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1 Evolution and Prospects of the Asymmetric Hydrogenation of
2 Unfunctionalized Olefins3 Cristiana Margarita and Pher G. Andersson*^{id}

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ABSTRACT: The catalytic enantioselective hydrogenation of prochiral olefins is a key reaction in asymmetric synthesis. Its relevance applies to both industry and academia as an inherently direct and sustainable strategy to induce chirality. Here we briefly recount the early breakthroughs concerning the asymmetric hydrogenation of largely unfunctionalized olefins, from the first reports to the advent of chiral Crabtree-like catalysts. The mechanism and its implications on the enantioselectivity are shortly discussed. The main focus of this Perspective lies on the more recent advances in the field, such as the latest developed classes of ligands and the opportunity to employ more Earth-abundant metals. Therefore, separate sections consider iridium N,P-, NHC-, P,S-, and -O,P-catalysts, and rhodium, palladium, cobalt, and iron catalysts. Finally, the remaining unsolved challenges are examined, and the potential directions of forthcoming research are outlined.

23 ■ INTRODUCTION

24 The enantioselective hydrogenation of olefins is currently
25 recognized as one of the most fundamental transformations in
26 asymmetric catalysis and represents an expedient strategy for
27 the creation of stereogenic centers in target molecules. The
28 process can rely on advantageous features such as excellent
29 atom economy, quantitative yields, and high levels of
30 enantioselectivity for a wide range of alkene substrates.¹ All
31 these factors contribute to the method's attractiveness for both
32 industrial applications and academic research. The field has
33 seen an impressive degree of development since the early
34 reports of successful asymmetric hydrogenation mediated by
35 Rh(I)- and Ru(II)-diphosphine chiral catalysts,² a discovery
36 leading up to the 2001 Nobel Prize awards to Noyori³ and
37 Knowles,²ⁱ and it has continued to draw the interest of
38 numerous research groups to date. The Rh(I) and Ru(II)
39 catalytic systems have since been applied extensively to
40 diversely functionalized olefins. They still constitute the optimal
41 choice for the synthesis of optically active α -amino acids and
42 many pharmaceutically relevant compounds. However, they
43 have mainly exhibited high efficiency and stereocontrol on
44 substrates possessing a coordinating group in proximity of the
45 C=C bond. With only a few exceptions,⁴ they resulted
46 prevalently in low activity and enantioselectivity when tested on
47 minimally functionalized olefins, which can be defined as those
48 not containing any coordinating functional group directly
49 connected to the double bond.⁵ In order to overcome these
50 limitations and open the field of asymmetric hydrogenation to
51 more general classes of olefins, different catalytic systems have

been developed and evaluated for alkenes lacking metal-
chelating functional groups. Among other purposes, the interest
in the enantioselective reduction of minimally decorated double
bonds is related to the possibility of stereocontrol on remote
alkyl regions in the synthesis of natural and biologically active
compounds.

The first promising reports of chiral catalysts able to
selectively handle unfunctionalized olefins involved metal-
locenes⁶ and organolanthanide⁷ complexes. They could hydro-
genate 2-phenyl-1-butene up to 96% enantiomeric excess (ee)
but required very low temperatures, a base for catalyst
activation, and complicated ligand preparation, which greatly
inhibited their further development. Nevertheless, outstanding
examples of metallocene catalysts were described by Buchwald,
who first reported on the use of a titanocene catalyst^{6h} for the
hydrogenation of trisubstituted nonfunctionalized olefins in up
to 99% ee, and later developed a zirconocene catalyst^{6m} for the
hydrogenation of the even more challenging class of
tetrasubstituted olefins with ee's exceeding 90%.

The central role that iridium currently plays in homogeneous
catalytic hydrogenation can be traced back to the development
of Crabtree's catalyst **1**, [Ir(cod)(PCy₃)(py)]⁺PF₆⁻ (Figure 1, ⁷³ fi

Figure 1. Crabtree's catalyst and Pfaltz's Ir-PHOX catalyst.

cod = 1,5-cyclooctadiene),⁸ an achiral cationic complex which
demonstrated exceptionally high activity toward olefins lacking
neighboring coordinating groups, surprisingly including also
tetrasubstituted olefins. The catalyst, employed as a crystalline
salt, showed good stability against oxidation, making it easier to
handle than most air-sensitive organometallic compounds,
despite its impressive reactivity. Crabtree's work opened the
possibility for further development of this kind of system in an
asymmetric version.

■ EARLY DEVELOPMENTS

In 1993, the groups of Helmchen,⁹ Williams,¹⁰ and Pfaltz¹¹
introduced the use of chiral phosphino-oxazoline N,P-ligands
(PHOX) in asymmetric catalysis. In 1997, Pfaltz used PHOX
ligands to generate the first series of chiral counterparts of

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Crabtree's catalyst (**2**, Figure 1) and successfully applied it to the asymmetric hydrogenation of imines.¹² Eventually, the catalysts were also employed in a number of aryl-substituted prochiral olefins, resulting in excellent enantioselectivity (98% ee for (*E*)- α -methylstilbene).¹³ At the same time, some important issues related to the catalyst stability were solved. It had already been observed by Crabtree that the Ir cationic catalyst suffered from deactivation due to the formation of hydride-bridged trimers. This problem was solved by Pfaltz, replacing the counteranion PF₆[−] with the more weakly coordinating species tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF[−]). This variation granted a dramatic increase in the reaction rate,¹⁴ and it also allowed lowering the catalyst loadings to less than 1 mol%.

These findings prompted enormous attention to the design of chiral Ir complexes with the purpose of expanding the substrate scope to include a broader variety of olefins, resulting in the preparation and screening of a large variety of Ir-N,P-ligated catalysts. It still constitutes a prioritized research goal for the enantioselective hydrogenation of unfunctionalized alkenes. The Pfaltz group continued to study and develop new versions of the PHOX complexes, modifying the ligand backbone, and built a library of very efficient catalysts for a variety of minimally functionalized olefins.¹⁵ Successive work included pyridine and quinoline rings in ligands' structures and allowed the remarkable asymmetric hydrogenation of purely alkyl-substituted substrates in high ee.¹⁶ An excellent application of these systems to total synthesis provided γ -tocopherol as a single diastereoisomer in 98% ee, controlling two stereocenters in one reductive step.^{16b} The various developed ligands also enabled the asymmetric hydrogenation of different classes of substrates, including allylic alcohols, α,β -unsaturated esters,¹⁷ furan derivatives,¹⁸ boronic esters,¹⁹ and tetrasubstituted olefins.²⁰

