DOI: 10.1002/adsc.200800797

Recent Advances in the Synthesis of 2-Imidazolines and Their Applications in Homogeneous Catalysis

Han Liu[a] and Da-Ming Du[b,*]

[a] College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, People's Republic of China
[b] School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing 100081, People's Republic of China
Fax: (+86)-10-6891-4985; e-mail: dudm@bit.edu.cn or dudm@pku.edu.cn

Received: December 19, 2008; Published online: March 12, 2009

Abstract: As an important class of heterocyclic scaffolds, 2-imidazolines have attracted the attention from the chemists interested in natural products, pharmaceutical chemistry, synthetic organic chemistry, coordination chemistry, and homogeneous catalysis. To fulfill the demand of structural diversity, many efficient methods towards 2-imidazolines, as well as modifications of traditional methods, have been reported in the past two decades. 2-Imidazolines have been developed as ligands in homogeneous catalysis, for the substitution on the nitrogen atom that provides an opportunity for fine-tuning of the electronic effect. This review summarizes recent advances in the synthesis of 2-imidazolines and their applications in homogeneous catalysis.

1 Introduction
2 Recent Advances in the Synthesis of 2-Imidazolines
2.1 Classification of Synthetic Methods
2.2 Synthesis of 2-Imidazolines from 1,2-Diamines (Method A)
2.3 Synthesis of 2-Imidazolines from β-Hydroxyamides (Method B)
2.4 Synthesis of 2-Imidazolines from Isocyanides and Imines (Method C)
2.5 Synthesis of 2-Imidazolines from *N*-Acyl Diamines (Method D)
2.6 Synthesis of 2-Imidazolines from Aziridines (Method E)
2.7 Synthesis of 2-Imidazolines from Azlactones and Imines (Method F)
2.8 Synthesis of 2-Imidazolines from Alkenes (Method G)
2.9 Miscellaneous (Method H)
3 Applications of 2-Imidazolines in Homogeneous Catalysis
3.1 Applications in Palladium-Catalyzed Reactions
3.2 Applications in Ruthenium-Catalyzed Reactions
3.3. Applications in Copper-Catalyzed Reactions
3.4 Applications in Other Metal-Catalyzed Reactions
3.5 Imidazolines as Organocatalysts
4 Conclusion

Keywords: asymmetric catalysis; homogeneous catalysis; imidazolines; organic catalysis; synthetic methods

1 Introduction

Imidazolines (dihydroimidazoles) are important five-membered heterocycles.[1] According to the position of the double bond, imidazolines can be classified as 2-imidazoline, 3-imidazoline, and 4-imidazoline (Figure 1). In some publications, benzimidazole and saturated imidazolidine were also named as imidazoline incorrectly. Among the 2-, 3-, and 4-imidazolines, the importance of 2-imidazolines is the highest, for their wide applications in different fields of chemistry (*vide infra*). The substitutions on the ring can be aryl, alkyl, and even heteroatom groups. The present review will be focused on the recent advances in synthetic methods towards 2-imidazolines, and their applications in homogeneous catalysis. Those 2-imidazolines with substitutions in which heteroatoms connect directly to the five-membered ring, such as 2-amino-, 2-alkoxy-, and 2-mercapto-2-imidazolines, will not be included.

2-Imidazolines can be found in natural product chemistry, pharmaceutical chemistry, organic synthesis, coordination chemistry, and homogeneous catalysis. The marine alkaloid 4,5-dihydro-6′-deoxybromotopsentin was isolated from a sponge which was identified as *Spongosorites* sp. with high cytotoxicity.[2] Since the discovery of the imidazoline receptor (imidazoline binding site, IBS) in 1984,[3] many bioactive

Han Liu was born in 1983 in Beijing in the Peoople's Republic of China. He obtained his B.Sc. degree from Peking University in 2005. He is now conducting his Ph.D. research at the College of Chemistry and Molecular Engineering of Peking University in the group of Prof. Da-Ming Du, focusing on the development and application of new chiral ligands in asymmetric catalysis.

Da-Ming Du was born in 1967 in Henan Province, People's Republic of China. He received his B.Sc. degree from Zhengzhou University in 1989, his M. Sc. and Ph.D. degrees from Nankai University in 1992 and 1995 under the supervision of Professor Jiben Meng and Professor Xiuzhong Zhou.. He took a Lecturer position at Shandong University in 1995. He was promoted to Associate Professor in 1997 at Shandong University, and during this period, he was a Visiting Scholar at The Chinese University of Hong Kong with Professor Thomas C. W. Mak and Professor Henry N. C. Wong from 1996 to 1997 and then a Postdoctoral Visiting Scholar at Hong Kong University of Science & Technology with Professor Paul R. Carlier from 1998 to 1999. He joined the College of Chemistry and Molecular Engineering of Peking University as an Associate Professor in 2001 after working for two years as a Postdoctoral Fellow with Professor Wenting Hua. In September 2008 he moved to Beijing Institute of Technology, and was appointed Full Professor. He received the Thieme Journal Award 2009. Professor Du's research interests are focused on catalytic asymmetric organic synthesis and the development of new synthetic methodologies.

