CATALYTIC ASYMMETRIC HYDROGENATION OF HETEROARENES

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INTRODUCTION

Asymmetric hydrogenation of unsaturated organic compounds has been established as one of the most efficient methods for the preparation of chiral, non-racemic substrates.[1] Among hydrogenation of various substrates, the asymmetric hydrogenation of heteroarenes provides a straightforward approach to a wide range of enantiomerically pure saturated heterocycles, which are subunits of many biologically active compounds.[2] In addition, multiple stereocenters can be created in a single step when multi-substituted heteroarenes are used as substrates. With these advantages and potential application, the development of an efficient, cost-effective method for asymmetric hydrogenation of heteroarenes is highly desirable.

However, the development of asymmetric hydrogenation of heteroarenes has been a challenging process in organic synthesis because the stability of heteroarenes and the presence of heteroatoms. More energy (10-20 kcal mol^{-1} per double bond) is required for hydrogenation of heteroaromatic compounds than hydrogenation of olefins, ketones or imines.[3] In addition, the basic heteroatoms can bind to the metal centers to deactivate the catalysts or simply serve as achiral ligands. Furthermore, in contrast to functionalized olefins and ketones, the lack of a secondary coordinating site in simple heteroarenes to interact with the metal center also accounts for the difficulties in achieving good enantioselectivity.

Despite these challenges, several catalyst systems have been developed for asymmetric hydrogenation of heteroarenes in the past decade.[4] Two basic strategies that have been employed to facilitate the asymmetric hydrogenation process are the use of bicyclic heteroarenes and the introduction of substituents next to or on the heteroatoms. The first strategy is exemplified by the hydrogenation of quinolines, indoles and benzofurans. In these substrates, the aromatic stabilization energy of the heteroaromatic ring is reduced,[3] thereby increasing reactivity towards hydrogenation. In the second strategy, the substituent is installed to weaken the binding between the heteroatom and metal center by virtue of a steric effect or alternatively to serve as a secondary coordination site to the catalyst. To understand the chemical reactivity and future potential of this transformation, methods for asymmetric hydrogenation of various heteroarenes will be discussed.

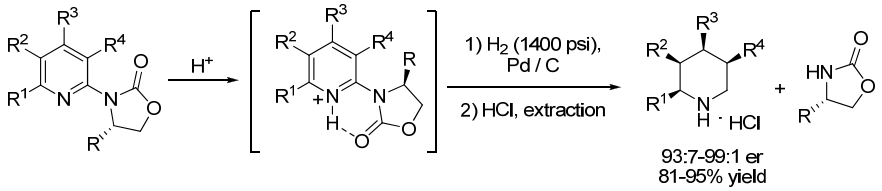
HYDROGENATION OF SIX-MEMBERED RING HETEROARENES

Pyridines

Early studies on asymmetric hydrogenation of pyridines used a $Rh(nbd)_2BF_4$/BINAP catalyst or a cinchona-modified heterogeneous catalyst,[5] but these catalysts suffered from low conversion and poor enantioselectivities. Initial reports of asymmetric hydrogenation of pyridines with an appended chiral auxiliary also gave low diastereoselectivities.[6]

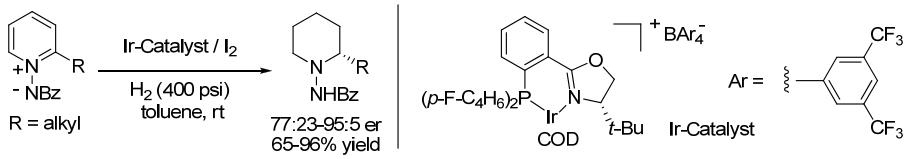
A significant breakthrough occurred when Glorius and co-workers reported a highly efficient method for the asymmetric hydrogenation of chiral *N*-(2-pyridyl)-oxazolidinones (Scheme 1).[7] Reductions of highly substituted pyridines are conducted in acetic acid using commercially available heterogeneous catalysts such as Pd/C, Rh/C and PtO_2, and result in good yield (81-95%) and high diastereoselectivities (93:7-99:1 dr). Multiple stereocenters can be created in a single step. The acidic conditions activate the substrate by protonating the pyridine starting material and suppress the catalyst poisoning property of the piperidine by protonating the piperidine product. The high diastereoselectivity is ascribed to strong hydrogen bonding between the pyridinium and oxazolidinone moiety. By forming a rigid intermediate, the R group on the oxazolidinone shields the top face leaving the bottom face accessible.

