RECENT ADVANCES IN CATALYTIC ASYMMETRIC SYNTHESIS OF CHIRAL PYRIDINE DERIVATIVES

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Abstract. *Chiral pyridines are important structural motifs widely found in pharmaceuticals, biologically active natural products, and chiral ligands. However, their catalytic asymmetric synthesis is challenging as pyridyl substrates are not tolerated in many established catalytic asymmetric reactions. In this review, the representative catalytic asymmetric reactions that work well for the synthesis of chiral pyridine derivatives are briefly summarized.*

Contents

1. Introduction

Pyridine is one of the most important heteroarenes in chemistry and medicine. In particular, chiral pyridine-containing functional molecules such as pharmaceuticals, natural products, and chiral ligands are of great importance (Figure 1).[1] Therefore, development of efficient methods to access pyridine-containing chiral architectures is highly desirable. Asymmetric catalysis has been recognized as an ideal approach to the construction of optically active compounds, and great success has been achieved in the past decades in this realm. However, catalytic asymmetric synthesis of chiral pyridine derivatives proves to be challenging due to the unique properties of pyridine, such as the Lewis basicity, coordinating ability of pyridine nitrogen, and π-deficient property. These properties either lead to catalyst deactivation or low reactivity of the reaction intermediate, thus resulting in poor compatibility with the catalytic system. Nonetheless, a range of catalytic asymmetric reactions that works well for pyridyl substrates have been disclosed. This short review includes the representative research works published up to the end of 2022, and the catalytic asymmetric reactions showing good compatibility with pyridines are summarized according to the reaction type. The representative reactions include: 1) catalytic asymmetric addition to unsaturated double bonds; 2) catalytic asymmetric reduction; 3) catalytic asymmetric cross-coupling; 4) catalytic asymmetric C−H functionalization.

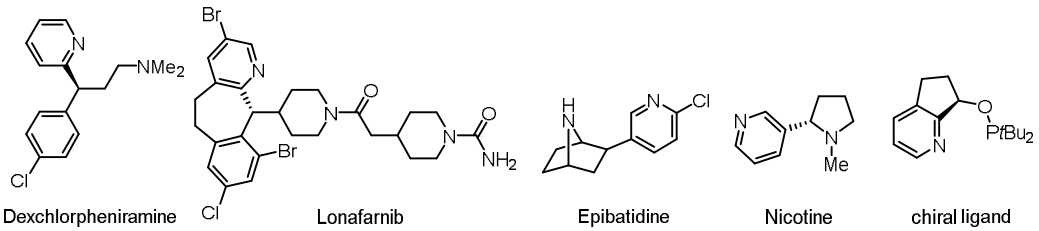
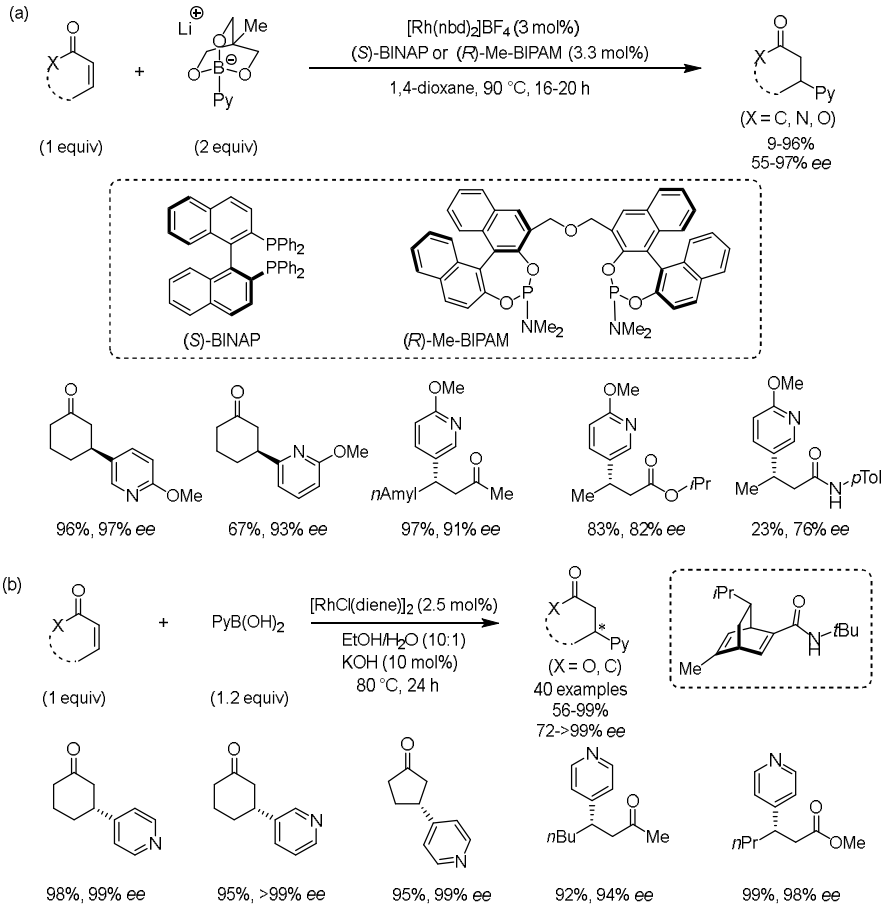


Figure 1. Representative chiral pyridine derivatives.

2. Catalytic asymmetric addition to unsaturated double bonds

Catalytic asymmetric addition to unsaturated double bonds represents one of the most versatile methods for the rapid construction of diverse chiral compounds. In recent years, many effective strategies have been developed to construct chiral pyridine derivatives based on this type of transformation, mainly including catalytic asymmetric hydropyridylation of olefins, catalytic asymmetric addition to alkenyl pyridines, and catalytic asymmetric addition to aryl/pyridyl imines.

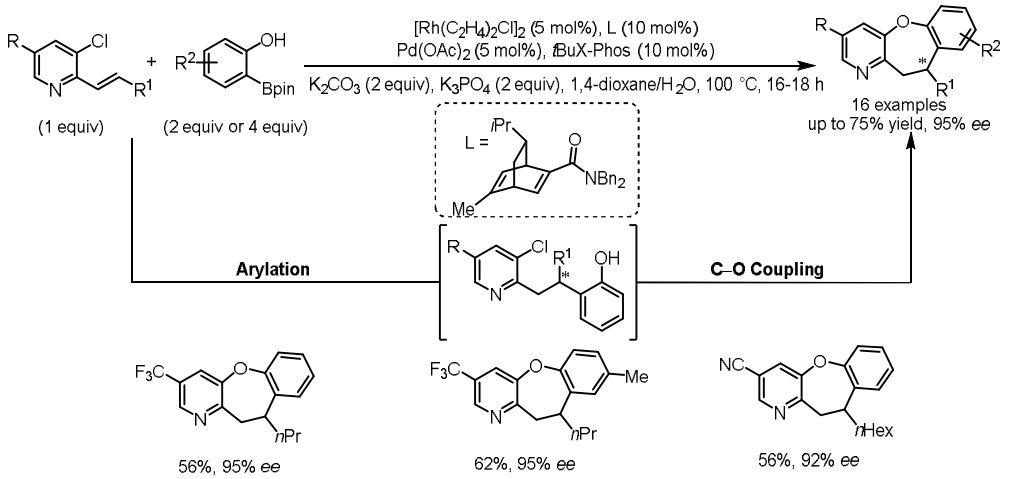
Catalytic asymmetric conjugate arylation of electron-deficient olefins with arylmetallic reagents provides a reliable approach to chiral molecules by installing the aryl moiety. Ideally, chiral pyridine derivatives can be obtained by using the pyridylmetallic reagents. However, extension of the arylmetallic reagents to pyridyl ones in the established systems is not easy. For instance, arylboron reagents are widely used in the asymmetric conjugate addition to electron-deficient olefins, but the pyridylboron reagents normally showed low reactivity. To address this issue, specially designed pyridylboron reagents (including lithium pyridyl(triol)borates and pyridyl *N*-methylimino diacetic acid boronates bearing a necessary blocking group next to the pyridine nitrogen) have been used. For example, Miyaura and coworkers[2] developed the rhodium-catalyzed asymmetric 1,4-addition of lithium pyridyl(triol)borates to *α,β*-unsaturated carbonyl compounds, and the OMe-substituent next to the pyridine nitrogen was found to be crucial (Scheme 1a).



