, bearing ionic substituents in place of the methyl groups of **1f**.[33] These pre-catalysts were employed in the CTH and in the CTH-based reductive amination of aldehydes in water.

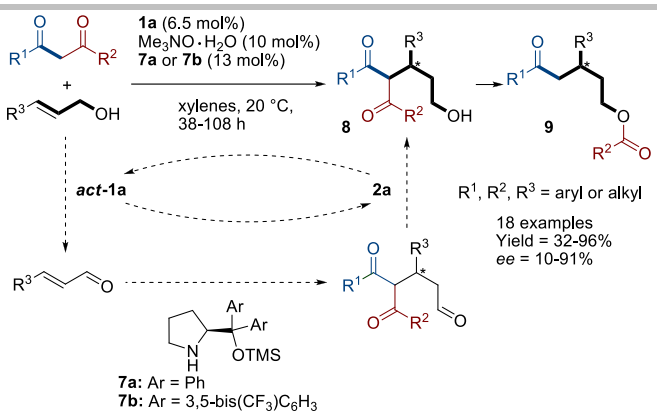
Pre-catalyst **1f** was also successfully employed by Benaglia and co-workers to promote the distereoselective hydrogenation of chiral ketimines (Scheme 9), affording the corresponding amines with good to excellent diastereomeric ratios and in higher yields compared to the Knölker's complex **1a**.[34] This methodology was also employed to synthesize three advanced intermediates of pharmaceutical active ingredients.



Scheme 9. Diastereoselective hydrogenation of chiral ketimines reported by Benaglia and co-workers.[34]

2.2. 'Hydrogen borrowing' (HB) processes

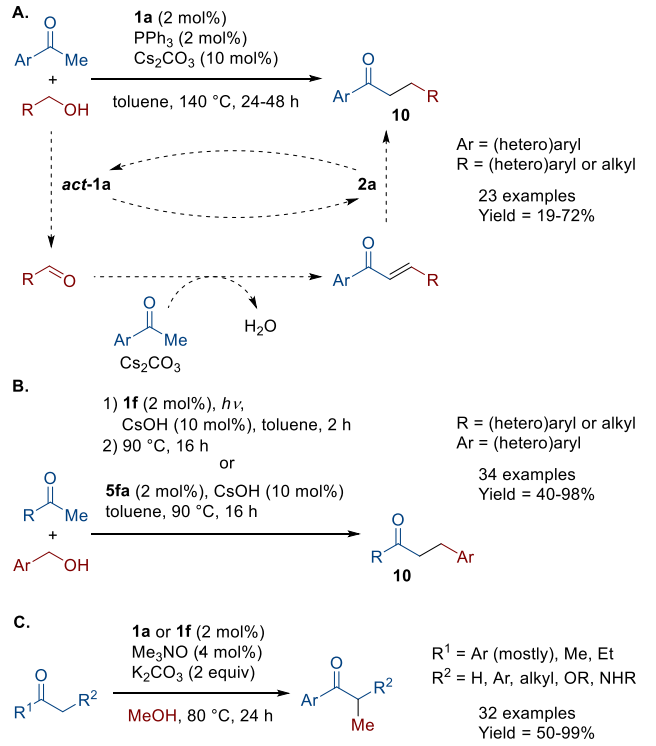
The ability of CICs/HCICs to reversibly transfer H_2 to polarized double bonds makes them attractive candidates for use in the so-called 'hydrogen borrowing' (HB) processes,[35] and this type of application has undergone tremendous developments in the last years.[36] Following up their first contribution of 2013 (which represents the first application of CICs in HB processes),[37] Quintard and Rodriguez reported in 2014 a dual catalytic cascade process providing access to the 3-alkylpentanol motif from allylic alcohols and 1,3-diketones.[38] As shown in Scheme 10, the in situ-generated catalyst ***act*-1a** promotes the dehydrogenation of allylic alcohols to α,β-unsaturated aldehydes. The aldehyde substrate undergoes the enantioselective Michael addition of the diketone mediated by a Jørgensen-type chiral amine (**7a** or **7b**), generating a chiral aldehyde which is then re-hydrogenated by HCIC **2a** to give the chiral alcohol intermediate **8**. The cascade is then closed by an intramolecular retro-Claisen reaction giving access to the chiral ketone (**9**). The methodology was illustrated by 13 examples (up to 96% yield, up to 91% *ee*) and also applied to the short synthesis of several key fragments of biologically active natural products.



Scheme 10. Dual catalytic cascade reaction (relying on CIC **1a** and iminium catalysis) for the enantioselective synthesis of the 3-alkylpentanol motif from 1,3-diketones and allylic alcohols.[38]

The same authors later reported a detailed mechanistic study on this tandem process and found that addition of a copper co-catalyst leads to a remarkable improvement of reaction scope and enantioselectivity.[39] They also extended this triple catalytic protocol (iron-, copper- and organo-catalysis) to β-ketoesters which underwent DBU-promoted lactonization to δ-lactones in the final step.[40]

In 2015, Sortais, Darcel and co-workers reported that the Knölker's complex **1a**, in the presence of Cs_2CO_3 and PPh_3, is able to promote the α-alkylation of (hetero)aryl-methyl ketones with primary alcohols.[41]

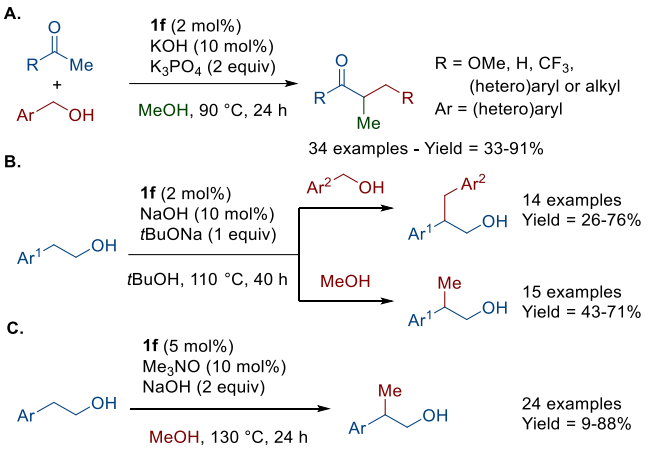


Scheme 11. HB α-alkylation of ketones reported by Sortais, Darcel and co-workers (A),[41] Poater, Renaud and co-workers (B),[30] and Morrill and co-workers (C).[42]

