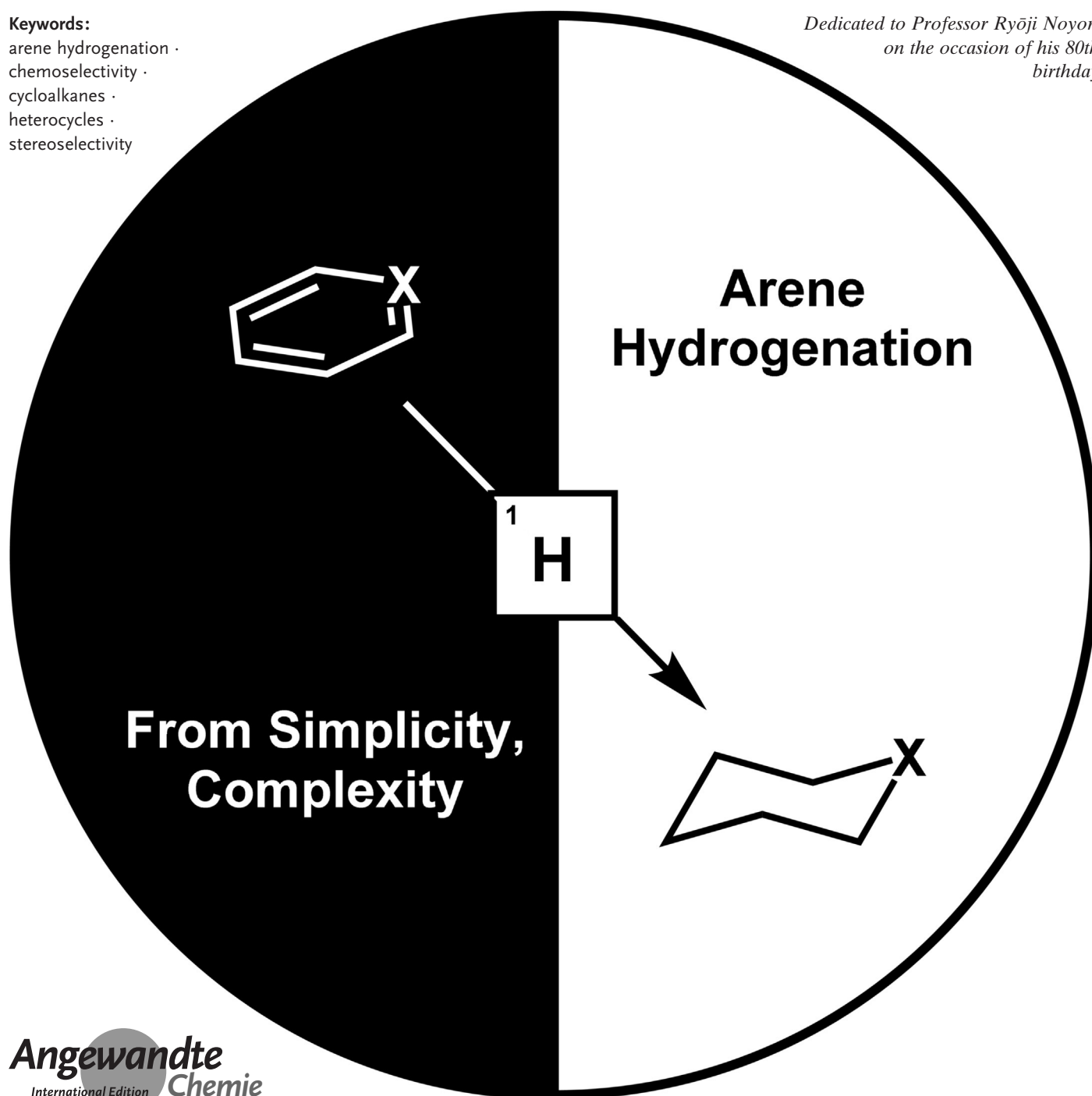


Arene Hydrogenation

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Selective Arene Hydrogenation for Direct Access to Saturated Carbo- and Heterocycles

*Mario P. Wiesenfeldt, Zackaria Nairoukh, Toryn Dalton, and Frank Glorius****Keywords:**arene hydrogenation ·
chemoselectivity ·
cycloalkanes ·
heterocycles ·
stereoselectivity*Dedicated to Professor Ryōji Noyori
on the occasion of his 80th
birthday*

Arene hydrogenation provides direct access to saturated carbo- and heterocycles and thus its strategic application may be used to shorten synthetic routes. This powerful transformation is widely applied in industry and is expected to facilitate major breakthroughs in the applied sciences. The ability to overcome aromaticity while controlling diastereo-, enantio-, and chemoselectivity is central to the use of hydrogenation in the preparation of complex molecules. In general, the hydrogenation of multisubstituted arenes yields predominantly the *cis* isomer. Enantiocontrol is imparted by chiral auxiliaries, Brønsted acids, or transition-metal catalysts. Recent studies have demonstrated that highly chemoselective transformations are possible. Such methods and the underlying strategies are reviewed herein, with an emphasis on synthetically useful examples that employ readily available catalysts.

1. Introduction

Arene hydrogenation transforms aromatic substrates into saturated carbo- and heterocycles. Classical methods, such as aromatic substitutions, condensations, and cross-coupling reactions, provide access to innumerable arene and heteroarene substrates. In turn, arene hydrogenation provides the most direct, retrosynthetically simple route to a vast, divergent range of cyclic saturated motifs (Figure 1). Its strategic value is reflected in a number of current multi-thousand ton scale industrial applications, such as the hydrogenation of benzene to cyclohexane (**1**)^[1] or cyclohexene (**2**)^[2] for nylon production, or the hydrogenation of thymol to (racemic) menthol (*rac*-**3**) in the Symrise menthol process.^[3] Arene hydrogenation is an important step in the valorization of biomass-derived platform chemicals such as furfural.^[4] Furthermore, arene hydrogenation and dehydrogenation are the key steps in the operation of liquid organic hydrogen carriers (LOHCs).^[5] The utilization of arene hydrogenation to access saturated functional molecules in the fine-chemical sector is gaining momentum. For example, the enantioselective hydrogenation of quinolines has enabled efficient access to enantioenriched tetrahydroquinoline alkaloids such as (–)-galipinine (**4**).^[6] A beautiful recent example would be the synthesis of (–)-jorunnamycin A and (–)-jorumycin (**5**) by the Stoltz group, whereby the core was constructed through an enantioselective isoquinoline hydrogenation-cyclization, thereby introducing a high level of complexity in a single operation.^[7] Likewise, arene hydrogenations have provided notable synthetic shortcuts to all-*cis*-(multi-)fluorinated cycloalkanes (e.g. **6**)^[8] and piperidines (e.g. **7**).^[9] The former motif (**6**) is of interest in materials science for its high polarity; the latter (**7**) combines two abundant design elements of medicinal chemistry. The chemo- and enantioselective hydrogenation of pyridines is the key step within a concise, multikilogram synthesis (7 steps, 38% overall yield) of a promising therapeutic against Type 2 diabetes (**8**).^[10] However, the implementation of this transformation towards a given target must satisfy three important conditions:

- 1) Reactivity: in contrast to the established hydrogenation of other unsaturated moieties such as alkenes,^[11] ketones,^[12]

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and imines/enamines,^[13] the hydrogenation of arenes is hindered by the added kinetic barrier resulting from the aromatic stabilization energy.

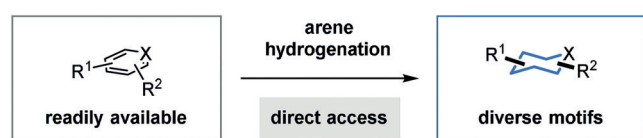
- 2) Stereoselectivity: the hydrogenation of multisubstituted arenes may form several product diastereomers; in general, the *cis* isomer is favored. Furthermore, substituted saturated carbo- and heterocycles are often chiral.
- 3) Chemoselectivity: elaborate substrates often exhibit competing side reactions—for example, concurrent hydrogenation of more reductively labile units, such as alkenes, or hydrodefunctionalizations.