Scheme 1. Asymmetric Hydrogenation of Chiral *N*-(2-Pyridyl)Oxazolidinones



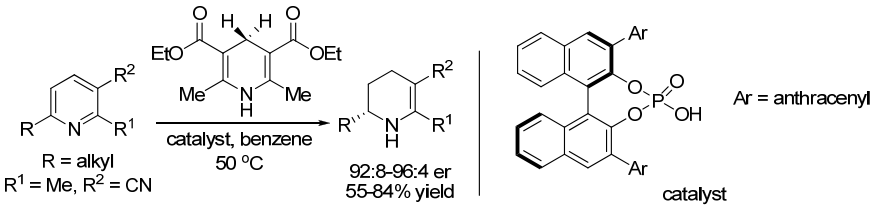
Charette and co-workers developed another asymmetric hydrogenation of pyridine derivatives using an achiral auxiliary and *N*-benzoyliminopyridinium ylides (Scheme 2).[8] Ir-phosphinooxazoline complexes are the best catalysts for this reaction. This method is best suited for the enantioselective hydrogenation of 2-substituted *N*-benzoyliminopyridinium ylides, and provides good yield (65-96%) and moderate enantioselectivities (77:23-95:5 er). The benzoylimino moiety serves as both an activator of substrates and a secondary coordinating group for the catalyst.

Scheme 2. Asymmetric Hydrogenation of *N*-Benzoyliminopyridinium Ylides



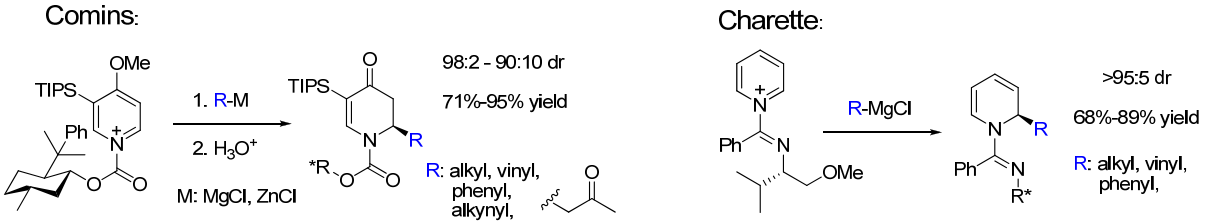
In addition to transition-metal complexes, organocatalysts have also been shown to be active for asymmetric hydrogenation of pyridines. Rueping and co-workers reported enantioselective reduction of pyridines in the presence of a BINOL phosphate Brønsted acid catalyst using Hantzsch dihydropyridine as the hydride source (Scheme 3).[9] The hydrogenation occurs with good yield (55-84%) and excellent enantioselectivities (92:8-96:4 er); however, the substrate scope is limited to certain 1,2,5-trisubstituted pyridines.

Scheme 3. Asymmetric Hydrogenation of Pyridines using Organocatalyst



Except for asymmetric hydrogenation, which establishes the stereocenters by C-H bond formation, there are other alternative methods to establish the stereocenters by C-C bond formation. The Comins[10] and Charette[11] groups developed procedures for 1,2-addition of carbon nucleophiles to pyridinium salts appended with a chiral auxiliary (Scheme 4). These additions proceed with moderate yield (68-95%) and good diastereoselectivities (90:10-98:2 dr), and the products can be further functionalized to establish trans stereocenters on the six-membered ring. However, these methods require the use of a chiral auxiliary and the scope of the carbon nucleophiles is limited.