As shown in Scheme 11 A, the alcohol substrate is dehydrogenated to aldehyde and then reacts with the in situ-generated ketone enolate in an aldol-dehydration sequence. The

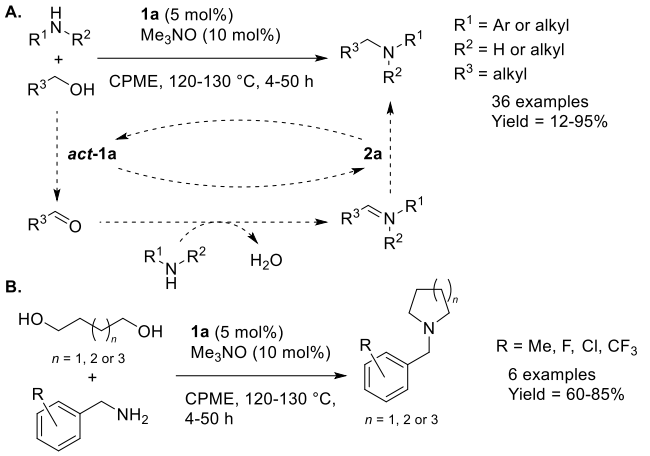
resulting α,β-unsaturated ketone then undergoes 1,4-reduction to form the alkylated product **10**. No explanation on the role of PPh_3 is provided by the authors. Poater, Renaud and co-workers also studied the α-alkylation of ketones using the highly active pre-catalysts **1f** and **5fa** (Scheme 8), extending the reaction scope to aliphatic ketones (Scheme 11 B).[30] Moreover, they carried out DFT studies from which the crucial role of the base counterion (Cs^+) in both the HT steps (alcohol dehydrogenation and 1,4-reduction) emerged. These studies also showed that the formation of catalyst ***act*-1f** upon ligand dissociation is more favored in the case of the PPh_3-substituted pre-catalyst **5fa** than with other analogs (including **1f**), thus shedding some light on the role of PPh_3 as additive in the above-discussed work of Sortais and Darcel.[41] Using pre-catalysts **1a** and **1f**, Morrill and co-workers later developed a standard protocol for the methylation and dimethylation of ketones in the presence of K_2CO_3,[42] covering a wide range of aromatic ketones (Scheme 11 C).

Very recently, Renaud and co-workers further unfolded the potential of pre-catalyst **1f**, which was employed in tandem HB processes involving four HT steps: on the one hand, a tandem three-component alkylation of methyl ketones was described, providing access to α-methylated substituted ketones in one pot (Scheme 12 A).[43]. On the other hand, the β-alkylation of alcohols with methanol and benzylic alcohols was reported (Scheme 12 B).[44] Almost simultaneously, a paper by Morrill and co-workers on the β-methylation of alcohols with methanol using pre-catalyst **1f** was also published (Scheme 12 C).[45]



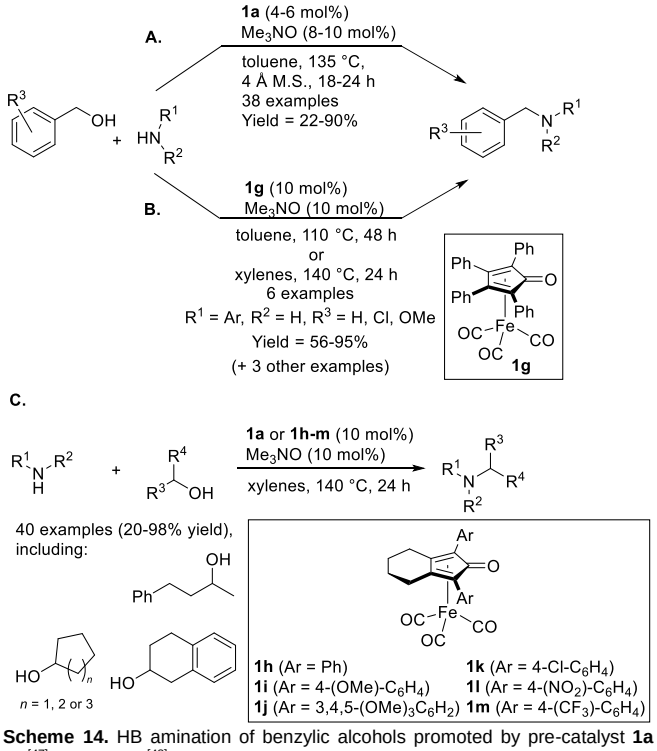
Scheme 12. Three-component HB alkylation of methyl ketones (A);[43] β-alkylation of alcohols reported by Renaud (B)[44] and by Morrill (C).[45]

In 2014, Feringa, Barta and co-workers reported the first application of CICs to the N-alkylation of amines with alcohols (or alcohol amination) using pre-catalyst **1a**.[46] This formal nucleophilic substitution proceeds via a CIC/HCIC-mediated sequence involving i) alcohol dehydrogenation, ii) imine formation and iii) imine reduction (Scheme 13 A). The reaction was performed using aromatic, benzylic and aliphatic amines (both primary and secondary). In terms of alcohols, the scope covered a number of primary aliphatic substrates (Scheme 13 A) and also three diols, which reacted with electron poor benzylamines to afford five-, six- and seven-membered nitrogen heterocycles (Scheme 13 B). Notably, environmentally friendly CPME was used as solvent for these transformations.



Scheme 13. CIC-catalyzed HB N-alkylation of amines with alcohols (A) and diols (B) originally reported by Feringa, Barta and co-workers.[46] CPME = cyclopentyl methyl ether.

