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N-Heterocyclic Carbenes in Asymmetric Hydrogenation

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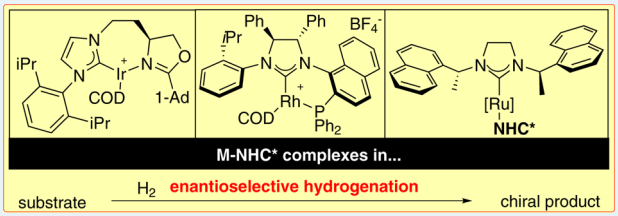
ABSTRACT: N-heterocyclic carbene (NHC)-metal complexes have become known as efficient catalysts for numerous transition metal catalyzed processes. An important application of many NHC-metal complexes is in the field of asymmetric catalysis, and this is achieved through the introduction of chiral information on the NHC ligands. Among the asymmetric transformations catalyzed by NHC-metal complexes is asymmetric hydrogenation, which is an attractive process for the synthesis of optically active compounds due to its high atom economy. However, to date, few chiral NHC-metal catalysts have been reported to be highly stereoselective for asymmetric hydrogenation. Over the past few years our group has made some significant breakthroughs within the field of asymmetric hydrogenation using chiral NHC catalysts. We have reported the NHC-Ru catalyzed asymmetric hydrogenation of a wide range of heterocyclic compounds with high regio- and enantioselectivity. The field of chiral NHC-metal complex catalyzed asymmetric hydrogenation is yet to be reviewed; this Perspective aims to provide a concise overview of NHC-metal catalyzed asymmetric hydrogenation to push the further development of this area of chemistry.

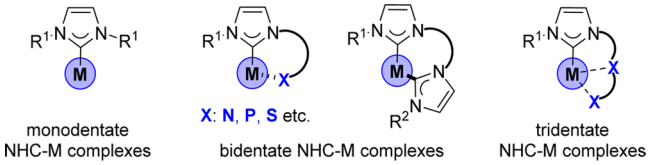


KEYWORDS: *catalysis, asymmetric hydrogenation, N-heterocyclic carbene, enantioselective catalysis, heteroarenes*

1. INTRODUCTION

Since Herrmann's seminal publication in 1995,[1] the field of NHC-metal complex catalysis has been widely explored, with complexes of numerous transition metals found to be highly efficient catalysts for a range of transformations.[2] Generally, NHC-metal complexes can be categorized on the basis of denticity, with monodentate, bidentate, and tridentate complexes reported in the literature (Scheme 1). With regard to bi- and tridentate systems, the NHC ligand incorporates either an additional NHC or a heteroatom capable of binding to the metal.

Scheme 1. Chiral NHC-Metal Catalysts Used in Asymmetric Hydrogenation



Herrmann and co-workers also pioneered the application of chiral NHC ligands in transition-metal catalysis,[3] and since then, many groups have contributed to the field of NHC-metal complex mediated asymmetric catalysis.[4] In terms of stereocontrol, however, the development of efficient chiral NHC ligands can be challenging due to the long distance between the NHC-metal center and chirality on either the N substituents or the backbone of the NHC. Additionally, the planar heterocyclic structure of NHCs and the free rotation of the NHC−metal bond allows the catalyst to adopt several conformations during a reaction. The stereochemical "topography" of chiral NHC ligands is also distinctly different from that of phosphine units, which means that structural motives which are privileged for chiral phosphine ligands are not directly transferable to the design of novel chiral NHC analogues.

Asymmetric hydrogenation is a fundamentally important transformation for synthesizing optically active compounds, as it displays perfect atom economy and can generally be performed under mild conditions.[5] The first efficient NHC-metal complex for asymmetric hydrogenation was reported in 2001 by Burgess.[6] Since 2011, our group has investigated NHC-Ru catalyzed enantioselective hydrogenation and has reported the highly enantioselective reduction of a range of heterocyclic compounds, namely quinoxalines, indolizines, pyridones, (benzo)furans, (benzo)thiophenes, flavones/chromones, and 1,5-benzothiazepinones. To the best of our knowledge the topic of NHC-metal catalyzed asymmetric hydrogenation has not yet been reviewed; hence, we endeavor to provide a concise overview of NHC-metal catalyzed asymmetric hydrogenation using H_2 gas. Sections 2 and 3 will focus on the hydrogenation of alkenes and ketones/imines and give an outline of the different NHC ligands utilized by the community, highlighting their characteristics. Section 4 provides an overview of our group's contribution to the field of (hetero)arene hydrogenation.

2. NHC-METAL COMPLEX CATALYZED ASYMMETRIC HYDROGENATION OF ALKENES

The metal-catalyzed asymmetric hydrogenation of alkenes has been widely employed in the synthesis of optically active compounds, especially by the pharmaceutical industry.[7] The

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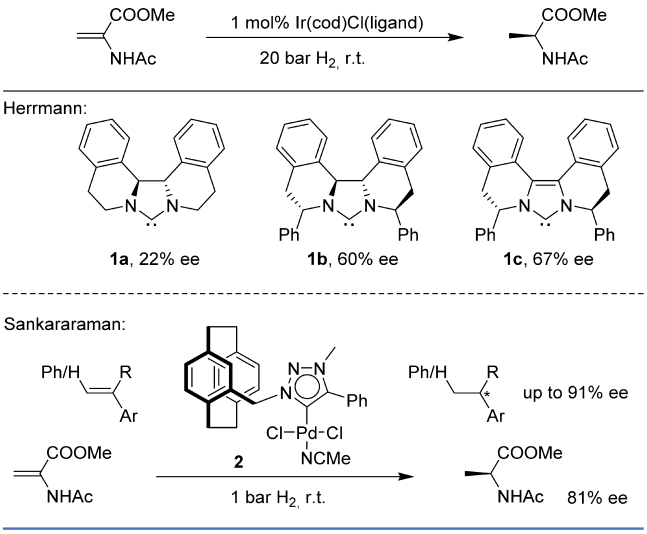
invention of new ligands is pivotal to the further development of this field. To date, numerous chiral NHC ligands have been developed for the asymmetric hydrogenation of alkenes. For the purpose of this review, we have classified the NHC ligands on the basis of their denticity (see Scheme 1).

2.1. Monodentate NHC ligands. Chiral monodentate NHC ligands have been frequently applied in asymmetric Pd catalyzed Suzuki−Miyaura reactions, asymmetric Ru catalyzed alkene metathesis reactions, and the asymmetric Rh(I) catalyzed conjugate addition of arylboronic acids to α-enones.[4] However, only two classes of rigid monocarbene ligands have proved to be effective for the asymmetric hydrogenation of alkenes.[8] The iridium complexes of ligands **1a−c**, developed by Herrmann et al., can be employed to hydrogenate methyl 2-acetamidoacrylate, providing the corresponding products with up to 67% enantiomeric excess (Scheme 2). In a recent

Scheme 2. Monodentate Carbenes for the Asymmetric Hydrogenation of Acetamidoacrylates and Alkenes