2-imidazoline-containing molecules have been synthesized and used as ligands, as illustrated in Figure 2. The research in this field has been reviewed recently.[4] In addition, 2-imidazolines have also been investigated as antihyperglycemic, anti-inflammatory, antihypertensive, antihypercholesterolemic, and antidepressant reagents. Due to the easy introduction of chirality on the imidazoline ring, some of them have been used as chiral auxiliaries in stereoselective synthesis of optical active compounds. As a structural analogue of 2-oxazolines,[5–9] 2-imidazolines have been developed as ligands in coordination chemistry. The substitutions on the nitrogen atom in the imidazoline ring provide opportunities for fine-tuning the elec-

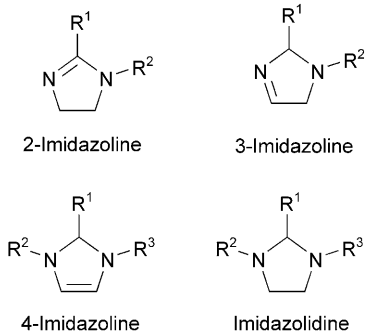


Figure 1. Classification of imidazolines.

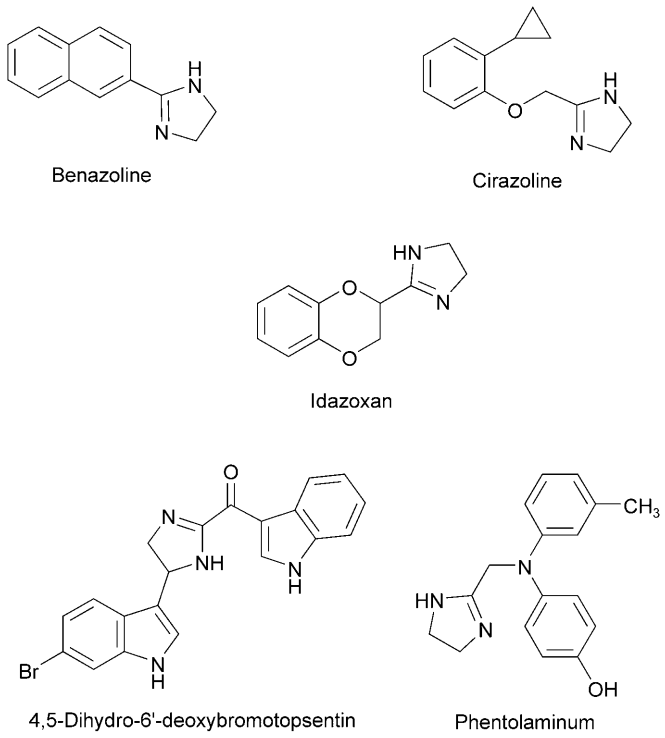


Figure 2. Natural and artificial bioactive 2-imidazoline compounds.

tronic effect. Some of the complexes show good catalytic activities in important chemical transformations, such as Suzuki–Miyaura coupling, Mizoroki–Heck reaction, Diels–Alder reaction, asymmetric allylic substitution, [3,3]sigmatropic rearrangement, Henry reaction, etc. In some cases, better yields and enantioselectivities than those obtained with corresponding oxazoline ligands can be achieved. Many transition metals such as Pd, Ru, Cu, Zn, Ir, Rh, and Ni, have been involved. 2-Imidazolines have also been used as organocatalysts in Staudinger lactam synthesis and Morita–Baylis–Hillman reaction, due to their higher basicity and nucleophilicity than oxazoline compounds. Their salts with strong acids have been used as chiral Brønsted acid catalysts.

The present review will be divided into two parts: synthetic methods towards 2-imidazolines developed in the past two decades, and applications of 2-imidazolines in homogeneous catalysis as ligands or organocatalysts. In the first part, both the methods for enantiopure imidazolines and racemic ones will be included. Some of them have been applied in the synthesis of chiral imidazoline ligands, which will be mentioned in the second part. The applications of imidazolines will be classified by the type of metals in the catalytic system, while the organocatalysis will be summarized alone.

2 Recent Advances in the Synthesis of 2-Imidazolines

2.1 Classification of Synthetic Methods

Since the first publication on 2-imidazoline compounds in 1888,[10] a plethora of synthetic methods from different starting materials have been developed. Some of them have been used for more than a half century and were reviewed in 1954.[11] During the past two decades, some novel methods towards 2-imidazolines, especially the diastereoselective and enantioselective formation of stereogenic centers, have been developed. The traditional methods have also been modified to improve their efficiency. On the basis of starting materials, the literature methods were classified into classes A to H, as illustrated in Figure 3. Method A can be further divided into five subclasses, considering the different source of C-1 in the imidazoline ring. Method H contains some unusual methods that have only been reported for specific substrates. Among these methods, Methods A, B, C, D, and E have been used in the asymmetric formation of 2-imidazolines. The chirality comes from both chiral starting materials (Methods A, B, D, and E) and chiral catalysts (Method C). In the synthesis of the chiral imidazoline ligands memtioned in the third part of the review, Methods A and B have been used more widely than the other six methods because of the easier availability of chiral amino alcohols and diamines.