Another class of notably effective catalysts involve C,N-ligands such as **3** (Figure 2), developed by Burgess.²¹ They

Figure 2. An example of Burgess's N-heterocyclic carbene catalysts.

contain an N-heterocyclic carbene (NHC) as coordination site in place of phosphines and provide high enantioselectivities for a range of trisubstituted minimally functionalized olefins and vinyl ethers.²²

Various classes of chiral N,P-ligands have been developed by the Andersson group. The investigation of different bicyclic heteroaromatic rings led to highly enantioselective hydrogenations by means of oxazole,²³ thiazole,²⁴ and imidazole-based²⁵ iridium catalysts **4**, **5**, and **6** (Figure 3). Other successful ligands were constructed around a 2-aza-norbornane chiral backbone (**7**, Figure 3).²⁶ The diverse nature of the different heterocycles also enables tuning the electron density on the N-donor atom, which in turn affects the electrophilicity of the iridium center. These iridium catalysts perform excellently on the typically tested trisubstituted nonfunctionalized olefins and also allow extending the substrate scope to

Figure 3. Catalysts developed by the Andersson group.

vinyl silanes,²⁷ fluorinated olefins,^{25,28} vinyl boronates²⁹ and enol phosphinates.³⁰

Several comprehensive reviews^{5,31} have covered these major advances in the asymmetric hydrogenation of nonfunctionalized olefins; hence, this Perspective is mainly focused on the recent reports in the field (up to 2016) and the potential future directions of research.

To evaluate the efficiency and selectivity of the catalytic systems in asymmetric hydrogenation, unfunctionalized trisubstituted olefins have generally been employed as benchmark substrates, especially 1,2-diarylethenes. In some cases disubstituted terminal olefins are also included in the screening, but reaching high enantioselectivity for these compounds has normally shown to be more problematic and might require more substrate-specific catalysts. Finally, exclusively alkyl-substituted and tetrasubstituted alkenes represent even more challenging substrates, appearing only in a limited number of reports.^{6m,20,32}

MECHANISM AND SELECTIVITY

The advent of iridium Crabtree-type chiral catalysts started the evolution of the hydrogenation of hindered alkenes without coordinating functional groups. The mechanistic aspects of the Ir-catalyzed hydrogenation and the origin of stereoselectivity have been studied and discussed by various contributors.³³ This section will shortly describe the proposed catalytic cycle most widely accepted today.

In 2003, Brandt and co-workers carried out density functional theory studies employing a truncated model for an Ir-N,P-catalyst and proposed the mechanism to involve an Ir(III)/Ir(V) catalytic cycle.³⁴ In that study, starting from complexes [Ir-(H)₂(N,P)(alkene)S]⁺ (alkene = ethane, S = solvent), the coordinated solvent molecule was replaced by a H₂ molecule, forming intermediate **A** (Figure 4). The migratory insertion step, which was identified as rate-determining due to the significant calculated energy barrier, occurred simultaneously and was also facilitated by the oxidative addition of the coordinated dihydrogen molecule to form the Ir(V) species **B**. Reductive elimination, liberating the alkane product, and coordination of new dihydrogen and alkene molecules regenerated species **A**. Kinetic studies have shown that the reaction is first-order in hydrogen pressure, but this could be related to H₂ diffusion in the solution, which can become rate-limiting when alkene hydrogenation is fast. It has been shown for Ir(PHOX) catalysts that the reaction is diffusion-limited at room temperature.^{14,15b,35} Successive extended calculations on the full structure of a reported Ir-N,P-catalyst further reinforced

Figure 4. Proposed Ir(III)/Ir(V) catalytic cycle.

Figure 5. (a) Quadrant selectivity model. (b) Hydrogenation of isomeric alkenes.

LATEST RESULTS

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It might seem that most issues have been largely overcome during decades of research on the asymmetric hydrogenation of olefins. This is certainly true in the sense that the large number of very efficient catalysts now available make it possible to achieve high enantioselectivities for a wide range of olefin classes, generally operating under mild conditions and at low catalyst loadings. Optimization efforts have predominantly revolved around the now well-established, wide variety of Ir-based catalysts, which continue to provide optimal results in the hydrogenation of various classes of substrates. However, some unsolved limitations in the applicability of these catalytic systems can still be found and will be analyzed herein after a discussion of recently published results. The selected reports regard exclusively catalytic systems that were applied to largely unfunctionalized olefins. Results on some unusual non-coordinating groups such as boronates are also covered. A very interesting part of the most recent advances involves the use of cheaper bulk metals as alternatives to iridium; therefore, successful examples of cobalt and iron catalysis are presented and arranged in separate sections.

The vast majority of reported research in asymmetric hydrogenation still concerns the use of Crabtree-type catalysts. Considerable advancements in the design of chiral ligands for iridium complexes have generated many innovative classes of catalysts, exploring diverse possibilities of tuning sterics and donor properties. For this reason, the large number of reports in iridium catalysis are grouped according to the donor atoms in the ligand coordination sites.

Iridium N,P-Catalysts. Recent advances in the development of ligands for Ir catalysis have been made by several research groups. For example, the group of Pàmies and Diéguez has lately been very active in the preparation of sugar-based ligands.³⁹ In particular, pyranoside phosphite-oxazoline structures **8** (Figure 6) were investigated, evaluating rigid biaryl moieties on the phosphorus to modularly generate a ligand library.

This approach afforded chiral iridium catalysts with improved substrate versatility, which achieved excellent ee's (up to 99%) for a broad range of unfunctionalized model alkenes: diaryl,

8

Figure 6. Pyranoside-based catalysts.

268 dialkyl, and cyclic trisubstituted, triaryl-substituted, and also
 269 1,1-disubstituted terminal olefins. Similarly, good results (>90%
 270 ee) were obtained for some of these substrates when using a
 271 simpler version of the ligands, having an *ortho*-tolyl phosphinite
 272 function.⁴⁰ The group also explored the possibility to carry out
 273 the hydrogenation of some olefins in propylene carbonate (PC)
 274 as an alternative, environmentally friendly solvent, still
 275 maintaining the excellent enantioselectivities. Another contri-
 276 bution by Pàmies and Diéguez showed that modification of
 277 previously developed phosphite-oxazoline catalysts to thiazo-
 278 line-containing analogues **9** (Figure 7) was beneficial for the

Figure 7. Selected results for biaryl-phosphite pyridine, phosphite-thiazoline, and phosphoramidite-based catalysts.