Scheme 1. Catalytic asymmetric hydropyridylation of *α,β*-unsaturated carbonyl compounds.

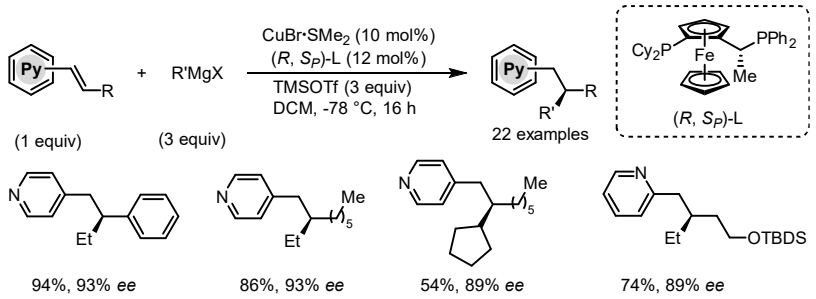
Boysen and coworkers also realized the catalytic asymmetric hydropyridylation of cyclohexanone, but only one entry using the 2-OMe-3-pyridylboron reagent was reported.[3] Recently, our group developed an efficient catalytic system for the rhodium-catalyzed asymmetric hydropyridylation of *α*,*β*-unsaturated carbonyl substrates. Pyridylboronic acids could be directly used and a wide range of *α*,*β*-unsaturated carbonyl substrates worked well (Scheme 1b). The use of bifunctional amide-diene ligand and alcohol solvent was found to be crucial for the success of the reaction.[4]

Electron-deficient azaarene-activated alkenes can be employed as the Michael acceptor, and the addition usually occurs regioselectively to generate chiral azaarenes bearing a *β*-stereogenic center.[5] Catalytic asymmetric addition to pyridine-activated alkenes have been successfully developed. In 2013, Lautens and coworkers[6a] developed a domino process leading to aza-dihydrodibenzoxepines by combining Rh-catalyzed asymmetric arylation of alkenyl pyridines and Pd-catalyzed intramolecular C–O coupling in one pot. Domino reactivity was discovered to depend on the electronics of the alkenyl pyridine, with electron-poor alkenyl pyridines producing optimal conversion into the desired products (Scheme 2). The same group also developed the combination of Rh-catalyzed asymmetric arylation of alkenyl pyridines with the Pd-catalyzed direct C–H arylation for the synthesis of chiral dihydrobenzoquinolines.[6b]



Scheme 2. Rh/Pd-catalyzed asymmetric synthesis of aza-dihydrodibenzoxepines from alkenyl pyridines.

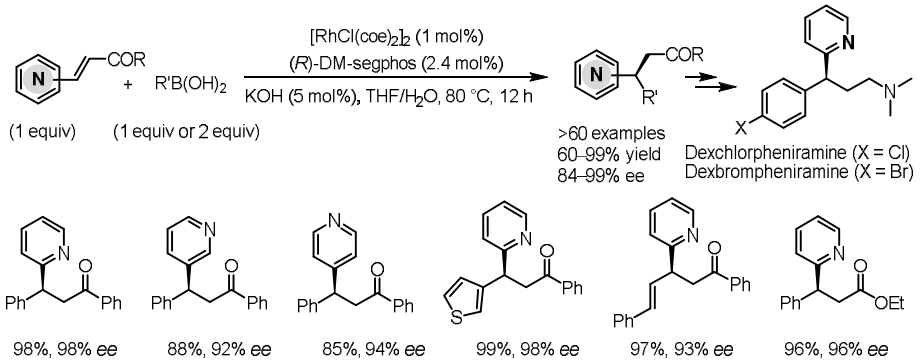
In 2017, Harutyunyan and coworkers[7] realized the catalytic asymmetric addition of Grignard reagents to poorly reactive *β*-substituted alkenyl pyridines (Scheme 3). The methodology involves reactivity enhancement of the alkenyl pyridine substrate *via* Lewis acid activation, and the enantioselectivity was controlled by the use of a chiral bisphosphine-ligated copper catalyst.



Scheme 3. Cu-catalyzed asymmetric addition of Grignard reagents to *β*-substituted alkenyl pyridines.

This method shows a broad substrate scope and good functional group tolerance, providing a useful access to chiral pyridines bearing a *β*-stereogenic center. A remaining challenge is that aryl Grignard reagents lead to poor enantioselectivity.

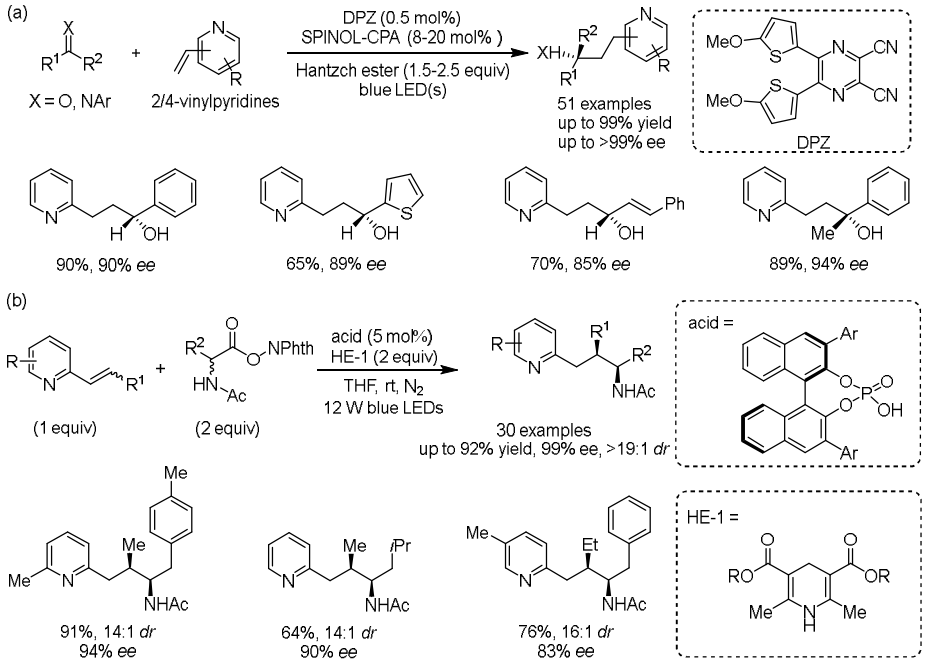
To construct chiral pyridines bearing an *α*-stereogenic center, the regioselectivity of the addition to alkenyl pyridines should be reversed. In 2020, our group developed a method for the construction of chiral pyridines bearing an adjacent stereogenic center by rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to carbonyl-activated alkenyl pyridines[8] (Scheme 4). The reaction features readily available reagents, commercially available catalyst/ligand, and a broad substrate scope with excellent enantiocontrol. Moreover, the method was successfully applied to the asymmetric synthesis of marketed drugs dexchlorpheniramine and dexbrompheniramine.