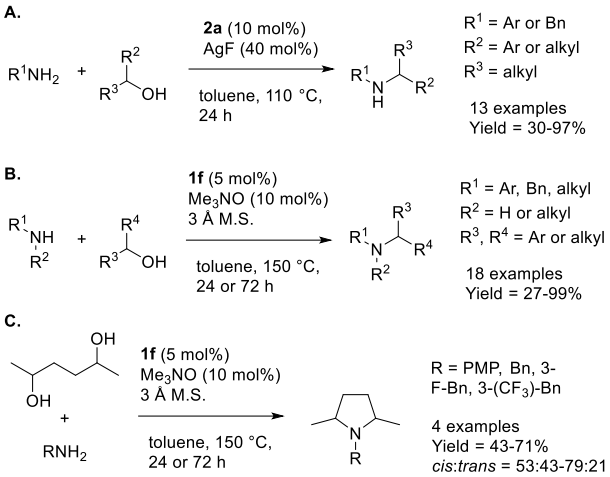
Following this breakthrough, the scope of CIC-catalyzed amination was expanded to the less reactive benzylic alcohols: Barta and co-workers achieved this goal optimizing the reaction conditions with CIC **1a** (Scheme 14 A),[47] whereas Wills and co-workers employed the tetraphenyl-substituted CIC **1g** (Scheme 14 B).[48] The Wills' group later developed a series of new CICs (**1h-m**, Scheme 14 C) and used them in the amination of several substrates, including a few secondary alcohols.[49]



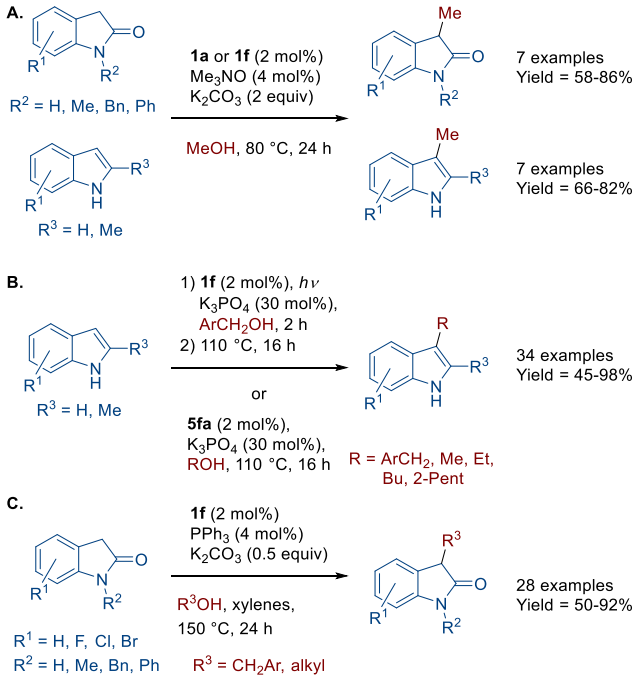
Scheme 14. HB amination of benzylic alcohols promoted by pre-catalyst **1a** (A)[47] and **1g** (B).[48] The CIC series developed by Wills and co-workers and its application to the HB amination (C).[49]

Secondary alcohols always proved poorly reactive in base metal-catalyzed HB amine alkylation:[50] until 2019, the only methodology relying on CICs/HCICs that covered a reasonably ample scope of secondary alcohols was the one reported by Zhao and co-workers in 2015 (Scheme 15 A).[51] However, the Zhao's reaction conditions require a rather high loading (10

mol%) of the sensitive isolated HCIC **2a** and a semi-stoichiometric amount of AgF (40 mol%) as co-catalyst, which remarkably reduces its practicality. Very recently, our group reported the successful use of the in situ-activated CIC **1f** to promote the HB amination of secondary alcohols (Scheme 15 B).[52] Owing to the high catalytic activity of **1f**, this methodology does not require any co-catalyst and gives good results with a number of substrates including – for the first time – a secondary diol, which reacts with primary amine to afford the corresponding 2,5-dimethylpyrrolidines (Scheme 15 C).



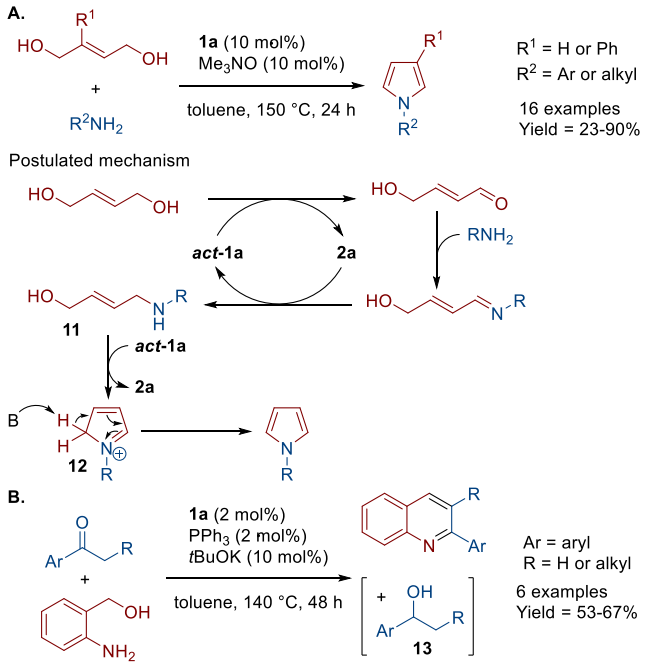
Scheme 15. HB amination of secondary alcohols with HCIC **2a**/AgF (A)[51] and with CIC **1f** (B, C).[52]



Scheme 16. HB methylation of 2-oxindoles and indoles reported by Morrill (A),[42] indole alkylation reported by Renaud and co-workers (B),[56] and alkylation of 2-oxindole reported by Morrill (C).[57]

In recent years, other CIC-catalyzed HB methodologies for amine alkylation with primary alcohols appeared in the literature: Feringa, Barta and co-workers reported the N-alkylation of unprotected aminoacids with fatty alcohols[53] and the decarboxylative N-alkylation of cyclic aminoacids[54] using the Funk-type complex **3aa** (Figure 1). Poater and Renaud described a protocol for the methylation and ethylation of aliphatic and aromatic amines promoted the highly active pre-catalyst **1f**.[55] Morrill and co-workers applied the same protocol employed for ketones – relying on CIC **1a** or **1f** (see Scheme 11 C) – to the methylation of amines and sulfonamides.[42] In the same paper, 2-oxindoles and 2-substituted indoles were also used as nucleophiles for the first time (Scheme 16 A). A more thorough study on indole alkylation was simultaneously reported by Renaud and co-workers using pre-catalysts **1f** and **5fa** (Scheme 16 B):[56] a series of benzylic as well as aliphatic alcohols were employed as alkylating agents. Very recently, Morrill and co-workers extended the scope of oxindole alkylation to several different 2-oxindoles and to a number of benzylic and aliphatic alcohols (Scheme 16 C).[57]

By definition, the concept of HB implies that, since an *even* number (2*n*) of HT elementary steps are involved, there is no net change of oxidation state at the end of the reaction. This is true for all the examples discussed above in this section. However, a few reactions have also been described which involve an *odd* number of HT steps (2*n* + 1, *n* = 1, 2, …) and thus are redox reactions, yet being somehow misleadingly termed as 'HB' reactions. Sundararaju and co-workers reported the **1a**-catalyzed synthesis of pyrroles starting from primary amines and but-2-ene-1,4-diol derivatives, which undergo a two-electron oxidation (Scheme 17 A).[58] According to the postulated mechanism, a HB amination initially occurs, affording the aminoalcohol intermediate **11**. The latter is dehydrogenated by catalyst ***act*-1a** to give the iminium ion **12** which, instead of being re-hydrogenated by HCIC **2a**, aromatizes to form the pyrrole product.