279 substrate scope.⁴¹ The hydrogenation of (*E*)- and (*Z*)-
 280 trisubstituted olefins resulted in high enantioselectivities as
 281 expected, but it was moreover possible to achieve exceptional
 282 ee's, in the range of 90–99%, for 1,1-disubstituted terminal
 283 olefins. Later studies implemented biaryl phosphites on
 284 pyridine-containing ligands, without the use of sugar frag-
 285 ments.⁴² This generated iridium catalysts **10** and **11** (Figure 7),
 286 whose structures resemble more closely Pfaltz's pyridine-based
 287 ligands^{16–19} and were found to give high stereoselectivity

toward both (*E*)- and (*Z*)-trisubstituted olefins, as well as more
 288 demanding dihydronaphthalenes and triaryl-substituted sub-
 289 strates (95–98% ee). Excellent results (90–99% ee) could also
 290 be achieved on several vinyl boronates and terminal olefins
 291 (>90% ee).

An interesting example of ligand design was reported when
 293 the Diéguez and Andersson groups collaborated to prepare and
 294 evaluate a library of catalysts containing the 2-aza-norbornane
 295 framework, an oxazoline or thiazole ring, and a biaryl phosphite
 296 moiety.⁴³ The resulting phosphoramidite-based ligands **12**
 297 (Figure 7) showed good versatility and resulted in hydro-
 298 genated products in higher ee's than the first generation of this
 299 type of ligands. Demanding terminal olefins were also well
 300 tolerated, and improved enantioselectivities were reached for a
 301 number of these compounds; however, some of the aryl-alkyl-
 302 substituted ones were still hydrogenated in moderate ee's due
 303 to competitive isomerization to the (*E*)-isomers.

A direct and powerful strategy to access chiral cyclohexanes
 305 by asymmetric hydrogenation of diversely functionalized 1,4-
 306 cyclohexadienes has been studied and optimized by the
 307 Andersson group.⁴⁴ Among the hydrogenation substrates,
 308 many examples of purely alkyl-substituted dienes can be
 309 found, for which thiazole- or imidazole-based iridium catalysts
 310 produced excellent enantioselectivities (up to 99%). The
 311 predominant formation of the *trans* isomer was observed for
 312 1,3-substituted carbocycles. Successively, the scope of this
 313 methodology has been further improved by fine variation of
 314 aryl substituents on the imidazole-type ligands (**6**, Figure 8),
 315 which afforded even more efficient, versatile, and enantio-
 316 selective catalysts.⁴⁵

An important feature to consider in this work lies in the
 318 possibility to preserve some of the double bonds on the cyclic
 319 structures, leaving room for further synthetic manipulations.
 320 This has proven to be consistently attainable in the case of

Figure 8. New generation of imidazole-based catalysts for the asymmetric hydrogenation of cyclohexadienes (selected results).

322 tetrasubstituted olefins. In addition, it was also found possible
 323 to discriminate between two differently trisubstituted olefins on
 324 some aryl-containing cyclohexadienes, and they could be
 325 converted to either monohydrogenated products or fully
 326 saturated chiral cyclohexanes, depending on hydrogen pressure
 327 and reaction time; in both cases, 99% ee was maintained
 328 (Figure 9).

Figure 9. Regioselective hydrogenation of cyclohexadienes.

329 In 2014, the synthesis of new pyridine-based N,P-ligands
 330 with a five-membered fused carbocycle (13, Figure 10) was

Figure 10. Examples of new pyridine- and proline-based catalysts.

331 described by Andersson and co-workers.⁴⁶ This group of
 332 catalysts differs from previous generations employing pyridine
 333 as a N-donor since they contain a carbon atom instead of
 334 oxygen as a linker between the ligand chiral backbone and the
 335 phosphorus. Earlier ligands with a P–O bond are generally less
 336 stable.^{16a} The results obtained in the asymmetric hydrogenation
 337 of some typically tested trisubstituted olefins proved the
 338 catalysts' efficiency, reaching full conversion and ee's in the
 339 range of other heterocyclic ligands (>90% ee). Thiazole-
 340 substituted ligands 14 (Figure 10) derived from proline also
 341 showed high activity and good enantioselectivities when used in
 342 the Ir-catalyzed hydrogenation of certain trisubstituted and
 343 endocyclic nonfunctionalized alkenes (84–97% ee).⁴⁷

344 Using the BIPI ligands class (15, Figure 11), which had
 345 already performed successfully in the Rh-catalyzed asymmetric
 346 hydrogenation of various functionalized olefins, a set of novel
 347 iridium catalysts was developed by Busacca, Qu, and
 348 Senanayake.⁴⁸ In order to apply this system to unfunctionalized
 349 olefins, a ligand optimization study was carried out, varying the
 350 substituents at the phosphorus and on the imidazoline ring.
 351 Having cyclohexyl groups on both functions and a fluorine
 352 atom on the naphthyl *peri*-position provided a very efficient
 353 catalyst for hydrogenating challenging tetrasubstituted olefins,
 354 yielding an excellent 96% ee for the model substrate 2,3-
 355 dimethylindene using 1 bar of H₂ (2 mol% of catalyst). A 90%
 356 ee was obtained for dimethyl dihydronaphthalene, and high
 357 selectivity was also achieved for two representative trisub-
 358 stituted olefins. Pyridyl-dihydrobenzoxaphosphole (BoQ-
 359 Phos) ligands 16 (Figure 11) were also evaluated in the Ir-
 360 catalyzed hydrogenations of unfunctionalized olefins.⁴⁹

Figure 11. BIPI, BoQPhos, and LalithPhos catalysts.

361 Although high conversions and good enantioselectivities (76–
 362 90% ee) were obtained for different substrates (Figure 11), the
 363 BIPI-derived catalysts 15 provided better results. The hydro-
 364 genation of prochiral unfunctionalized dihydronaphthalenes
 365 was improved with the design of new phosphine-oxazoline
 366 ligands 17 (LalithPhos, Figure 11), and various 1-aryltetralins
 367 were thus obtained in ee's higher than 90% using 1 atm of H₂.⁵⁰

368 The group of Van der Eycken has investigated chiral
 369 ferrocene-derived N,P-ligands 18 (Figure 12), whose iridium

Figure 12. Ferrocene N,P-catalysts.

370 complexes were tested in the hydrogenation of unfunctional-
 371 ized olefins.⁵¹ A 91% ee was observed for (*E*)- α -methylstilbene
 372 at 50 bar of H₂. Moderate enantioselectivities were found for
 373 dihydronaphthalene substrates and 2,3-dimethylindene, while
 374 an excellent result was achieved for α -ethylstyrene (>99% ee).