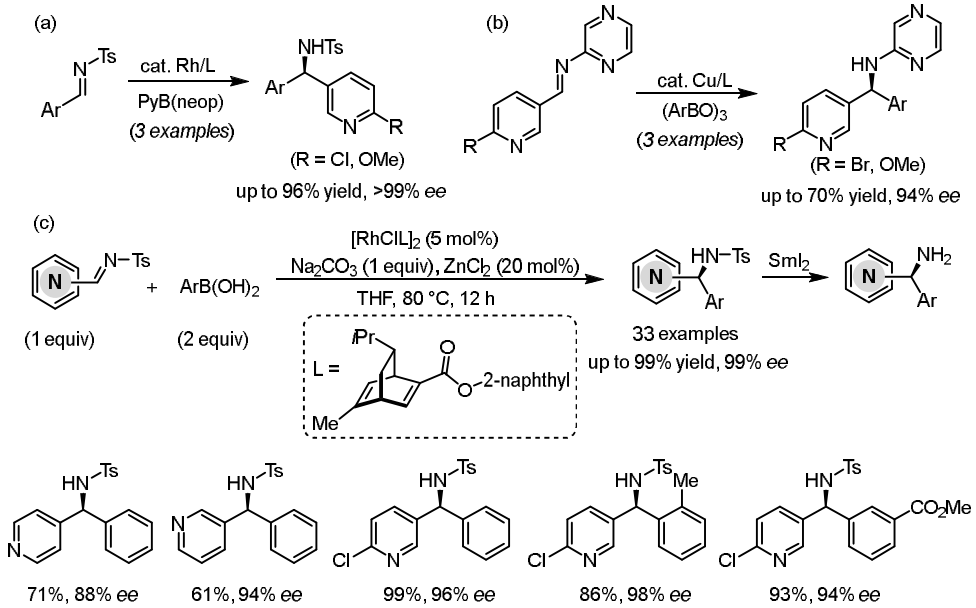
Scheme 4. Rh-catalyzed asymmetric addition of organoboronic acids to carbonyl-activated alkenyl pyridines.

In addition to the construction of stereocenters at the *α*- and *β*-positions of pyridine, the formation of enantioenriched *γ*-functionalized pyridines by conjugate addition to alkenyl pyridines is also viable. In 2019, Jiang and coworkers[9] developed an enantioselective addition of prochiral radicals to alkenyl pyridines *via* visible-light-driven cooperative photoredox and asymmetric catalysis. With a chiral Brønsted acid catalyst to activate the substrate and control the enantioselectivity, a series of prochiral ketyl and *α*-aminoalkyl radical species generated from aldehydes, ketones, and imines through single-electron transfer reduction could readily undergo conjugate addition to alkenyl pyridines, leading to various *γ*-secondary/tertiary hydroxyl- and amino-group substituted pyridines in high yields and good enantioselectivities (Scheme 5a). In 2022, Lu *et al.*[10] established a visible-light-induced, photocatalyst-free enantioselective hydroalkylation of alkenyl pyridines with chiral Brønsted acid catalysis. This approach provides highly efficient access to pharmaceutically important enantioenriched pyridine derivatives featuring adjacent *β* and *γ* tertiary stereocenters (Scheme 5b).

The asymmetric addition to carbon-nitrogen double bonds such as asymmetric pyridylation of imines and asymmetric addition to pyridyl imines provides opportunities for the synthesis of chiral pyridine derivatives featuring the amino group. Initially, chiral auxiliary and chiral reagents were usually used for the asymmetric synthesis.[11] The catalytic asymmetric pyridylation of imines was a challenging task, and the Lin group reported the rhodium-catalyzed asymmetric addition of 3-pyridylboronates to aryl imines.[12] However, the pyridyl reagent was limited to the 4-Cl/OMe-substituted 3-pyridyl ones (Scheme 6a). Zhou and coworkers developed the copper-catalyzed asymmetric arylation of 3-pyridyl imines with arylboroxines, but an unremovable pyrazine directing group was required (Scheme 6b).[13] In 2022, our group reported the rhodium-catalyzed asymmetric addition of simple arylboronic acids to pyridyl imines.[14] The catalytic system tolerates a range of pyridyl imines and arylboronic acids to produce the chiral pyridines in good yields and enantioselectivities. Moreover, the protective group could be easily removed to deliver the free amine product (Scheme 6c).



Scheme 5. Chiral pyridines bearing a γ-stereogenic center by asymmetric addition to alkenyl pyridines.

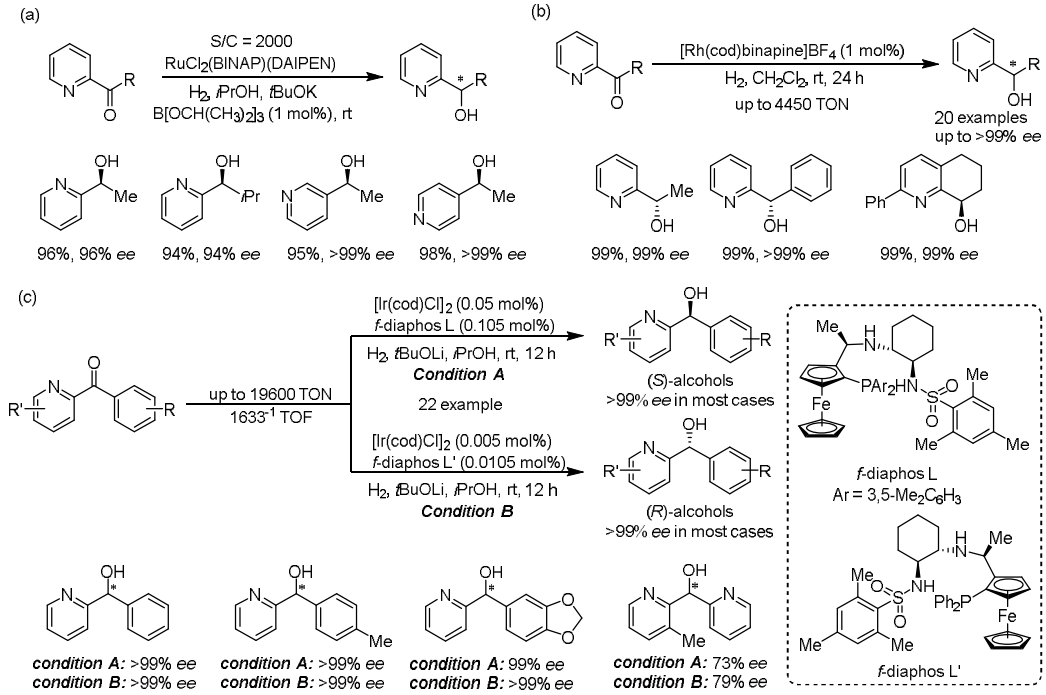


Scheme 6. Synthesis of chiral pyridines by catalytic asymmetric addition to imines.

3. Catalytic asymmetric reduction

Catalytic asymmetric reduction of pyridine-based ketones, olefins and imines provides a practical strategy for the synthesis of chiral pyridine derivatives. With an appropriate choice of chiral catalyst, several reductants such as hydrogen gas, boranes, and silanes can be used to achieve the asymmetric reduction of pyridyl substrates.

An early representative work was reported by Noyori[15] on the hydrogenation of pyridyl ketones with *trans*-$RuCl_2$[(*R*)-xylBINAP]-[(*R*)-daipen] as the catalyst and with the addition of isopropyl borate to inhibit pyridine coordination. However, this method is limited to the asymmetric reduction of alkyl-pyridyl ketones (Scheme 7a). Afterwards, several groups applied the chiral Ru catalyst in the asymmetric hydrogenation of aryl-pyridyl ketones, but only the *ortho*-substituted-aryl substrates showed high enantioselectivities.[16] In 2015, Zhang *et al.*[17] developed an effective method for the asymmetric hydrogenation of 2-pyridine alky/aryl ketones using [Rh(COD)binapine]BF_4 as the catalyst, affording 2-pyridine-alky/aryl alcohols in excellent yields and enantioselectivities (Scheme 7b). In 2019, Zhong *et al.*[18] presented an efficient and practical protocol for the highly enantioselective hydrogenation of the non-*ortho*-substituted 2-pyridyl aryl ketones by employing the Ir/*f*-diaphos catalytic system, affording chiral alcohols in up to >99% *ee* with a TON of up to 19600 and a TOF of 1633 h^{-1} (Scheme 7c).