Arguably the kinetic barrier was surmounted in 1901, with the first report on the hydrogenation of benzene by Sabatier and Senderens.^[14] Today, the hydrogenation of almost all known arene and heteroarene motifs can be achieved using a variety of available catalyst systems. Such catalyst systems include both homogeneous metal complexes and heterogeneous catalysts, such as metal (nano-)particles and surface-supported catalysts.^[15a–d] Nevertheless, the low reactivity of a particular arene substrate often constrains the selection of catalyst systems, especially for strongly stabilized benzene derivatives, and hence may lead to alternative challenges such as enantio- or chemoselectivity. The development of transformations with predictable selectivity remains demanding and research into such reactions is an emerging field. The objectives of this Review are to discuss these recent efforts from the perspective of the organic chemist, to help the reader to judge whether or not a desired hydrogenation reaction is facile, and to suggest which catalyst system should

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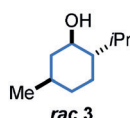
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Established – simple bulk chemicals

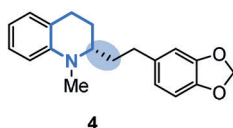


industrial cyclohexane & cyclohexene syntheses

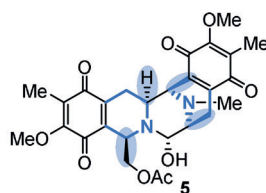


rac menthol – Symrise menthol process

Emerging – complex fine chemicals



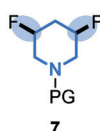
3 steps
(–)-galipinine



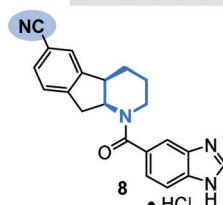
16 steps
(–)-joromycin



1 step
formerly 12



1 step
formerly 5



7 steps
formerly 15

Challenges

- stereocontrol: *cis/trans* enantioselectivity
- labile FG substituents at reactive arene
- further reducible sites

Figure 1. Arene hydrogenation provides direct access to diverse carbonyl and heterocycle motifs.

be tried preferentially. A perspective for future work will be outlined in the process. Such a review cannot be comprehensive; recent reviews have been published focusing on various aspects of arene hydrogenation^[15] or dearomatization reactions in a broader sense.^[16]

2. Stereoselective Arene Hydrogenation

2.1. Diastereoselective Arene Hydrogenation

The hydrogenation of disubstituted arenes may generate two diastereomers of the saturated product. Arene hydrogenation generally proceeds with high *cis* selectivity, although the *trans* isomer is usually thermodynamically favored. The *cis* isomer would result from a non-interrupted coordination of the catalyst to the arene during the hydrogenation. The formation of the *trans* isomer requires a π facial exchange, for example through a catalyst dissociation-reassociation sequence from a chiral, dearomatized diene or olefin intermediate, prior to further hydrogenation. It can be argued that such a rearrangement is unlikely to occur, since the further hydrogenation of the dearomatized intermediates should be faster than the initial dearomatization of the stabilized aromatic substrate. In addition, the catalyst would have to bind to the sterically more hindered π face following the facial exchange to then give the *trans* isomer. Nonetheless, the binding affinity of the metal catalyst to the particular species and π face, and ultimately the *cis* selectivity, is dependent on the reaction conditions as well as the electronic and steric properties of the substrate and those of the catalyst. In most cases, the *trans* isomer is indeed formed as a minor product. Recently, the Marks group disclosed a catalyst system that exclusively delivers the *cis* isomer.^[17] The group had previously reported on supported, single-site^[18] organozirconium catalysts which consist of a cationic $\text{Cp}^*\text{Zr}(\text{alkyl})_2$ ($\text{Cp}^* = \text{C}_5\text{Me}_5$) precatalyst tethered to an anionic sulfated zirconiumoxide support.^[19] The different selectivities of the new $\text{Cp}^*\text{Zr}(\text{benzyl})_2$ precatalyst (**13**) compared to the previous single-site $\text{Cp}^*\text{ZrMe}_2/\text{ZrS}$ precatalyst (**12**) were demonstrated with the hydrogenation of hexadeuterobenzene (**9**; Figure 2A). Precatalyst **12** delivered a statistical 1:3 mixture of $\alpha\alpha\alpha$ - (or all-*cis*-) hexadeuterocyclohexane (**10**) and $\alpha\beta\alpha$ - (or *cis-trans-cis*-) hexadeuterocyclohexane (**11**). This result suggests that the sequential pairwise hydrogen transfer occurred randomly to both π faces.^[20] In contrast, the new precatalyst **13** delivered all-*cis*-isotopomer **10** exclusively. Careful mechanistic investigations revealed that the active species derived from **13** still included one benzoate substituent, whereas the active catalyst derived from **12** was completely hydrogenolyzed to the zirconium dihydride. Counterintuitively, the benzoate species derived from **13** had a lower binding affinity to the partially hydro-



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Zackaria Nairoukh obtained his PhD in organic chemistry under the supervision of Prof. Jochanan Blum at the Hebrew University of Jerusalem in 2014. He then joined Prof. Ilan Marek's group at the Technion-Israel Institute of Technology for postdoctoral research in the area of metal-mediated stereoselective transformations. In 2017 he joined Prof. Frank Glorius's group at the Westfälische Wilhelms-Universität Münster as a Minerva postdoctoral fellow, where he is currently researching chemoselective arene hydrogenation.

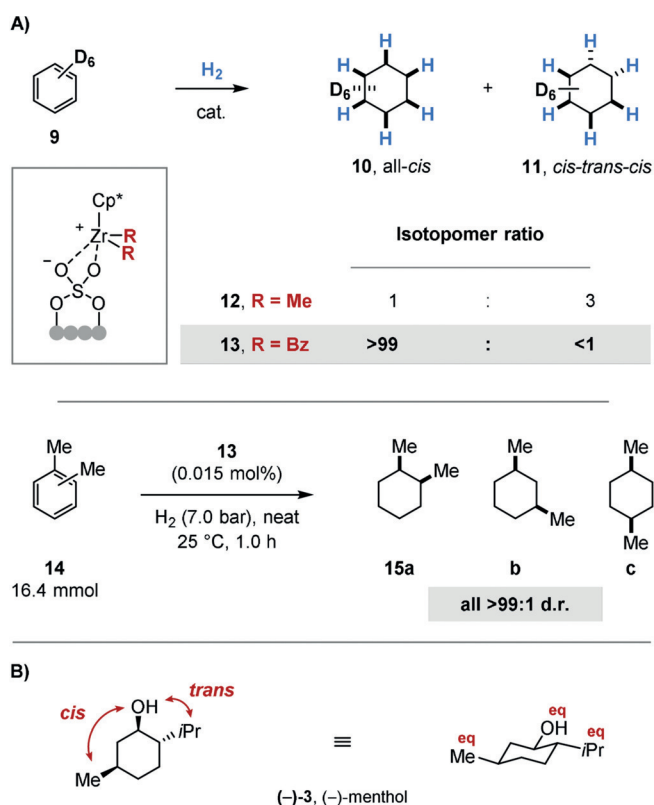


Figure 2. A) Highly *cis*-selective arene hydrogenation using a supported, single-site organozirconium precatalyst (**13**). B) Relative stereochemistry of (-)-menthol ((-)-3) and its most stable conformation. Eq: equatorial orientation.

generated diene or olefin species, thus prompting the authors to conclude that the π facial exchange in the previous system should not involve the dissociation of intermediates from the metal center. Precatalyst **13** provides highly *cis*-selective access to various alkylated cyclohexanes (**14**), which can be subsequently diversified to give more complex molecules. This is noteworthy, since the high electrophilicity of the catalyst prevents the use of substrates containing polar functional groups.

In some cases, the *trans* isomers of the multisubstituted saturated carbo- and heterocyclic products can be accessed from their *cis* analogues through nucleophilic substitution reactions; however, a *trans*-selective hydrogenation would be both more general and direct. Notably, the hydrogenation of

para-xylene using a pyridine(diamine) molybdenum catalyst reported by the Chirik group delivers the product with a 1:1 d.r.^[21] Moreover, the Symrise methanol process includes a rare example of an arene hydrogenation that gives the racemic *trans* product as the major isomer.^[22] The hydrogenation is conducted at high temperatures and the observed product selectivities reflect the thermodynamic equilibria of the diastereomers. Each substituent of menthol lies in an equatorial orientation, thus making it the lowest energy isomer (Figure 2B).^[23] Furthermore, the unwanted diastereoisomers and enantiomers can be recycled to give a >90% overall yield for (-)-menthol.^[3] To the best of our knowledge, however, no general procedures for *trans*-selective arene hydrogenation are known.

