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ASYMMETRIC HYDROGENATION OF SIX-MEMBERED MONOCYCLIC *N*-HETEROAROMATIC COMPOUNDS

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Abstract – Six-membered chiral cyclic amines are important skeletal structures found in natural products as well as bioactive species. Asymmetric hydrogenation of six-membered *N*-heteroaromatic compounds is considered one of the most straightforward protocols for preparing six-membered chiral cyclic amines, because asymmetric hydrogenation is an atom economical reaction and applicable to industrial scales. In this review, we summarize the development of asymmetric hydrogenation of six-membered *N*-heteroaromatic compounds, such as pyridines, pyrazines, pyrimidines, and pyridones.

1. INTRODUCTION

Chiral cyclic amines are important molecular motifs that are abundant in natural alkaloids and biologically active compounds, and are key intermediates for preparing agrichemicals, drugs, fragrances, and so on. Accordingly, intensive synthetic studies have been directed toward not only constructing such cyclic amine skeletons, but also controlling the stereochemistry on poly-substituted cyclic amines. Although asymmetric hydrogenation of *N*-heteroaromatic compounds is a rational and straightforward synthetic route that is environmentally benign, atom economical, and industrially applicable, the reduction of *N*-heteroaromatic compounds is considered difficult due to their aromaticity. Recently, optically active cyclic amines were prepared by asymmetric hydrogenation of six-membered *N*-heteroaromatic compounds, such as quinolines[1] and quinoxalines,[2] and five-membered compounds, such as indoles,[3] imidazoles,[4] and pyrroles,[5] using transition metal catalysts bearing chiral ligands (Figure 1).[6] In this review, we summarize the development of asymmetric hydrogenation of six-membered *N*-heteroaromatic compounds, such as pyridines, pyrazines, pyrimidines, and pyridones.

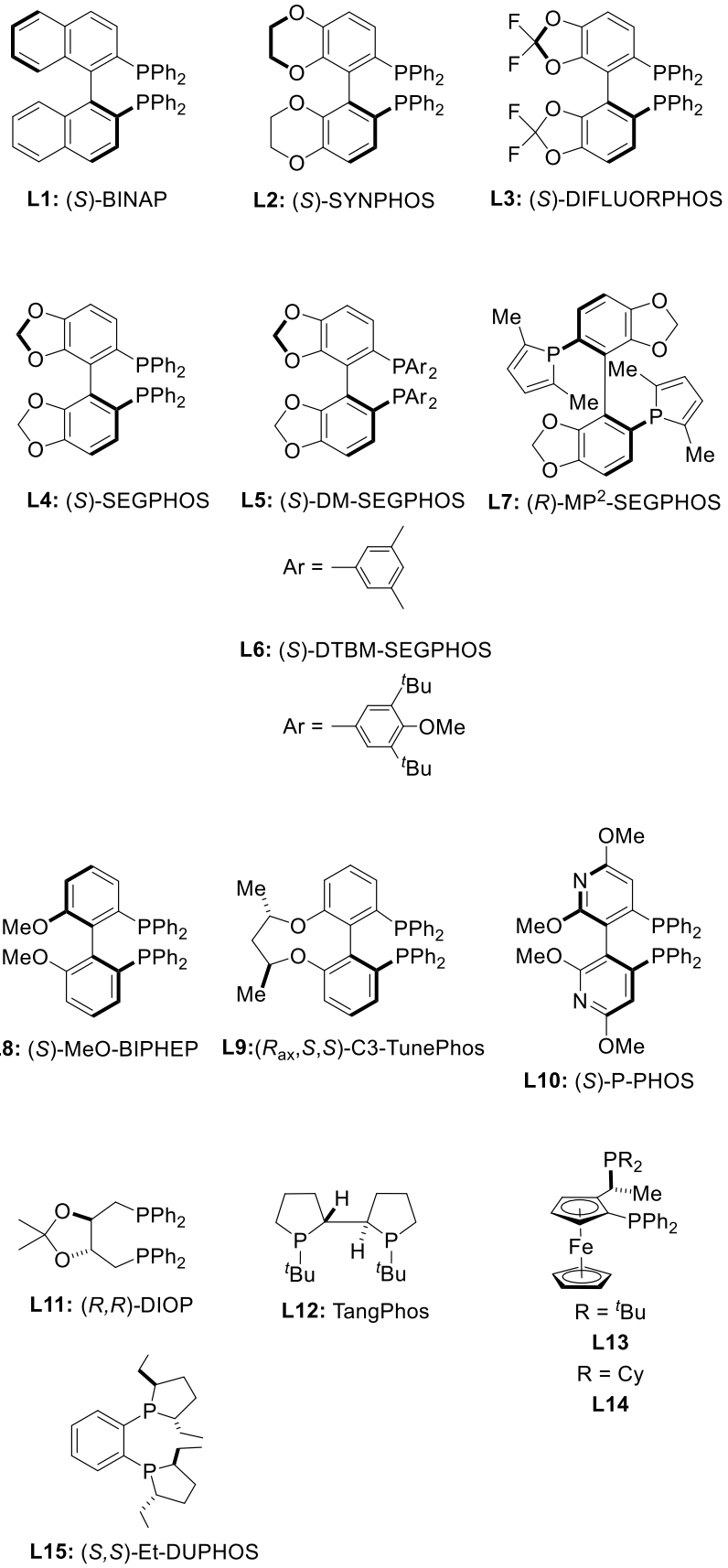
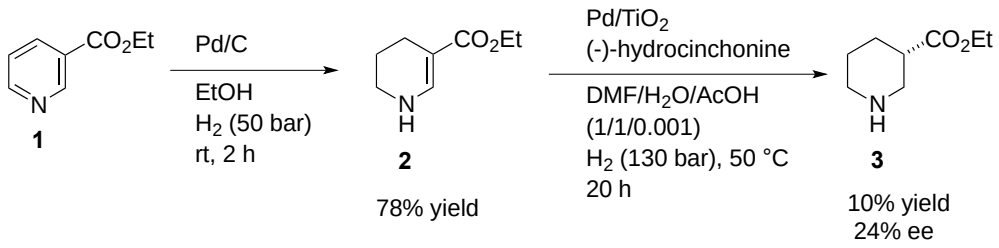