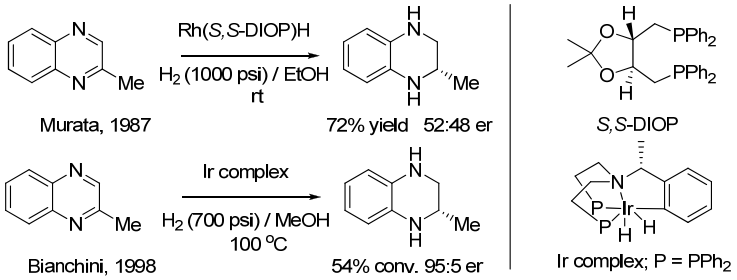
Scheme 4. Alternative Methods to Establish Stereocenter



Quinoxalines, Quinolines and Isoquinolines

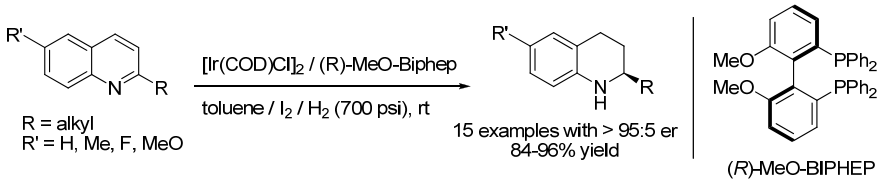
The first example of asymmetric hydrogenation of bicyclic heteroarenes was reported by Murata and co-workers (Scheme 5).[12] 2-Methylquinoxaline is reduced to tetrahydro-2-methyl quinoxaline using Rh[(*S*,*S*-DIOP)]H as the catalyst to give low enantioselectivity (52:48 er). A significant improvement was reported by Bianchini and co-workers using an orthometalated iridium dihydride complex (Scheme 5).[13] The hydrogenation of the same substrate gives good enantioselectivity (95:5 er), although the conversion (54%) is modest.

Scheme 5. Pioneering Work on Asymmetric Hydrogenation of Quinoxalines



Zhou and co-workers reported the first efficient method for asymmetric hydrogenation of quinolines with $[Ir(COD)Cl]_2$-MeO-BIPHEP catalyst and iodine as an additive (Scheme 6).[14] The reduction of a variety of 2-substituted quinolines occurrs with high yield (84-96%) and excellent enantioselectivities (>95:5 er). The choice of additive has a dramatic impact on the turnover number and enantioselectivity, and only iodine and other halogen additives such as NBS or NIS result in excellent conversion and enantioselectivity. Since the introduction of the Ir-MeO-BIPHEP catalyst system, several other efficient phosphine and phosphite ligands have been developed for asymmetric hydrogenation of quinolines using the same Ir-precursor.[15] Some representative ligands are shown in Figure 1.

Scheme 6. Iridium-Catalyzed Asymmetric Hydrogenation of Quinolines



Although phosphine and phosphite ligands are generally used, asymmetric hydrogenation of quinolines can also be achieved by using phosphine-free catalysts. Fan and co-workers recently developed a chiral diamine-based iridium catalyst with trifluoroacetic aicd as additive for the asymmetric hydrogenation of quinolines (Scheme 7).[16] The reduction of 2-substituted quinolines proceeds with excellent yield (90-99%) and enantioselectivities (>97:3 er) without the rigorous exclusion of air.