2.2. Enantioselective Arene Hydrogenation

The enantioselective hydrogenation of arenes has been extensively explored following the first highly enantioselective ($\geq 90\%$ *ee*) example reported in 1998.^[24] These efforts have been detailed comprehensively in a number of recent reviews.^[15g–j] Multiple strategies have been developed to affect chiral induction. Chiral auxiliaries may be attached to the substrate, thus facilitating a diastereoselective hydrogenation and hence enantioselective access to the chiral, saturated product upon removal of the chiral auxiliary. For example, the Glorius group developed a diastereoselective hydrogenation of pyridines using the Evans auxiliary (Figure 3).^[25] The reaction employs an achiral heterogeneous catalyst such as Pd(OH)₂/C in acetic acid. The acidic medium is believed to play three important roles in the reaction. Firstly, hydride attack is facilitated by formation of a pyridinium ion. Secondly, catalyst poisoning by the Lewis basic substrate (**16**) or product is minimized by protonation. Thirdly, protonation locks the conformation of the chiral auxiliary, thus sterically blocking catalyst association on one face (**18**). The method allows the construction of up to three stereocenters. The chiral auxiliary may be cleaved in situ and recovered quantitatively. This means of enantioselective access to chiral piperidines in a single operation has been applied in organic synthesis.^[25b] Although other methods that employ chiral auxiliaries for the enantioselective hydrogenation of benzoic or furanoic acid derivatives exist,^[26] the formation of a rigid conformation that effectively shields one face is nontrivial. The introduction and removal of the



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Frank Glorius is a Full Professor of Organic Chemistry at the Westfälische Wilhelms-Universität Münster. His research program focuses on the development of new concepts for catalysis in areas such as C–H activation, smart screening and data analysis, photocatalysis, and N-heterocyclic carbenes in organocatalysis, as surface modifiers, and in (asymmetric) arene hydrogenation.

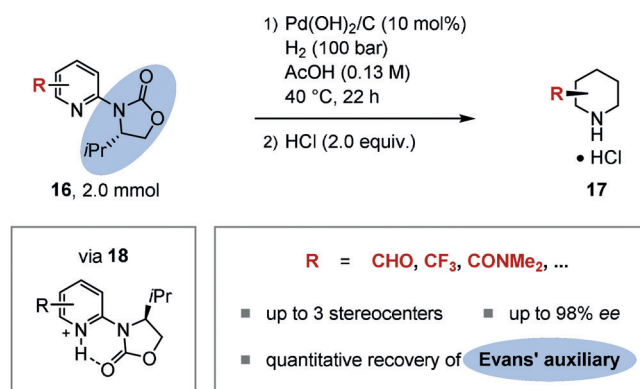


Figure 3. Enantioselective synthesis of piperidines by the diastereoselective hydrogenation of pyridines using the Evans auxiliary.

stoichiometric chiral auxiliary must be facile, which presents difficulties if it cannot be readily synthesized from the chiral pool and/or recovered, thereby limiting the scope of this underlying strategy.

An elegant strategy that addresses this problem was advanced by Rueping et al. and later others.^[27] They discovered that a catalytic chiral phosphoric acid additive (e.g. **21**) can be employed to activate basic N-heteroarenes such as 2-substituted quinolines (**19**) and the imine intermediates in the enantioselectivity-determining step for hydride transfer (**23**; Figure 4). Either a Hantzsch ester (**20**) or molecular hydrogen in combination with an achiral transition-metal catalyst may act as a hydride source. Although limited to basic N-heteroarene substrates, this strategy is synthetically useful: in particular, the transfer hydrogenation showed a good tolerance of functional groups and is readily applicable on a laboratory scale.

The use of homogeneous metal complexes with chiral ligands is, in principle, the most general strategy, and several privileged catalyst systems have emerged (Figure 5). The combination of iridium with chiral bisphosphine ligands

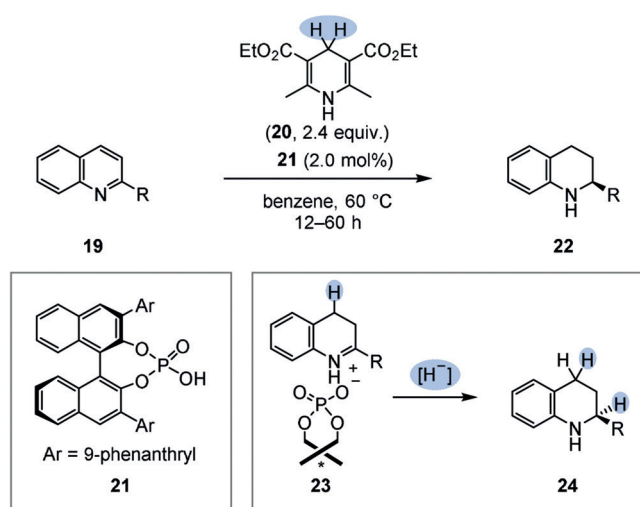
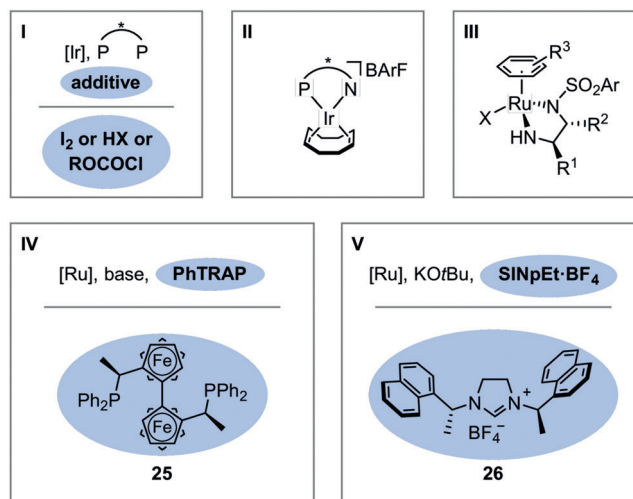


Figure 4. Enantioselective transfer hydrogenation of 2-substituted quinolines (**19**) using a chiral Brønsted acid catalyst (**21**).



- I** Scope: electron-poor N-heteroarenes Tunable by P–P* variation
- II** Scope: N/O-heteroarenes Tunable by PHOX variation
- III** Scope: arenes with a polarized carbonyonium/iminium moiety Tunable by diamine or arene ligand variation
- IV** Broad arene scope: N/N,O-heteroarenes, carbocycles Less tunable: privileged ligand
- V** Broad arene scope: N/O-/N,O-/S-heteroarenes, carbocycles Less tunable: privileged ligand

Figure 5. Established transition-metal-based catalyst systems for the enantioselective hydrogenation of (hetero-)arenes and some relevant characteristics.

(catalyst system **I**) has been studied intensively following its introduction by the group of Y.-G. Zhou.^[6] In most cases, the catalyst system is used in combination with an additive. For example, iodine promotes hydrogenation by oxidation of the iridium(I) precatalyst to the active iridium(III) species.^[28] Chloroformates^[29] or Brønsted acids^[30] bind to the basic nitrogen atom of the heteroarene, thereby activating it for the dearomative hydride attack and preventing catalyst poisoning by the Lewis-basic substrates or products. Halide-bridged iridium(III) dimers, which have been studied by the Mashima group,^[31] represent an alternative precatalyst with a similar active species.^[31c] The scope of catalyst system **I** includes a wide variety of electron-poor N-heteroarenes, and the catalyst system can be tuned to match a particular substrate by exploiting the facile accessibility of chiral bisphosphines. In addition to chiral bisphosphines, chiral P,N ligands such as phosphine-oxazolines (PHOX) have been employed in combination with iridium (**II**) by the Charette^[28d] and Pfaltz groups.^[32] In contrast to the (more nucleophilic) active iridium(III)-monohydride species^[28e] of precatalyst **I**, the active species of the iridium-PHOX catalyst system (**II**) is an acidic iridium(III)-dihydride complex,^[33] which is applicable to electron-poor and electron-rich N-heteroarenes as well as O-heteroarenes. Chiral ruthenium complexes can also catalyze the enantioselective hydrogenation of (hetero-

)arenes. For example, analogues of Noyori's transfer hydrogenation catalyst (**III**) have been employed by the groups of Q.-H. Fan and A. S. C. Chan, as well as others, for the hydrogenation of arenes bearing polarized carbonyl or iminium moieties.^[34] In addition, the Kuwano group has advanced the use of combinations of the privileged *trans*-chelating chiral 2,2'-bis[1-(diphenylphosphino)ethyl]-1,1'-biferrocene (PhTRAP) ligand (**25**) with a ruthenium precursor under basic conditions (**IV**).^[35] The catalyst system is applicable to a broad range of divergent arene and heteroarene motifs.^[36] Of particular note is the ability of the catalyst to effect hydrogenation of strongly aromatic naphthalene.^[36d] In terms of its divergent scope of applicable (hetero-)arenes, this catalyst system is, arguably, surpassed only by the ruthenium bis(N-heterocyclic carbene) (NHC) catalyst system (**V**)^[37] developed by the Glorius group, which was originally inspired by Chaudret's complex.^[38] This catalyst system can be prepared by deprotonation of the chiral NHC precursor (**26**)^[37g] in the presence of a ruthenium source. Notably, this system can even catalyze the hydrogenation of thiophenes and benzothiophenes, which lead to strongly coordinating saturated products.^[37c] Other catalyst systems based on rhodium or palladium^[39] have yet to demonstrate the general applicability of those discussed above.