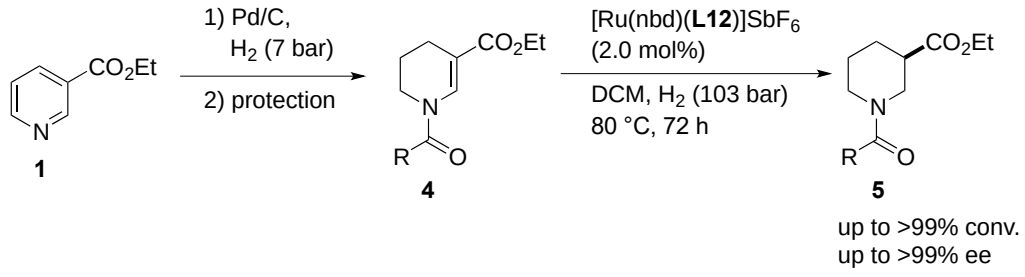
Figure 1. Chiral Diphosphine Ligands

2. DEAROMATIZATION OF PYRIDINES FOLLOWED BY ASYMMETRIC HYDROGENATION

Early reports of the asymmetric hydrogenation of pyridines were categorized into a common strategy of (I) dearomatization, where the pyridine π-conjugated system was first partially broken by appropriate reduction, followed by (II) asymmetric hydrogenation of the resulting cyclic olefins. Studer *et al.* applied heterogeneous catalysts for asymmetric hydrogenation of ethyl nicotinate (**1**): in the first reduction, a heterogeneous palladium catalyst afforded ethyl 1,4,5,6-tetrahydropyridine-3-carboxylate (**2**), whose subsequent asymmetric hydrogenation was catalyzed by another heterogeneous palladium catalyst modified with (-)-hydrocinchonine to give ethyl piperidine-3-carboxylate (**3**) in 24% ee (Scheme 1).[7] Zhang *et al.* later modified the second step of Studer's original synthetic route by introducing an *N*-protecting group, and asymmetric hydrogenation of *N*-acylated vinylogous amides **4** (R = Me, Ph, ^{t}Bu, OMe, OBn, and O^{t}Bu) was achieved by a rhodium(I)/TangPhos catalyst system to give the corresponding amides **5** in up to 99% ee (Scheme 2).[8] Both examples required the formation of cyclic enamines, which were stabilized by the conjugation of the C=C bond and ester groups prior to the final asymmetric hydrogenation. This was attributed to the general instability and easy aromatization of dihydropyridines.[9] Tetrahydropyridines were strategically used for subsequent hydrogenation.



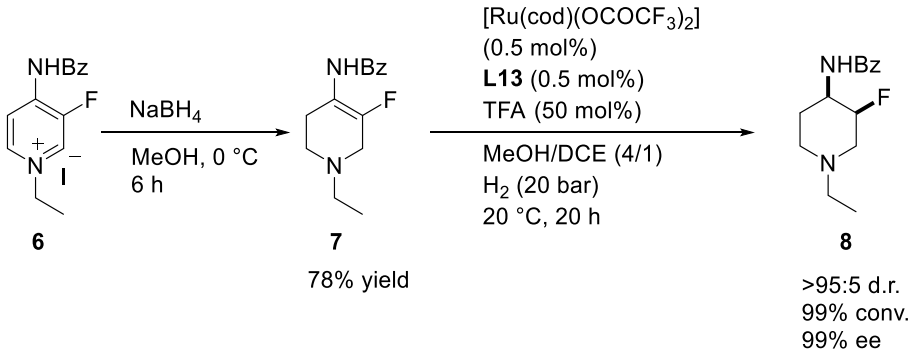
Scheme 1. Two-step Hydrogenation of Ethyl Nicotinate (**1**)



Scheme 2. Asymmetric Hydrogenation of *N*-Acyl Vinylogous Amides **4**

On the other hand, Stumpf *et al.* synthesized fluoropiperidine **8** by two-step reductions starting from pyridinium salt **6**. The first step was a hydride reduction by $NaBH_4$ in MeOH to give **7** as a partially hydrogenated product, which was further hydrogenated by a catalyst system of

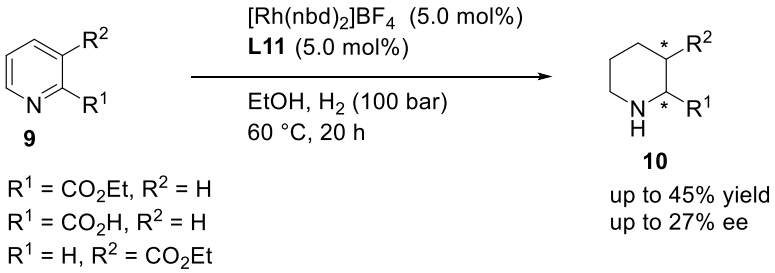
[Ru(cod)(OCOCF$_3$)$_2$]/JOSIPHOS to give **8** with high enantioselectivity (99% ee) while maintaining the fluorine group intact (99% of F content) (Scheme 3).[10]