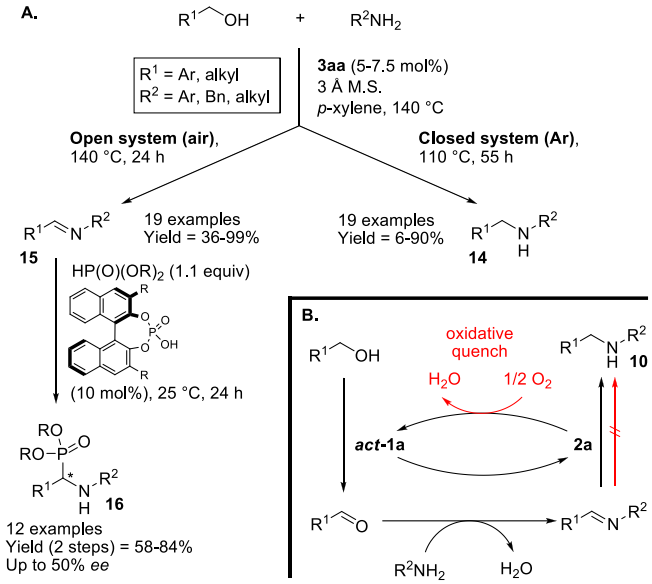


Scheme 17. Oxidative cyclization of but-2-ene-1,4-diol derivatives reported by Sundararaju (A),[58] and the quinoline synthesis described Sortais, Darcel and co-workers (B).[41]

The authors did not clarify whether there is a terminal oxidant or **2a** spontaneously releases H_2 to give back ***act*-1a**. Sortais, Darcel and co-workers reported a Friedländer-type reaction generating quinolines from 2-aminobenzyl alcohol and ketones (Scheme 17 B).[41] Similarly to the previous example, this is an

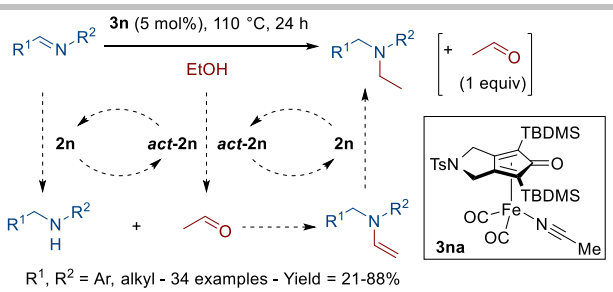
oxidative process, as H_2 generated from alcohol dehydrogenation is not re-incorporated into the product. It is likely that the starting ketone acts as terminal oxidant in this case, since the corresponding alcohol **13** was detected in the reaction mixture.

Very recently, Hultzsch and Hofmann demonstrated the possibility to switch between HB-type reactivity and oxidative reactions by simply modifying the experimental conditions (Scheme 18 A).[59] The reaction of benzylic alcohols with various amines in the presence of pre-catalyst **3aa** and molecular sieves gave high yields of the amination products (**14**) when performed in a closed vessel under argon. However, when the reaction was performed in an open vessel under air, imines (**15**) were the only products. The authors propose that, in the latter case, an oxidative quenching of the activated catalyst **2a** occurs by reaction with O_2, so that the imine reduction step is bypassed (Scheme 18 B). A two step-one pot enantioselective reaction was also developed, in which the in situ-formed imine is converted by dialkylphosphites into α-*N*-alkylaminophosphonates (**16**) in the presence of a chiral phosphoric acid catalyst (Scheme 18 A).



Scheme 18. Effect of the reaction conditions on the outcome of alcohol amination (A), and proposed mechanism of the aerobic quench of catalyst **2a** (B).[59]

Finally, in 2018 Gandon, Bour and co-workers reported the synthesis of tertiary amines by imine ethylation with EtOH in the presence of the Funk-type pre-catalyst **3na** (Scheme 19).[60] The reaction is a reductive process in which 2 equiv of EtOH are consumed: 1 equiv is incorporated in the reaction product, and 1 equiv serves as terminal reducing agent, generating acetaldehyde as byproduct. The authors proposed the mechanism shown in Scheme 19 on the basis of several deuteration experiments and DFT calculations, and the reaction scope was thoroughly investigated.

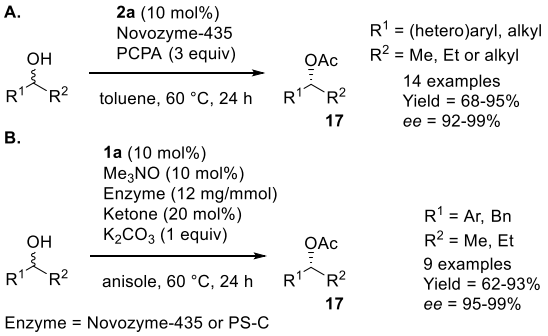


R1, R2 = Ar, alkyl - 34 examples - Yield = 21-88%

Scheme 19. The CIC-catalyzed reductive imine ethylation developed by Gandon, Bour and co-workers.[60] TBDMS = *tert*-butyldimethylsilyl.