Together, these chiral transition-metal-based catalyst systems facilitate the highly enantioselective hydrogenation of a variety of heteroaromatic scaffolds (Figure 6). A summary of catalysts and conditions for each product motif can be found in the appendices of the recent reviews by the group of Y.-G. Zhou.^[15g,j] Each method, however, remains limited in terms of functional-group tolerance and the substrate substitution pattern, particularly of the reactive aromatic ring. A certain substrate may require reoptimization of the reaction conditions, possibly benefiting from the tunability offered by catalyst systems **I–III**. Furthermore, there is a notable difference in the number of synthetic studies dedicated to the respective arene substrates. The hydrogenations of quinolines and, to a lesser extent, those of quinoxalines, isoquinolines, indoles, and pyridines are particularly well-explored. Possible reasons include their more facile hydrogenation or a greater demand for the chiral product motif. In either case, well-explored motifs might be comparatively more easily incorporated within a synthesis. Benzene derivatives, the archetypical arenes, present an obvious gap in the scope of all the current catalyst systems. This can be attributed to the high resonance energy (36 kcal mol⁻¹) of benzene. For comparison, only 25 kcal mol⁻¹ of resonance energy is lost during the (semi-)hydrogenation of naphthalene.^[40] This difference in resonance energy would

							>30
1	1	2	1	1	1	1	
1	1	9	7	9	1	1	
2	1	1	1	4	1	9	
1	1	2	2	1	2	1	
1	1	1	3	1	2	0	

Figure 6. Overview of the substrate scope of (highly) enantioselective arene hydrogenations catalyzed by chiral transition-metal catalysts and the respective number of published synthetic methods ($\geq 90\%$ ee, minimum two substrates).

likely be reflected in the energies of the respective transition states. As a result, very few catalysts are able to surmount the activation barrier associated with the hydrogenation of benzene.^[41a] In particular, homogeneous catalysts are generally unsuitable for the hydrogenation of benzene derivatives. A significant number of homogeneous precatalysts for the hydrogenation of benzene are known, but they have been shown to form heterogeneous active catalysts in situ. This vexing problem has been covered in excellent reviews by Widegren and Finke and, independently, by Dyson.^[41] Although enantioselective, heterogeneous catalyst systems are known,^[42] the development of such systems requires different, less established strategies compared to their homogeneous counterparts.

3. Chemoselective Arene Hydrogenation

For the purpose of this Review, we define three major chemoselectivity challenges in the area of arene hydrogenation:

- 1) Other reducible sites present in functionalized arenes are usually hydrogenated in preference;
- 2) Multicyclic arenes incorporate several potentially reactive aromatic rings;
- 3) Hydrodefunctionalizations can occur for arenes bearing substituents with functional groups that are directly attached to the reactive aromatic ring.

These challenges are in addition to those pertaining to aromatic stability, steric hindrance at the ring, and poisoning effects. However, research into such challenges, exemplified by the (enantioselective) hydrogenation of the strongly aromatic naphthalenes,^[36d] the highly coordinating thiophenes,^[37c] or of triphenylphosphine,^[43] represent interesting subtopics in themselves. Herein, methods that provide solutions for the outlined chemoselectivity challenges are discussed, with a focus on those dealing with the most challenging, strongly aromatic benzene and pyridine derivatives, since we assume that the control of the chemoselectivity should be most difficult with these substrates. Furthermore, we would consider that methods using commercially available or readily prepared catalyst systems can be expected to find more immediate application in organic synthesis and are discussed preferentially.

3.1. Preferential Hydrogenation of Arenes in the Presence of Easily Reducible Moieties

Carbonyl groups are a common reducible unit in organic chemistry. Whereas carboxylic acid derivatives are generally well-tolerated, ketones and aldehydes are normally hydrogenated preferentially over arenes. The chemoselective hydrogenation of arenes in the presence of these functional groups has been the focus of a number of studies.^[44]

For example, the chemoselective hydrogenation of phenol (**27**) to cyclohexanone (**28**) was targeted because of the huge commercial demand for the product. Since cyclohexanone is

an intermediate in the total hydrogenation of phenol to cyclohexanol (**29**), several reports disclose selectivity towards cyclohexanone at low conversion. A remarkably simple solution was discovered by the groups of Jiang and Han.^[44c] Through the use of a catalyst system consisting of (commercial) heterogeneous palladium catalysts (e.g. Pd/C or Pd/Al₂O₃) and Lewis acids (e.g. AlCl₃ or ZnCl₂), quantitative conversions are combined with essentially 100% selectivity for cyclohexanone (Figure 7 A). The authors assume that the

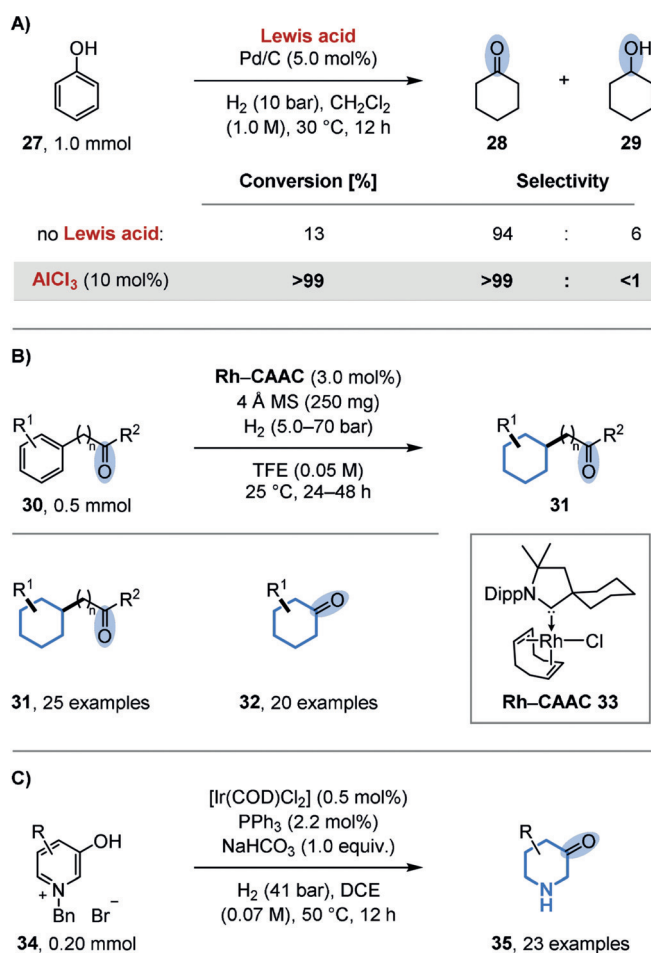


Figure 7. Chemoselective hydrogenation of arenes in the presence of ketones. A) Effect of a Lewis acid on the partial hydrogenation of phenol (**27**). B) Chemoselective hydrogenation of aromatic ketones (**30**) using rhodium-CAAC complexes (e.g. **33**). C) Chemoselective partial hydrogenation of 3-hydroxypyridinium salts (**34**). COD = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol.

Lewis acid activates the phenol for hydrogenation but reduces the rate of the further hydrogenation of cyclohexanone by coordination. Since catalytic amounts of the Lewis acid are sufficient, the interaction of the palladium catalyst with the Lewis acid may offer an alternative mechanistic rationale. In 2015 the Zeng group disclosed a general and selective method for the preferential hydrogenation of arenes in the presence of ketones (Figure 7 B).^[44i] The authors discovered that the use of rhodium precatalysts containing strongly electron-donating cyclic (alkyl)(amino)carbenes (CAACs; e.g. **33**)

were key to achieving high selectivities. These ligands, as well as their rhodium complexes, had previously been introduced by the Bertrand group as part of their impressive research program on strongly electron-donating carbenes.^[45] Other rhodium complexes, including those derived from related classical, less electron-donating imidazolium-derived NHCs, provided either low conversions or low selectivities. The authors assumed that the highly electron-rich metal center, as a result of the CAAC ligands, would favor arene binding through back-donation into the antibonding π orbitals of the arene. Although slight variations of the conditions were required to ensure preservation of the ketone functionality for all the substrates, the broad applicability of the catalyst system is impressive, since it includes multiple additional functional groups attached to the (hetero-)arene substrates. With a slight variation of the conditions, the system is also applicable to the semihydrogenation of phenols. On the basis of a mercury drop test, the authors initially assumed the active catalyst to be homogeneous in nature. A recent mechanistic study by the Bullock group, however, which included kinetic studies, quantitative poisoning experiments,^[46] and analytical techniques (Rh K-edge XAFS, STEM, IR), indicated that rhodium nanoparticles are the active species.^[47] Finally, the group of Y.-G. Zhou disclosed a method dedicated to the synthesis of 3-piperidones (**35**) starting from activated, benzyl-protected hydroxypyridinium salts (**34**; Figure 7C).^[44g] The scope includes unsubstituted, 2-/4-alkyl- and 2-/4-aryl-substituted substrates, while tolerating various remote functional groups. The disclosed semihydrogenation of such 3-hydroxypyridines is more difficult than that of 2-hydroxypyridines, which form stable amides upon hydrogenation. Consequently, a variety of cyclohexanones and other saturated carbo- and heterocycles containing ketones can be prepared by hydrogenation, often obviating the need for protecting groups or subsequent reoxidations.