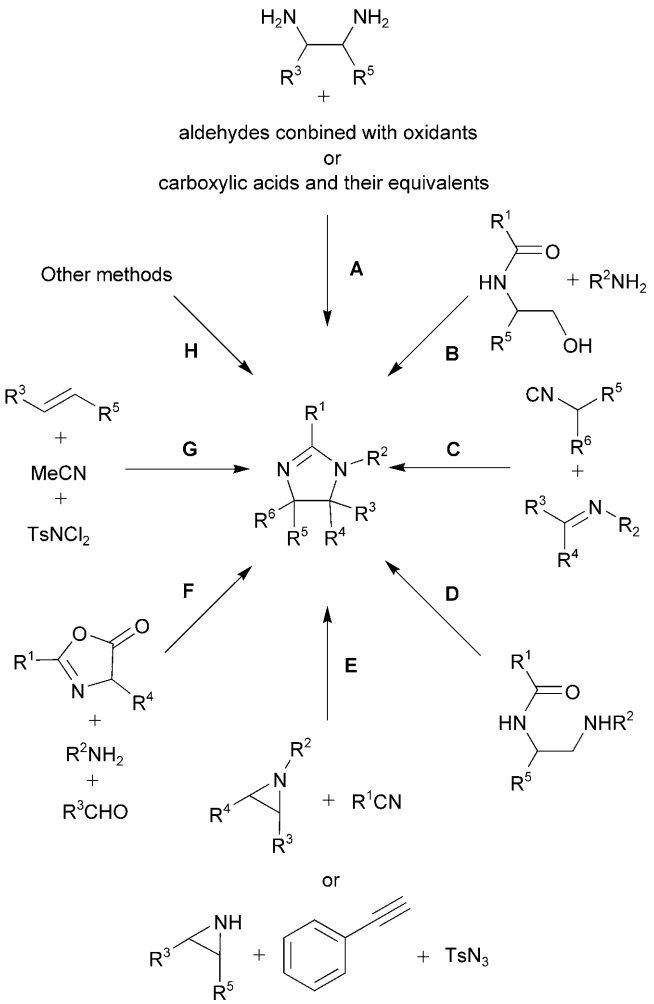


Figure 3. Classification of different synthetic methods towards 2-imidazolines.

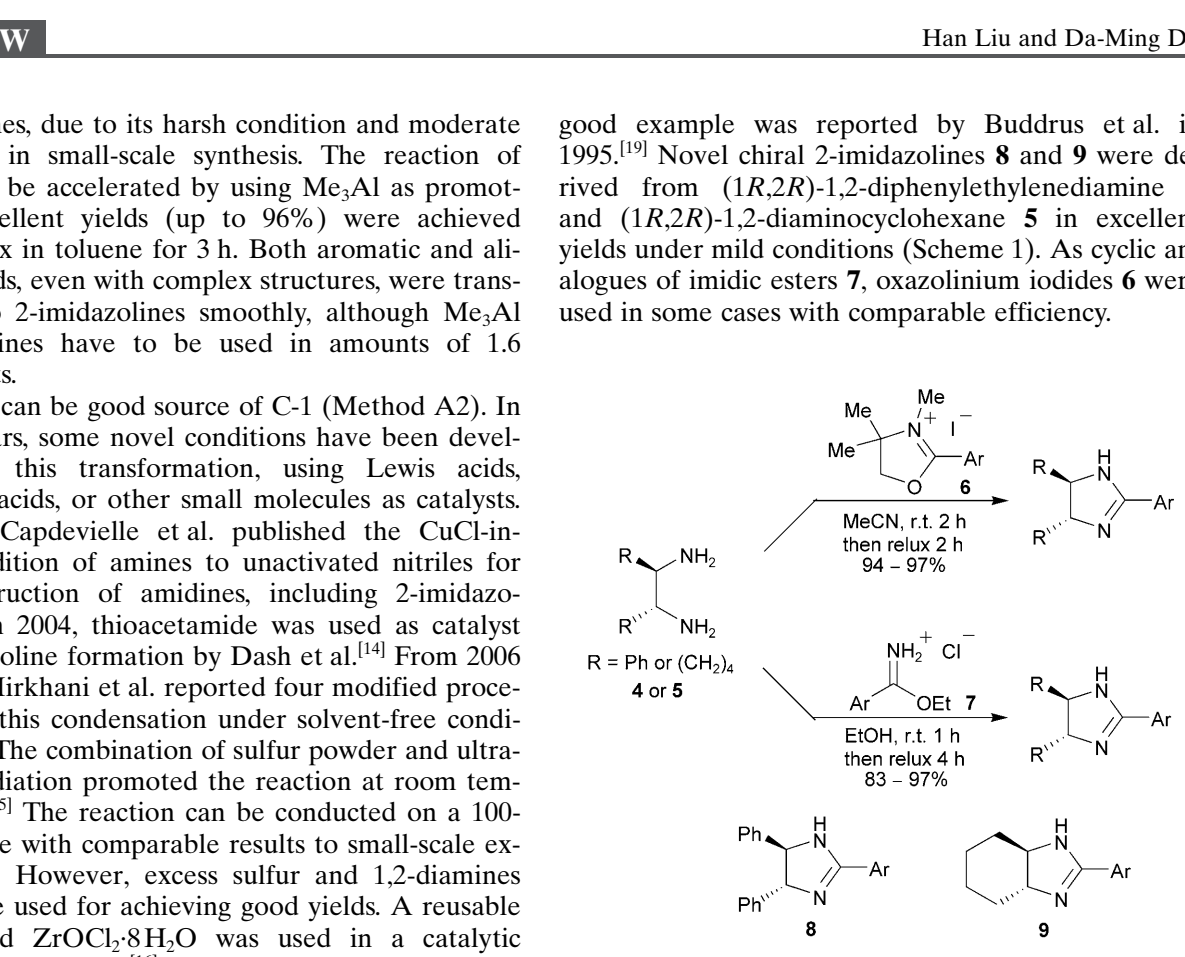
2.2 Synthesis of 2-Imidazolines from 1,2-Diamines (Method A)