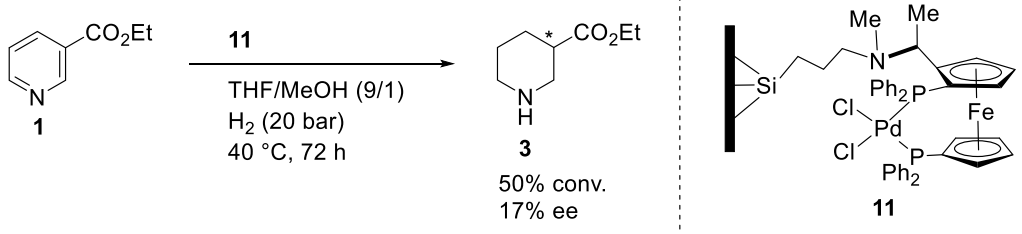
Scheme 3. Synthesis of *N*-[(3*S*,4*R*)-1-Ethyl-3-fluoropiperidin-4-yl]benzamide (**6**)

3. DIRECT ASYMMETRIC HYDROGENATION OF PYRIDINES

In general, direct asymmetric hydrogenation of pyridines is quite difficult because of the coordination of the products, such as piperidines, to catalytically active metal centers and unpredictable racemization through tautomerization among partially hydrogenated imines and enamines. There are two reports of direct asymmetric hydrogenation of nicotinic esters **9**: one was a homogeneous catalyst system, in which [Rh(nbd)$_2$]BF$_4$/(*R*,*R*)-DIOP served as a catalyst for the direct asymmetric hydrogenation of **9** to give the corresponding piperidine derivatives **10** in moderate conversion and with low enantioselectivity (up to 27% ee) (Scheme 4);[11] and the other was a heterogeneous palladium catalyst supported on mesoporous silica **11** for asymmetric hydrogenation of **1**, giving **3** in 17% ee (Scheme 5).[12]

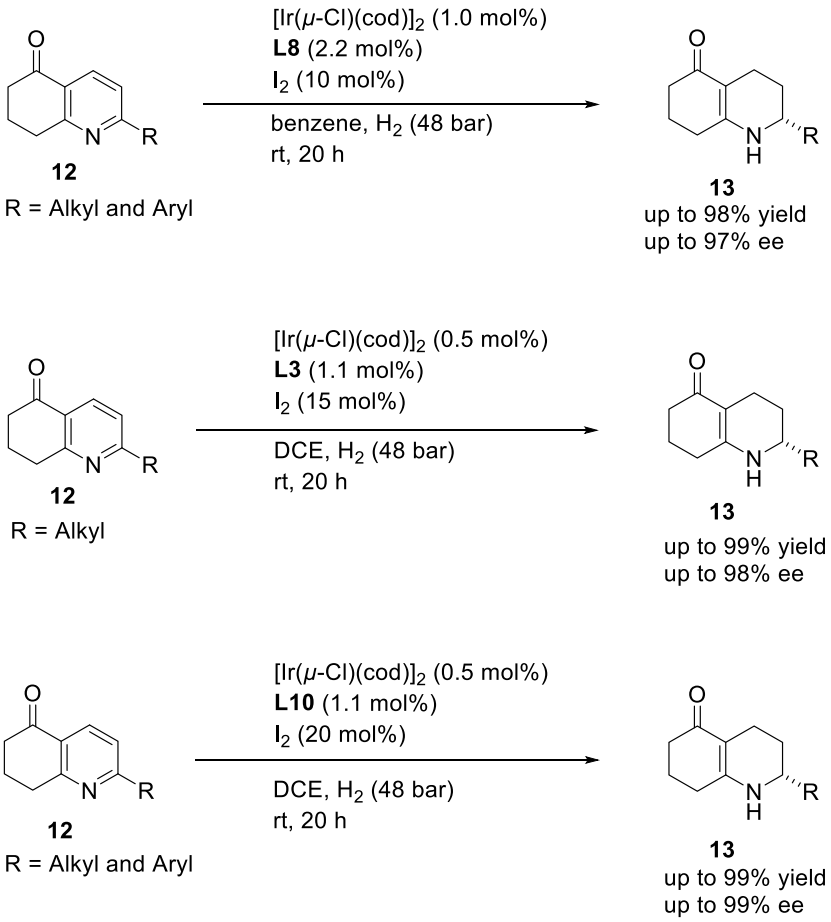


Scheme 4. Asymmetric Hydrogenation of Pyridine Derivatives **9**



Scheme 5. Asymmetric Hydrogenation of Ethyl Nicotinate (**1**) Using **11**

A catalyst system of [Ir(μ-Cl)(cod)]$_2$/(*S*)-MeO-BIPHEP was applied for asymmetric hydrogenation of 7,8-dihydro-quinolin-5(6*H*)-ones **12** to give the corresponding partially hydrogenated cyclic olefins **13**, conjugated α,β-unsaturated ketones with excellent enantioselectivities (up to 97% ee).[13] Similarly, use of other chiral diphosphine ligands such as (*R*)-DIFLUORPHOS (**L3**) and (*S*)-P-PHOS (**L10**) afforded **13** in up to 99% ee with S/C ratio up to 1000 (Scheme 6).[14,15] In these reactions, I_2 functioned as an oxidant to generate iridium(III) species by oxidative addition[16,17]