Strategically, the chemoselective hydrogenation of arenes in the presence of alkenes is even more relevant, since comparatively broadly applicable protection or reoxidation reactions are not known. Foremost, an industrial process for the semihydrogenation of benzene to cyclohexene has been developed by Asahi Chemical Industry Co., Ltd.^[2] The product is an important intermediate in the production of cyclohexanone for the manufacture of nylon. The process uses zinc-based Lewis acid additives, which are believed to stabilize the alkene through coordination, and an innovative, four-phase reactor consisting of a solid catalyst layer surrounded by an aqueous layer, the organic phase, and gas-phase H_2 . This setup is believed to favor partial hydrogenation owing to the higher solubility of benzene relative to cyclohexene in the aqueous layer.^[48] The partial hydrogenation of benzene to cyclohexadiene is even more challenging, since the reaction is endergonic. As a result, cyclohexadienes have so far only been synthesized in small quantities by hydrogenation, whereas cyclohexene can be produced in 60% yield on an industrial scale.^[49] The chemoselective hydrogenation of phenyl rings in the presence of acyclic alkenes has been observed, but no general method is known.^[50]

The chemoselective hydrogenation of heteroarenes in the presence of alkenes is, however, more common, likely owing

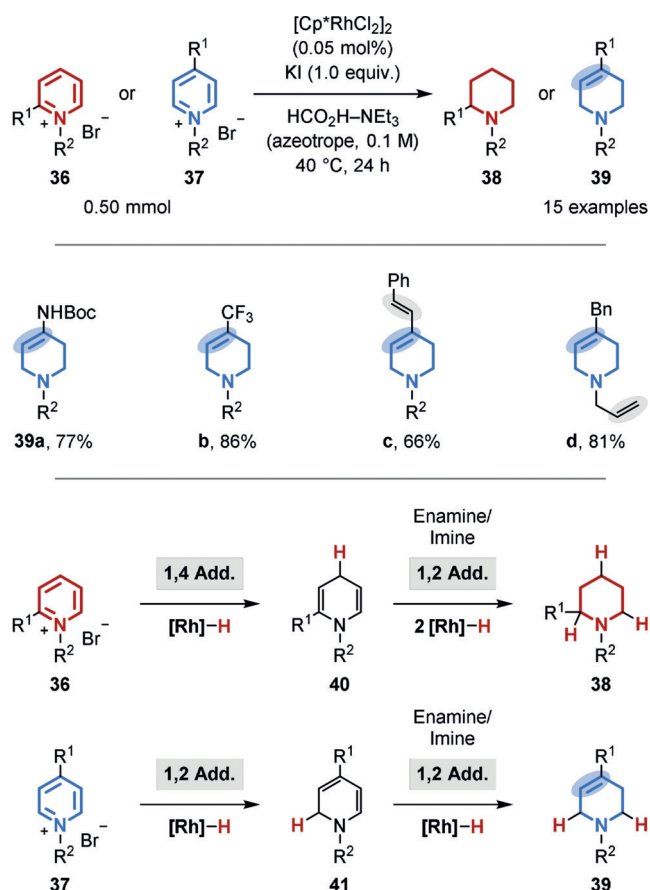


Figure 8. Chemoselective transfer hydrogenation of pyridinium salts.

to the reduced aromaticity and inherent bond polarization.^[51] For example, a general method for the chemoselective, semihydrogenation of 4-substituted pyridinium salts (**37**)^[52] was disclosed by the Xiao group (Figure 8).^[51b] The transformation uses an azeotropic mixture of formic acid and triethylamine as the hydrogen source, a commercial rhodium catalyst in low loading (turnover number (TON) up to 9000), and potassium iodide as an additive. Whereas 2-substituted pyridinium salts (**36**) gave predominantly perhydrogenated piperidines (**38**), 4-substituted pyridinium salts (**37**) provided the semihydrogenated, 3,4-unsaturated tetrahydropiperidines (**39**) almost exclusively. The authors explained this surprising result by steric blocking of the 1,4-hydride addition in the case of the 4-substituted substrates (**37**). As a result, one double bond remains that cannot isomerize to a polarized iminium species (**39**). The tolerance of the catalyst system for unpolarized double bonds is further highlighted by the preservation of the acyclic double bonds in **39c,d**. Moreover, a chemoselective hydrogenation of quinolines catalyzed by an inexpensive cobalt catalyst was disclosed by the Beller group (Figure 9). In addition to an alkene within a stilbene motif (**44a**), even an alkyne within a tolane motif (**44b**) as well as an aldehyde (**44c**) were well-tolerated.^[51d]

The preservation of nitriles during the hydrogenation of heteroarenes is known.^[53] For example, a recent synthesis of a promising Type 2 diabetes inhibitor (**8**) by a team from Boehringer Ingelheim and the University of Pennsylvania

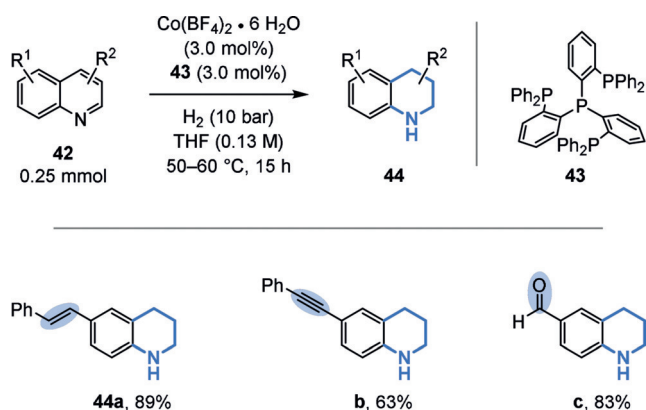


Figure 9. Chemoselective hydrogenation of quinolines in the presence of an alkene, an alkyne, and an aldehyde.

involved the chemoselective hydrogenation of indenopyridinium salt **46** in the presence of a nitrile group as a key step (Figure 10).^[10a] Although heterogeneous catalysts proved inadequate owing to competing side reactions such as nitrile reduction, an extensive screening of homogeneous catalyst systems revealed a combination of iridium and a dihydrobenzoxaphosphole ligand **47** to be well-suited for the desired transformation. The product **48** was formed in an excellent yield on a multikilogram scale, with complete preservation of the nitrile group and with good enantioselectivity. **48** was efficiently converted into the desired product (**8**) by deprotection, kinetic resolution, and subsequent amide coupling. In total, the therapeutic agent **8** was obtained in excellent overall yield (38%) in a concise seven-step sequence. The chemoselective arene hydrogenation offers a significant synthetic shortcut compared to the previous route (15 steps, less than 3% overall yield).

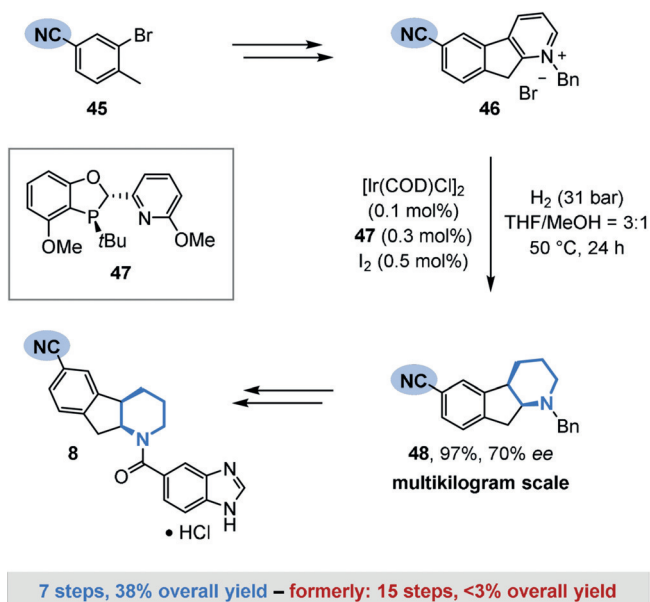


Figure 10. Boehringer Ingelheim's synthesis of a potent therapeutic agent (**8**) against Type 2 diabetes by the chemoselective hydrogenation of pyridinium salt **46**.