375 Sigman recently reported a novel strategy for the enantio-
 376 selective hydrogenation of 1,1-diaryl-substituted olefins, which
 377 relies on a remote coordinating effect deriving from a *meta*
 378 substituent on one of the aromatic rings.⁵² In particular,
 379 methoxy functionalities were studied as *meta* directing groups,
 380 providing an expansion of the substrate scope compared to the
 381 Ru and Rh catalytic systems, which required oxygen directing
 382 groups in the *ortho* position. The use of the new proline-
 383 derived phosphoramidite (PhosPrOx) ligands 19 (Figure 13)
 384 afforded remarkable ee's (up to 93%) in the hydrogenation of
 385 1,1-diaryl-substituted olefins without an *ortho* substituent.
 386 However, the requirement for a 3,5-dimethoxy substitution
 387 on one of the aryls in the substrate in order to reach high
 388 enantioselectivity is still limiting the scope of this new

Figure 13. Remotely directed asymmetric hydrogenation of 1,1-diaryl- and 1,1-dialkyl-alkenes.

Scheme 1. Retrosynthesis of Clickphine N,P-Ligands

developed in 2015 by Reek and van Maarseveen.⁵⁶ Chirality 418 is induced to the ligand libraries from a single copper catalyst, 419 and the process allows the variation of up to four substituents 420 on the triazole-phosphine structure in two reaction steps. These 421 iridium complexes were evaluated in the hydrogenation of 422 largely unfunctionalized olefins; while good ee's were obtained 423 for both examples of (*E*)-trisubstituted (90%) and terminal 424 aryl-alkyl-disubstituted substrates (75%), they could not equal 425 the excellent results obtained with other classes of Ir-N,P- 426 catalysts. On the other hand, a promising enantioselectivity of 427 87% was achieved in the case of a more demanding 428 tetrasubstituted substrate, with very few higher values reported 429 so far. 430

Iridium N-Heterocyclic Carbene (NHC) Catalysts. In a 431 recent study comparing different NHC,N-ligands,⁵⁷ Burgess 432 concluded that imidazolynilidene **23**, imidazolylidene **3**, and 433 benzimidazolylidene **24** structures (Figure 15) show negligible 434 f15

Figure 15. Comparison of NHC,N-catalysts.

differences in catalytic performance in the Ir-catalyzed 435 asymmetric hydrogenation of largely unfunctionalized alkenes. 436 The test substrates were reduced with enantioselectivities 437 comparable to those previously reported for this class of 438 ligands, obtaining excellent results (up to 99% ee) in the case of 439 (*E*)-trisubstituted olefins. 440

In 2013, Pfaltz developed a series of NHC-pyridine ligands 441 (**25**, Figure 16) containing five-, six-, and seven-membered 442 carbocycles.⁵⁸ These structures combine the features of some of 443 the most successful ligands available to date, and their iridium 444 catalysts proved to be very efficient in the hydrogenation of 445 different unfunctionalized olefins. 446

High levels of enantioselectivity (>90%) were observed, even 447 for (*Z*)-trisubstituted (94% ee) and endocyclic substrates (96% 448 ee). Although they did not outperform Burgess's system **3** in 449

Figure 14. Benzimidazole-derived N,P-ligand.

methodology. Zhou applied the same concept via remote 389 carboxyl group coordination in the hydrogenation of 1,1-diaryl- 390 and 1,1-dialkylethenes.⁵³ For the former, the directing COOH 391 group was placed in the *ortho* position of one of the aryl 392 substituents and could be readily removed by one-pot 393 decarboxylation, accessing chiral unfunctionalized 1,1-diaryl- 394 ethanes in high yields and excellent enantioselectivity. These 395 structures are the core of many biologically active compounds. 396 The catalysts contained spiro phosphine-oxazoline ligands **20** 397 (Figure 13) and successfully operated at 0.25 mol% loading and 398 6 atm of H₂ on a broad scope of diarylethene acids (96 to >99% 399 ee). Also for dialkyl substrates, high enantioselectivities were 400 achieved (89–99% ee), resulting in useful chiral γ -methyl fatty 401 acids. Asymmetric iridium-catalyzed hydrogenations have 402 generally relied on steric differentiation in order to reach high 403 stereoselectivity, while the coordination strategy had been a 404 prerogative of Rh- and Ru-mediated processes. Insight into this 405 interesting new strategy in asymmetric hydrogenation and its 406 potential has been highlighted by Reek.⁵⁴ 407

The synthesis of chiral benzimidazole-based ligands **21** 408 (Figure 14) was reported in 2014 by Müller, and their first 409

application in the asymmetric hydrogenation of (*E*)- α -methyl- 410 stilbene provided encouraging results (up to 90% ee).⁵⁵ 411 Optimization of the ligands structure is still to be accomplished, 412 but it could lead to a new competitive class of catalysts in the 413 future. 414

An alternative strategy involving one-pot Cu-catalyzed 415 cycloadditions for the facile preparation of tunable triazole- 416 containing N,P-ligands **22** (Clickphine, Scheme 1) was 417

Figure 16. Application of NHC-pyridine catalysts (selected results).

Figure 17. Examples of application of P,S-catalysts.

Iridium O,P-Catalysts. In 2011, Pfaltz and co-workers reported the synthesis and evaluation of L-proline-based O,P-ligands **29** (Figure 18) in Ir-catalyzed hydrogenations.⁶² These

Figure 18. Proline-derived P,O-ligands.

chiral amido- and ureaphosphines can coordinate transition metals through the carbonyl oxygen atom and can be prepared from inexpensive precursors. It was shown that full conversion and excellent enantioselectivities (up to 99% ee) could be obtained, for example, in the hydrogenation of (*E*)- α -methylstilbene, with a performance comparable to that of the best N,P-systems. These O,P-complexes proved, however, to be less stable than proline-based N,P-catalysts and were therefore generated *in situ* prior to the hydrogenation reaction. These catalysts did not outperform other highly enantioselective N,P-iridium complexes in the case of minimally functionalized trisubstituted olefins, but they have been successfully applied to

Rhodium. A dinuclear Rh(III) complex (**30**, Figure 19) derived from chiral diphosphine ligands was reported for the

hydrogenation of olefins without directing groups, in contrast to conventional results for Rh(I) species.⁶⁴ The approach relies on the dissociation into the corresponding mononuclear monohydride Rh(III) as active species. The precatalyst is a chloride-bridged dinuclear rhodium complex, and a number of structures were generated from a series of chiral diphosphine ligands. Employing bulkier diphosphine ligands resulted in higher activity and selectivity in the hydrogenation of (*E*)- α -methylstilbene (up to 95% ee) using 30 bar of H₂ at 80 °C in toluene, with 1 mol% catalyst loading and 2 mol% of *n*-Bu₄NCl as additive. Excellent results (87–98% ee) were also obtained for a range of methylstilbene derivatives with various aryl substituents. High enantioselectivity could also be achieved in the hydrogenation of alkenyl boranes (85 and 93% ee).