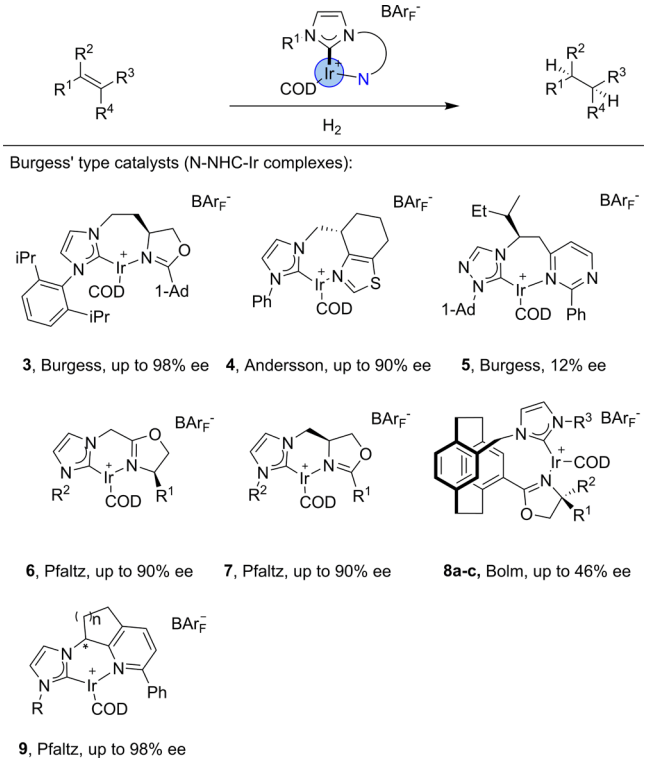


publication, Sankararaman and co-workers established a mesoionic NHC with a planar chiral paracyclophane moiety for the hydrogenation of various C═C bonds with ee values of up to 91% (Scheme 2).

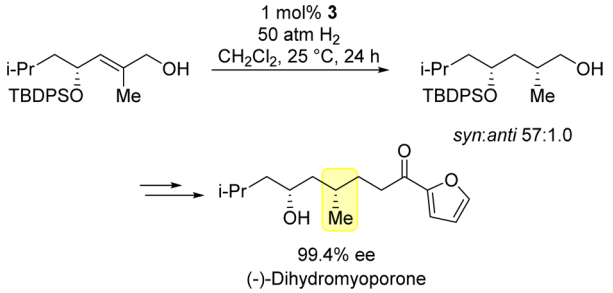
2.2. Bidentate NHC Ligands Incorporating Nitrogen Units. In 2001, Burgess and co-workers reported a small library of NHC-oxazoline-Ir complexes for the enantioselective hydrogenation of nonfunctionalized alkenes.[6,9] Complex **3** proved best for this reaction, affording the corresponding product with up to 98% ee and 99% yield (Scheme 3). Notably, exchanging the catalyst 1-adamantyl and *N*-diisopropyl phenyl substituents on the oxazoline and NHC with less sterically demanding groups was found to greatly decrease the enantioselectivity of the catalyst. This is the first literature report of asymmetric hydrogenation using NHC ligands. It is worth noting that Burgess' catalyst **3** was also applied in the asymmetric hydrogenation of a diverse range of alkenes, such as 1,3-dienes and functionalized monoenes.[10] Moreover, catalyst **3** was utilized in the synthesis of natural products, such as (−)-dihydromyoporone, generating the highlighted stereocenter with a *syn*:*anti* ratio of 57:1 (Scheme 4).[11] The application of the NHC-oxazoline-iridium complexes in asymmetric hydrogenation was reviewed by Burgess in 2012.[12]

Building upon the structural features of Burgess' catalyst **3**, numerous other *N*-NHC-metal complexes have been developed

Scheme 3. Development of *N*-NHC-Metal Catalysts for Alkene Hydrogenation



Scheme 4. Application of Catalyst 3 in the Synthesis of (−)-Dihydromyoporone



for application in the asymmetric hydrogenation of alkenes (Scheme 3). In 2006, Andersson and co-workers developed the efficient chiral NHC-thiazole iridium complex **4**, also containing a seven-membered chelate ring, for the asymmetric hydrogenation of unfunctionalized trisubstituted olefins.[13] A large variety of substrates were hydrogenated by the Ir-NHC-thiazole catalyst **4**, with excellent conversion and enantioselectivities ranging from 34% to 90%. In 2007, Burgess also prepared the seven-membered-ring chelating ligand **5**, with a triazole-NHC core. The catalyst exhibited high activity but very low levels of enantioselectivity (12% ee) in the asymmetric hydrogenation of (*E*)-1,2-diphenylpropene.[14]

Pfaltz and co-workers developed two oxazoline-NHC-Ir complexes (**6** and **7**), bearing six-membered chelate rings.[15] Though complexes **6** and **7** displayed high reactivity and good selectivity (up to 90% ee), Burgess' catalyst **3** was found to give superior levels of enantioinduction for most substrates. Interestingly, while catalyst **3** required sterically demanding substituents on the NHC and oxazoline ring, less sterically demanding substituents on catalysts **6** and **7** provided better

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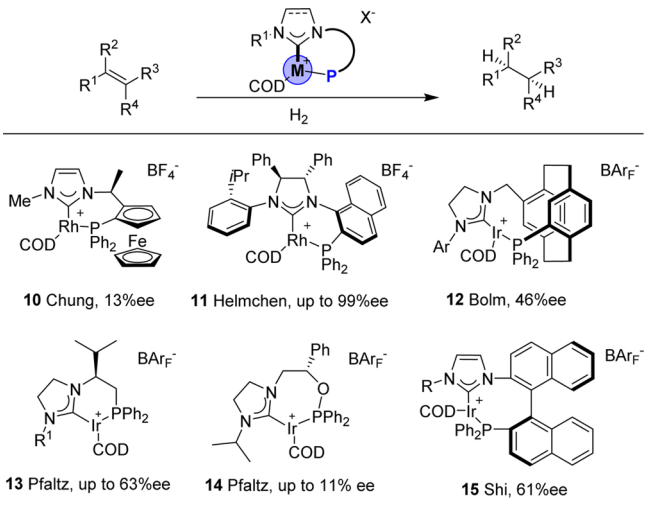
results. Bolm and co-workers have also contributed to this class of nitrogen-containing bidentate Ir-NHC catalysts, with the synthesis of **8**, containing a planar chiral [2.2]paracyclophane scaffold. The catalyst was found to afford up to 46% ee in the asymmetric hydrogenation of simple and functionalized alkenes.[16] The latest contribution in the development of new *N*-NHC-Ir catalysts was made by Pfaltz in 2013. A series of chiral bidentate pyridine-NHC-Ir complexes (**9**) were reported and evaluated in the asymmetric hydrogenation of alkenes.[17] In terms of the enantioselectivities and substrate scopes, Pfaltz's research on the pyridine-containing Ir-NHC catalytic system made a very useful complement to Burgess' catalyst **3**. Of note, these iridium C,N complexes are excellent catalysts for the hydrogenation of acid-sensitive substrates, presumably due to the lower acidity of iridium hydride intermediates produced from Ir-NHC complexes.