Synthesis of imidazolines from 1,2-diamines is the first class of methods developed by chemists. The biggest advantage of this method is the easy introduction of chirality by using enantiopure 1,2-diamines. Considering the similarity between 2-imidazolines and amides in structure, carboxylic acids or esters are naturally used as the source of C-1 (Method A1). A 1:1 mixture of diamine and carboxylic acid or ester is heated directly at high temperature (150 °C or higher) with removal of the water or alcohol formed in the condensation process. This method is not widely used in the synthesis of chiral 2-imidazolines from chiral

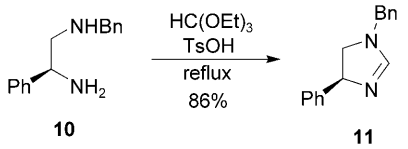
1,2-diamines, due to its harsh condition and moderate efficiency in small-scale synthesis. The reaction of esters can be accelerated by using Me_3Al as promoter.[12] Excellent yields (up to 96%) were achieved after reflux in toluene for 3 h. Both aromatic and aliphatic acids, even with complex structures, were transformed to 2-imidazolines smoothly, although Me_3Al and diamines have to be used in amounts of 1.6 equivalents.

Nitriles can be good source of C-1 (Method A2). In recent years, some novel conditions have been developed for this transformation, using Lewis acids, Brønsted acids, or other small molecules as catalysts. In 1993, Capdevielle et al. published the CuCl-induced addition of amines to unactivated nitriles for the construction of amidines, including 2-imidazolines.[13] In 2004, thioacetamide was used as catalyst for imidazoline formation by Dash et al.[14] From 2006 to 2008, Mirkhani et al. reported four modified procedures for this condensation under solvent-free condition.[15–18] The combination of sulfur powder and ultrasonic irradiation promoted the reaction at room temperature.[15] The reaction can be conducted on a 100-mmol scale with comparable results to small-scale experiments. However, excess sulfur and 1,2-diamines have to be used for achieving good yields. A reusable Lewis acid $ZrOCl_2 \cdot 8H_2O$ was used in a catalytic amount under reflux.[16] The yield can be improved by changing the condition from reflux to ultrasonic or microwave irradiation. The catalyst can be reused for at least four times without loss of activity. Another two heterogeneous catalysts, silica sulfuric acid (SSA)[17] and 12-tungstophosphoric acid (TPA)[18] supported on silica, were developed for the synthesis of 2-imidazolines, as well as oxazolines and thiazolines. Both of the supported catalysts were used under reflux and can be recovered by filtration and dried at elevated temperature (60 °C for SSA and 100 °C for silica supported TPA).

As activated equivalents of carboxylic acids, imidic esters (imidates) **1**, orthoesters **2**, and DMF-DMA **3** (Figure 4) have been used in the synthesis of 2-imidazoline compounds (Method A3). Imidic esters can be generated from the corresponding amides by treatment with Et_3OBF_4 (Meerwein's salt), or from nitriles by treatment with HCl (gas) in alcohol or MeONa. In the former two cases, the salts of imidic esters can be isolated as crystals through filtration before use. This method has been widely used in the synthesis of chiral imidazolines from chiral 1,2-diamines. One good example was reported by Buddrus et al. in 1995.[19] Novel chiral 2-imidazolines **8** and **9** were derived from (1*R*,2*R*)-1,2-diphenylethylenediamine **4** and (1*R*,2*R*)-1,2-diaminocyclohexane **5** in excellent yields under mild conditions (Scheme 1). As cyclic analogues of imidic esters **7**, oxazolinium iodides **6** were used in some cases with comparable efficiency.



Scheme 1. Synthesis of chiral 2-imidazolines from diamines and imidates or oxazolinium iodides (Method A3).



Scheme 2. Synthesis of chiral 2-imidazoline from orthoformate and diamine (Method A3).