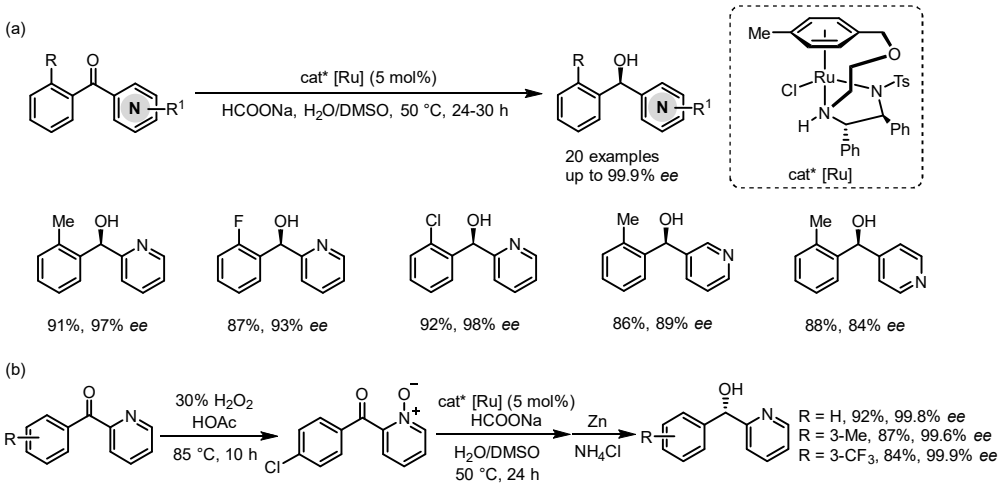


Scheme 7. Catalytic asymmetric hydrogenation of pyridyl ketones.

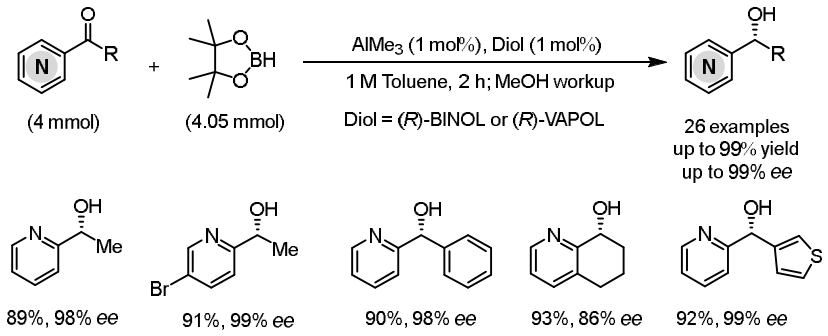
Asymmetric transfer hydrogenation is also a popular method for asymmetric reduction due to its operational simplicity and avoidance of the use of hazardous hydrogen gas and a pressure vessel. In 2017, Jiang *et al.*[19] developed an efficient asymmetric transfer hydrogenation of pyridyl-aryl ketones with a bifunctional oxo-tethered ruthenium complex as the catalyst and sodium formate as the reductant in aqueous solution (Scheme 8a). Interestingly, the reduction products with opposite configuration were obtained when non-*ortho*-substituted *N*-oxide of pyridyl aryl ketones were used (Scheme 8b).

In 2019, Rueping *et al.*[20] developed a versatile protocol for highly enantioselective hydroboration of 2-pyridyl ketones utilizing an in situ formed aluminum complex bearing readily available VANOL-,

VAPOL-, and BINOL-based ligands. The ligands could be fully recovered and reused. The protocol is suitable for a wide range of substrates and has a high tolerance to functional groups (Scheme 9).



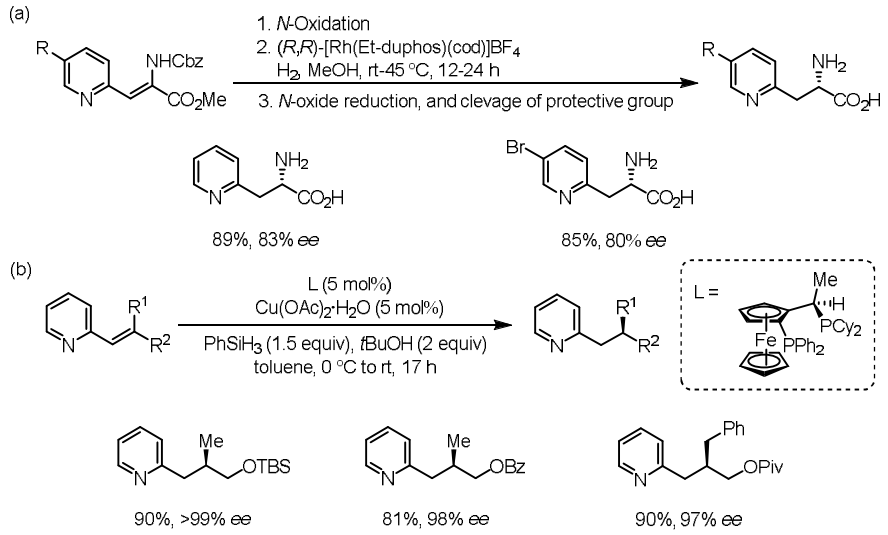
Scheme 8. Catalytic asymmetric transfer hydrogenation of pyridyl ketones.



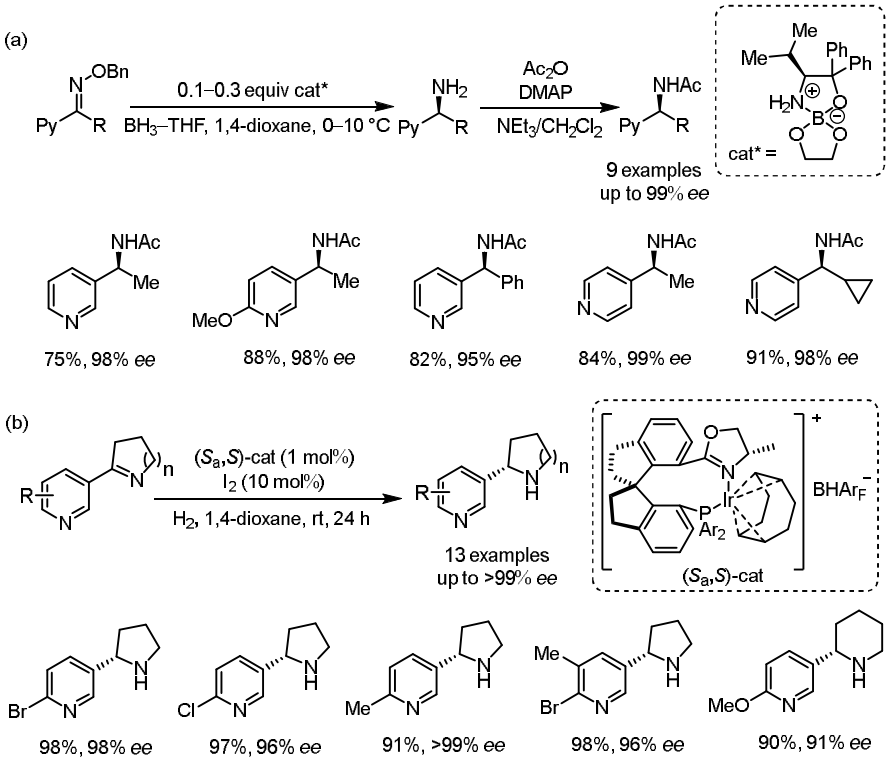
Scheme 9. Catalytic asymmetric hydroboration of pyridyl ketones by aluminum catalysis.

Asymmetric reduction of multi-substituted alkenyl pyridines provides another applicable approach to chiral pyridines. Reddy *et al.*[21] developed a novel method for enantioselective synthesis of (2-pyridyl)alanines by converting (2-pyridyl)dehydroamino acid derivatives to the corresponding *N*-oxides followed by asymmetric hydrogenation using a chiral rhodium catalyst. The corresponding pyridyl alanines were obtained with 80-83% *ee* upon *N*-oxide reduction and cleavage of the protecting group (Scheme 10a). In 2009, Lam *et al.*[22] successfully realized the copper-catalyzed asymmetric conjugate reductions of *β*,*β*′-disubstituted 2-alkenyl pyridines (Scheme 10b).