2.3. Bidentate Phosphine-NHC Ligands. Considering the extensive use of highly effective chiral phosphine ligands in the field of asymmetric hydrogenation, the development of novel chiral NHC ligands incorporating a phosphine moiety for use in asymmetric hydrogenation is a reasonable progression. In 2003, Chung and co-workers disclosed the first chiral bidentate phosphine-NHC-Rh complex, **10**, inspired by Josiphos, for the asymmetric hydrogenation of dimethyl itaconate; unfortunately only 13% ee was obtained (Scheme 5).[18] Helmchen reported

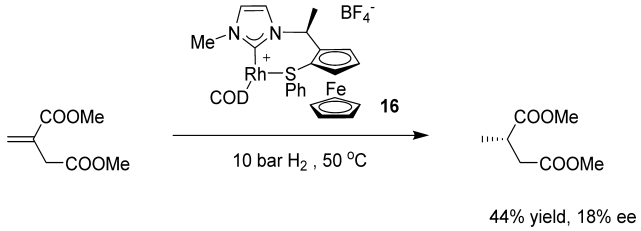
Scheme 5. Used Bidentate Chiral *P*-NHC-Metal Complex Catalysts



the bidentate chiral phosphine-NHC-Rh complexes **11**, containing an imidazoline moiety and a stereogenic *N*-naphthyl axis, for the asymmetric hydrogenation of α,β-unsaturated esters with up to 99% ee obtained.[19] In the same year, phosphine-NHC-Ir-complexes **12**, containing a planar chiral [2.2]paracyclophane scaffold, were reported by Bolm and exploited in the asymmetric hydrogenation of simple and functionalized alkenes, giving enantiomerically enriched products with up to 46% ee.[20] In 2006, Pfaltz also developed phosphine-NHC-Ir complexes **13** and **14**, which were used in the hydrogenation of unfunctionalized and functionalized alkenes.[21] However, the highest ee observed was 63%. More recently, Shi and co-workers designed a series of new chiral phosphine-NHC-Ir complexes **15**, incorporating a 1,1′-binaphthyl unit as the chiral framework, for the asymmetric hydrogenation of several olefins, but only up to 61% ee was obtained.[22]

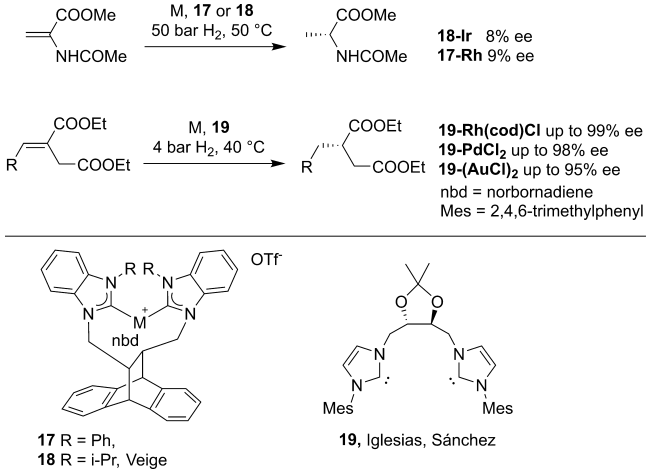
2.4. Bidentate Sulfur-NHC Ligands. While bidentate NHC ligands containing N donors and P donors have been explored extensively in the asymmetric hydrogenation of alkenes, the use of bidentate NHC complexes containing sulfur as a donor is underexplored. To date, only one *S*-NHC-metal complex has been reported as a hydrogenation catalyst, by Chung and co-workers.[18] Unfortunately, the reduction of dimethyl itaconate using *S*-NHC-Rh complex **16** afforded the corresponding product in 44% yield with only 18% ee (Scheme 6).

Scheme 6. Planar Chiral *S*-NHC-Rh Complex for Hydrogenation of Dimethyl Itaconate



2.5. Bidentate Bis-NHC Ligands. In 2009, Veige reported bidentate bis-NHC-Ir and Rh complexes **17** and **18**, derived from chiral ethano-anthracene. These complexes were utilized in the asymmetric hydrogenation of methyl 2-acetamidoacrylate with full conversion but very low ee (9%) (Scheme 7).[23] This is

Scheme 7. Chiral Bidentate Bis-NHC-Metal Complexes in Asymmetric Hydrogenation



the first example of chelating bis-NHC ligands in asymmetric hydrogenation. In 2010, Sánchez and co-workers reported another bis-NHC ligand bearing a chiral dioxolane framework for asymmetric hydrogenation (Scheme 7).[24] They synthesized a series of bis-NHC-Au, -Pd, and -Rh complexes **19**, which displayed significant activities for the hydrogenation of a range of alkenes. Remarkably, the hydrogenation of (*E*)-diethyl 2-benzylidenesuccinate was achieved by using the rhodium catalyst **19**-Rh(cod)Cl with 99% ee.

2.6. Tridentate NHC Ligands. In 2010, Sánchez and co-workers developed a novel family of tridentate *C,N,N*-pincer-type complexes, containing Au, Pd, and Rh (**20**). These

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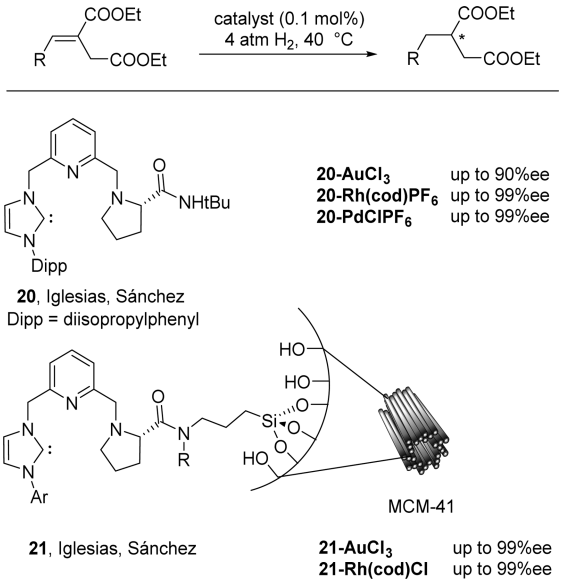
complexes were first applied to the enantioselective hydrogenation of diethyl 2-benzylidenesuccinates (Scheme 8).[25]

Scheme 8. *C,N,N*-Pincer Gold, Palladium, and Rhodium Complexes and Their Immobilization on Mesoporous Silica

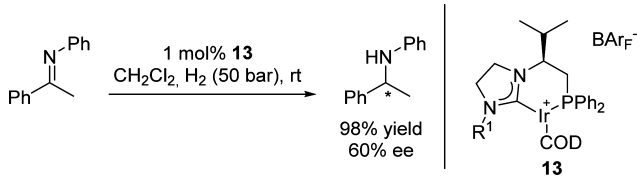


Additionally, the Au and Rh complexes were successfully immobilized on ordered mesoporous silica **21** and utilized in the hydrogenation of diethyl itaconate and diethyl 2-benzylidenesuccinate.[26] While the supported Rh(I) catalysts **21**-Rh(cod)Cl showed higher activity in comparison to the Au(III) catalysts **21**-$AuCl_3$, both afforded high levels of enantiomeric excess (ee > 98%) and both catalysts could be recycled and reused up to four times without loss of activity. We believe that, following this catalyst-immobilization strategy, many highly active and enantioselective heterogeneous asymmetric catalysts for hydrogenation could be successfully developed in the future.

3. NHC-METAL COMPLEX CATALYZED ASYMMETRIC KETONE/IMINE HYDROGENATION

The catalysis of ketone hydrogenation using hydrogen gas with chiral NHC-metal complexes has yet to be reported, even though the asymmetric hydrogenation of ketones/imines has been widely documented using other ligands.[27] Surprisingly, there is only one example of an NHC-metal complex catalyzed asymmetric hydrogenation of imines, reported by Pfaltz in 2006 using complex **13** (Scheme 9).[21] Given the importance of chiral secondary alcohols and amines, the development of efficient chiral NHC-metal catalysts for imine/ketone hydrogenation is a worthy research challenge. However, a greater mechanistic understanding of NHC-metal catalyzed hydrogenation may first be required to aid the design of an efficient chiral NHC-metal catalyst.