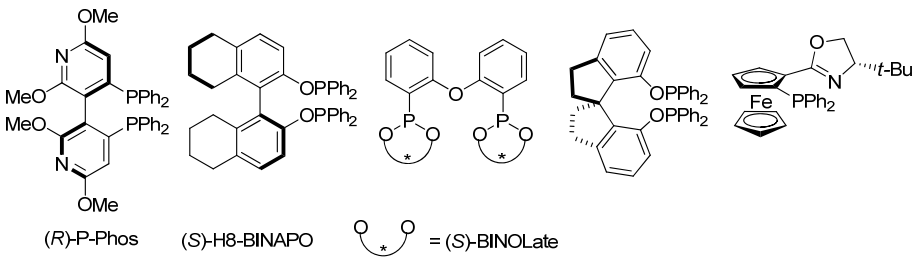
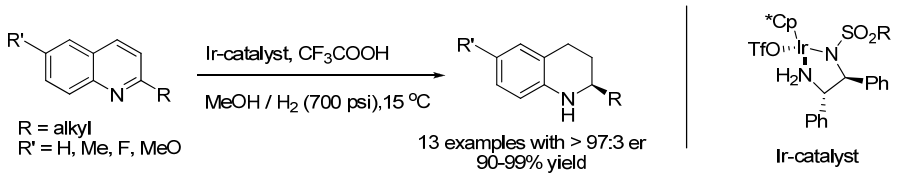


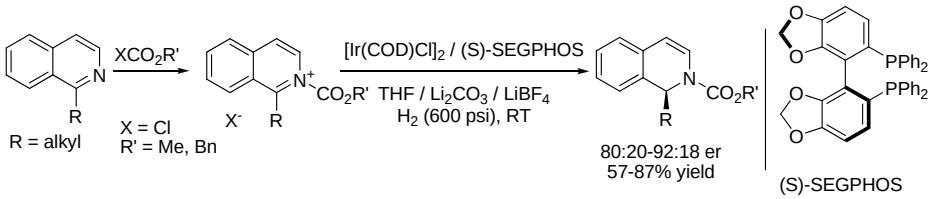
Figure 1. Other Efficient Ligands for Asymmetric Hydrogenation of Quinolines

Scheme 7. Diamine-Based Iridium Catalyst for Asymmetric Hydrogenation of Quinolines



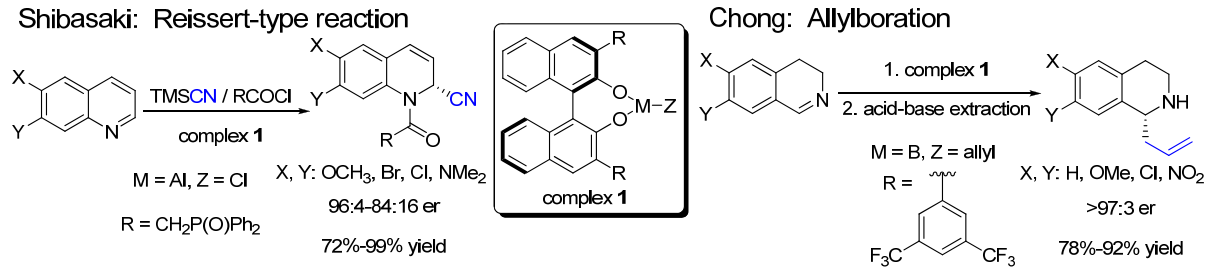
Because isoquinolines can bind more strongly to metal centers than 2-substituted quinolines, low conversions were observed with isoquinoline substrates under standard conditions for hydrogenation of quinolines. However, Zhou and co-workers showed that by exploiting the activating ability of substituents at nitrogen atom, the reduction could occur smoothly with moderate to good yield (57-87%) and enantioselectivities (80:20-92:18 er) (Scheme 8).[17] Chloroformates are used as activating agents to block the nitrogen binding site as well as to lower the electron density of the aromatic ring.