Asymmetric reduction of ketoimine-type pyridyl substrates is also feasible. In 2008, De Jesús *et al.*[23] developed a spiroborate ester-catalyzed enantioselective borane reduction of heteroaryl and heterocyclic ketoxime esters, and the asymmetric borane reduction of 3- and 4-pyridyl-derived *O*-benzyl ketoxime ethers was achieved (Scheme 11a). In 2015, Zhou *et al.*[24] realized the first highly enantioselective hydrogenation of cyclic imines bearing a pyridyl group by using iridium catalyst with a chiral spiro phosphine-oxazoline ligand. The reaction provides a direct catalytic route to the synthesis of chiral nicotine analogues. The key to successful hydrogenation is the inclusion of an *ortho* substituent on the pyridyl ring of the substrates to reduce the coordinating ability of the pyridine *N* atom (Scheme 11b).



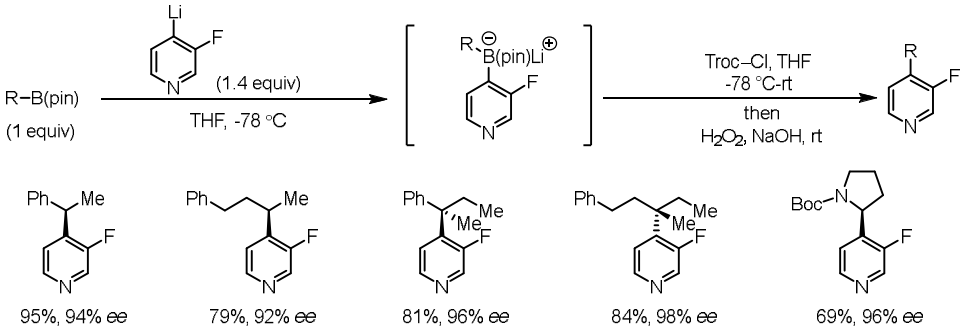
Scheme 10. Catalytic asymmetric reduction of alkenyl pyridines.



Scheme 11. Catalytic asymmetric reduction of pyridyl ketoximes and ketoimines.

4. Catalytic asymmetric cross-coupling

Catalytic asymmetric cross-coupling reactions have been intensively studied, but the coupling of pyridyl reagents is a challenging task. However, several catalytic systems have been reported that are able to tolerate pyridyl substrates. Early examples required the use of chiral reagents to achieve a stereospecific coupling under transition-metal catalysis.[25] Aggarwal *et al.*[26] developed a method for the stereospecific coupling of secondary and tertiary boronic esters with lithiated azaarenes under transition-metal-free conditions. The process involves initial boronate complex formation followed by addition of Troc-Cl, which activates the nitrogen and induces 1,2-migration. Oxidative workup furnishes the coupled product with complete stereospecificity (Scheme 12).



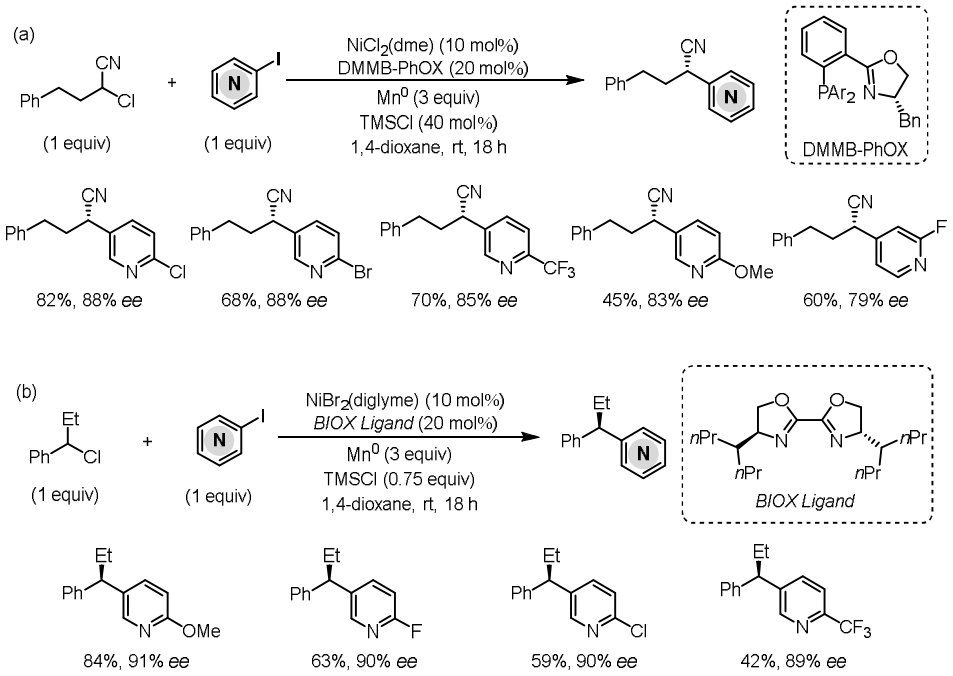
Scheme 12. Stereospecific coupling of boronic esters with pyridyl lithium reagents.

Reisman *et al.*[27] developed the Ni-catalyzed asymmetric reductive cross-coupling of heteroaryl iodides and *α*-chloronitriles. A chiral PHOX ligand was identified to be effective in promoting the reaction, providing *α*,*α*-disubstituted nitriles in good yields and with high enantioselectivities. This is the first example of a Ni-catalyzed asymmetric reductive cross-coupling reaction that tolerates *N*- and *S*-heterocyclic coupling partners, including a range of pyridines (Scheme 13a). In 2017, the same group developed[28] a new chiral bioxazoline ligand, which promoted the Ni-catalyzed asymmetric reductive cross-coupling between heteroaryl iodides and benzylic chlorides, and pyridyl substrates were well tolerated in this system (Scheme 13b).

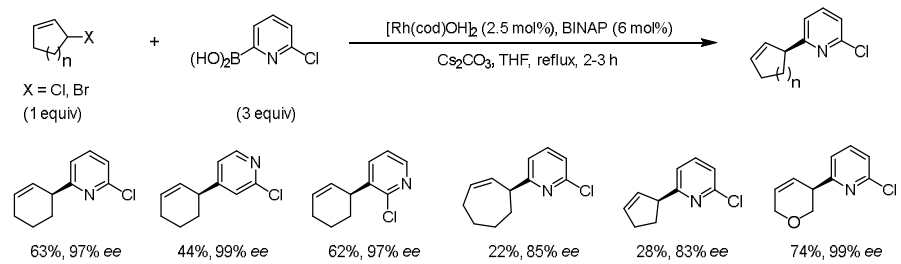
Suzuki–Miyaura reaction of pyridyl substrates was challenging in typical catalytic systems. Fletcher *et al.*[29] developed a rhodium-catalyzed asymmetric Suzuki–Miyaura reaction between organoboronic acids with allylic halides. Although unsubstituted pyridylboronic acids were unsuitable, the reaction system tolerated the *ortho*-halogen-substituted ones (Scheme 14). In 2020, Liu *et al.*[30] established a copper-catalyzed enantioconvergent radical Suzuki-Miyaura C(sp^3)−C(sp^2) cross-coupling of racemic alkyl halides with B(mac)-derived boronate esters, and several 3-pyridyl substrates were shown to be tolerated.