2.3 Enantioselective applications

Two main strategies have been followed to develop enantioselective catalytic methodologies involving CICs/HCICs: i) dual catalysis combining an achiral Fe-complex and a chiral catalyst; ii) use of chiral Fe-complexes.[61] Only the former approach, pioneered by Beller and co-workers in 2011 using HCIC **2a** and chiral phosphoric acids,[62] has allowed so far to achieve satisfying levels of enantioselectivity, whereas highly effective chiral CICs are still to be discovered. In 2016, Rueping and co-workers reported a highly effective dynamic kinetic resolution (DKR) of chiral secondary alcohols in the presence of HCIC **2a** and Novozyme-435 – an immobilized lipase from *Candida antarctica* (Scheme 20 A).[63] This enzyme is able to promote the selective acetylation of the *R*-enantiomer of the alcohol in the presence of *p*-chlorophenyl acetate (PCPA), whereas the Fe-complex has the role of racemizing the less reactive enantiomer (*S*). A number of alcohols were converted into the corresponding acetates (**17**) in good yields and with very high *ee* values. Shortly after, Bäckvall and co-workers also reported a similar DKR methodology (Scheme 20 B) which has the advantage of employing the air-stable racemization pre-catalyst **1a** (activated in situ with Me_3NO) instead of the highly sensitive catalyst **2a**.[64] Under the optimized conditions, either Novozyme-435 or PS-C (a lipase derived from *Burkholderia cepacia* bacteria) were employed as enantioselective catalyst, and phenyl acetate was used as acetylating agent.

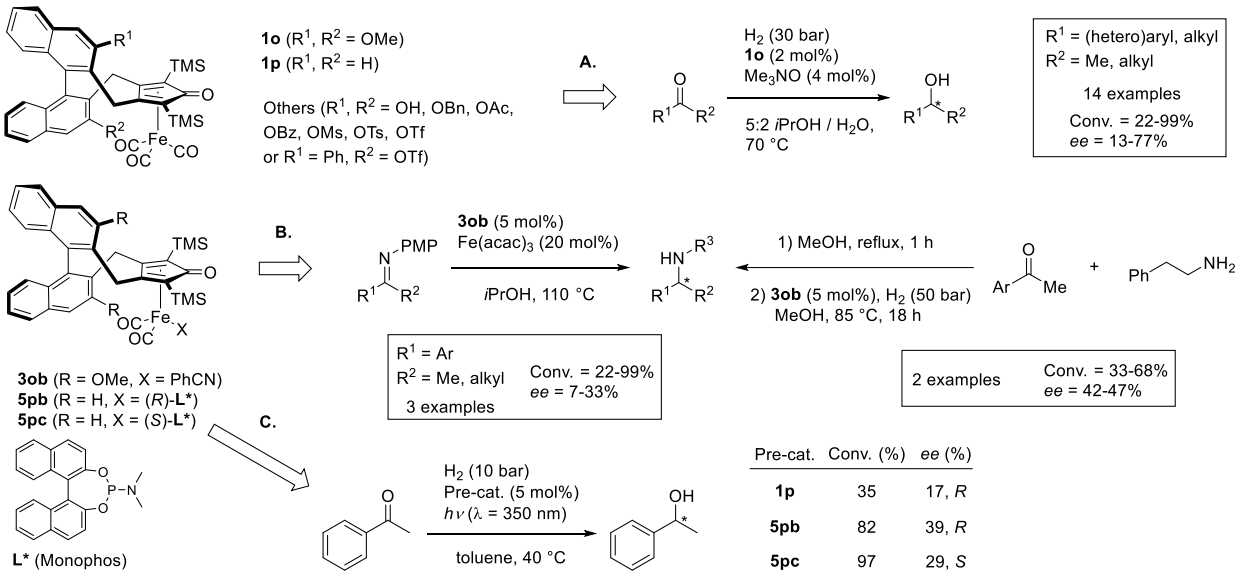


Scheme 20. DKR of secondary alcohols reported by Rueping and co-workers,[63] and Bäckvall and co-workers.[64] PCPA = *p*-chlorophenyl acetate.

The use of chiral CICs, pioneered by Berkessel and co-workers[65] and Wills and co-workers,[66] was recently pursued by several groups. The main difficulty in the design of new chiral complexes is that the cyclopentadienone ring is flat: if stereogenic elements are introduced at the cyclopentadienone substituents, in the commonly accepted hydrogen-transfer transition state they sit too far apart from the incoming substrate

to effectively transfer the stereochemical information (Figure 3 A).[66] If, alternatively, one CO is replaced with a chiral ligand,[65] in the activated form **2** the Fe atom becomes stereogenic (Figure 3 B), and the co-presence of catalyst diastereomers may lead to low stereocontrol.

In 2015, we reported the synthesis of a small library of chiral CICs derived from (*R*)-1,1'-bi-2-naphthol (BINOL) and differing from each other in the substitution at the 3,3'-positions of the binaphthyl motif (Scheme 21).[67] Although in these CICs the stereogenic axis is remote from the functional groups involved in catalysis, we expected that the rigid binaphthyl framework and the presence of protruding substituents at its 3,3' positions could secure reasonable stereocontrol.



Scheme 21. Chiral (*R*)-BINOL-derived CICs developed by our group, and their applications in the AH of ketones (A)[67] and of C=N bonds (B);[25a] effect of the replacement of a CO with a chiral ligand (C).[61]

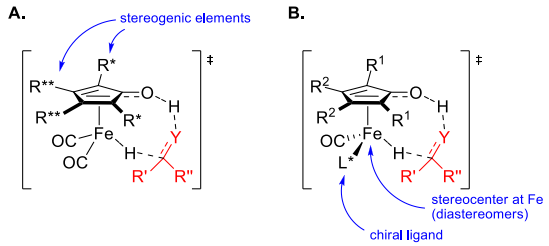
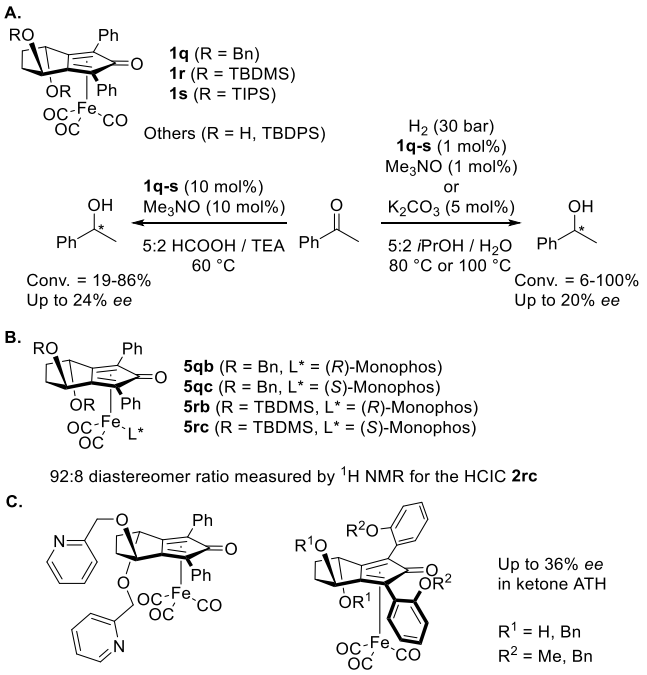


Figure 3. Reasons of the difficulty in developing effective chiral CICs for enantioselective HT reactions when a chiral cyclopentadienone ligand is used (A), or a chiral ligand is coordinated to iron (B).