In comparison to the chemoselective hydrogenation of arenes bearing ketones, alkenes, or nitriles, the chemoselective hydrogenation of arenes bearing other unsaturated moieties such as nitro groups, imines, azides, sulfoxides, or others is less explored. Nevertheless, it cannot necessarily be concluded that their presence causes a greater challenge in terms of chemoselectivity.^[54]

3.2. Regioselective Hydrogenation of Aromatic Substrates Bearing Multiple Aromatic Moieties

In substrates bearing multiple aromatic moieties, the ring with the lowest resonance energy is generally hydrogenated in preference. For example, it is well-documented that the hydrogenation of quinolines, isoquinolines, and their analogues occurs at the least aromatic, heteroaromatic ring (Figure 11).^[55] A general rationale for the strength of the

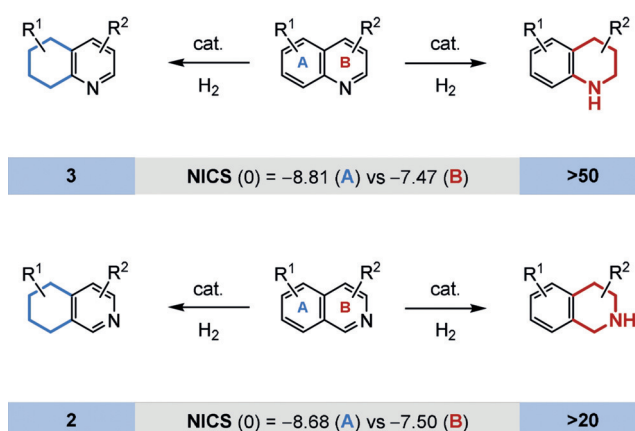


Figure 11. Regioselective hydrogenation of quinolines and isoquinolines and the respective number of published synthetic methods ($\geq 50\%$ yield, at least two substrates). The NICS(0) value refers to the center of the ring.

aromatic stabilization energy of a particular ring can often be obtained from the easily calculated nucleus-independent chemical shift (NICS) values.^[56] The NICS value identifies the hypothetical chemical shift inside the aromatic ring. As a result of the ring current, the values are strongly negative. Consequently, aromatic rings with a more negative NICS value can be expected to show a stronger aromatic character. It is tempting to rely purely on such values for the estimation of the reactivity of an aromatic ring during hydrogenation, but the NICS value, like other parameters that estimate aromaticity, can produce some curious results.^[57] Moreover, regioselectivity in the hydrogenation of fused aromatic rings is dependent on the electronic and steric properties of the substrate. For example, the regioselectivity of the hydrogenation of free indole derivatives can switch from the less aromatic N-containing ring to the carbocyclic rings when electron-withdrawing substituents are present on the N-containing ring.^[58] Such groups destabilize the formation of the reactive iminium salt intermediates. Furthermore, installation of the Evans bulky chiral oxazolidone in quinolines

facilitates the regioselective reduction of the carbocyclic ring.^[25c]

In contrast, a catalyst-controlled, regioselective hydrogenation of the more aromatic ring, which is not purely governed by substrate electronic or steric effects, is a desirable goal. For example, the groups of Borowski and Sabo-Etienne showed that a series of anthracene and acridine derivatives were regioselectively hydrogenated at their external carbocyclic rings using Chaudret's electron-rich ruthenium complex (**50–53**; Figure 12).^[38] The authors rationalized this

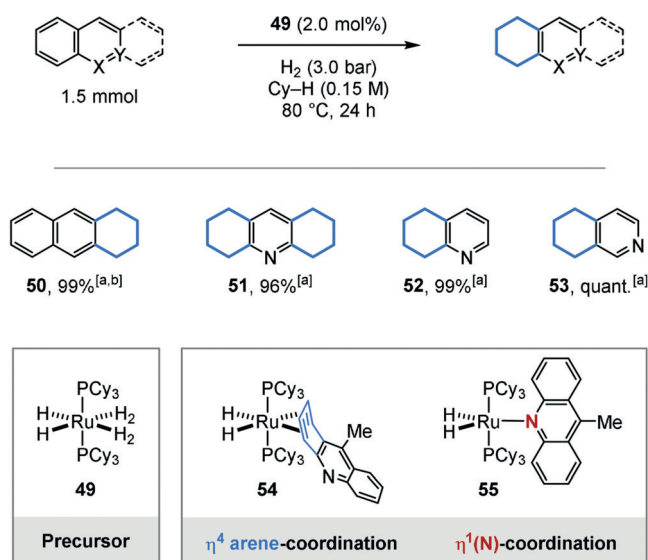


Figure 12. Regioselective hydrogenation of polycyclic aromatic compounds using Chaudret's complex (**49**). It was suggested that a preferential Ru- η^4 -arene coordination determines the regioselectivity. [a] GC yields. [b] 1 h reaction time. Cy=cyclohexyl.

observation with the preferential η^4 -arene coordination (**54**), which is accompanied by a loss of aromaticity compared to the $\eta^1(N)$ mode (**55**). Complex **54** could be characterized by NMR spectroscopy.

Inspired by the reactivity of Chaudret's complex (**49**), the Glorius group developed a related, NHC-based catalyst system (Figure 13 A).^[37a] Interestingly, the regioselectivity was strongly dependent on the NHC ligand. Further ligand variation culminated in the development of chiral catalyst system **V** for the homogeneous enantioselective hydrogenation of (hetero-)arenes. The chiral ruthenium-PhTRAP catalyst system developed by the Kuwano group (**IV**) also showed a preference for the carbocyclic ring over the less aromatic N-containing ring in quinolines and isoquinolines (Figure 13 B).^[36e,g] A large bite angle of the employed bisphosphine was key to achieving chemoselective hydrogenation.

The chemoselective hydrogenation of naphthols has been investigated because of the synthetic interest in the regioisomers of tetrahydronaphthols, which are common motifs in secondary metabolites. A chemoselective hydrogenation of the phenol ring was achieved by the Huang group

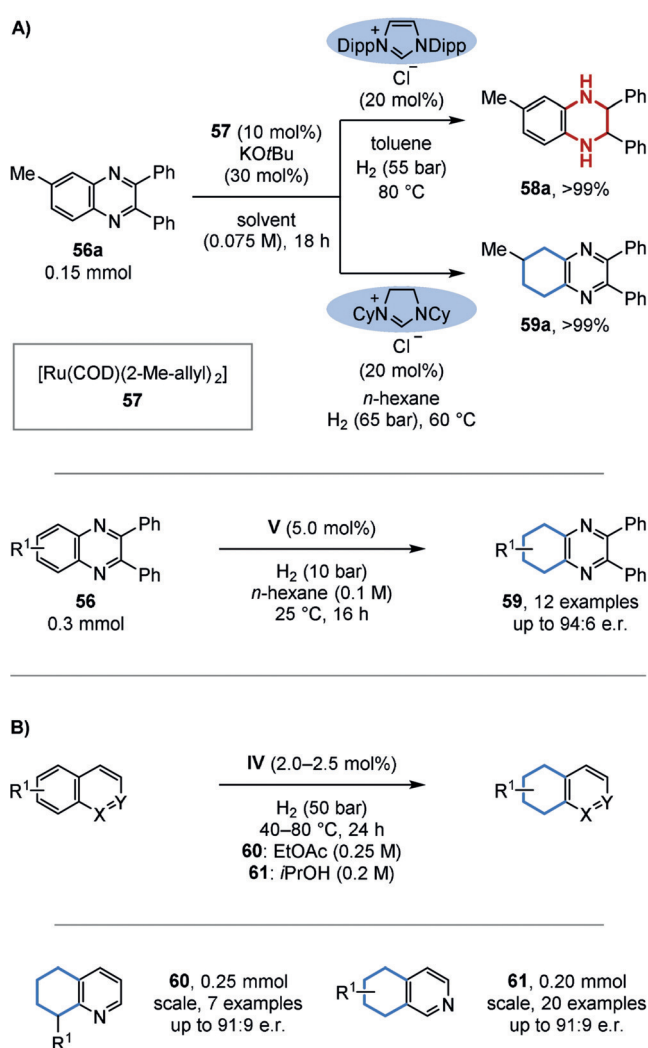


Figure 13. A) Regio- and enantioselective hydrogenation of quinoxalines. B) Regio- and enantioselective hydrogenation of quinolines and isoquinolines. Dipp = 2,6-diisopropylphenyl.

using ruthenium pincer complex **64**.^[59a] Since no reaction occurred in the absence of a hydroxy group, the authors proposed that the hydrogenation proceeds via a non-aromatic ketone tautomer (**67**; Figure 14 A). The opposite regioselectivity, as achieved by the Zeng group, can be achieved with a heterogeneous catalyst that is prepared in situ from $[\text{Rh}(\text{COD})\text{Cl}]_2$ and polymethylhydrogen siloxane (PMHS) as the hydrogen source.^[59b] It is possible that the hydrosilane also acts to protect the alcohol, thus forming a stable silyl-enol species that prevent the formation of activated ketone tautomers. This may drive the reaction to the sterically more accessible benzene ring (Figure 14 B).