5. Catalytic asymmetric C−H functionalization

The enantioselective C−H functionalization of pyridines is an atom- and step-economical method for the synthesis of enantioenriched pyridine derivatives, and much effort has been devoted to this approach. A seminal study was conducted by Jordan and coworkers, in which a chiral Cp−Zr complex was used to promote C−H alkylation of 2-picoline with 1-hexene, and 58% *ee* was achieved.[31] A breakthrough was made by Hou and coworkers,[32] and a cationic half-sandwich Sc complex was developed to furnish the asymmetric alkylation of 2-substituted pyridines using various 1-alkenes with up to 96% *ee* (Scheme 15a). Shi *et al.*[33] developed a highly regio- and enantioselective Ni(0)-catalyzed *endo*-selective C−H cyclization of pyridines with alkenes. An unprecedented enantioselective C−H activation at pyridyl 3- or 4-positions was enabled by bulky chiral *N*-heterocyclic carbene ligands. This protocol provides an atom- and step-economical way to access a variety of chiral bi- and polycyclic pyridines, including 5,6,7,8-tetrahydroquinolines and 5,6,7,8-tetrahydroisoquinolines (Scheme 15b). Ye *et al.*[34] developed a Ni-Al bimetallic catalytic system to realize the asymmetric C2−H alkylation of pyridines with 1,3-dienes. Notably, this catalytic system enables efficient C2-alkylation of a wide range of pyridines, including the unsubstituted pyridine (Scheme 15c).



Scheme 13. Catalytic asymmetric reductive cross-coupling of pyridyl iodides.

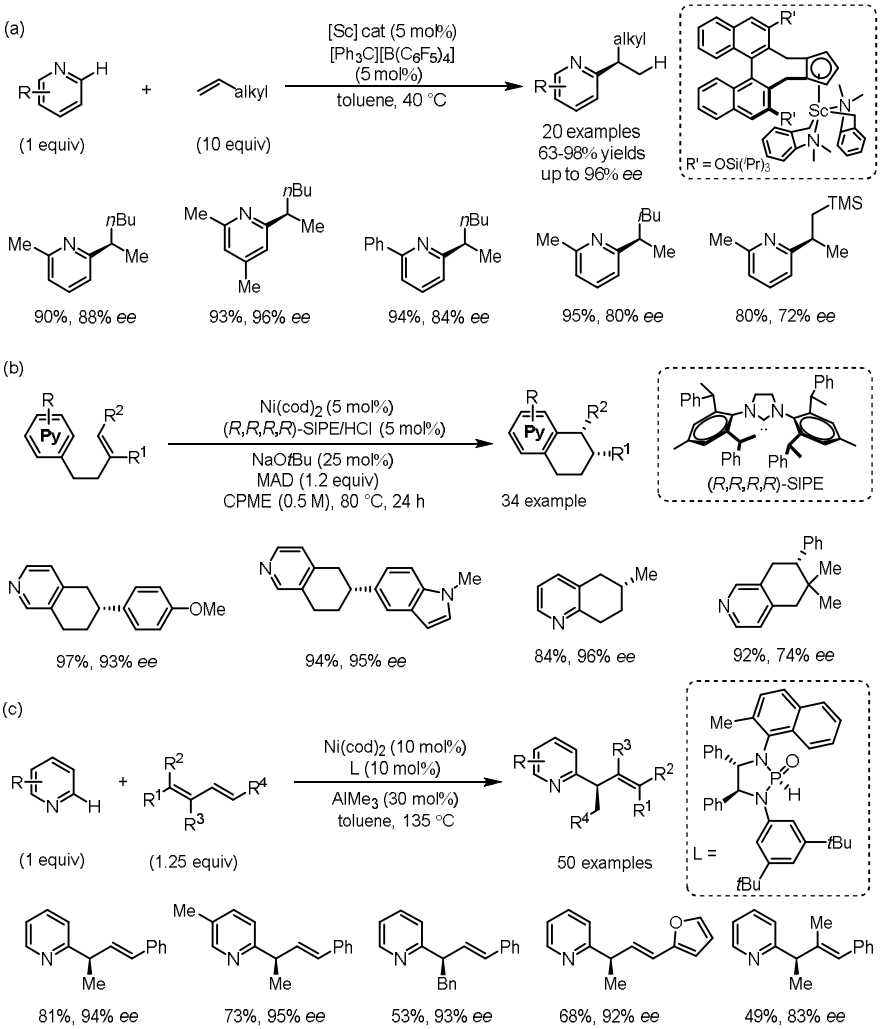


Scheme 14. Rh-catalyzed asymmetric Suzuki-Miyaura coupling of pyridylboronic acids with allylic halides.

In addition to direct C(sp^2)–H functionalization on the pyridine ring, asymmetric C–H functionalization on the side chain is also feasible. For example, the enantioselective α-C(sp^3)–H functionalization of alkylpyridines has been developed. In 2008, Trost *et al.*[35] reported a method for employing 2-methylpyridines in palladium-catalyzed asymmetric allylic alkylation (Scheme 16a). Later, the same group realized[36] the highly regio-, diastereo-, and enantioselective allylic alkylation of higher-order 2-substituted pyridines (Scheme 16b). In 2018, a Pd-catalyzed asymmetric side-chain C(α)-allylation of 2-alkylpyridines without an external base was developed by Sawamura and coworkers.[37] The D-isomannide-based monodentate diamidophosphite ligands enabled the highly linear- and enantioselective allylation with good functional group compatibility (Scheme 16c).

Direct elaboration of readily accessible alkenyl pyridines is also a viable strategy for the synthesis of highly functionalized pyridines. For example, Wang and Li[38] employed 2-alkenyl pyridines as a type of activated alkene for enantioselective intermolecular cross Rauhut−Currier reactions with 3-aroyl acrylates and 2-ene-1,4-diones. With an amino acids-based chiral phosphine catalyst, highly valuable chiral pyridine building blocks were synthesized in good yields and high enantioselectivities (Scheme 17a). In addition, pyridine-directed asymmetric C–H functionalization of arenes was also developed. Li *et al.*[39] reported a

highly enantioselective iridium-catalyzed C−H borylation of diaryl(2-pyridyl)methanes with the chiral pyridine-derived bidentate N,B-ligands. The resulting borylation products could be readily transformed into various chiral tri(hetero)arylmethane compounds (Scheme 17b).



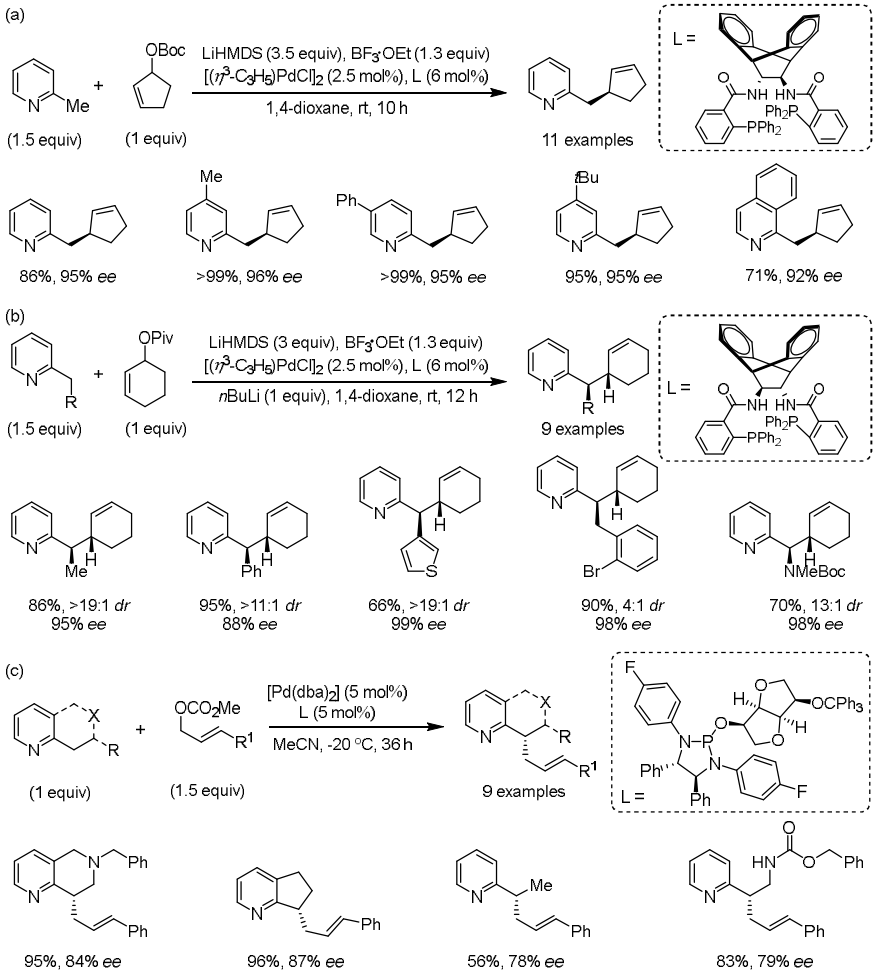
Scheme 15. Catalytic asymmetric C−H alkylation of pyridines.