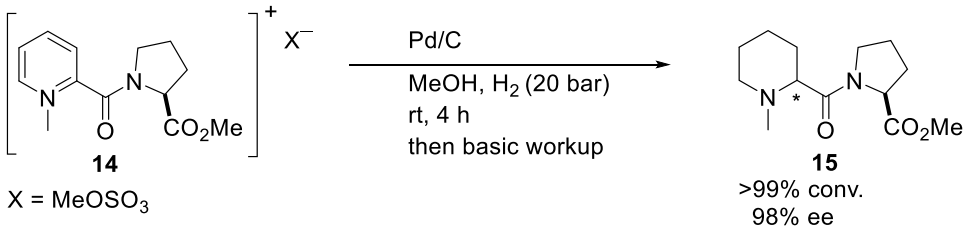


Scheme 6. Asymmetric Hydrogenation of **12**

4. ASYMMETRIC HYDROGENATION OF PYRIDINIUMS

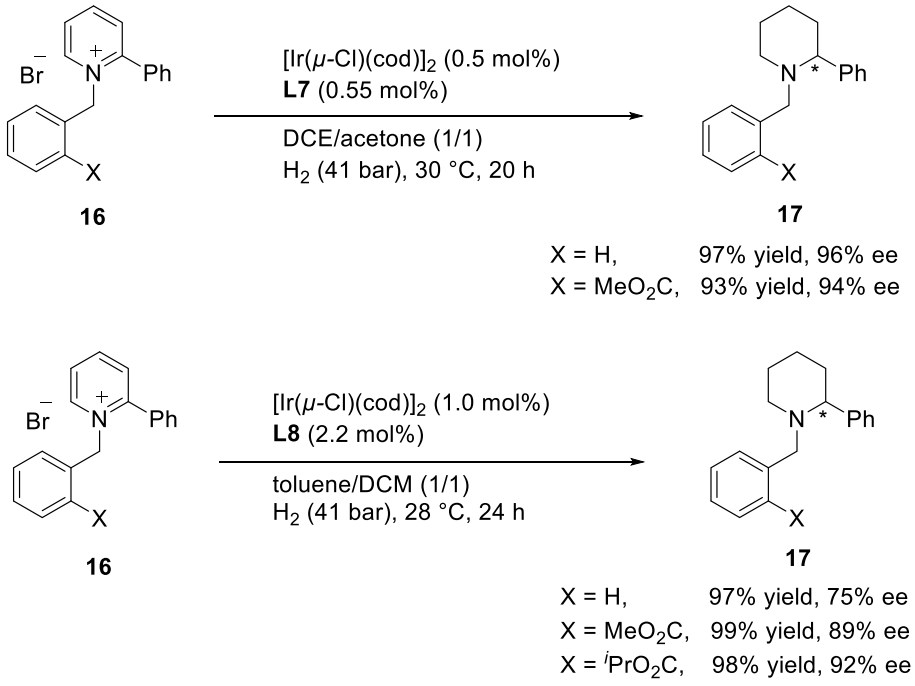
N-Protection

Introduction of an alkyl group, such as methyl and benzyl group, onto a nitrogen atom of pyridines to give pyridinium cation dramatically improved the catalytic performance for hydrogenation in terms of decreasing the charge density of the pyridine ring, and preventing the tight coordination of a nitrogen atom of the product amines to a catalyst. The first example of such an alkylation strategy was reported in a heterogeneous catalyst system in which hydrogenation of *N*-methylated pyridinium salt **14** proceeded smoothly and asymmetric induction depended on the auxiliary (*S*)-proline moiety (Scheme 7).[18]



Scheme 7. Asymmetric Hydrogenation of *N*-Methylated Pyridinium Salt **14**

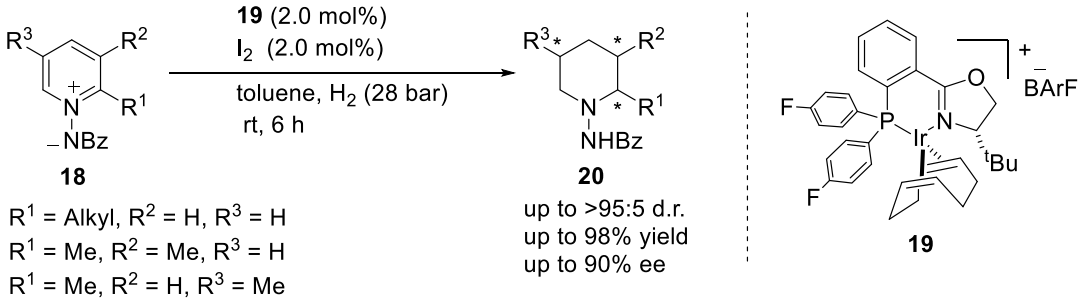
Two research groups independently reported the same asymmetric hydrogenation of **16** using iridium catalysts combined with different chiral diphosphine ligands such as (*R*)-MP^2-SEGPHOS (**L7**) and (*S*)-MeO-BIPHEP (**L8**) (Scheme 8).[19,20] In the case of [IrCl(cod)]$_2$/(*S*)-MeO-BIPHEP, (carboalkoxy)methyl substituents at the ortho position of the benzyl group led to slight improvements in enantioselectivity due to coordination of the (carboalkoxy)methyl substituents. Recently, Zhou and co-workers applied the asymmetric hydrogenation of *N*-protected pyridinium salts to 3-hydroxypyridinium salts to synthesis *trans* 6-substituted piperidin-3-ols using [IrCl(cod)]$_2$/(*S,S*)-f-Binaphane.[21]



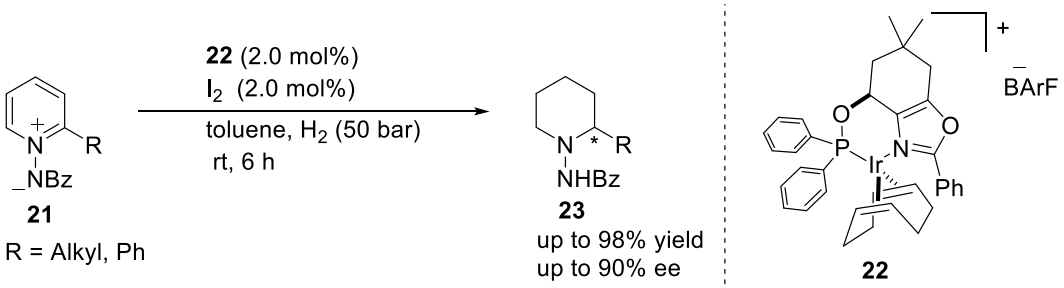
Scheme 8. Asymmetric Hydrogenation of Pyridinium Salts **16**