Orthoesters have also been used in the synthesis of chiral 2-imidazolines. In 1996, Jones et al. reported the synthesis of chiral 2-imidazoline **11** from $HC(OEt)_3$ and unsymmetrical chiral diamine **10** (Scheme 2).[20] The substitution on the amino group was important for the location of the double bond. The reaction was catalyzed by TsOH in refluxed $HC(OEt)_3$. In some cases, DMF-DMA **3** was used as an equivalent of $HC(OEt)_3$ with higher activity for the easy extrusion of Me_2NH and MeOH.[21]

Compared with the former mentioned methods, the synthesis of 2-imidazolines **14** from ethylenediamine **12** and aldehydes **13** (Method A4) has only been investigated in the past three years (Scheme 3). Considering the different oxidation states of C-1 in imidazolines compared with aldehydes, oxidants are needed after the *in situ* generation of imidazolidine inter-

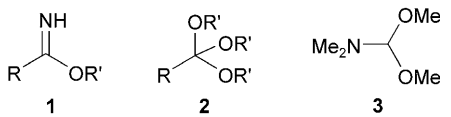
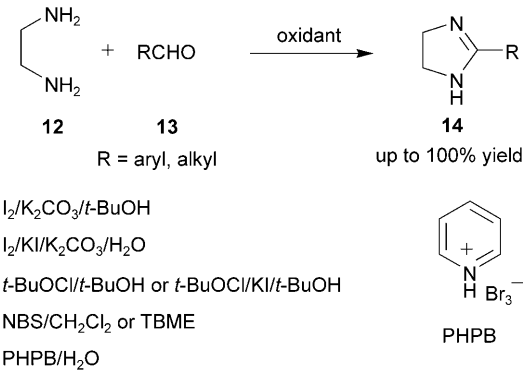
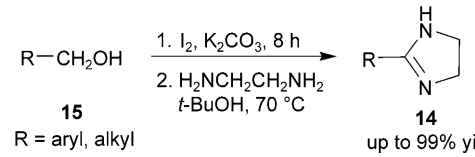


Figure 4. Some activated equivalents of carboxylic acids.



Scheme 3. Synthesis of 2-imidazolines from aldehydes and diamines (Method A4).



Scheme 4. One-pot synthesis of 2-imidazolines from primary alcohols and diamines (Method A4).

mediates. Different oxidation systems have been developed for this transformation. In 2005, Fujioka and Kita et al. reported NBS as oxidant in CH_2Cl_2.[22,23] Both aromatic and aliphatic aldehydes were transformed into the corresponding 2-imidazolines in good yields. In their screening, NIS and NCS also gave comparable results. In 2006, Konwar et al. and Togo et al. reported I_2 as oxidant in water and *t*-BuOH, respectively.[24,25] The mechanism of the oxidation involves *N*-iodination followed by elimination of HI. Further oxidation by diacetoxyiodobenzene gave imidazoles in high yields.[25]

In 2007, Togo et al. reported a direct synthesis of 2-imidazolines **14** from ethylenediamine **12** and primary alcohols **15**.[26] The oxidation of alcohols to aldehydes and formation of imidazolines can be conducted in one-pot (Scheme 4). Other cheap and convenient oxidants such as *t*-BuOCl,[27] *t*-BuOCl/KI,[27] and PHPB (pyridinium hydrobromide perbromide),[28] were also developed. Comparable good results can be achieved in most cases. In addition to ethylenediamine, other chiral 1,2-diamines have also been used successfully in this reaction.

Other equivalents of carboxylic acid such as thioimidic esters (thioimidates) **16**, dithioesters **17**, and chlorodicyanovinylbenzene **18** (Figure 5), can also be used as C-1 sources (Method A5). In 1999, Mioskowski et al. reported the modified 2-imidazoline synthesis from thioimidic esters.[29] The salt of thioimidates were generated from the corresponding nitriles and thiophenol in the presence of HBr (gas) in Et_2O. The

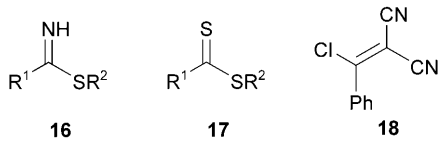


Figure 5. Some equivalents of carboxylic acids.

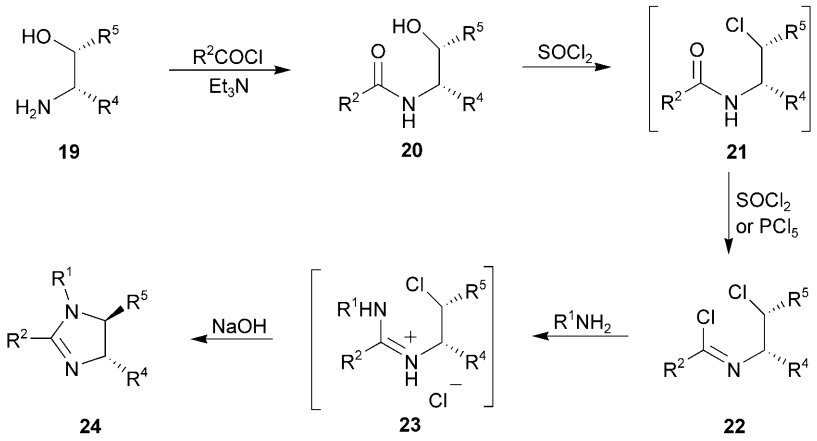
condensation of 1,2-diamines with thioimidic esters took place smoothly at room temperature with good yields, indicating the higher reactivity of thioimidic esters than imidic esters. In 1981, Levesque et al. reported the condensation of dithioesters with diamines under mild conditions.[30] Chlorodicyanovinylbenzene **18** can be considered as an equivalent of benzoyl chloride.[31] One molar equivalent of malonitrile and HCl was extruded during the condensation through a retro-Knoevenagel reaction and addition-elimination.