6. Miscellaneous reactions

Directly installing acyl, alkyl, and aryl groups on electron deficient heteroaromatic rings like pyridines can be achieved through Minisci-type reactions. A significant breakthrough was reported by Phipps *et al.*[40] in 2018, which described an enantioselective Minisci-type addition of in situ generated *α*-amino radicals to pyridines by cooperative catalysis of an iridium photocatalyst and a chiral Brønsted acid catalyst (Scheme 18).

Taking advantage of the electron-deficient property of pyridine, an asymmetric dearomatizing addition/oxidative rearomatization strategy was developed to construct chiral pyridines. In 2018, Buchwald *et al.*[41] developed the copper-catalyzed C−C bond-forming dearomatization of pyridines, and the chiral

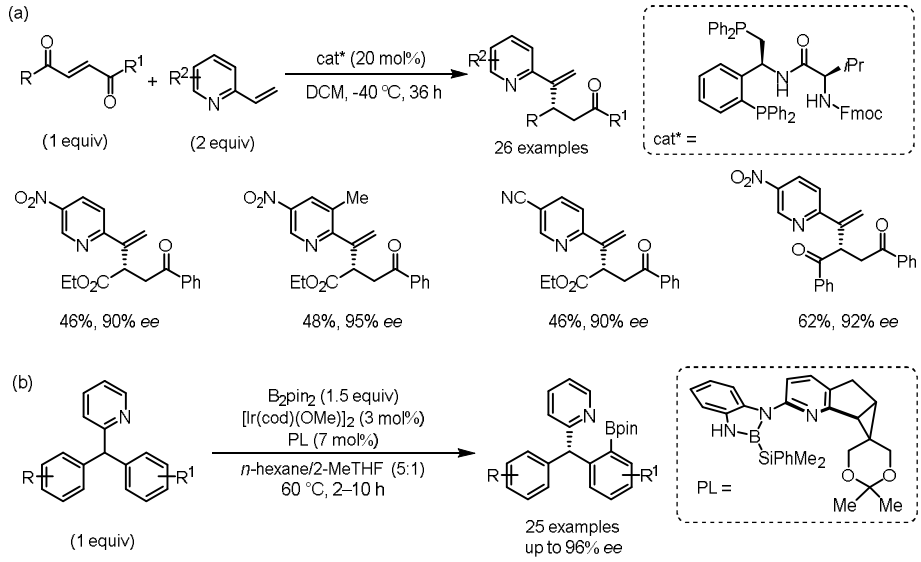
addition products could be oxidized to the corresponding chiral pyridines using oxygen or air. This protocol enables one-pot syntheses of highly enantioenriched C4-functionalized pyridines from pyridines and simple alkenes (Scheme 19).



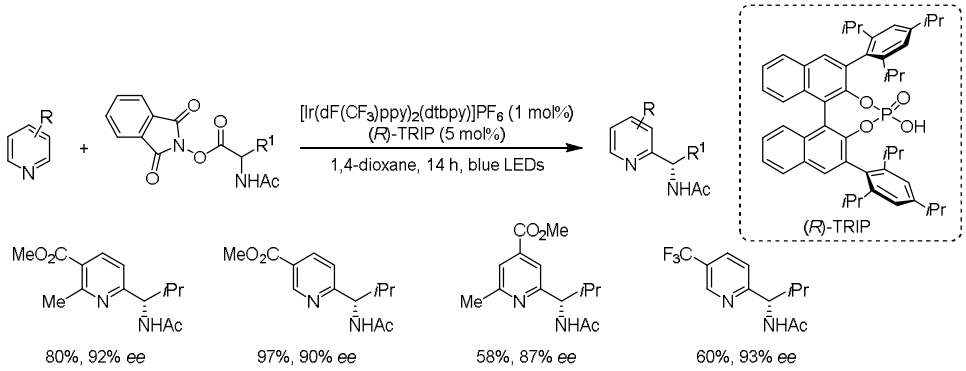
Scheme 16. Catalytic asymmetric C−H functionalization of alkylpyridines.

Intermolecular cycloaddition reaction is a useful tool to generate complex ring systems with continuous stereogenic centers. In 2019, Trost *et al.*[42] developed an efficient method for the construction of chiral heteroaryl-substituted cycles *via* palladium-catalyzed asymmetric cycloaddition. Most classes of nitrogen-containing aromatics including pyridines are compatible substrates (Scheme 20).

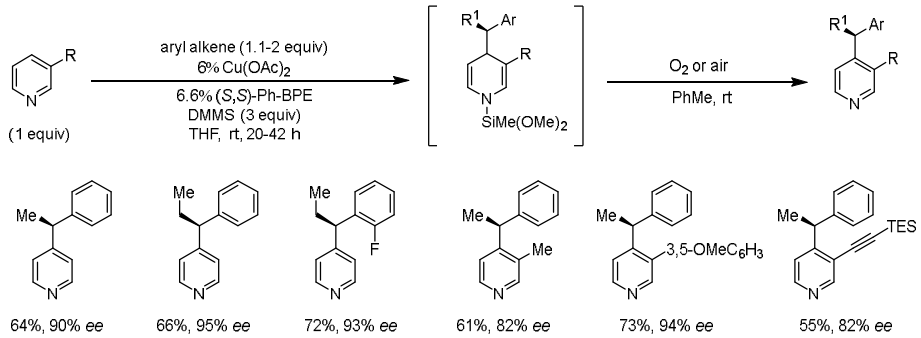
Compared to asymmetric transformations of pyridines and pyridyl substrates, asymmetric de novo construction of pyridines provides a novel approach to synthetically challenging chiral pyridines. In 2021, Liu *et al.*[43] developed a nickel-catalyzed enantioselective [2+2+2]-cycloaddition of alkynes with alkyne-tethered malononitriles for the construction of densely substituted pyridines that contain an adjacent all-carbon quaternary center (Scheme 21).



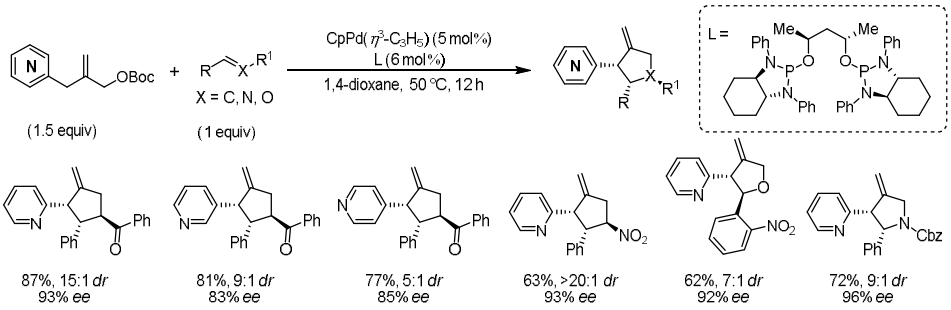
Scheme 17. a) Catalytic asymmetric C–H functionalization of alkenyl pyridines. b) Iridium-catalyzed C–H borylation of diaryl(2-pyridyl)methanes.