Indeed, a 30-40% increase of the *ee* was observed with the 3,3'-disusbstituted complexes in acetophenone asymmetric hydrogenation when compared to the unsubstituted complex **1p**. The best performing pre-catalyst **1o** (OMe in the 3,3'-positions) gave enantiomeric excesses in ketone hydrogenation ranging from 13% to 77% (Scheme 21 A). Yet moderate, these are the highest *ee* values reported so far using chiral CICs. Derivatives possessing large aromatic substituents at the 3,3'-binaphthyl positions turned out to be synthetically inaccessible. We tested our chiral catalysts for ketimine AH and AH-based ketone reductive amination (Scheme 21 B), and we obtained low to moderate *ee* values using the Funk-type complex **3ob**.[25a] Finally, we applied the Berkessel's approach[65] to CIC **1p**, replacing one of its CO with (*R*)- or (*S*)-Monophos (Scheme 21 C). We reasoned that the formation of a stereocenter at iron, occurring upon activation, could take place under the influence of the chiral ligands, leading to the preferential formation of one of the two possible epimers at iron. The diastereosomeric complexes **5pb** and **5pc** showed a matched/mismatched effect in acetophenone AH, but the enantioselectivity was modest in both cases (39% and 29% *ee*, respectively).

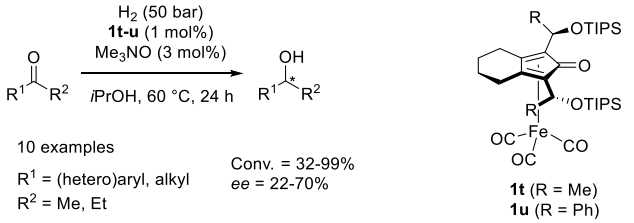


Scheme 22. The chiral complexes with C_2-symmetric cyclopentadienone ligand developed by Wills and co-workers,[68] and their catalytic applications (A). Complexes generated by ligand exchange with a chiral phosphoramidite ligand (B). Second-generation pre-catalysts (C).[69]

In 2016, Wills and co-workers reported a series of chiral CICs (**1q-s** and others) bearing a C_2-symmetric cyclopentadienone ligand and differing from each other in the protection of the OH

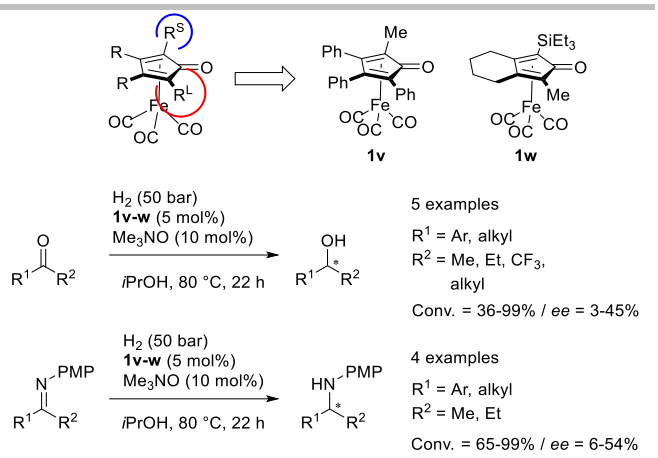
groups located on the fused six-membered ring (Scheme 22 A).[68] These pre-catalysts were tested in the asymmetric transfer hydrogenation and in the asymmetric hydrogenation of acetophenone giving modest enantiocontrol (up to 24% *ee*). Following the Berkessel's approach,[65] four complexes (**5qb**, **5qc**, **5rb**, **5rc**) were generated by exchange of one CO with either (*R*)- or (*S*)-Monophos (Scheme 22 B). The latter complex **5rc** was converted into the corresponding HCIC, possessing a stereogenic Fe-center. ^{1}H NMR analysis showed the formation of two epimers at iron in a 92:8 ratio. Despite this, the complexes showed very low activity and enantioselectivity in acetophenone AH and ATH. The same authors synthesized additional members of this chiral CIC series featuring modified substituents at the oxygen atoms and/or at the 2,5-positions of the cyclopentadienone ring (some examples are shown in Scheme 22 C), but no improvement in terms of enantioselectivity was obtained.[69] It is likely that the low stereocontrol displayed by these complexes is due to the large distance between the stereocenters and the functional groups involved in catalysis (i.e., the Fe-center and the cyclopentadienone's C=O group).

Very recently, De Wildeman and co-workers reported new chiral CICs possessing a C_2-symmetric cyclopentadienone ligand with stereocenters at positions 2,5 – i.e., closer to the C=O group involved in the catalytic activity (Scheme 23).[70] This kind of design led to a slight improvement in terms of enantioselectivity compared to the Wills' pre-catalysts, although the *ee* values remained moderate. Free rotation of the bonds connecting the stereocenters to the cyclopentadienone ring may be a possible explanation for the limited improvement.