2.3 Synthesis of 2-Imidazolines from β-Hydroxyamides (Method B)

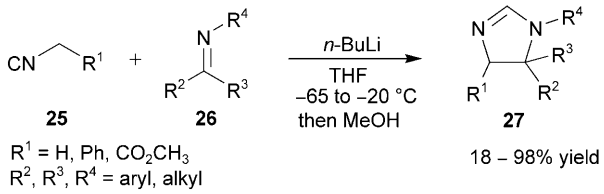
Although Method A provides an access to chiral 2-imidazolines, the major drawback is that the method is more efficient for C_2-symmetrical 1,2-diamines than C_1-symmetrical ones. In the latter case, the chiral diamines have to be synthesized in several steps from amino alcohols. To overcome the limitation of Method A, Casey et al. reported a general one-pot route for the preparation of enantiopure 2-imidazolines **24** from more accessible β-hydroxy amides **20** which have been widely used as materials of oxazolines and thiazolines.[32] As illustrated in Scheme 5, the chloroethyl amides **21** are generated by treating β-hydroxy amides **20** with thionyl chloride under reflux. The highly active imidoyl chlorides **22** are formed by treating chloroethyl amides **21** with thionyl chloride or PCl_5, depending on the different R^2 groups. The desired 2-imidazolines **24** can be obtained after substitution and NaOH-mediated annulation through the proposed amidinium intermediates **23**. A wide range of acyl chlorides and amines, including formyl chloride and ammonia (dissolved in $CHCl_3$), can be good substrates in this process. This method has been widely used in the synthesis of chiral 2-imidazoline ligands (*vide infra*).

2.4 Synthesis of 2-Imidazolines from Isocyanides and Imines (Method C)

In 1977, Schöllkopt et al. reported the synthesis of 2-imidazolines **27** from α-metalated isocyanides and imines **26** (Scheme 6).[33] The isocyanides **25** were metalated by *n*-BuLi at low temperature and reacted with unactivated imines smoothly to form 2-lithiated



Scheme 5. Synthesis of 2-imidazolines from β-hydroxyamides (Method B).



Scheme 6. Synthesis of 2-imidazolines from lithiated isocyanides and imines (Method C).

imidazolines, which were quenched by methanol or other electrophiles. Both activated and unactivated isocyanides were successfully used because of the high basicity of *n*-BuLi. A similar procedure has been developed by van Leusen et al. using α-substituted TosMIC as activated isocyanide.[34]

In 1996, Hayashi et al. developed an Au(I)-catalyzed Mannich-type reaction of isocyanoacetate **28** with *N*-sulfonylimines **29**.[35] The desired 2-imidazolines **30** can be obtained in quantitative yields with >90:10 *cis* selectivity by the catalysis of 1 mol% Au(I) compound. Another catalyst $RuH_2(PPh_3)_4$ for this reaction was reported by Lin et al. in 1997.[36] The *trans*-**30** were formed preferably with 95:5 selectivity in this work. The *cis*-**30** can also be efficiently transformed to *trans*-**30** by treatment with Et_3N in CH_2Cl_2.[35] Compared with the former examples, the transition metal-catalyzed processes provide us with access to both *cis* and *trans* isomers under mild conditions from the same materials (Scheme 7). Other catalysts such as NHC-CuCl **31**[37] and pincer-Pd(II) **32**[38] were also developed recently with *trans* selectivity (Figure 6).

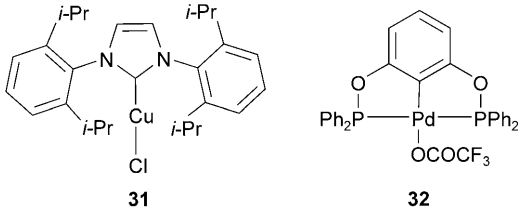
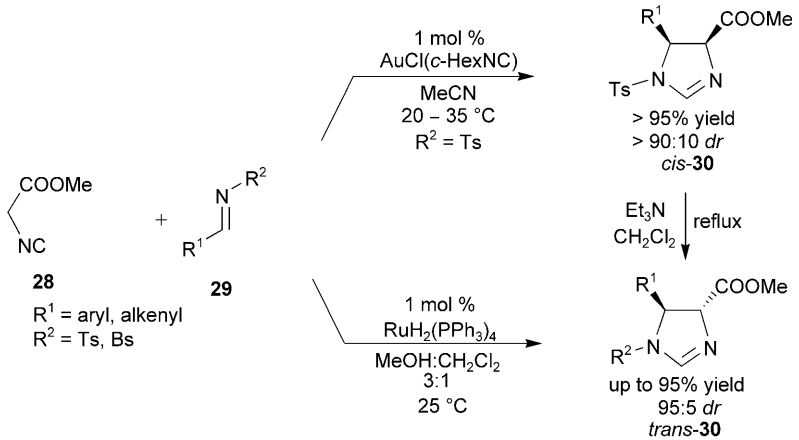
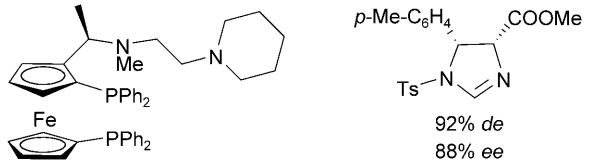


Figure 6. Pincer complexes as catalysts for 2-imidazoline synthesis.