Scheme 9. NHC-Metal Catalyzed Asymmetric Hydrogenation of Imines

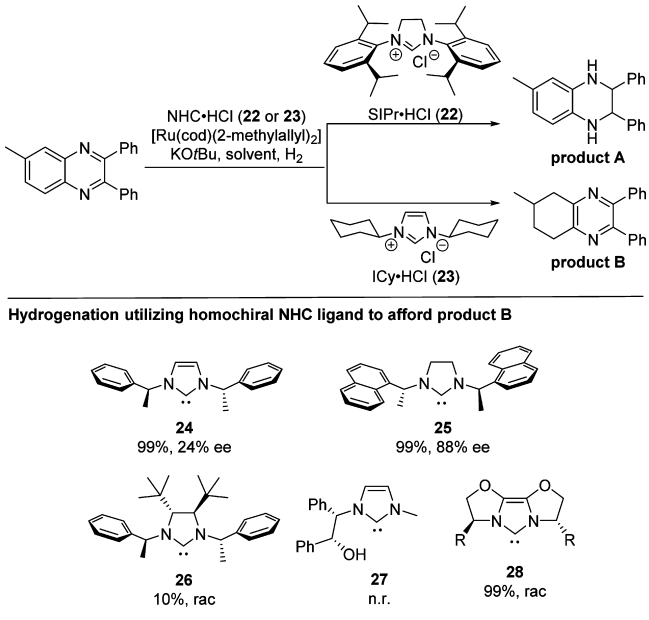


4. NHC-METAL COMPLEX CATALYZED ASYMMETRIC HYDROGENATION OF (HETERO)ARENES

In addition to the asymmetric hydrogenation of alkenes, the asymmetric hydrogenation of (hetero)arenes represents an attractive approach toward saturated or partially saturated cyclic molecules, enabling the installation of multiple stereocenters in a single step. However, despite a few impressive advances,[28] the asymmetric hydrogenation of (hetero)arenes suffers from limitations, with many challenges yet to be addressed. Most transition-metal catalysts that have been explored are generally only effective for the hydrogenation of N-heterocycles and related systems. The selective homogeneous asymmetric hydrogenation of carbocyclic rings, and many other classes of heterocycles, still poses a substantial challenge.

4.1. Discovery of a Novel and Robust NHC-Ru Catalytic System: Enantioselective Hydrogenation of Aromatic Carbocyclic Rings. Following work by Chaudret, Borowski, and Sabo-Etienne on the remarkable ability of a ruthenium-hydride complex to hydrogenate stable (hetero)-arenes,[29] our group became interested in exploring this concept, with the view to develop a novel transition metal NHC catalyst. Initial studies revealed that the combination of Ru(cod)(2-methylallyl)$_2$ and in situ deprotonated imidazolium or imidazolidinium salts provided an efficient catalytic system capable of hydrogenating quinoxalines.[30] The reaction showed great sensitivity to the nature of the carbene ligand. Employing the carbene precursor SIPr·HCl (**22**), we observed reduction of the N-heterocycle, providing product A, reactivity which is typical of other catalyst systems (Scheme 10). Interestingly, changing the ligand to ICy·HCl (**23**) resulted in complete inversion of the regioselectivity, resulting in reduction of the carbocycle, yielding product B (Scheme 10). Pleasingly, the chiral NHCs **24**−**28** tested in this reaction were also selective for the reduction of the carbocycle, while phosphine ligands gave no reactivity at all. The most successful chiral motif was

Scheme 10. Ligand Screening for Asymmetric Quinoxaline Hydrogenation



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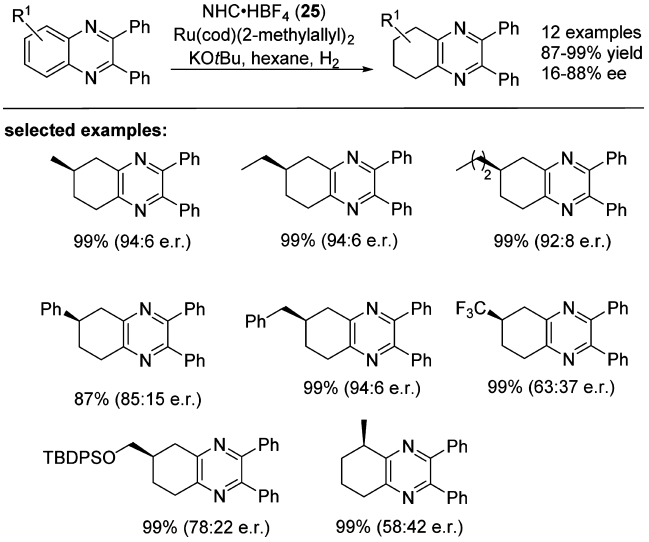
based on the arylethyl framework (**24** and **25**), initially described by Hermann as the first class of chiral NHC.[3] Backbone chirality (**26**), as well as a second coordination site on the ligand (**27**), resulted in low or no conversion. The IBiox ligands **28** were reactive; however, no enantioinduction was observed. Among the NHCs tested, the 1-(1-naphthyl)-ethylamine-derived ligand **25** proved best, displaying high reactivity, regioselectivity, and enantioselectivity (Scheme 10).

A variety of 6-alkyl-substituted quinoxalines were hydrogenated in excellent yields, high regioselectivities, and good enantioselectivities (80−88% ee) under the optimized conditions. Notably, this represents the first example of the asymmetric hydrogenation of carbocyclic rings of aromatic compounds (Scheme 11). Interestingly, replacing the 6-alkyl

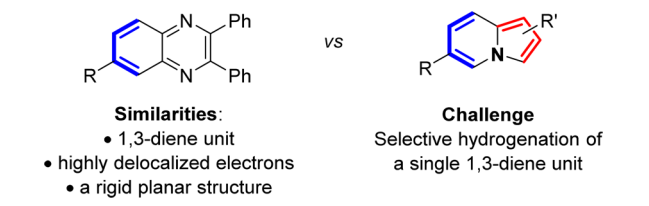
Scheme 11. Scope of the NHC-Ru Catalyzed Asymmetric Hydrogenation of Quinoxalines



substituent with a phenyl ring was found to decrease the reaction's enantioselectivity, as did changing the position of the alkyl substituent from the 6- to the 5-position.

4.2. From Carbocycle to N-Bridged Heterocycles: A Key Rigid 1,3-Diene Unit. When considering the structure of quinoxalines, several important features can be summarized: they contain an electron-deficient ring system with highly delocalized electrons and a rigid 1,3-diene unit (Scheme 12).

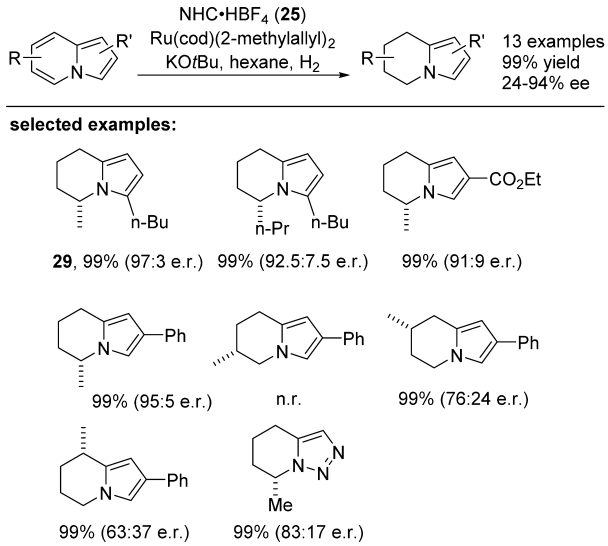
Scheme 12. Comparison of the Core Structures of Quinoxalines and Indolizines



The rigid 1,3-diene unit is also present in the core structure of indolizines, and has properties similar to those of the carbocycle of quinoxaline. Thus, we rationalized that indolizines may also be interesting hydrogenation substrates for our NHC-Ru catalyst. Indolizines, however, posed the additional challenge of selectively reducing one of the two 1,3-diene units (i.e., pyridyl and pyrrole) in the molecule (Scheme 12). Prior to this work, only a few heterogeneous catalytic systems had been reported for the hydrogenation of partially saturated indolizidines and the asymmetric hydrogenation of aromatic indolizines was unknown in the literature.