Scheme 8. Iridium-Catalyzed Asymmetric Hydrogenation of Isoquinolines



Other alternate methods to establish the stereocenters by C-C bond formation include Reissert-type reaction of quinolines developed by Shibasaki[18] and allylboration of cyclic imines developed by Chong (Scheme 9).[19] These reactions proceed with moderate yield (72-99%) and enantioselectivities (84:16-97:3 er), and some hydrogen-sensitive function groups (such as cyano, allyl) can be introduced. However, no other carbon nucleophiles can be used to give similar products with comparable yield and stereoselecitivity.

Scheme 9. Alternate Methods to Establish Stereocenter



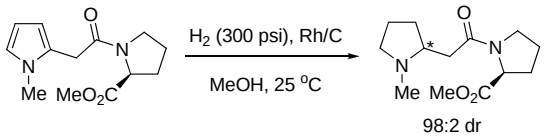
HYDROGENATION OF FIVE-MEMBERED RING HETEROARENES

Pyrroles and Indoles

For the diastereoselective hydrogenation of pyrroles, Tungler and co-workers reported the the stereoselective reduction of a pyrrole appended with (*S*)-proline (Scheme 10).[20] The chiral

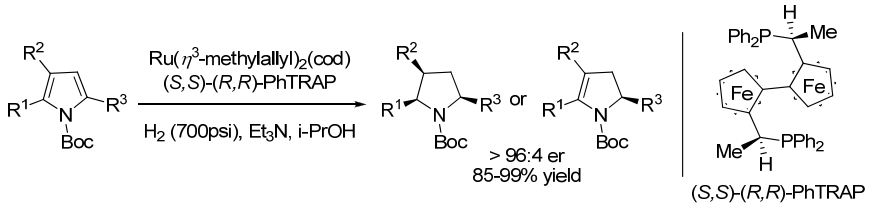
(2-pyrrolyl)acetamide is subjected to hydrogenation using a Rh/C catalyst in methanol, to give a pyrrolidine derivative with excellent diastereoselectivity (98:2 dr). However, this method is only applied to the reduction of (2-pyrrolyl)acetic acid derivatives.

Scheme 10. Diastereoselective Hydrogenation of Pyrroles



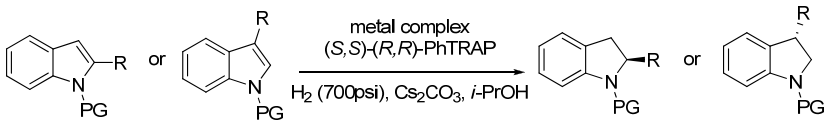
Recently, Kuwano and co-workers disclosed a highly enantioselective hydrogenation of *N*-Boc-pyrroles (Scheme 11).[21] The hydrogenation of *N*-Boc-pyrroles proceeds with good enantioselectivities (>96:4 er) by using a chiral Ru(η^3-methylallyl)$_2$(cod)-(*S,S*)-(*R,R*)-PhTRAP catalyst. The substrates can be mono-substituted or 2,3,5-trisusbstituted with a large substituent at the 5-position. Studies have shown that the reaction occurs by initial reduction of the less substituted carbon-carbon double bond. Dihydropyrroles are obtained when all substituents in the trisubstituted substrate are aryl groups, because the following hydrogenation of the carbon-carbon double bond is obstructed by steric repulsion between the aryl groups.

Scheme 11. Ru-Catalyzed Enantioselective Hydrogenation of Pyrroles



For the asymmetric hydrogenation of indoles, Kuwano and co-workers reported that both rhodium and ruthenium complexes with PhTRAP ligand are efficient catalysts.[22] The choice of catalyst largely depends on the protecting groups on nitrogen. The Ru(η^3-methylallyl)$_2$(cod) catalyst is best suited for substituted *N*-Boc indoles, while the [Rh(nbd)$_2$]SbF$_6$ is efficient for 2-substituted *N*-Ac indoles and 3-substituted *N*-Ts indoles (Table 1).