3.3. Chemoselective Hydrogenation of Arenes with Directly Attached Labile Functional Groups

During our extensive studies on arene hydrogenation we have identified the challenging hydrogenation of arenes bearing functional groups directly attached to the reactive

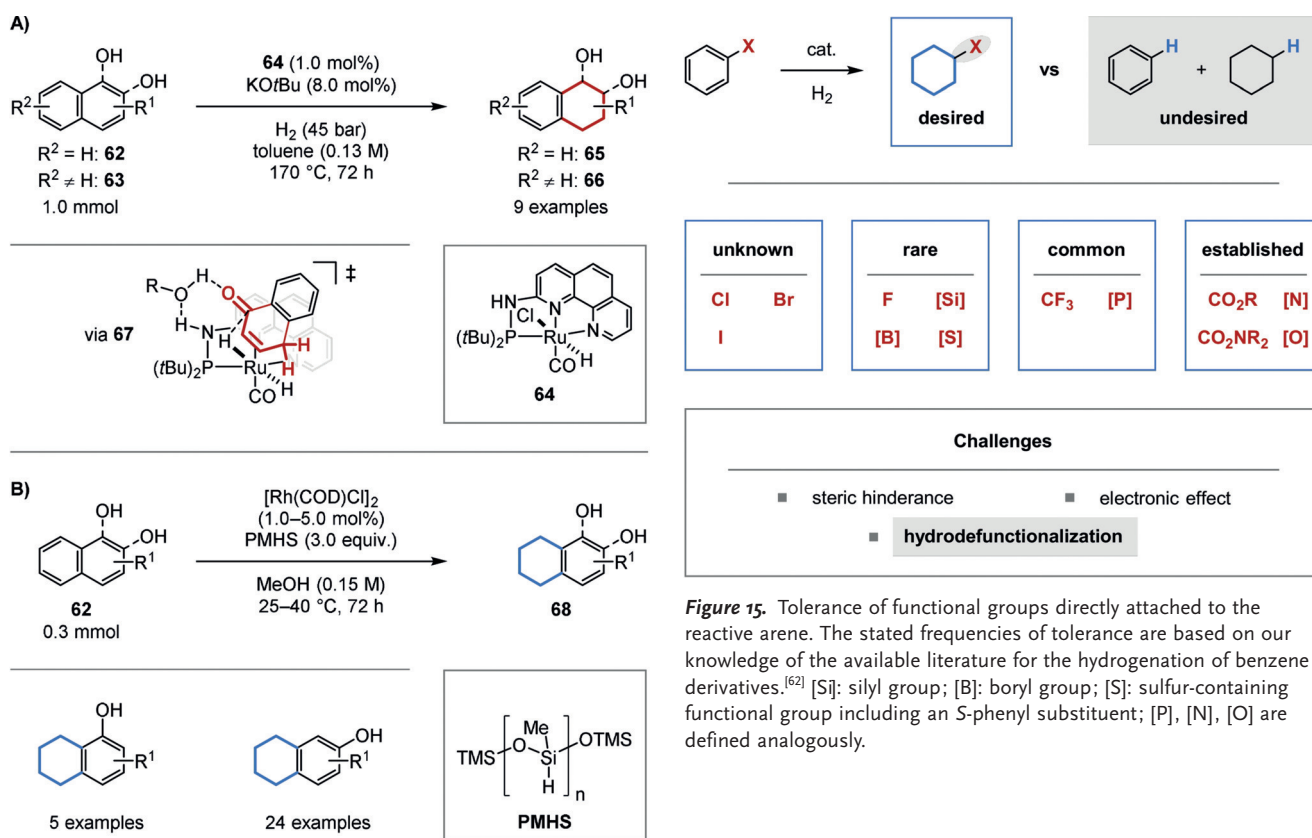
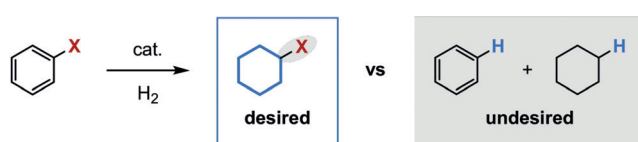


Figure 14. A) Regioselective hydrogenation of naphthols (**62**, **63**) to the 1,2,3,4-tetrahydronaphthols (**65**, **66**). B) Regioselective hydrogenation of naphthols to 5,6,7,8-tetrahydronaphthols (**68**). TMS = trimethylsilyl.

aromatic ring as a limit to the synthetic utility of the transformation. Such functional groups could greatly increase the value of the products by altering the physical properties or by serving as a handle for the incorporation of the saturated motifs into more complex structures. In general terms, the functionalization of arenes is more facile than that of the saturated products.^[60] Naturally, the tolerance of functional groups is dependent on their chemical properties. Many groups such as carboxylic acids/esters, amines,^[61] amides, and alcohols/ethers are commonly tolerated (Figure 15). Other less frequently tolerated functional groups, when directly attached to the arene, may sterically hinder the productive coordination of the arene to the catalyst. Additionally, certain functional groups may negatively influence the electronic properties of the arene at the reaction center. Finally, new mechanistic pathways for hydrodefunctionalization may become feasible because of the proximity of the functional group to the catalyst during arene hydrogenation, or as a result of the formation of dearomatized intermediates in which the functional group is activated for hydrodefunctionalization. For example, dearomatization may render the functional group in a newly allylic position.

The application of fluorinated, saturated compounds has been widely explored in the fields of agrochemistry, pharmaceuticals, and materials science.^[63] Research by the O'Hagan group has demonstrated the potential of all-*cis*-multifluori-



unknown	rare	common	established
Cl Br I	F [Si] [B] [S]	CF ₃ [P]	CO ₂ R [N] CO ₂ NR ₂ [O]

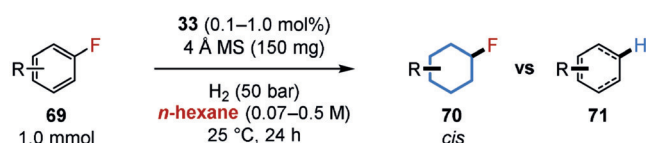
Challenges	
steric hindrance	electronic effect
hydrodefunctionalization	

Figure 15. Tolerance of functional groups directly attached to the reactive arene. The stated frequencies of tolerance are based on our knowledge of the available literature for the hydrogenation of benzene derivatives.^[62] [Si]: silyl group; [B]: boryl group; [S]: sulfur-containing functional group including an *S*-phenyl substituent; [P], [N], [O] are defined analogously.

nated cycloalkanes (e.g. **6**) as highly polar building blocks.^[64] Inspired by O'Hagan's work, we became interested in developing a *cis*-selective hydrogenation procedure that tolerates fluorine substituents directly attached to the reactive arene (Figure 16).^[8b] However, the transformation of inexpensive (multi-)fluorinated arenes (**69**) into such molecules needed to overcome the well-known hydrodefluorination side reaction (to **71**). Although the C–F bond is very strong, several mechanistic pathways are known to lead to a net hydrodefluorination.^[65] We observed, however, that the formation of the undesired products is decreased when the Bertrand–Zeng complex **33** is used as a precatalyst under mild conditions. Furthermore, the choice of solvent proved crucial, with nonpolar *n*-hexane giving a highly selective hydrogenation.^[66] It is possible that less polar solvents decrease the rate of defluorination mechanisms proceeding via a polar intermediate. Likewise, the higher solubility of hydrogen gas in nonpolar solvents might affect the rate of the desired hydrogenation relative to the undesired hydrodefluorination.^[67] Furthermore, polar solvents may interact with, and alter the structure of, the active catalyst. The developed conditions provide convenient access to *cis*-stereodefined (multi-)fluorinated building blocks containing a second functional group for further derivatization (e.g. **70 a–c**), saturated fluorinated heterocycles (e.g. **72**) and polar all-*cis*-multifluorinated cycloalkanes (e.g. **6**). Some of the reaction products are currently being made commercially available.^[68]