The hydrogenation of substituted indolizines, utilizing the NHC-Ru catalyst derived from NHC ligand **25**, was found to provide tetrahydroindolizines, such as **29**.[31] Exclusive hydrogenation of the six-membered pyridine ring was observed. This regioselectivity can be justified by the electron delocalization of the fused N-bridged heterocycle, which affords a less aromatic and hence more easily reduced pyridine. Employing the optimized conditions, we hydrogenated a variety of indolizines, as shown in Scheme 13. Additionally, 1,2,3-triazolo[1,5-

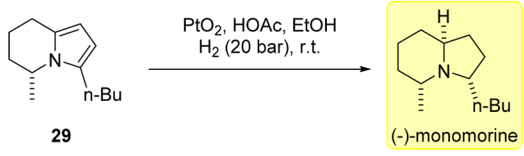
Scheme 13. NHC-Ru Complex Catalyzed Asymmetric Hydrogenation of Indolizines



a]pyridines were also hydrogenated with moderate enantiomeric ratio under the optimized conditions, constituting the first example of the asymmetric hydrogenation of this ring system.

Following asymmetric hydrogenation of the six-membered ring, the further heterogeneous hydrogenation of the remaining pyrrole ring of tetrahydroindolizine **29** was explored utilizing Jefford's heterogeneous catalyst,[32] to provide the enantiomer of the natural product (−)-monomorine (Scheme 14).

Scheme 14. Synthesis of (−)-Monomorine



Similar to the case for indolizines, pyridones are another electron-poor pyridine-like ring system with reduced aromaticity (also contains a 1,3-diene unit). Usually monocycles are more difficult to hydrogenate as, following the reaction, there is no aromatic stabilization retained in the molecule. Here, *N*-methylation locks the less aromatic amide structure and helps the hydrogenation reaction to proceed in high yields (Scheme 15).[33] Many different substitution patterns were possible in this

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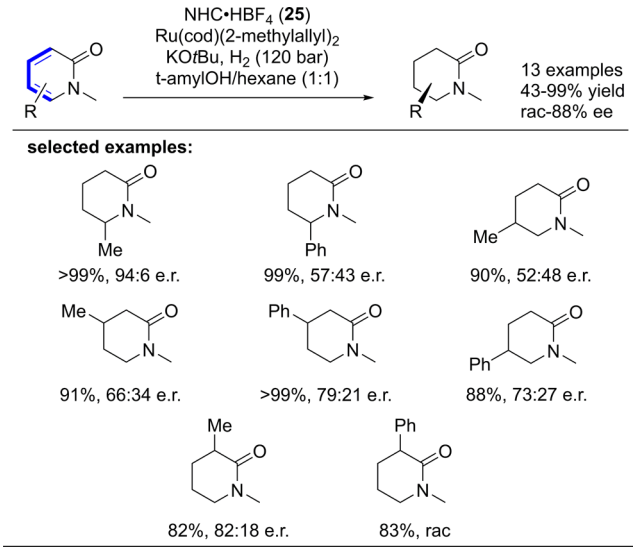
reaction, although the obtained enantioselectivities were rather low.

Scheme 15. NHC-Ru Complex Catalyzed Asymmetric Hydrogenation of Pyridones

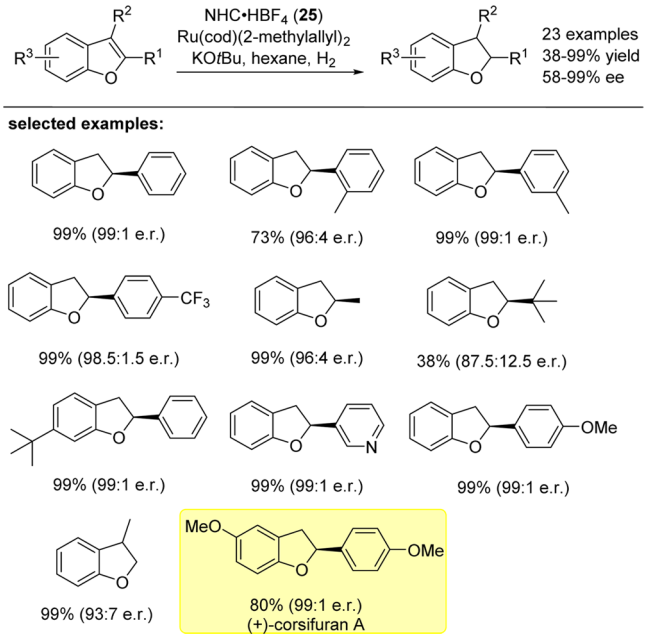


4.3. Exploring the Hydrogenation of Electron-Rich Five-Membered Heteroarenes. Having successfully shown that our NHC-Ru system was an efficient catalyst for the hydrogenation of electron-deficient six-membered carbocycles and heteroarenes, we next explored the catalyst's reactivity toward electron-rich bicyclic aromatics: namely, benzofurans. Pleasingly, application of the previously described catalyst system, utilizing homochiral NHC ligand **25**, to the hydrogenation of 2-substituted benzofurans resulted exclusively in reduction of the heterocyclic ring. The 2,3-dihydrobenzofurans were obtained with excellent enantioinduction when the 2-substituent was an aryl group (Scheme 16).[34] While small 2-alkyl substituents gave products with good enantiomeric excess, sterically demanding 2-alkyl substituents were found to reduce both the yield and ee. Only two reports, with very limited substrate scope, can be found for the asymmetric hydrogenation of benzofurans prior to 2014,[35] with this being the first example of highly asymmetric hydrogenations of aryl-substituted benzofurans to the best of our knowledge.

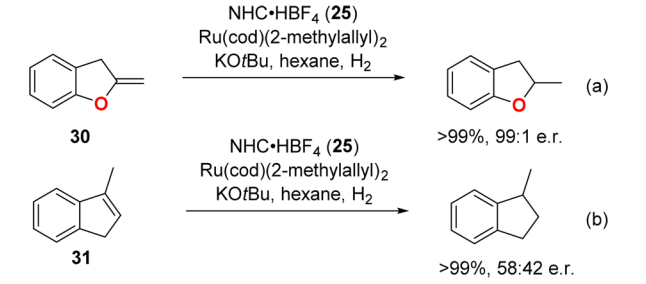
While the structure and mode of action of the catalyst are not yet known, we believe that the oxygen atom in benzofurans is pivotal and responsible for the enantioselectivity. To investigate this hypothesis, nonaromatic 2,3-dihydrobenzofuran **30** was subjected to the optimized reaction conditions. As anticipated, the hydrogenated product was obtained in quantitative yield with the same enantiomeric ratio as the hydrogenation product of 2-methylbenzofuran (Scheme 17a). Further, a drastic decrease in enantioselectivity was observed when 3-methylindene (**31**) was hydrogenated (Scheme 17b). These results support the hypothesis that the oxygen atom in the substrate is important for enantioinduction.