Charette *et al*. demonstrated an asymmetric hydrogenation of activated pyridine derivatives, *N*-iminopyridinium ylides **18**, mediated by an iridium complex **19** bearing phosphinooxazoline (Scheme 9).[22] The benzoylimino moiety served as both an activator of pyridines and a directing group for the

catalyst. Later, Andersson and collaborators reported the same asymmetric hydrogenation of *N*-iminopyridinium ylides **21** to give **23** in up to 90% ee using an iridium catalyst **22** (Scheme 10).[23]



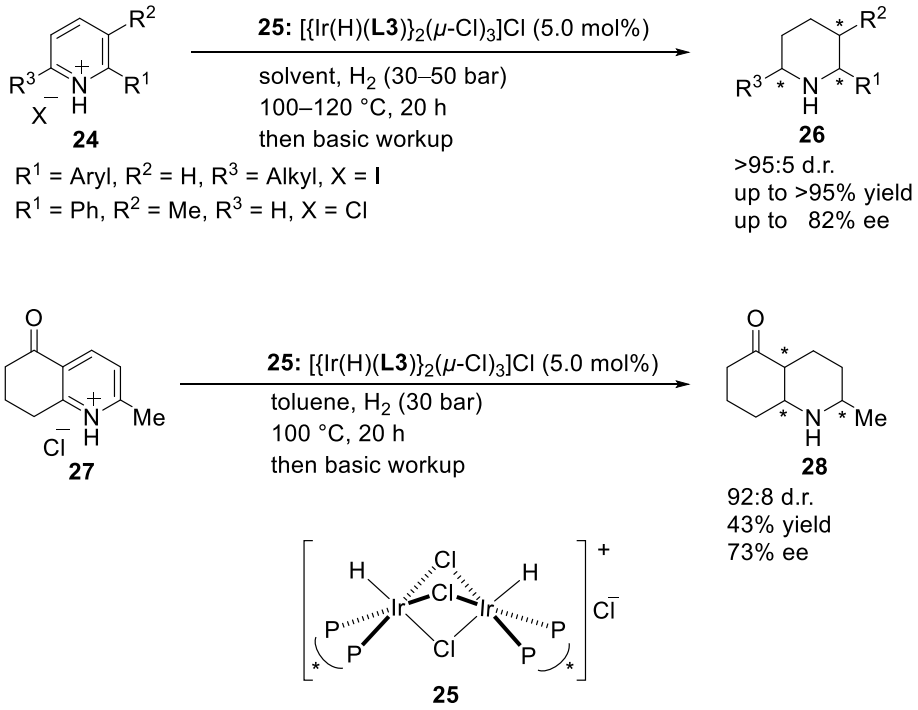
Scheme 9. Asymmetric Hydrogenation of *N*-Iminopyridinium Ylides **19**



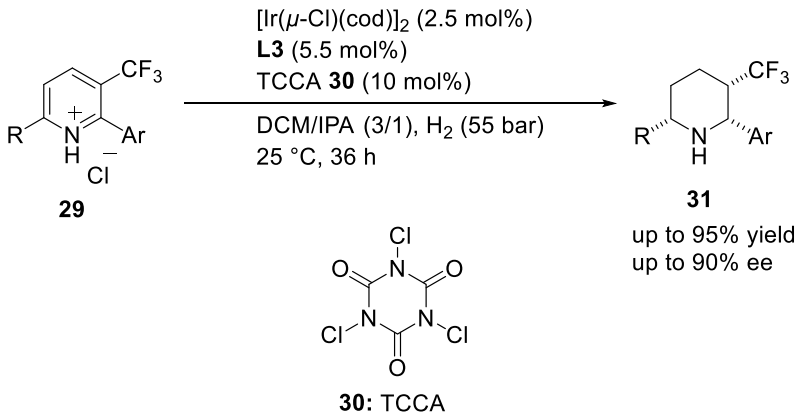
Scheme 10. Asymmetric Hydrogenation of *N*-Iminopyridinium Ylides **22**

Salt Formation by Brønsted Acids

Brønsted acids such as HX (X = Cl, Br, I) and acetic acid are commonly used to form the corresponding pyridinium salts as well as isoquinolinium salts. We previously reported that asymmetric hydrogenation of 2-substituted quinolinium HX salts afforded better enantioselectivity than that of the corresponding neutral substrates.[24] Recently, we found that asymmetric hydrogenation of pyridinium salts proceeded smoothly to give the corresponding products in high enantioselectivity.[25] Asymmetric hydrogenation of multi-substituted pyridinium salts **24** was hydrogenated by dinuclear iridium(III) catalysts **25** bearing chiral atropisomeric diphosphine ligands to give the corresponding piperidines **26** after a simple basic work up (Scheme 11). In addition, trisubstituted pyridine **27** was also hydrogenated to give the corresponding piperidine **28** with three chiral centers. In this reaction, we observed a unique chemoselectivity. Pyridine rings were hydrogenated with a tolerance for carbonyl groups. Zhou *et al.* applied the HCl salt formation strategy to the asymmetric hydrogenation of trisubstituted pyridinium salts **29**, giving **31** in up to 90% ee (Scheme 12).[26] To improve the catalytic activity and enantioselectivity, 10 mol% of amount of TCCA (**30**) was added as a halogen source which oxidize a low-valent iridium species.[17,27]