Despite the generality of the former strategy, fluorinated pyridine derivatives were not tolerated, presumably as a result of catalyst deactivation by the Lewis-basic N-heterocycles. We therefore developed an alternative method that provided diastereoselective access to a broad range of

Conditions



Solvent screen – R = 4-OTBS (70a)

Polarity	Solvent	Yield (70a) [%]	Selectivity		
↑	TFE	24	32	:	68
	CH ₂ Cl ₂	77	83	:	17
	Et ₂ O	91	91	:	9
	<i>n</i> -hexane	95	96	:	4

Scope – over 30 examples – up to 20 mmol scale

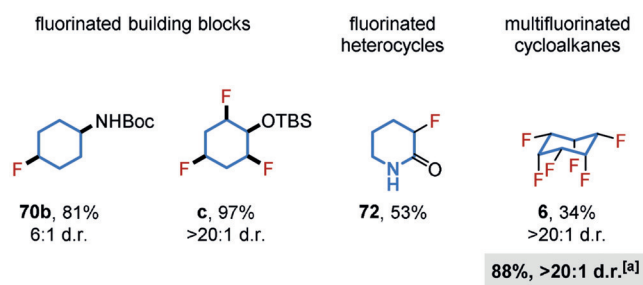
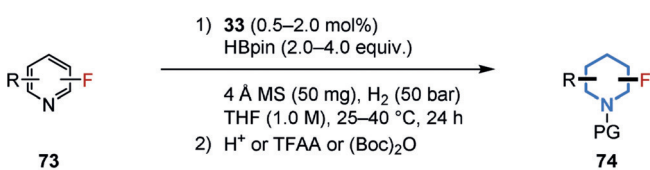


Figure 16. Chemoselective hydrogenation of fluorinated arenes.

[a] New conditions using 450 mg SiO₂ instead of 4 Å MS.

substituted, all-*cis*-(multi-)fluorinated piperidines in a single operation. We believe the reaction occurs via a pyridine dearomatization by HBPIn, followed by the total saturation of the boron-protected, dearomatized intermediates (Figure 17).^[9b] Versatile (multi-)fluorinated building blocks and



Scope – over 40 examples – up to 10 mmol scale

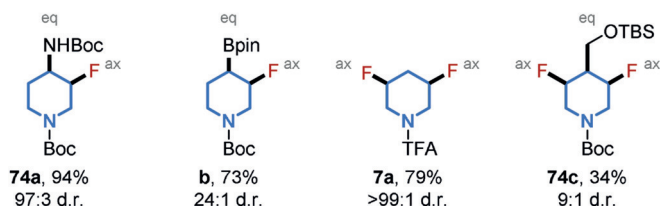
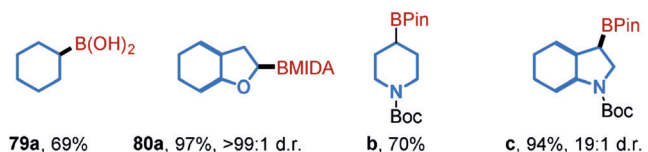
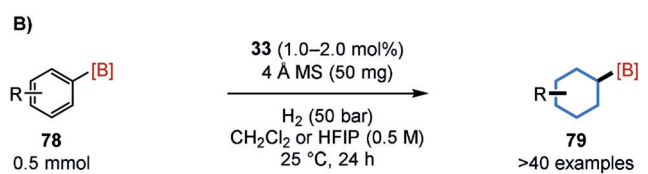
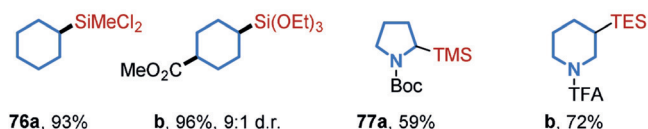
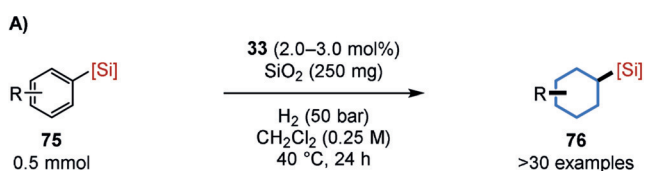


Figure 17. Chemoselective hydrogenation of fluorinated pyridines. Defined orientations of the substituents were determined. PG = protecting group (H, TFA, or Boc), TFAA = trifluoroacetic anhydride.

motifs containing further functional groups, such as fluorinated aminopiperidine 74a, a common fragment in medicinal chemistry, were obtained and commercialized (e.g. 74a–c and 7a).^[68] The straightforward preparation of these motifs enabled determination of the axial/equatorial orientation of the substituents by NMR spectroscopy.^[69]

The successful hydrogenation of fluorinated arenes inspired us to develop procedures for the hydrogenation of arenes decorated with other synthetically useful functional groups attached to the reactive arene. Silyl groups are widely utilized within organic synthesis, materials science, pharmaceutical, agrochemical, and fragrance research;^[70] however, silylated saturated carbo- and heterocycles represent a synthetic challenge for many established transformations.^[71] Making use of the facile accessibility of silylated arenes (75), a general, *cis*-selective procedure to access such products was provided by an arene hydrogenation catalyzed by rhodium-CAAC 33 (Figure 18A).^[72] Notably, the syntheti-

Figure 18. Chemoselective procedures for the hydrogenation of A) silylated and B) borylated arenes. HFIP = Hexafluoroisopropanol, MIDA = *N*-Methyliminodiacetate.

cally most useful alkoxy- and halosilyl substituents were well-tolerated, thus generating the products (76a,b) that can be used as building blocks in polymer chemistry or organic synthesis.^[73] During optimization, a significant enhancement of the yield was observed when using increased amounts of the silica gel additive. This positive effect was also applied to the previously low-yielding hydrogenation of very highly fluorinated arenes and facilitated almost quantitative yields

(6; Figure 16). Interestingly, no such effect was detected with the previously employed 4 Å molecular sieves (MS). A general synthetic study was likewise performed for the hydrogenation of borylated arenes (**78**; Figure 18B).^[74a] Under the optimal reaction conditions, boronic acids (**79 a**) as well as a wide range of boron protecting groups (**80 a–c**) were well-tolerated. The further tolerance of several other functional groups allows access to (substituted) borylated carbo- and heterocycles, which were obtained with high *cis* selectivities. These products can readily be derivatized via the boryl group. A notable, closely related study was disclosed recently by the Zeng group.^[74b]

4. Conclusions

Arene hydrogenation is an increasingly important strategic transformation for the direct preparation of saturated carbo- and heterocycles; such transformations are already applied on a multithousand ton scale in industry. The demand for such compounds in the fine-chemicals sector has prompted further development of diastereo-, enantio-, and chemoselective methods for the hydrogenation of functionalized arenes.

A high level of (*cis*-)diastereoselectivity is typically inherent to the transformation. Enantioselective methods make use of chiral auxiliaries, chiral phosphoric acids, or chiral transition-metal catalysts. In particular, the use of chiral transition-metal catalysts facilitates general access to valuable product motifs, such as piperidines. Moreover, complex, desirable structures can be generated using highly chemoselective methods. Such challenges have been solved for arenes bearing reducible functional groups, polycyclic arenes, and for arenes bearing directly attached, labile functional groups.

Although many interesting synthetic applications can be realized with current technologies, many challenges remain. Most importantly, from a synthetic chemistry perspective, the existing methods are often limited in scope, which makes their application to complex substrates difficult. In addition, we consider the development of methods that overcome the following unsolved challenges to be most relevant:

- *trans*-selective arene hydrogenation;
- catalytic, enantioselective hydrogenation of simple benzene derivatives or phenols;
- arene hydrogenation at low or even ambient pressure.

Research in each of these areas will benefit from further mechanistic understanding, which is often limited by the high hydrogen pressures required, and the innovation of new catalyst systems.

Given the inability of the vast majority of homogeneous catalysts to hydrogenate monocyclic benzene derivatives, the enantioselective hydrogenation of these substrates may eventually be realized under enantioselective, heterogeneous catalysis. Finally, the development of a user-friendly, tunable homogeneous catalyst for the hydrogenation of monocyclic benzene derivatives, analogous to Wilkinson's catalyst for the hydrogenation of alkenes, would open up a means to ration-

ally approach existing selectivity challenges and undoubtedly revolutionize the field.

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Conflict of interest

M.P.W., Z.N., and F.G. are inventors on German patent applications 102017106467.2 and 102018104201.9, held and submitted by Westfälische Wilhelms-Universität Münster. These patent applications cover methods for the synthesis of fluorinated cyclic aliphatic and heterocyclic compounds. See Figures 16 and 17.

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