4.4. From Bicyclic Heterocycles to Monocyclic Heterocycles. In spite of the prominence of the tetrahydrofuran skeleton in a range of natural product classes, there are few reported examples of the asymmetric hydrogenation of substituted furans.[36] Hence, we next explored our catalytic system for the hydrogenation of monocyclic oxygen-containing

Scheme 16. NHC-Ru Complex Catalyzed Asymmetric Hydrogenation of Benzofurans



Scheme 17. Investigation into the Influence of Oxygen within the Substrate



heteroarenes. Unfortunately, initial examination of the asymmetric hydrogenation of monosubstituted furans using our NHC-Ru catalyst resulted in only racemic products. Further investigation, however, demonstrated that our system is highly efficient for the asymmetric hydrogenation of diverse 2,5-disubstituted aryl alkyl furans and 2,4-disubstituted furans (Scheme 18).[37] Moderate to good conversions, diastereoselectivities, and enantioselectivities were obtained for the hydrogenation of 2,5-disubstituted aryl alkyl furans. For all of the 2-methyl-4-aryl-substituted furans, the corresponding tetrahydrofurans were achieved as a single *cis* diastereoisomer with high conversions and outstanding enantiomeric excesses.

Because of the absolute configuration of the major *cis* enantiomer formed, and our knowledge of the enantioinduction achieved for hydrogenation of 2-substituted benzofurans, a possible catalytic pathway for the hydrogenation of 2,5-disubstituted furans was proposed (Scheme 19). Initially, enantiodetermining hydrometalation of the less sterically hindered face of the alkyl-substituted double bond, to form the two possible dihydrofuran stereoisomers **I1** and **I2**, is proposed to occur. The major 2*R*,5*R*-*cis* enantiomer then forms via sequential hydrometalation of **I1** and recoordination at the remaining double bond (path A, Scheme 19). Alternatively, the second stereocenter could be formed via formation of a Ru-π-

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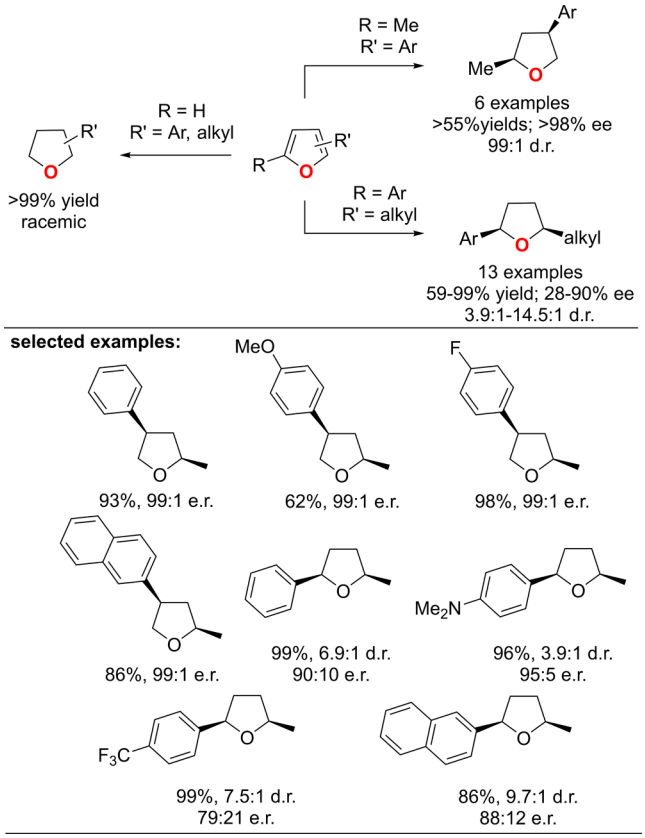
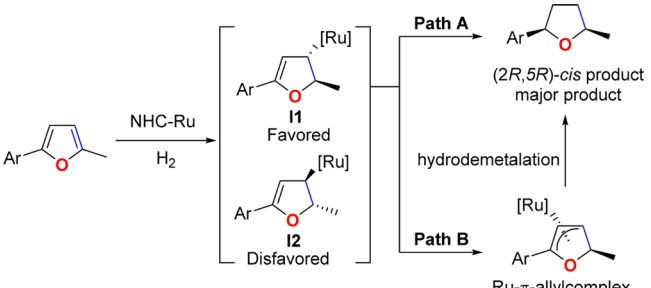
Scheme 18. NHC-Ru Complex Catalyzed Hydrogenation of Substituted Furans



Scheme 19. Proposed Mechanism for the Asymmetric Hydrogenation of 2,5-Disubstituted Furans

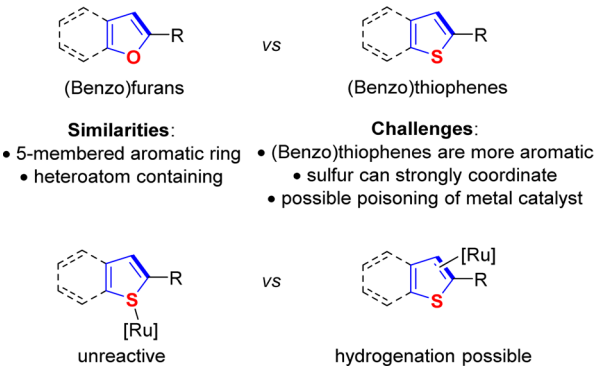


Path A, Sequential hydrodemetalation and recoordination
Path B, Isomerization

allyl complex followed by its hydrodemetalation (path B, Scheme 19).

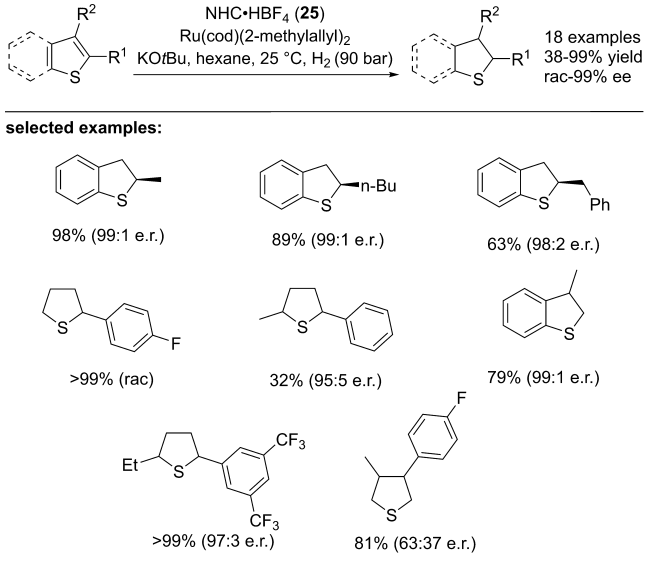
4.5. *S* Effect: Hydrogenation of Thiophenes and Benzothiophenes. Having investigated the hydrogenation of oxygen-containing five-membered heteroarenes, we turned our attention toward the sulfur-containing thiophene and benzothiophene ring systems (Scheme 20). While (benzo)-furans sometimes display reactivity similar to that of (benzo)-thiophenes in numerous organic transformations, sulfur-containing substrates can often be problematic in transition metal catalyzed processes due to sulfur's potential to strongly coordinate to and poison metal catalysts (Scheme 20). This is highlighted by the fact that, prior to our report, there existed no homogeneous catalytic system in the literature for the hydrogenation of substituted benzothiophenes and thiophenes.