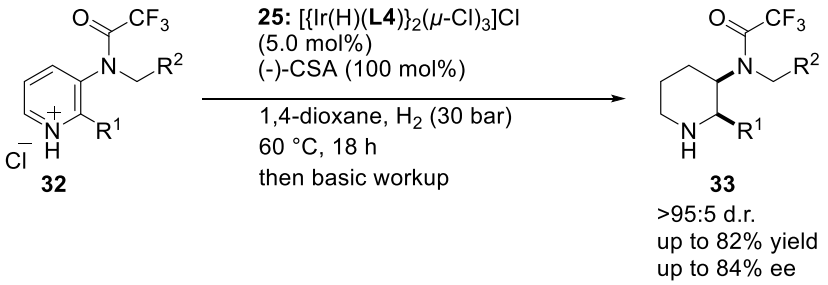


Scheme 11. Asymmetric Hydrogenation of Pyridinium Salts **24** and **27** Catalyzed by Iridium Complex **25**



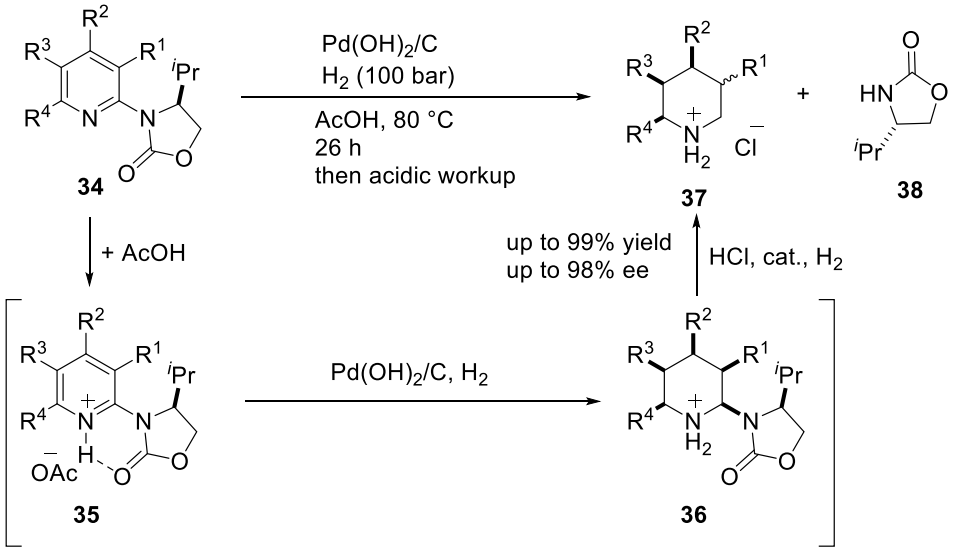
Scheme 12. Asymmetric Hydrogenation of Pyridinium Salts **29**

We also reported the synthesis of NK1 receptor antagonist derivatives **33** using Ir-catalyzed asymmetric hydrogenation of 3-amido-2-arylpyridinium salts **32**. We found that the addition of (-)-10-camphorsulfonic acid [(-)-CSA] and the use of trifluoroacetyl amide resulted in a higher yield and enantioselectivity in an asymmetric hydrogenation of 3-amido-2-arylpyridinium salts (Scheme 13).[28]

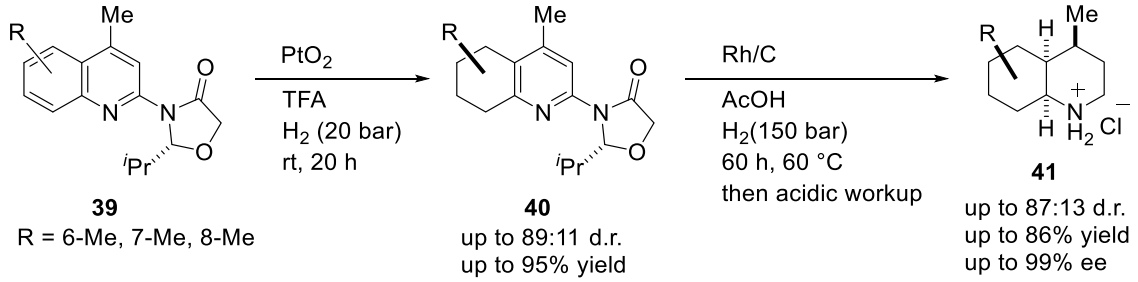


Scheme 13. Synthesis of NK1 Receptor Antagonist Derivatives Using Ir-Catalyzed Asymmetric Hydrogenation of **32**

Glorius *et al.* reported the hydrogenation of pyridines **34** bearing a chiral oxazolidinone moiety at the 2-position catalyzed by heterogeneous Pd/C, producing chiral piperidines **37** with highly controlled multiple stereogenic centers (Scheme 14).[29] In this reaction, it was predicted that the initial formation of the acetate salts of **35** was followed by hydrogenation to give the corresponding 2-oxazolidinonyl piperidines **36**, which were spontaneously converted to the products **37** by the elimination of (*S*)-4-isopropyloxazolidin-2-one (**38**). Similarly, Glorius *et al.* reduced quinoline derivatives **39** with a chiral oxazolidinone moiety at the 2-position: the initial ring-reduction was conducted by PtO_2 to give 4-alkyl-5,6,7,8-tetrahydroquinolines **40**, whose further hydrogenation afforded **41** with high *cis*-selectivity and high enantioselectivity after an acidic workup (Scheme 15).[30]