Palladium. An interesting report in palladium catalysis involves a chiral [2,2]paracyclophane-based 1,2,3-triazol-5-ylidene Pd complex (**31**, [Figure 20](#)) containing a labile

acetonitrile ligand.⁶⁵ It was employed to hydrogenate prochiral
olefins under mild conditions in methanol (1 atm H₂, 30–35
°C). When tested on (*E*)- α -methylstilbene and a naphthalene-
substituted terminal alkene, it produced nearly quantitative
yields and promising levels of enantioselectivity (84–87% ee).
Ligand improvement and screening could result in a substrate
scope expansion for this type of catalytic system.

Cobalt. An early report by Pfaltz had presented an efficient cobalt catalyst for the enantioselective reduction of α,β -unsaturated esters.⁶⁶ More recently, Chirik's work made an important contribution to the asymmetric hydrogenation of largely unfunctionalized olefins using cobalt catalysis. This paves the road for the use of more earth-abundant metals; an obviously attractive option in terms of cost and environmental advantages. Cobalt bis(imino)pyridine complexes **32** (Figure 21) have also been successfully employed in the asymmetric hydrogenation of challenging terminal aryl,alkyl-substituted olefins and furnished the corresponding saturated products in high enantioselectivity (>90% ee).⁶⁷ A particularly remarkable result is the excellent 96% ee observed in the formation of 1-

methyldindane. Hopmann recently presented a quantum 548
mechanical study of the chiral CoBIP catalysts, providing 549
information about their properties, activation paths and 550
asymmetric hydrogenation mechanism.⁶⁸ Competitive alkene 551
isomerization was shown to play a role in the overall process, 552
affecting also the observed enantioselectivities. 553

Successively, high-throughput screening of numerous chiral bidentate phosphine ligands in combination with different cobalt precursors allowed the identification of a suitable catalytic system for the asymmetric hydrogenation of (*E*)- α -methylstilbene.⁶⁹ Ultimately, a Biphep derivative (ligand **33**, Figure 21) was found to be highly stereoselective, resulting in 83% conversion and 94% ee, after 20 h using 34 atm of H₂. The catalyst loadings are higher (10 or 5 mol%) than those commonly used for iridium catalysts (1 mol% or less), but these results certainly prove cobalt to be a valuable asset for efficient and versatile hydrogenation of largely unfunctionalized olefins.

Both Lu and Chirik reported the Co-catalyzed enantio-
selective hydrogenation of several 1,1-diarylethenes in 2016. In
Lu's case,⁷⁰ a stable cobalt complex containing an oxazoline
iminopyridine chiral ligand (**34**, [Figure 21](#)) was used as
precatalyst. In the presence of NaBHET₃ in toluene and using 1
atm of H₂ at room temperature, it was possible to reach full
conversion and 90% ee for substrates with an *ortho*-Cl group,
which provided a unique effect to achieve high enantio-
selectivities. When the alkene scope was evaluated, enantio-

selectivities up to 95% ee were observed for α -alkylstyrenes. The Cl group could then be removed or used for further functionalizations with excellent yields, describing a convenient way to obtain various chiral 1,1-diarylethanes.

In Chirik's report, cobalt bis(imino)pyridine complexes proved very successful in the asymmetric hydrogenation of cyclic unfunctionalized olefins, such as aryl-substituted indenenes and dialins (up to 99% ee).⁷¹ In a comparative study, both isomeric *exo*- and *endocyclic* alkenes were hydrogenated in good to high enantioselectivity (up to 95% ee), with a tendency to show opposite stereochemical outcomes. Moderate ee's (up to 77%) were obtained for 1,1-diarylethenes when *ortho* substitution was present. A remarkable application of the catalytic system is the multigram-scale reduction of 4-methyl-1,2-dihydronaphthalene (93% ee), carried out in neat alkene using 0.1 mol% of chiral cobalt complex. Co-hydride species were rapidly generated in the presence of H₂ and were identified by means of NMR and X-ray diffraction, providing some information about the chiral environment around the cobalt.

Iron. Aryl-substituted bis(imino)pyridine iron dinitrogen complexes **35** (Figure 22) were described as efficient base metal

Figure 22. Iron catalysts for the hydrogenation of simple olefins.

catalysts, exhibiting high turnover frequencies for the hydrogenation of unfunctionalized trisubstituted and challenging tetrasubstituted olefins, employing iron loadings as low as 0.3 mol% at room temperature.⁷² Recent optimization of the ligand design using more electron-rich structures improved the performance.⁷³ This work could furnish valuable insight for the development of an asymmetric version of iron catalytic systems.

Another class of iron catalysts was reported where the active species are generated *in situ* by reduction of stable Fe(II) complexes with LiAlH₄.⁷⁴ The use of bidentate N,N-ligands resulted in excellent activity in the hydrogenation of styrene, which was fully saturated in less than 1 h using 30 atm of H₂ with 0.1 mol% catalyst loading. A particularly efficient catalyst was then obtained using a pincer bipyridine ligand (**36**, Figure 22), which provided full conversion after 3 h using 10 atm of H₂ at 0.01 mol% catalyst loading. Styrenes and aliphatic terminal olefins were also hydrogenated with high reaction rates; however, it was necessary to increase the temperature to 50 °C in the case of disubstituted olefins. This contribution also makes it possible to envision further developments toward Fe-based asymmetric hydrogenation catalysts.