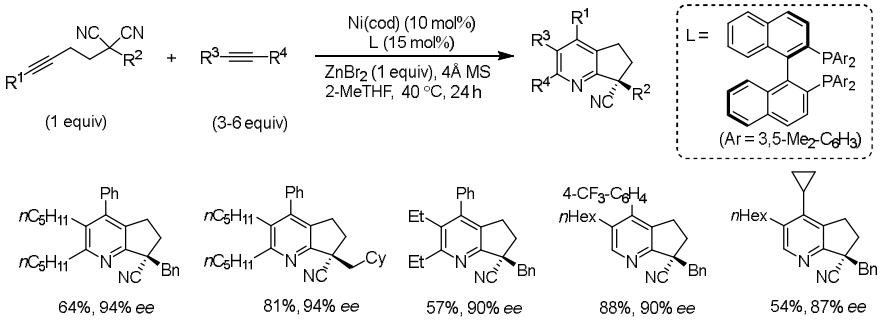
Scheme 18. Catalytic asymmetric Minisci-type addition to pyridines.



Scheme 19. Synthesis of chiral pyridines *via* Cu-catalyzed asymmetric dearomatization.



Scheme 20. Synthesis of chiral pyridines by Pd-catalyzed asymmetric cycloaddition.



Scheme 21. Synthesis of chiral pyridines by asymmetric de novo construction of the pyridine ring.

7. Conclusion

In summary, significant achievements have been made in catalytic asymmetric synthesis of chiral pyridine derivatives, and structurally diverse chiral pyridines can be efficiently accessed through catalytic asymmetric addition, catalytic asymmetric reduction, catalytic asymmetric cross-coupling, and catalytic asymmetric C−H functionalization among other strategies. Despite the considerable progresses, there is still room for improvement and development of approaches to chiral pyridines. For example, most of the current methods relies on the use of noble-metals as catalyst, development of base-metal catalysis and/or organocatalysis is highly desirable; limitation on the scope of pyridyl substrates remains a non-negligible problem, and general methods that work well for structurally diverse 2-, 3-, and 4-pyridyl substrates are rare; introduction of the state-of-the-art technologies such as biocatalysis, photolysis, and electrocatalysis may lead to greener and more efficient methods for synthesis of chiral pyridines.

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References

1. a) Taylor, R. D.; MacCoss M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845-5859. b) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475-3478. c) Yang, G.; Zhang, W. *Chem. Soc. Rev.* **2018**, *47*, 1783-1810.
2. Yu, X.-Q.; Yamamoto, Y.; Miyaura, N. *Synlett* **2009**, *2009*, 994-998.
3. Albrecht, F.; Sowada, O.; Fistikci, M.; Boysen, M. M. K. *Org. Lett.* **2014**, *16*, 5212-5215.
4. Ye, B.; Yao, J.; Wu, C.; Zhu, H.; Yao, W.; Jin, L.; Dou, X. *ACS Catal.* **2022**, *12*, 2434-2440.
5. Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831-845.

6. a) Friedman, A. A.; Panteleev, J.; Tsoung, J.; Huynh, V.; Lautens, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 9755-9758. b) Lied, F.; Brodnik Žugelj, H.; Kress, S.; Štefane, B.; Glorius, F.; Lautens, M. *ACS Catal.* **2017**, *7*, 1378-1382.
7. Jumde, R. P.; Lanza, F.; Pellegrini, T.; Harutyunyan, S. R. *Nat. Commun.* **2017**, *8*, 2058.
8. Zhu, H.; Yin, L.; Chang, Z.; Wang, Y.; Dou, X. *Adv. Synth. Catal.* **2020**, *362*, 3142-3147.
9. Cao, K.; Tan, S. M.; Lee, R.; Yang, S.; Jia, H.; Zhao, X.; Qiao, B.; Jiang, Z. *J. Am. Chem. Soc.* **2019**, *141*, 5437-5443.
10. Guo, J.; Xie, Y.; Lai, Z. M.; Weng, J.; Chan, A. S.; Lu, G. *ACS Catal.* **2022**, *12*, 13065-13074.
11. Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-3740.
12. Chen, Y. J.; Cui, Z.; Feng, C. G.; Lin, G. Q. *Adv. Synth. Catal.* **2015**, *357*, 2815-2820.
13. Wu, C.; Qin, X.; Moeljadi, A. M. P.; Hirao, H.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2019**, *131*, 2705-2709.
14. Hu, Y.; Wang, C.; Zhu, H.; Xing, J.; Dou, X. *Adv. Synth. Catal.* **2022**, *364*, 531-535.
15. Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749-1751.
16. a) Chen, C.; Reamer, R. A.; Chilenski, J. R.; McWilliams, C. J. *Org. Lett.* **2003**, *5*, 5039-5042. b) Tao, X.; Li, W.; Ma, X.; Li, X.; Fan, W.; Xie, X.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z. *J. Org. Chem.* **2012**, *77*, 612-616.
17. Yang, H.; Huo, N.; Yang, P.; Pei, H.; Lv, H.; Zhang, X. *Org. Lett.* **2015**, *17*, 4144-4147.
18. Nian, S.; Ling, F.; Chen, J.; Wang, Z.; Shen, H.; Yi, X.; Yang, Y.-F.; She, Y.; Zhong, W. *Org. Lett.* **2019**, *21*, 5392-5396.
19. Wang, B.; Zhou, H.; Lu, G.; Liu, Q.; Jiang, X. *Org. Lett.* **2017**, *19*, 2094-2097.
20. Lebedev, Y.; Polishchuk, I.; Maity, B.; Dinis Veloso Guerreiro, M.; Cavallo, L.; Rueping, M. *J. Am. Chem. Soc.* **2019**, *141*, 19415-19423.
21. Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Org. Lett.* **2001**, *3*, 3157-3159.
22. Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386-10387.
23. Huang, K.; Merced, F. G.; Ortiz-Marciales, M.; Meléndez, H. J.; Correa, W.; De Jesús, M. *J. Org. Chem.* **2008**, *73*, 4017-4026.
24. Guo, C.; Sun, D. W.; Yang, S.; Mao, S. J.; Xu, X. H.; Zhu, S. F.; Zhou, Q. L. *J. Am. Chem. Soc.* **2015**, *137*, 90-93.
25. a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538-3539. b) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191-13193. c) Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856-16868.
26. Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 10958-10961.
27. Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480-10483.
28. Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2017**, *139*, 5684-5687.
29. Schäfer, P.; Palacin, T.; Sidera, M.; Fletcher, S. P. *Nat. Commun.* **2017**, *8*, 15762.
30. Jiang, S. P.; Dong, X. Y.; Gu, Q. S.; Ye, L.; Li, Z. L.; Liu, X. Y. *J. Am. Chem. Soc.* **2020**, *142*, 19652-19659.
31. Rodewald, S.; Jordan, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 4491-4492.
32. Song, G.; O, W. W. N.; Hou, Z. *J. Am. Chem. Soc.* **2014**, *136*, 12209-12212.
33. Zhang, W. B.; Yang, X. T.; Ma, J. B.; Su, Z. M.; Shi, S. L. *J. Am. Chem. Soc.* **2019**, *141*, 5628-5634.
34. Li, J. F.; Pan, D.; Wang, H. R.; Zhang, T.; Li, Y.; Huang, G.; Ye, M. *J. Am. Chem. Soc.* **2022**, *144*, 18810-18816.
35. Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092-14093.
36. Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056-12057.
37. Murakami, R.; Sano, K.; Iwai, T.; Taniguchi, T.; Monde, K.; Sawamura, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 9465-9469.
38. Qin, C.; Liu, Y.; Yu, Y.; Fu, Y.; Li, H.; Wang, W. *Org. Lett.* **2018**, *20*, 1304-1307.
39. Song, P.; Hu, L.; Yu, T.; Jiao, J.; He, Y.; Xu, L.; Li, P. *ACS Catal.* **2021**, *11*, 7339-7349.
40. Proctor, R. S.; Davis, H. J.; Phipps, R. J. *Science* **2018**, *360*, 419-422.
41. Gribble Jr., M. W.; Guo, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 5057-5060.

42. Trost, B. M.; Jiao, Z.; Hung, C. I. *Angew. Chem. Int. Ed.* **2019**, *58*, 15154-15158.
43. Cai, J.; Bai, L.-G.; Zhang, Y.; Wang, Z.-K.; Yao, F.; Peng, J.-H.; Yan, W.; Wang, Y.; Zheng, C.; Liu, W.-B. *Chem* **2021**, *7*, 799-811.