Scheme 14. Hydrogenation of Pyridines bearing Chiral Auxiliaries **34**

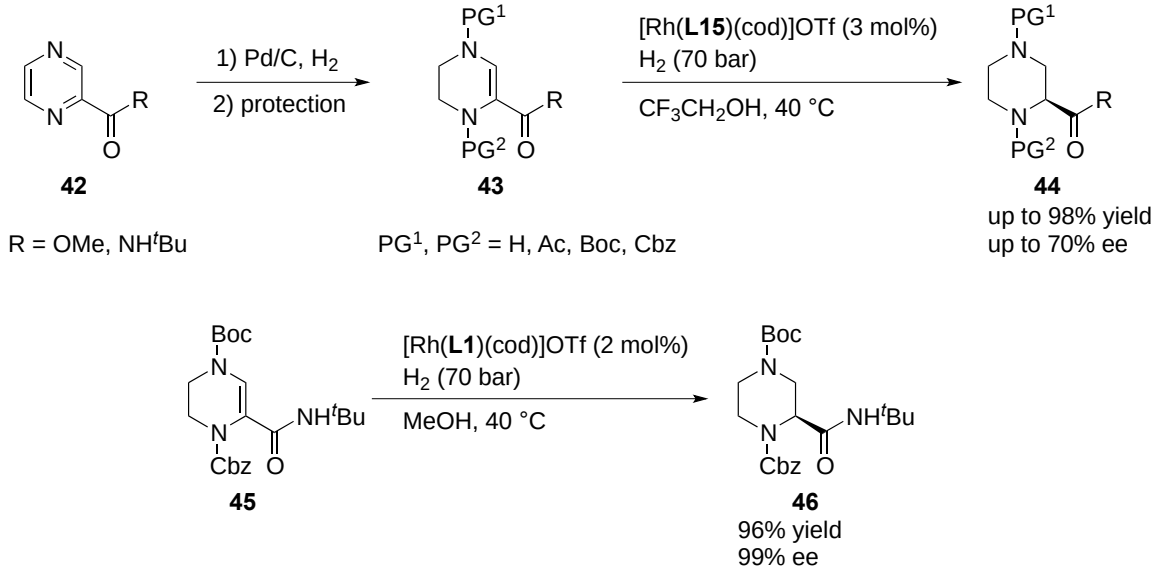


Scheme 15. Rh/C Catalyzed Hydrogenation of **40**

5. ASYMMETRIC HYDROGENATION OF OTHER SIX-MEMBERED *N*-HETEROAROMATIC COMPOUNDS

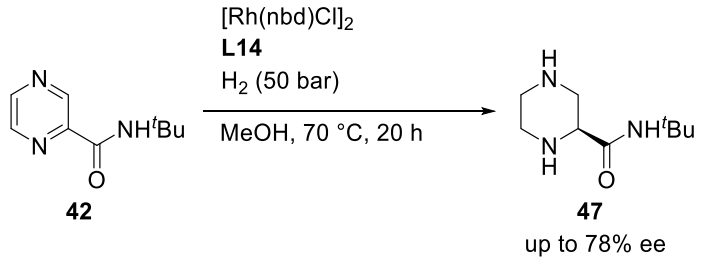
Asymmetric Hydrogenation of Pyrazines

Asymmetric hydrogenation of pyrazines was developed for preparing chiral piperazine structures that are often found in bioactive compounds. The asymmetric hydrogenation of amido-substituted pyrazines is an especially attractive protocol as chiral amido-substituted piperazines comprise a part of the skeleton of Indinavir, an HIV-protease inhibitor. Rossen *et al*. reported the asymmetric hydrogenation of ester- and amido-substituted pyrazines using a two-step reduction. The first reduction was the hydrogenation of pyrazines **42** and subsequent protection of two NH groups to give conjugated alkenes **43**. The second reduction was the asymmetric hydrogenation of **43** to give ester- and amido-substituted chiral piperazines **44** (Scheme 16).[31] In this reaction, protecting groups on the nitrogen atoms of **43** were indispensable for increasing the enantioselectivity: amido-substituted conjugated alkenes **45** protected by Boc and Cbz



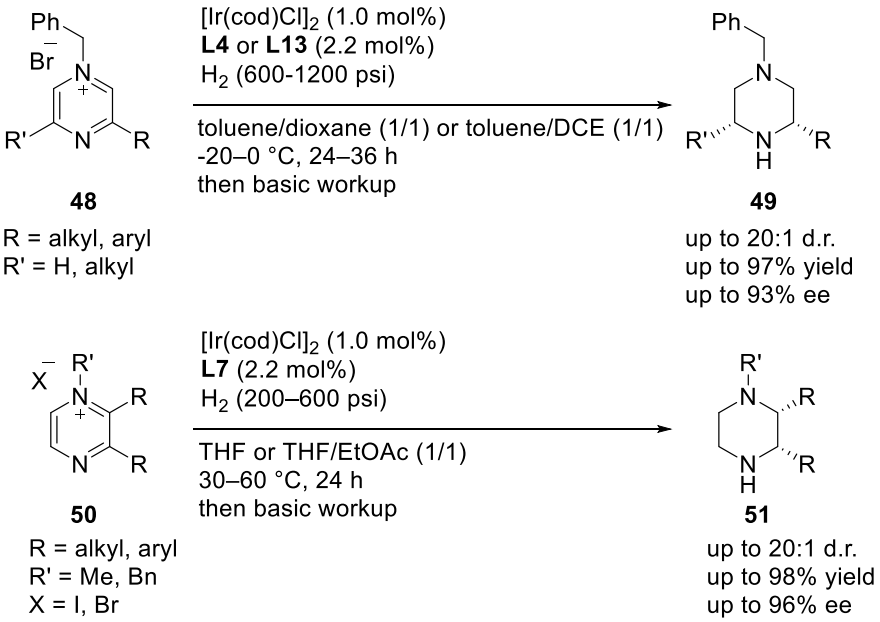
Scheme 16. Two-step Asymmetry Hydrogenation of Ester- and Amido-substituted Pyrazines **42**

groups resulted in excellent enantioselectivity (99%) to afford **46** in 96% yield. As a more straightforward method, Fuchs reported the asymmetric hydrogenation of the pyrazine **42** catalyzed by a rhodium(I) complex bearing a chiral diphosphine ligand **L14** to give the amido-substituted chiral piperazine **47** in 78% ee (Scheme 17).[32]