Scheme 20. Comparison of the Core Structures of (Benzo)furans and (Benzo)thiophenes and Potential (Benzo)thiophene-Ru Binding Modes



On the basis of our knowledge of the NHC-Ru catalyst, we were confident that the asymmetric hydrogenation of (benzo)-thiophenes was possible, as the strong σ-donating capacity of the carbene ligand with the metal center should favor η^2-(C,C)-substrate−metal interactions through attractive π-back-donation into the π-bond of the substrate (Scheme 20). Additionally, Ru(II) complexes generally display very weak S coordination. Pleasingly, following optimization, we found 2- and 3-alkyl-substituted benzothiophenes and 2,5-disubstituted thiophenes were hydrogenated efficiently, providing products with excellent enantioselectivities (Scheme 21).[38] Similar to the

Scheme 21. NHC-Ru Complex Catalyzed Asymmetric Hydrogenation of (Benzo)thiophenes



case for monosubstitued furans, monosubstituted thiophenes could be reduced quantitatively, but only to provide the racemic products (Scheme 21). 2-Aryl or 3-aryl-substituted benzothiophenes were found to be unreactive under the optimized conditions. In comparison to (benzo)furans, the hydrogenation of (benzo)thiophenes exhibited some noticeable differences, with lower conversions achieved and a narrower scope of effective substrates. The further optimization of our NHC ligand is potentially required to address these limitations.

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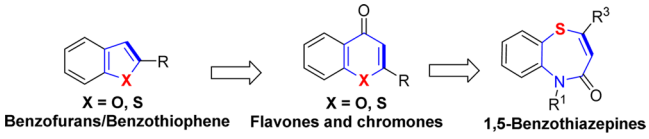
4.6. Ring Size: From Five-Membered Rings to Six- and Seven-Membered Rings. Having systematically explored the hydrogenation of oxygen and sulfur-containing five-membered heteroarenes, we next focused our attention on six-membered oxygen- and sulfur-containing heterocycles as well as seven-membered sulfur-containing heterocycles (Scheme 22). First,

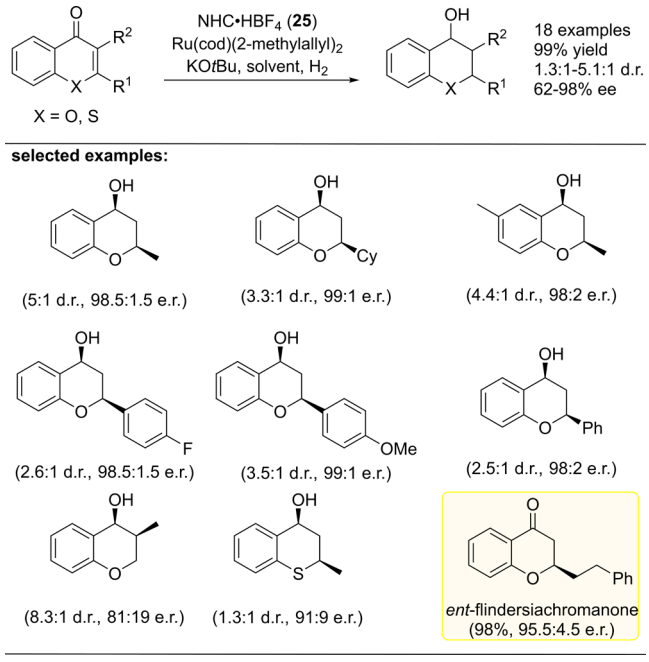
Scheme 22. Comparison of the Structure of Oxygen/Sulfur Containing Heterocycles



flavones and chromones were selected as interesting substrates, as optically active flavonoids and chromanoids are extensively represented in natural product cores.[39] Despite this, the asymmetric hydrogenation of flavones and chromones remained largely unexplored. Structural analogies can be found on comparison of benzofurans and flavone/chromones, which both contain double bonds within a benzannulated oxygenated ring system, indicating that analogous asymmetric hydrogenation may be possible.

With our privileged NHC-Ru complex as the catalyst, the hydrogenation of chromones provided the corresponding chromanoid with excellent enantioselectivities and good diastereomeric ratios (5:1). The catalyst system proved to be efficient for the enantioselective hydrogenation of a variety of 2-substituted flavones and chromones (Scheme 23).[40] A significant decrease in enantioselectivity was observed when 3-substituted chromone was hydrogenated under the optimized conditions. Thiochromenone could also be hydrogenated under the same conditions, but with very low diastereoselectivity. These chiral flavanols and chromanols could be further oxidized

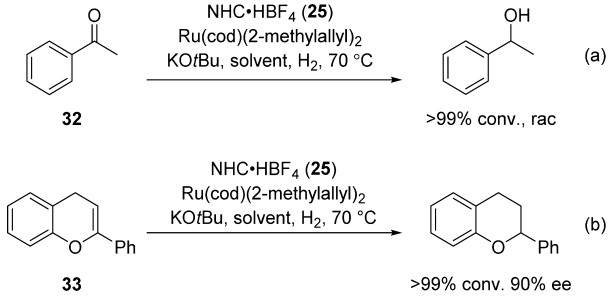
Scheme 23. NHC-Ru Catalyzed Asymmetric Hydrogenation of Chromones and Flavones



to deliver various enantiomerically enriched flavanones and chromanones in excellent yields.

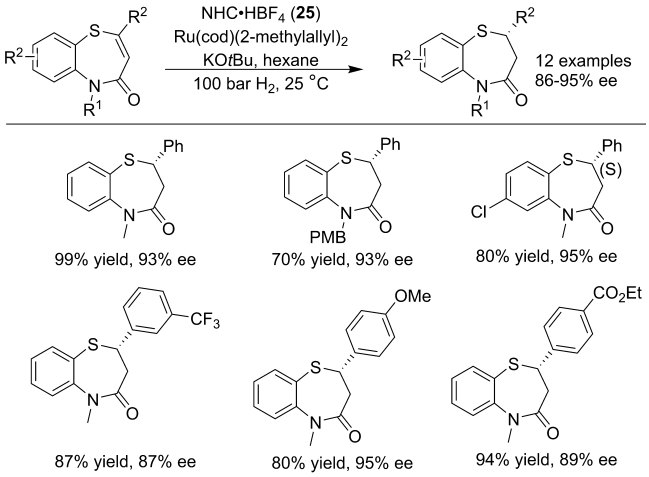
The poor diastereoselectivity observed suggested that the catalyst system was not highly selective for the asymmetric hydrogenation of ketones. To verify this hypothesis, the hydrogenation of acetophenone (**32**) was undertaken, resulting in formation of the racemic alcohol (Scheme 24a). In contrast, hydrogenation of the carbon−carbon double bond of chromene **33** afforded the saturated product with high enantioselectivity (Scheme 24b).

Scheme 24. NHC-Ru Catalyzed Hydrogenation of Acetophenone 32 and Chromene 33



Moreover, it was found that the NHC-Ru catalytic system could be successfully extended to the asymmetric hydrogenation of the vinyl thioether motif of the seven-membered, sulfur-containing heterocycles 1,5-benzothiazepinones with excellent ee values (up to 95%), high yields (up to 99%), and good functional group tolerance (Scheme 25),[41] which

Scheme 25. NHC-Ru Catalyzed Hydrogenation of 1,5-Benzothiazepinones



provides a direct method to access optically active 1,5-benzothiazepine, a versatile pharmacophore in the field of pharmaceutical research.[42] Surprisingly, while hydrogenation has been intensely studied, the asymmetric hydrogenation of seven-membered heterocycles remains rare.