CONCLUSIONS AND OPEN CHALLENGES

The development of chiral Crabtree-type catalysts has notably expanded the field of homogeneous asymmetric hydrogenation of nonfunctionalized olefins, providing complementarity to Rh

and Ru systems. Examining the scope of the catalysts that are currently available for the asymmetric hydrogenation of largely unfunctionalized olefins, it seems clear that careful ligand optimization and control of the reaction conditions allow reaching high enantioselectivities for many different substrate classes. One drawback of this approach is the lack of generality of the catalysts; it is still difficult to generate a single catalyst that would tolerate a large number of olefins bearing substituents of diverse nature. However, recent investigations, especially in iridium catalysis, continue to produce new powerful systems, advancing toward the goal of increased functional group tolerance. The main limitation that still concerns the majority of asymmetric hydrogenations is the necessity to operate on pure geometrical isomers; (*E*)- and (*Z*)-trisubstituted olefins are generally found to produce opposite enantiomers of the alkane products, canceling the chance of achieving high stereoselectivity when both are present. The reason for this undesired behavior lies in the mode the catalysts are discriminating between the prochiral faces of the olefin, with the favored coordination being dictated by the less substituted carbon atom rather than the prochiral center. Therefore, a catalytic system that would be able to select directly on the prochiral carbon, regardless of alkene geometry, is much sought after, as it would enable the asymmetric hydrogenation of *E/Z* mixtures to yield enantiomerically pure products. This issue is even more relevant in the case of unfunctionalized olefins, since the presence of functional groups on the substrates facilitates both the stereoselective synthesis of either (*E*)- or (*Z*)-isomers and also their separation.

Another open challenge concerns the development of efficient systems for hindered tetrasubstituted olefins. This class of substrates has always proved very demanding, and reports of highly enantioselective hydrogenations are still scarce. One interesting feature of tetrasubstituted olefins is certainly the opportunity to generate two contiguous stereocenters in a single reaction; thus, efforts in the development of improved catalysts for these sterically challenging compounds are easy to foresee.

Other demanding substrates are also represented by olefins that contain non-coordinating groups such as silanes or halides. In the latter case, the hydrogenation is further complicated by competing dehalogenation processes, an issue still to be overcome by development of new catalytic systems.

In addition to handling these difficult classes of alkenes, it would also be highly desirable to directly saturate aromatic rings, which would be one of the most interesting opportunities for the asymmetric hydrogenation of minimally functionalized substrates. Several efficient catalysts have been developed for the asymmetric hydrogenation of various classes of heteroarenes, and these advances have been reviewed in detail by Zhou and Glorius.⁷⁵ Some examples of catalytic hydrogenation of benzene rings have been reported,⁷⁶ but still the substrate scope remains very narrow, and this research area is also likely to expand in the future.

The formation of multiple stereocenters from the asymmetric hydrogenation of polyene substrates is of undoubtable interest, and the usefulness of this strategy has been elegantly demonstrated in natural products preparation.^{16b,77} On the other hand, polyenes can also offer many other interesting post-hydrogenation synthetic possibilities if the catalytic system can be tuned to react with one olefin while leaving others untouched and available for further functionalization. It

would represent a powerful synthetic tool to induce chirality, especially in complex structures containing many double bonds. Examples of regioselective iridium catalysts have been recently reported⁴⁵ and can surely offer a hint for future studies on this subject.

Finally, a fundamental area of investigation lies in the search for catalysts based on more cost-effective and environmentally friendly Earth-abundant metals, exemplified by recent works in cobalt and iron catalysis. In the former case, some excellent results for the asymmetric hydrogenation of unfuctionalized olefins have already been reported, and the optimization of catalytic activity and stability are plausible lines of forthcoming development. In the case of Fe-catalyzed hydrogenation of olefins, the challenge is instead to design an efficient asymmetric variant of the newly developed achiral systems.

Taking the above-mentioned considerations into account, one can conclude that many fascinating aspects and opportunities of the asymmetric hydrogenation of minimally functionalized olefins remain to be explored and that the design of innovative catalysts capable of overcoming the remaining issues would provide fundamental contributions to the field.

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Notes

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REFERENCES

- (1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive asymmetric catalysis: I-III*; Springer: Berlin, 1999. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000.
- (2) (a) Evans, D.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Nature* **1965**, 208, 1203. (b) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, 7, 942. (c) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445. (d) Dang, T. P.; Kagan, H. B. *J. Chem. Soc. D* **1971**, 481. (e) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10. (f) Tanaka, M.; Ogata, I. *J. Chem. Soc., Chem. Commun.* **1975**, 735a. (g) Kawabata, Y.; Tanaka, M.; Ogata, I. *Chem. Lett.* **1976**, 5, 1213. (h) Hayashi, T.; Tanaka, M.; Ogata, I. *Tetrahedron Lett.* **1977**, 18, 295. (i) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, 99, 5946. (j) Knowles, W. S. *Acc. Chem. Res.* **1983**, 16, 106. (k) Bakos, J.; Tóth, I.; Heil, B.; Markó, L. *J. Organomet. Chem.* **1985**, 279, 23. (l) Inagaki, K.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Organomet. Chem.* **1997**, 531, 159.
- (3) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumabayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, 109, 5856.
- (4) (a) Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, 502, 169. (b) Schmid, R.; Broger, E. A.; Cereghetti, M.; Cramer, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, 68, 131. (c) Forman, G. S.; Ohkuma, T.; Hems, W. P.; Noyori, R. *Tetrahedron Lett.* **2000**, 41, 9471.
- (5) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, 105, 3272.
- (6) (a) Cesarotti, E.; Ugo, R.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1979**, 18, 779. (b) Paquette, L. A.; McKinney, J. A.; McLaughlin, M. L.; Rheingold, A. L. *Tetrahedron Lett.* **1986**, 27, 5599. (c) Halter-