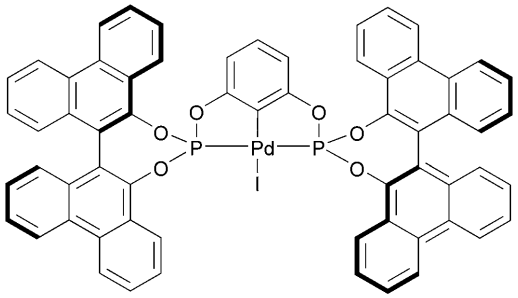


Scheme 7. Synthesis of 2-imidazolines from activated isocyanides and imines (Method C).



33 34

Figure 7. Ferrocene-derived diphosphine ligand for asymmetric synthesis of 2-imidazolines.



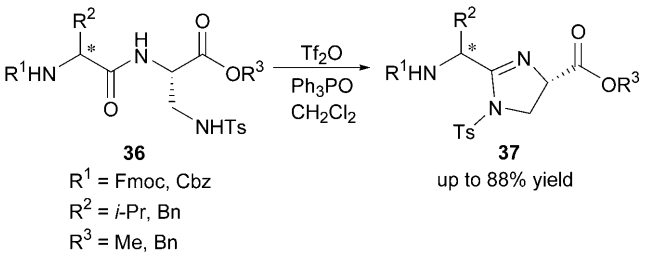
35

Figure 8. Chiral pincer complex containing the VAPOL unit.

The first asymmetric form of this reaction was reported by Lin et al. in 1999,[39,40] using Me_2SAuCl and ferrocene-derived diphosphine ligand **33**[41] which has been successfully used in the reaction of isocyanide with aldehydes. The catalyst also showed good reactivity and enantioselectivity in this reaction. The desired products **34** were obtained with up to 88% *ee* by the action of 0.5 mol% catalyst at room temperature (Figure 7). Compared with the reaction of aldehydes, $(c\text{-HexNC})_2AuBF_4$ gave inferior results than Me_2SAuCl.

In 2008, Szabó et al. reported a recent example of this asymmetric reaction.[42] On the basis of their former work on pincer-Pd(II) catalysts **32**,[38] a novel chiral pincer complex **35** containing a VAPOL unit (Figure 8) was synthesized. Up to 98% combined yield for diastereomers and 86% *ee* for *cis* isomers were achieved, while no diastereoselectivity was observed. Other pincer complexes containing modified BINOL units gave lower *ee* but moderate selectivities for *trans* isomers.

This reaction can also be conducted in a three-component form, using primary amines and aldehydes or ketones for the *in situ* generation of imines.[43–45] The desired products with up to four substitutions on the 4 and 5 positions can be obtained without a metal catalyst at room temperature. The reaction can be further improved by adding AgOAc as catalyst. Primary amines with hydroxy or double bond units can be involved, and more complex products can be obtained using isophthaldehyde or hexane-1,6-diamine. No asymmetric form of the three-component reaction has been developed till now.



36 37

R^1 = Fmoc, Cbz
R^2 = *i*-Pr, Bn
R^3 = Me, Bn

up to 88% yield

Scheme 8. Synthesis of 2-imidazoline-containing amino acids and peptides (Method D).

2.5 Synthesis of 2-Imidazolines from *N*-Acyl Diamines (Method D)

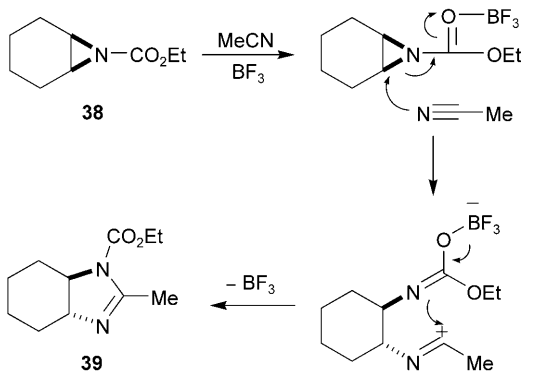
In 2004, You and Kelly developed an efficient route for 2-imidazoline formation from *N*-acyl diamines **36** mediated by Tf_2O and Ph_3PO.[46] This method has good functional group compatibility and can be used for the synthesis of imidazoline-containing amino acids **37**, as illustrated in Scheme 8. The oxygen atom in the amide group is transformed to a leaving group and substituted by TsNH in the side chain, which is different from the oxazoline formation. No racemization of the two chiral centers was observed in this reaction. Compared with method A, the only difference is that the *N*-acyl diamine is isolated as intermediate in this case. Such a variation provides us with an opportunity to use chiral carboxylates without loss of optical purity.