Further derivatizations of the reduced products were also performed in this study to demonstrate the synthetic utility of the method. First, we demonstrated that **34** can be successfully converted to the unprotected 2,3-dihydro-1,5-benzothiazepinone **35** without any loss of enantiomeric excess under strongly Brønsted acidic conditions (Scheme 26a). Moreover, the

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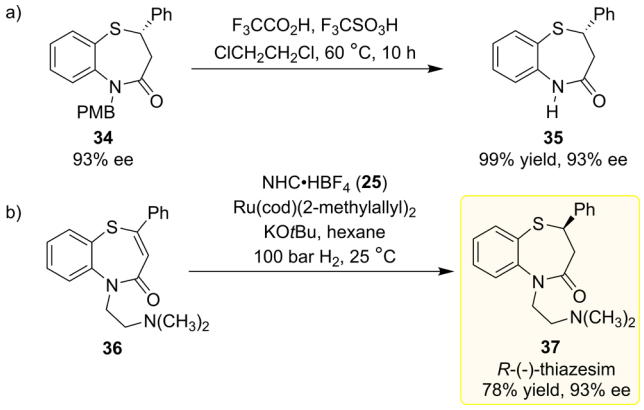
Scheme 26. Applications of the Asymmetric Hydrogenation Reaction



asymmetric hydrogenation of the unsaturated 1,5-benzothiazepinone **36**, bearing a tertiary amine moiety, was found to proceed readily, affording the seven-membered heterocyclic antidepressant drug (*R*)-(−)-thiazesim (**37**) with 93% ee and 78% yield (Scheme 26b),[43] which constitutes one of the most straightforward processes for the asymmetric synthesis of thiazesim to date.

4.7. Comments on our NHC-Ru Catalyst System. In this Perspective, we presented the highly enantioselective hydrogenation of ten different heterocycles with one catalyst system based on ruthenium and the homochiral NHC ligand SINpEt (**25**). The broad applicability of this system to a range of different (hetero)arenes is remarkable, with efficient, asymmetric hydrogenation of carbocycles and nitrogen-, oxygen-, and sulfur-containing five, six- and seven-membered heterocycles being developed (Scheme 27).

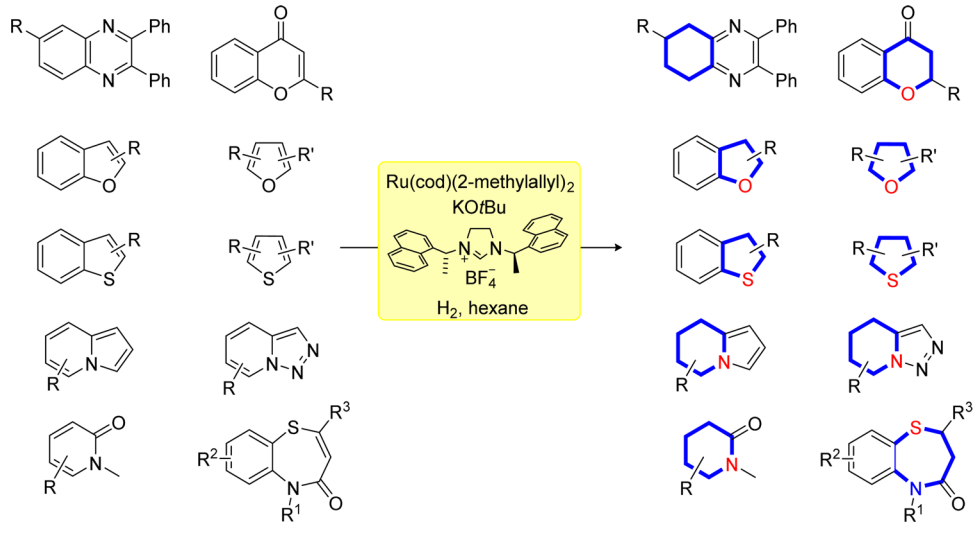
While we continue to investigate the catalyst's mode of reactivity and enantioinduction, we assume that the naphthalene groups on the ligands are required not only to enable the selectivity but also to provide stability to the catalyst complex. Exchanging them for aliphatic groups generally results in unstable complexes, which give poorly reproducible hydrogenation results. To investigate the nature of the catalyst, we performed kinetic investigations for the hydrogenation of 2-methylbenzofuran.[34a] The presence of an induction time shows that the preformed bis(NHC)ruthenium complex is a precatalyst, which is activated under a hydrogen atmosphere. The activation presumably occurs via hydrogenation of the naphthyl moieties on the ligand, providing tetrahydronaphthalene substituents in the active catalyst. It is truly remarkable that a monodentate NHC, presumably the only spectator ligand in the active catalyst, can create a chiral environment capable of giving enantioselectivities comparable to those of established chiral bis-phosphine ligands.

5. SUMMARY AND OUTLOOK

This general perspective has given a clear outline of the application of NHC-metal complexes as catalysts in the asymmetric hydrogenation of alkenes, imines, and (hetero)arenes. As described above, many NHC-metal complexes have been applied to the hydrogenation of alkenes. While only two families of rigid monodentate NHC-metal complexes have been reported for the asymmetric hydrogenation of alkenes, numerous bi- and tridentate NHC-metal complexes have been reported with varying levels of success. Particularly exciting are the high levels of enantioinduction achieved using tridentate NHC-metal complexes of Au, Rh, and Pd and the immobilization of the catalyst system on ordered mesoporous silica, providing a recyclable catalyst system. Nevertheless, the efficiency and chiral control of most NHC-metal complexes in the hydrogenation of alkenes is still far from that of the analogous phosphine-metal complexes. Moreover, there are still no suitable and effective chiral NHC ligands for the enantioselective hydrogenation of diverse ketones and imines.

With regard to the NHC-metal complex catalyzed asymmetric hydrogenation of (hetero)arenes, to date, only the Ru-NHC complex reported by our group has been found to afford high reactivities and enantioselectivities.[44] Utilizing a single NHC ligand (**25**) and a ruthenium precursor, we have been able to achieve the asymmetric hydrogenation of a range of electronically diverse carbocycles and nitrogen-, oxygen-, and sulfur-containing (hetero)arenes, which truly demonstrated the power of NHC ligands in the hydrogenation of (hetero)arenes. Moreover, Zeng recently demonstrated that the aromatic ring of aryl ketones and phenols can be smoothly and

Scheme 27. NHC-Ru Catalyzed Highly Enantioselective Hydrogenation of Nine Diverse Heterocycles



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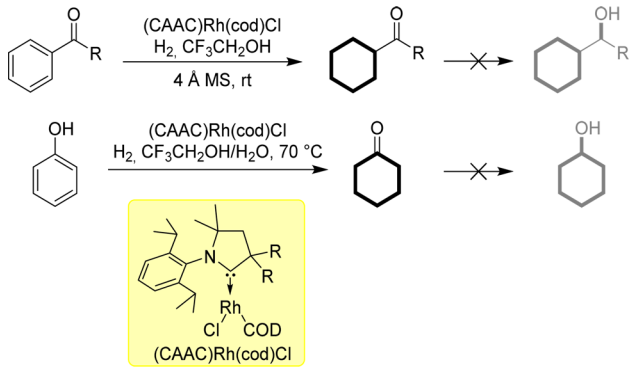
regioselectively hydrogenated using an electron-rich carbene-Rh complex (Scheme 28).[45] While only achiral ligands have

Scheme 28. CAAC-Rh Catalyzed Hydrogenation of Benzene and Phenol Derivatives in the Presence of Ketones



been employed to date, the superior selectivity and reactivity of the NHC-Rh catalyst in comparison to those of systems based on phosphines will hopefully lead to a renewed interest by the community in this fascinating ligand class. Research in the area of NHC ligand design and synthesis is ongoing within our research group to develop new ligands, which will provide orthogonal reactivities and selectivities.

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Notes

The authors declare no competing financial interest.

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