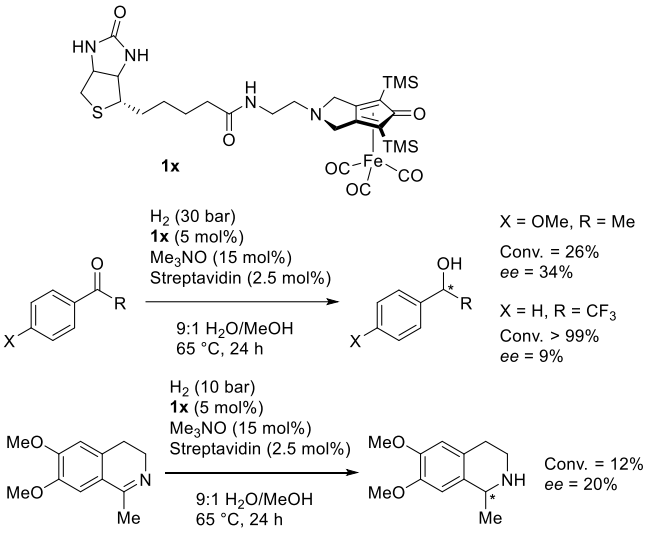
Scheme 23. The chiral complexes recently reported by De Wildeman and co-workers and their applications in ketone AH.[70]

In the attempt to bring the stereochemical information as close as possible to the CIC's functional groups involved in HT, we recently developed several chiral CICs endowed with a stereogenic plane due to the presence of different substituents at position 2 and 5 of the cyclopentadienone ring (Scheme 24).[71,72] We surmised that a large difference in size between these substituents could lead to effective stereodiscrimination between the substrate's enantiofaces. Six racemic complexes were synthesized and tested in ketone and ketimine hydrogenation, and it was found that increasing the size of the 'large' substituent R^L beyond a certain extent led to a drop of catalytic activity. Thus, the two complexes **1v** and **1w**, reaching a compromise between activity and R^L/R^S difference in size, were resolved by semipreparative chiral HPLC. The enantiopure complexes were tested in the AH of several ketones and ketimines, and low to moderate *ee* values were obtained.



Scheme 24. The chiral CICs with stereogenic plane developed by our group and their applications in ketone and ketimine AH.[71] PMP = *p*-methoxyphenyl.

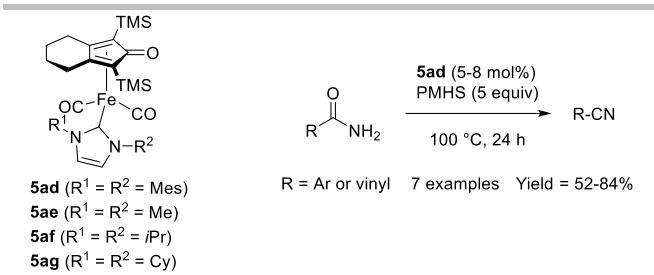
Finally, Ward, Renaud and co-workers addressed the issue of developing chiral CICs for enantioselective reductions following a supramolecular, bio-inspired approach (Scheme 25). They synthesized several biotinylated CICs, which were incorporated as cofactors in streptavidin and used to promote the AH of two ketones and one ketimine in aqueous environment.[73] With the best performing CIC (**1x**), the effect of incorporation into streptavidin was evident but, nevertheless, the enantioselectivity remained very poor in absolute terms.



Scheme 25. Use of the in situ generated biohybrid pre-catalyst **1x** ⊂ streptavidin reported by Ward, Renaud and co-workers.[73]

3. Other applications

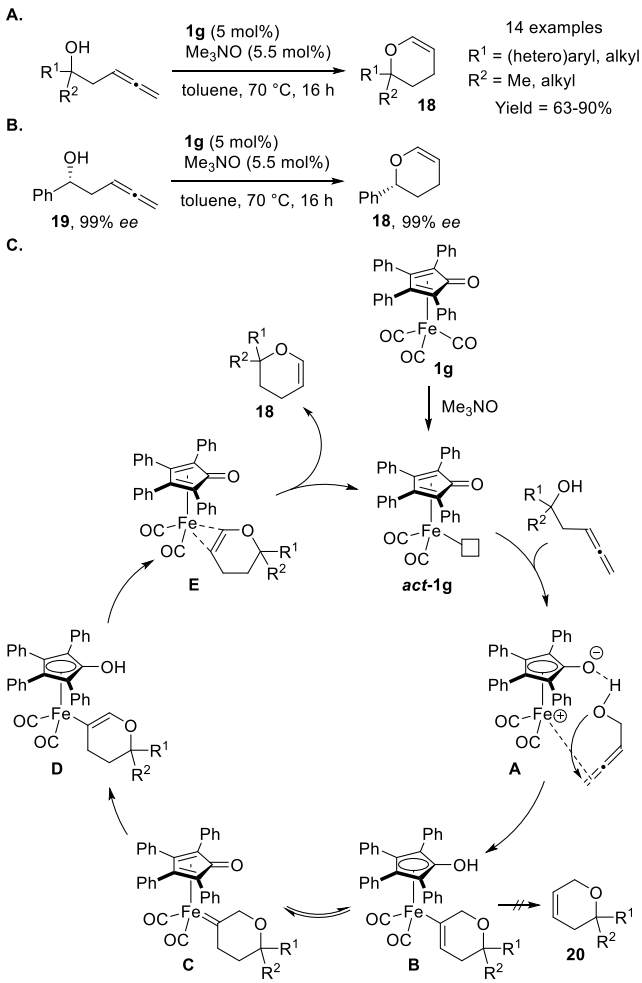
While the first catalytic applications and most further developments of CICs were in reactions involving HT steps, in the last years these iron complexes have been reported to promote also different types of reactivity. In 2015, Darcel, Sortais and co-workers described the synthesis and characterization of several new CICs in which one of the CO ligands is replaced by an NHC.[74]



Scheme 26. Some of the NHC-substituted CICs reported by Sortais, Darcel and co-workers,[74] and their application in the dehydration of primary amides. PMHS = polymethylhydrosiloxane.

These derivatives (some of which are shown in Scheme 26) were able to promote the dehydration of primary amides to nitriles in fair to good yields, whereas the corresponding CIC **1a** – i.e., the Knölker's complex – was catalytically inactive. The reaction scope was investigated with complex **5ad** and found to cover a number of aromatic and α,β-unsaturated primary amides. No reaction mechanism was proposed by the authors.