- man, R. L.; Vollhardt, K. P. C.; Welker, M. E.; Blaaser, D.; Boese, R. *J. Am. Chem. Soc.* **1987**, 109, 8105. (d) Halterman, R. L.; Vollhardt, K. P. *C. Organometallics* **1988**, 7, 883. (e) Pino, P.; Galimberti, M. *J. Organomet. Chem.* **1989**, 370, 1. (f) Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* **1990**, 112, 4911. (g) Grossman, R. B.; Doyle, R. A.; Buchwald, S. L. *Organometallics* **1991**, 10, 1501. (h) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, 115, 12569. (i) Gibis, K.-L.; Helmchen, G.; Huttner, G.; Zsolnai, L. *J. Organomet. Chem.* **1993**, 445, 181. (j) Paquette, L. A.; Sivik, M. R.; Bzowej, E. I.; Stanton, K. J. *Organometallics* **1995**, 14, 4865. (k) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, 9, 2377. (l) Schwink, L.; Knochel, P. *Chem. - Eur. J.* **1998**, 4, 950. (m) Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, 121, 4916.
- (7) (a) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, 114, 2761. (b) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, 116, 10241. (c) Haar, C. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1996**, 15, 1765. (d) Roesky, P. W.; Denninger, U.; Stern, C. L.; Marks, T. J. *Organometallics* **1997**, 16, 4486.
- (8) Crabtree, R. *Acc. Chem. Res.* **1979**, 12, 331.
- (9) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, 34, 1769.
- (10) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, 34, 3149.
- (11) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 566. (b) von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefebvre, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, 5, 573. (c) Koch, G.; Pfaltz, A. *Tetrahedron: Asymmetry* **1996**, 7, 2213.
- (12) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. - Eur. J.* **1997**, 3, 887.
- (13) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, 37, 2897.
- (14) Smidt, S. P.; Zimmermann, N.; Studer, M.; Pfaltz, A. *Chem. - Eur. J.* **2004**, 10, 4685.
- (15) (a) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1999, 1814. (b) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, 12, 442. (c) Bernardinelli, G. H.; Kündig, E. P.; Meier, P.; Pfaltz, A.; Radkowski, K.; Zimmermann, N.; Neuburger-Zehnder, M. *Helv. Chim. Acta* **2001**, 84, 3233. (d) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, 40, 4445. (e) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, 4, 4713. (f) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, 344, 40. (g) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, 6, 2023. (h) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, 347, 61. (i) Schönleber, M.; Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, 350, 2033.
- (16) (a) Drury, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, 43, 70. (b) Bell, S.; Wüstenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, 311, 642. (c) Woodmansee, D. H.; Müller, M.-A.; Neuburger, M.; Pfaltz, A. *Chemical Science* **2010**, 1, 72.
- (17) Woodmansee, D. H.; Müller, M.-A.; Tröndlin, L.; Hörmann, E.; Pfaltz, A. *Chem. - Eur. J.* **2012**, 18, 13780.
- (18) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, 45, 5194.
- (19) Ganić, A.; Pfaltz, A. *Chem. - Eur. J.* **2012**, 18, 6724.
- (20) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2007**, 46, 8274.
- (21) (a) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, 123, 8878. (b) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, 125, 113.
- (22) Zhu, Y.; Burgess, K. *Adv. Synth. Catal.* **2008**, 350, 979.
- (23) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. *G. J. Am. Chem. Soc.* **2004**, 126, 14308.
- (24) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. *G. J. Am. Chem. Soc.* **2006**, 128, 2995.
- (25) Kaukoranta, P.; Engman, M.; Hedberg, C.; Bergquist, J.; Andersson, P. *G. Adv. Synth. Catal.* **2008**, 350, 1168.