Table 1. Ru- or Rh-Catalyzed Enantioselective Hydrogenation of Indoles



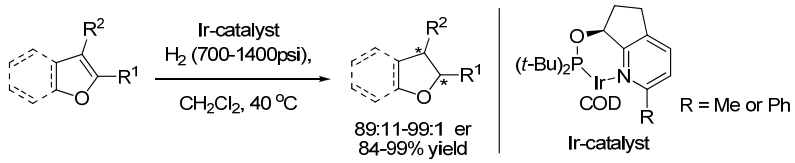
Metal Complex	PG	Substitution Pattern	Yield (%)	er
Ru(η^3-methylallyl)$_2$(cod)	Boc	2- and 3- substituted	85-99	93:7-97:3
[Rh(nbd)$_2$]SbF$_6$	Ac	2-substituted	83-98	93:7-97:3
[Rh(nbd)$_2$]SbF$_6$	Ts	3-substituted	71-96	97:3-99:1

Furans and Benzofurans

The first attempt at catalytic asymmetric hydrogenation of furans was reported by Takaya and co-workers in 1995.[23] 2-Methylfuran is reduced to (*S*)-2-methyltetrahydrofuran with moderate enantioselectivity (75:25 er) using $Ru_2Cl_4[(R)\text{-BINAP}]_2(NEt_3)$ as catalyst. Subsequent studies focused on developing chiral rhodium catalyst,[5a] but these Rh-catalysts suffer from low conversion and poor enantioselectivities.

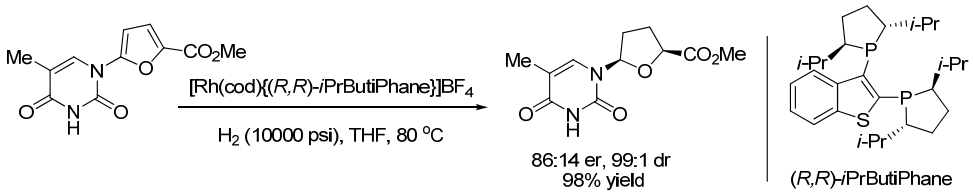
A significant breakthrough is the development of an Ir-catalyst with pyridine-phosphinite ligand by Pfaltz and co-workers (Scheme 12).[24] The hydrogenation of furans and benzofurans proceeds with good yield (84-99%) and enantioselectivities (89:11-99:1 er). The choice of the substituents at the phosphorus atom in the ligand strongly affects the catalytic activity as well as the enantioselectivity. The ligand with a bulky electron-rich $(t\text{-Bu})_2P$ group is found to be the best ligand.

Scheme 12. Ir-Catalyzed Enantioselective Hydrogenation of Furans and Benzofurans



Albert and co-workers reported the rhodium-catalyzed asymmetric hydrogenation of 5-thyminyl-2-furoate (Scheme 13).[25] Using a DuPHOS-type bisphosphine ligand, *i*Pr-ButiPhane, the reduction yields the cisproduct with excellent diastereoselectivity (99:1 dr) and moderate enantioselectivity (86:14 er). Surprisingly, no reduction of the thymine moiety is observed in the transformation. However, no expanded substrate scope is reported for this Rh-catalyzed asymmetric hydrogenation of furans.

Scheme 13. Rh-Catalyzed Asymmetric Hydrogenation of Furan Derivative



CONCLUSION

The asymmetric hydrogenation of heteroarenes has received growing interest in the past decade, due in part to the fundamental challenges as well as to the potential utility in organic synthesis. The use of bicyclic heteroarenes and the introduction of secondary coordinating groups or a chiral auxiliary have aided in the asymmetric hydrogenation of a variety of heteroaromatic

compounds. Despite these recent advances, the development of synthetically useful methods is still in its infancy and is currently limited by substrate scope and lack of product complexity. Further mechanistic understanding and methodological exploration will likely advance the synthetic utility of this class of hydrogenation and bring increased attention to this challenging area.

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