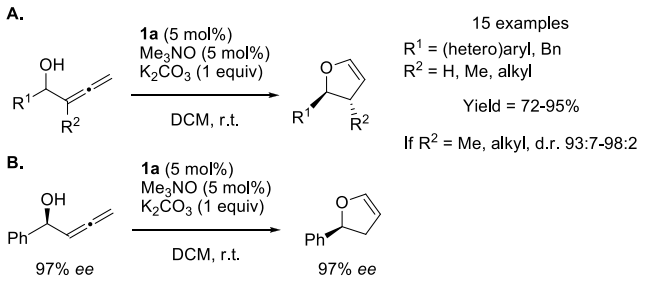
In 2017, El Sepelgy, Cavallo, Rueping and co-workers[75] reported the application of CICs to the carboetherification of allenols (Scheme 27), a type of transformation that had been described shortly before by Bäckvall and co-workers using the Shvo's ruthenium catalyst.[76]



Scheme 27. CIC-catalyzed 6-*endo* cyclization of β-allenols (A, B), and catalytic cycle (C) proposed by El Sepelgy, Cavallo, Rueping and co-workers.[75]

A screening of CICs and experimental conditions led to the use of the tetraphenyl-substituted complex **1g** (activated in situ with Me_3NO) at 70 °C. Under the optimized reaction conditions, several β-allenols were cyclized in good yields (Scheme 27 A). Remarkably, complete retention of configuration was observed upon cyclization of the chiral alcohol **19** (Scheme 27 B), meaning that the carboetherification is much faster than the previously discussed alcohol racemization (see Section 2.3). On the basis of deuterium-labeling experiments and DFT calculations, the authors proposed a mechanism (Scheme 27 C) similar to the one reported for the reaction catalyzed by the Shvo's ruthenium catalyst,[76] in which the non-innocent cyclopentadienone ligand plays a crucial role. Indeed, catalyst ***act*-1g** is able to coordinate the allene fragment while forming, at the same time, a hydrogen bond with the substrate's OH (Scheme 27 B, intermediate **A**). In this way, the substrate is activated to undergo a 6-*endo* cyclization, which occurs with concomitant formation of the hydroxycyclopentadienyl form of the ligand. The iron vinylidene complex **B** is then converted in the isomeric form **D** via the carbene intermediate **C**. This isomerization consists of two consecutive proton transfer steps mediated by the cyclopentadienone/hydroxycyclopentadienyl oxygen atom. Finally, the iron vinylidene species **D** undergoes protodemetalation, thus releasing the 3,4-dihydro-2*H*-pyran product **18**. Remarkably, the 3,6-dihydro-2*H*-pyran product **20** is not observed because the protodemetalation of **C** is disfavored compared to that of **D**.

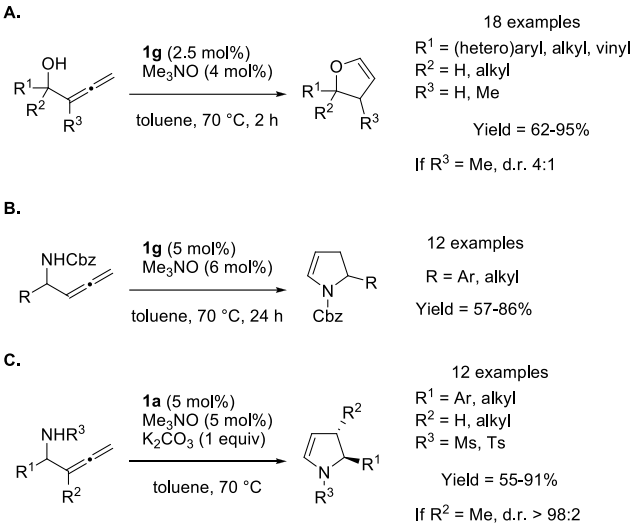
Shortly after the Rueping's report, Yang, Himo, Bäckvall and co-workers published a paper describing the carboetherification of α-allenols promoted by the Knölker's complex **1a** (Scheme 28).[77] Under the optimized conditions, the reaction proceeds at room temperature in the presence of **1a** (5 mol%)/Me_3NO (5 mol%)/K_2CO_3 (1 equiv) and covers a range of substrates (Scheme 28 A) including some chiral allenols, which retain their absolute configuration (Scheme 28 B) and cyclize with a high level of diastereoselectivty. For this reaction, on the basis of deuterium-labeling experiments and DFT calculations the authors proposed a mechanism substantially similar to the one shown above for β-allenols (Scheme 27).



Scheme 28. CIC-catalyzed 5-*endo* cyclization of α-allenols (A, B) reported by Yang, Himo, Bäckvall and co-workers.[77]

El Sepelgy, Rueping and co-workers later extended their methodology relying on pre-catalyst **1g** to the synthesis of five-membered oxygen- and nitrogen-heterocycles by cyclization of, respectively, α-allenols (Scheme 29 A) and protected α-allenic amines (Scheme 29 B).[78] Very recently, the synthesis of nitrogen-heterocycles using *N*-sulfonamide substrates was also investigated by Himo and Bäckvall using pre-catalyst **1a** in the presence of Me_3NO and K_2CO_3 (Scheme 29 C).[79] The cyclization gave good yields with several sulfonamides and,

remarkably, the reaction forming a new stereocenter occurred with very high diastereoselectivity.



Scheme 29. CIC-catalyzed cyclization of α-allenols (A) and α-allenic *N*-Boc amines (B) reported by El Seplegy and Rueping.[78] Cyclization of allenic sulfonamides recently described by Himo, Bäckvall and co-workers.[79]

4. Conclusions

CICs have become the object of a fast-growing interest in the area of homogeneous catalysis because they are cheap and robust pre-catalysts that can effectively promote – alone or in combination with other catalysts – a number of synthetic transformations. Moreover, they represent a demonstration of the deep effect that a non-innocent ligand may exert on the catalytic properties of a 'challenging' metal such as iron – notoriously difficult to harness for two-electron processes. Remarkable progress has been made in CIC-catalyzed redox processes – i.e. their first reported catalytic application – owing also to the development of new pre-catalysts featuring increased catalytic activity. Additionally, some progress has been made in the development of chiral complexes for enantioselective reductions. However, the type of application which has undergone the most tremendous development is represented by hydrogen borrowing processes, including ketone and amine alkylation with alcohols and tandem reactions in which CICs are combined with additional catalysts. Last but not least, it has been shown that the applicability of CICs is not limited to reactions involving hydrogen transfer step(s), but also to processes featuring different mechanisms where, again, the cyclopentadienone/hydroxycyclopentadienyl ligand plays a crucial role. We believe that the most important future challenges in this field are: i) achieving a further increase of the catalytic activity, which will allow to perform the reactions under milder conditions with a benefit for the process chemo-, regio- and stereo-selectivity; ii) developing truly effective chiral CICs, which will pave the way to a wide range of potential applications in enantioselective catalysis.

Keywords: iron catalysis • (cyclopentadienone)iron complexes • homogeneous catalysis • reductions • hydrogen borrowing reactions

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