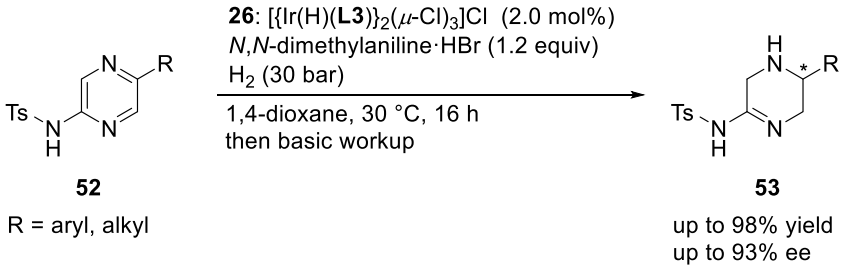
Scheme 17. Rh-Catalyzed Asymmetric Hydrogenation of Amido-substituted Pyrazine **42**

In 2016, Zhou *et al.* reported that formation of the pyrazinium salts with benzyl bromide and iodomethane facilitated asymmetric hydrogenation catalyzed by iridium(I) complexes bearing chiral diphosphine ligands at low temperature. This reaction was applied to the wide range of mono- and disubstituted pyrazines **48** and **50** to give the corresponding mono- and disubstituted piperazines **49** and **51**, respectively, in high yields and with high enantioselectivities (Scheme 18).[33]



Scheme 18. Asymmetric Hydrogenation of Pyrazinium Salts **48** and **50** Catalyzed by Iridium(I) Complexes with Chiral Diphosphine Ligands

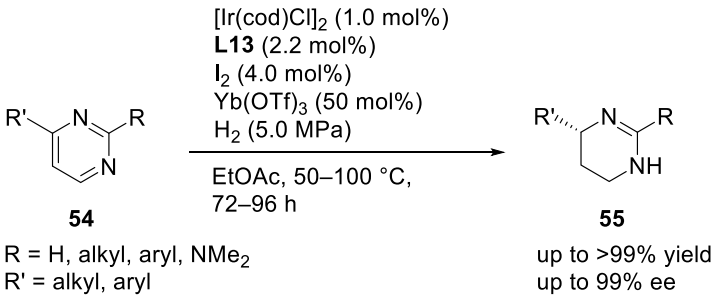
Quite recently, we found that tosylamido-substituted pyrazines **52** are hydrogenated at ambient temperature by dinuclear iridium(III) complex **26** to give tetrahydropyrazines **53** in high yields and with high enantioselectivities (Scheme 19).[34] Because the basicity of **52** is too low to form HCl salts, we added *N*,*N*-dimethylanilinium bromide to trap the amine products that severely retarded the catalytic reaction.



Scheme 19. Asymmetric Hydrogenation of Tosylamido-substituted Pyrazines **52** Catalyzed by Iridium(III) Complex **26** with *N*,*N*-Dimethylanilinium Bromide

Asymmetric Hydrogenation of Pyrimidines

Kuwano *et al.* reported an asymmetric hydrogenation of pyrimidines **54** to produce chiral cyclic amidines **55** (Scheme 20).[35] This reaction requires lanthanide triflates as the Lewis acid to improve not only the catalytic activity, but also the enantioselectivity, as Lewis acids prevented the aromatization of dihydrogenated intermediates. Furthermore, the coordination of pyrimidines to lanthanide triflate facilitated the initial reduction of the N=C double bond of pyrimidines.

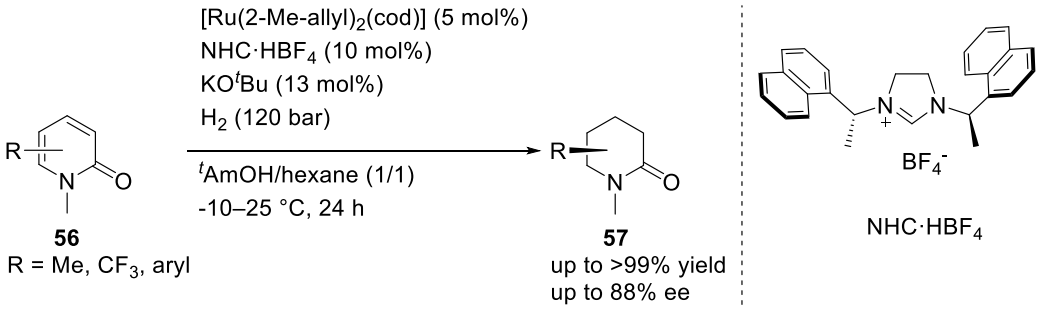


Scheme 20. Asymmetric Hydrogenation of Pyrimidines **54** Catalyzed by Iridium(I) Complex

Asymmetric Hydrogenation of Pyridones

Glorius *et al*. reported an asymmetric hydrogenation of *N*-protected pyridones **56** with the Ru complex bearing a chiral NHC ligand to give *N*-protected dimethylpiperidin-2-one **57** (Scheme 21).[36] Although 1,6-dimethylpyridone afforded 1,6-dimethylpiperidin-2-one in excellent yield (>99%) and with good enantioselectivity (88% ee) in this catalyst system, 1,3-, 1,4-, and 1,5-dialkyl-substituted, and

aryl-substituted pyridones were not competent substrates and the corresponding products had low enantioselectivity. In contrast, Consiglio *et al.* and Wills *et al.* attempted an asymmetric hydrogenation of pyridones with Ru catalysts bearing chiral diphosphine ligand **L8** and chiral diamido ligand, respectively; however, the products were obtained in low yield or with low enantioselectivity.[37]



Scheme 21. Asymmetric Hydrogenation of Pyrimidone **56** Catalyzed by Ruthenium Complex

ACKNOWLEDGEMENT

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