- 815 (26) (a) Li, J.-Q.; Paptchikhine, A.; Govender, T.; Andersson, P. G. *Tetrahedron: Asymmetry* **2010**, *21*, 1328. (b) Trifonova, A.; Diesen, J. 883
816 S.; Andersson, P. G. *Chem. - Eur. J.* **2006**, *12*, 2318. 884
817 (27) Källström, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Org. Biomol. Chem.* **2012**, *10*, 8539. 885
818 *Adv. Synth. Catal.* **2006**, *348*, 2575. 886
819 (28) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. 887
820 Am. Chem. Soc.* **2007**, *129*, 4536. 888
821 (29) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 1556. 889
822 *Chem. Commun.* **2009**, 5996. 890
823 (30) Cheruku, P.; Diesen, J.; Andersson, P. G. *J. Am. Chem. Soc.* 891
824 **2008**, *130*, 5595. 892
825 (31) (a) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. 893
826 *Chem. Rev.* **2014**, *114*, 2130. (b) Woodmansee, D. H.; Pfaltz, A. *Eur. J. Org. Chem.* 894
827 **2011**, *47*, 7912. (c) Halterman, R. L. *Comprehensive* 895
828 *Asymmetric Catalysis: Supplement 2*; Springer: Berlin, 2004. (d) Rose- 896
829 blade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. (e) Pàmies, O.; 897
830 Andersson, P. G.; Diéguez, M. *Chem. - Eur. J.* **2010**, *16*, 14232. 898
831 (f) Cadu, A.; Andersson, P. G. *Dalton Trans.* **2013**, *42*, 14345. 899
832 (32) Co, T. T.; Kim, T.-J. *Chem. Commun.* **2006**, 3537. 900
833 (33) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. 901
834 Chem.* **1977**, *141*, 205. (b) Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, 902
835 T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183. (c) Crabtree, R. 903
836 H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. 904
837 M.; Morris, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 6994. (d) Dietiker, R.; 905
838 Chen, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 5513. (e) Fan, Y.; Cui, X.; 906
839 Burgess, K.; Hall, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 16688. (f) Mazet, 907
840 C.; Smidt, S. P.; Meuwly, M.; Pfaltz, A. *J. Am. Chem. Soc.* **2004**, *126*, 908
841 14176. 909
842 (34) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem. - Eur. J.* **2003**, 910
843 *9*, 339. 911
844 (35) Sun, Y.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. 912
845 G. *J. Am. Chem. Soc.* **1996**, *118*, 1348. 913
846 (36) Church, T. L.; Rasmussen, T.; Andersson, P. G. *Organometallics* 914
847 **2010**, *29*, 6769. 915
848 (37) (a) Hopmann, K. H.; Bayer, A. *Organometallics* **2011**, *30*, 2483. 916
849 (b) Hopmann, K. H.; Frediani, L.; Bayer, A. *Organometallics* **2014**, *33*, 917
850 2790. (c) Sparta, M.; Riplinger, C.; Neese, F. *J. Chem. Theory Comput.* 918
851 **2014**, *10*, 1099. 919
852 (38) Gruber, S.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 1896. 920
853 (39) Mazuela, J.; Norrby, P.-O.; Andersson, P. G.; Pàmies, O.; 921
854 Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634. 922
855 (40) Mazuela, J.; Pàmies, O.; Diéguez, M. *Eur. J. Inorg. Chem.* **2013**, 923
856 *2013*, 2139. 924
857 (41) Mazuela, J.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2013**, *5*, 925
858 2410. 926
859 (42) Mazuela, J.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, 927
860 *355*, 2569. 928
861 (43) Biosca, M.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; 929
862 Diéguez, M. *Chem. - Eur. J.* **2015**, *21*, 3455. 930
863 (44) (a) Cadu, A.; Paptchikhine, A.; Andersson, P. G. *Synthesis* **2011**, 931
864 *2011*, 3796. (b) Paptchikhine, A.; Itto, K.; Andersson, P. G. *Chem.* 932
865 *Commun.* **2011**, *47*, 3989. 933
866 (45) Peters, B. K.; Liu, J.; Margarita, C.; Rabten, W.; Kerdphon, S.; 934
867 Orebom, A.; Morsch, T.; Andersson, P. G. *J. Am. Chem. Soc.* **2016**, 935
868 *138*, 11930. 936
869 (46) Quan, X.; Parihar, V. S.; Bera, M.; Andersson, P. G. *Eur. J. Org.* 937
870 *Chem.* **2014**, *2014*, 140. 938
871 (47) Yotapan, N.; Paptchikhine, A.; Bera, M.; Avula, S. K.; Vilaivan, 939
872 T.; Andersson, P. G. *Asian J. Org. Chem.* **2013**, *2*, 674. 940
873 (48) Busacca, C. A.; Qu, B.; Grêt, N.; Fandrick, K. R.; Saha, A. K.; 941
874 Marsini, M.; Reeves, D.; Haddad, N.; Eriksson, M.; Wu, J.-P.; 942
875 Grinberg, N.; Lee, H.; Li, Z.; Lu, B.; Chen, D.; Hong, Y.; Ma, S.; 943
876 Senanayake, C. H. *Adv. Synth. Catal.* **2013**, *355*, 1455. 944
877 (49) Qu, B.; Samankumara, L. P.; Savoie, J.; Fandrick, D. R.; Haddad, 945
878 N.; Wei, X.; Ma, S.; Lee, H.; Rodriguez, S.; Busacca, C. A.; Yee, N. K.; 946
879 Song, J. J.; Senanayake, C. H. *J. Org. Chem.* **2014**, *79*, 993. 947
880 (50) Qu, B.; Samankumara, L. P.; Ma, S.; Fandrick, K. R.; Desrosiers, 948
881 J.-N.; Rodriguez, S.; Li, Z.; Haddad, N.; Han, Z. S.; McKellop, K.; 949
882 Pennino, S.; Grinberg, N.; Gonnella, N. C.; Song, J. J.; Senanayake, C. 950
883 H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14428. 951
884 (51) Bert, K.; Noel, T.; Kimpe, W.; Goeman, J. L.; Van der Eycken, J. 952
885 *Org. Biomol. Chem.* **2012**, *10*, 8539. 953
886 (52) Bess, E. N.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 646. 954
887 (53) Song, S.; Zhu, S.-F.; Yu, Y.-B.; Zhou, Q.-L. *Angew. Chem., Int.* 955
888 *Ed.* **2013**, *52*, 1556. 956
889 (54) Besset, T.; Gramage-Doria, R.; Reek, J. N. H. *Angew. Chem., Int.* 957
890 *Ed.* **2013**, *52*, 8795. 958
891 (55) Weemers, J. J. M.; Sypaseuth, F. D.; Bäuerlein, P. S.; van der 959
892 Graaff, W. N. P.; Filot, I. A. W.; Lutz, M.; Müller, C. *Eur. J. Org. Chem.* 960
893 **2014**, *2014*, 350. 961
894 (56) Wassenaar, J.; Detz, R. J.; de Boer, S. Y.; Lutz, M.; van 962
895 Maarseveen, J. H.; Hiemstra, H.; Reek, J. N. H. *J. Org. Chem.* **2015**, *80*, 963
896 3634. 964
897 (57) Khumsubdee, S.; Fan, Y.; Burgess, K. *J. Org. Chem.* **2013**, *78*, 965
898 9969. 966
899 (58) Schumacher, A.; Bernasconi, M.; Pfaltz, A. *Angew. Chem., Int. Ed.* 967
900 **2013**, *52*, 7422. 968
901 (59) Coll, M.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, *355*, 969
902 143. 970
903 (60) Borràs, C.; Biosca, M.; Pàmies, O.; Diéguez, M. *Organometallics* 971
904 **2015**, *34*, 5321. 972
905 (61) Biosca, M.; Coll, M.; Lagarde, F.; Brémond, E.; Routaboul, L.; 973
906 Manoury, E.; Pàmies, O.; Poli, R.; Diéguez, M. *Tetrahedron* **2016**, *72*, 974
907 2623. 975
908 (62) Rageot, D.; Woodmansee, D. H.; Pugin, B.; Pfaltz, A. *Angew.* 976
909 *Chem., Int. Ed.* **2011**, *50*, 9598. 977
910 (63) Rageot, D.; Pfaltz, A. *Helv. Chim. Acta* **2012**, *95*, 2176. 978
911 (64) Kita, Y.; Hida, S.; Higashihara, K.; Jena, H. S.; Higashida, K.; 979
912 Mashima, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 8299. 980
913 (65) Dasgupta, A.; Ramkumar, V.; Sankararaman, S. *RSC Adv.* **2015**, 981
914 *5*, 21558. 982
915 (66) Pfaltz, A. *Bull. Soc. Chim. Belg.* **1990**, *99*, 729. 983
916 (67) Monfette, S.; Turner, Z. R.; Semproni, S. P.; Chirik, P. J. *J. Am.* 984
917 *Chem. Soc.* **2012**, *134*, 4561. 985
918 (68) Hopmann, K. H. *Organometallics* **2013**, *32*, 6388. 986
919 (69) Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, 987
920 M. T.; Chirik, P. J. *Science* **2013**, *342*, 1076. 988
921 (70) Chen, J.; Chen, C.; Ji, C.; Lu, Z. *Org. Lett.* **2016**, *18*, 1594. 989
922 (71) Friedfeld, M. R.; Shevlin, M.; Margulieux, G. W.; Campeau, L.- 990
923 C.; Chirik, P. J. *J. Am. Chem. Soc.* **2016**, *138*, 3314. 991
924 (72) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, 992
925 *126*, 13794. 993
926 (73) Yu, R. P.; Darmon, J. M.; Hoyt, J. M.; Margulieux, G. W.; 994
927 Turner, Z. R.; Chirik, P. J. *ACS Catal.* **2012**, *2*, 1760. 995
928 (74) Guo, N.; Hu, M.-Y.; Feng, Y.; Zhu, S.-F. *Org. Chem. Front.* **2015**, 996
929 *2*, 692. 997
930 (75) (a) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* 998
931 **2012**, *112*, 2557. (b) Chen, Z.-P.; Zhou, Y.-G. *Synthesis* **2016**, *48*, 999
932 1769. (c) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. *ACS Catal.* **2016**, 1000
933 *6*, 5978. 1001
934 (76) Wei, Y.; Rao, B.; Cong, X.; Zeng, X. *J. Am. Chem. Soc.* **2015**, *137*, 1002
935 9250. 1003
936 (77) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129. 1004
937