2.6 Synthesis of 2-Imidazolines from Aziridines (Method E)

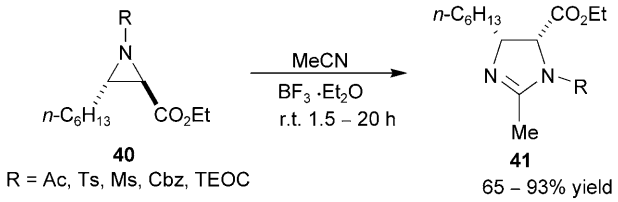
In 1973, Nozaki et al. reported the BF_3-mediated synthesis of imidazolines from aziridines and nitriles.[47] In this pioneering work, the *cis*-1,2-dialkyl-substituted aziridine **38** gave specifically *trans* product **39**. Both acetonitrile and benzonitrile were used in this reaction at 81 and 100 °C, respectively. On the basis of this result, an S_N2 mechanism was proposed by the authors, as illustrated in Scheme 9.

In 1992, this method was expanded to more substrates by Zwanenburg et al., such as *N*-protected aziridines **40** derived from ethyl 2-nonenoate (Scheme 10).[48] In this work, the reaction took place smoothly at room temperature and the *cis* products **41** were obtained in up to 91% yield as single diastereomers.

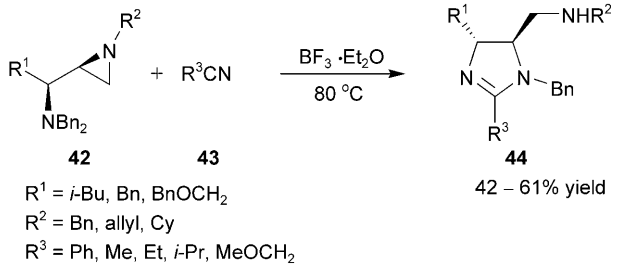
In 2004, Concellón et al. investigated the chiral induction in this reaction.[49] The enantiopure aziridines **42** with a dibenzylamino group on the α-carbon reacted with different nitriles **43** by the catalysis of the $BF_3{\cdot}Et_2O$ complex (Scheme 11). The *N*-benzyl-4,5-disubstituted imidazolines **44** were obtained in enantiopure form instead of the predicted 5-substituted prod-



Scheme 9. Mechanism for the BF_3-mediated 2-imidazoline synthesis (Method E).



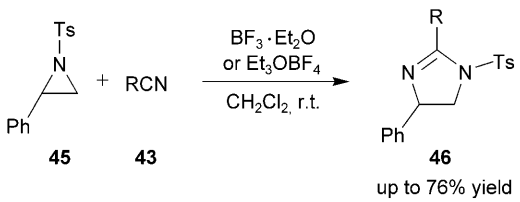
Scheme 10. Synthesis of 2-imidazolines from aziridines and acetonitrile (Method E).



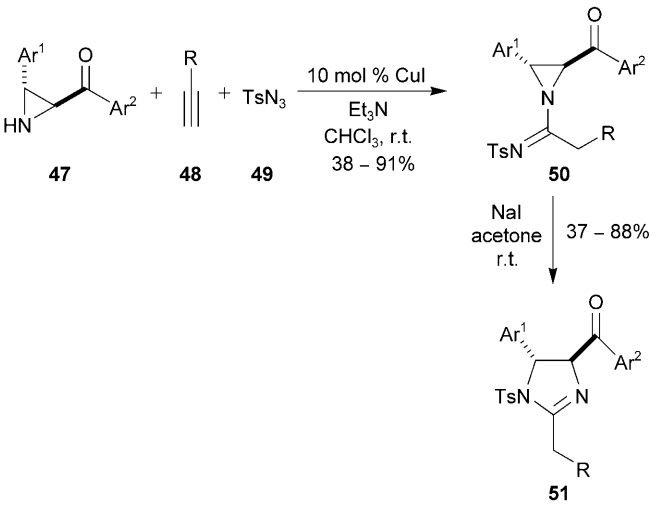
Scheme 11. Chiral induction in 2-imidazoline synthesis (Method E).

uct. In the proposed mechanism, the aziridine ring is opened by the vicinal dibenzylamino group by the catalysis of BF_3, and a new aziridinium species is formed. The newly formed ring is transformed to imidazoline through nucleophilic attack of nitrile followed by ring closure, in which a benzyl group is removed by nitrile as *N*-benzylamide.

In the same year, Singh et al. reported the reaction of 1-tosyl-2-phenylaziridine **45** with a series of nitriles **43** under the catalysis of $BF_3{\cdot}Et_2O$ or Meerwein's salt (Scheme 12).[50,51] When enantiopure aziridine was used, only racemic product **46** was obtained, indicating the S_N1 nature of the ring-opening step, which is due to the ability of the phenyl group to stabilize the vicinal carbocation. In the case of 2,3-disubstituted aziridines containing one phenyl group, the nitriles attack selectively the phenyl-substituted carbon.



Scheme 12. Synthesis of 5-phenyl-2-imidazolines from aziridine and nitriles (Method E).



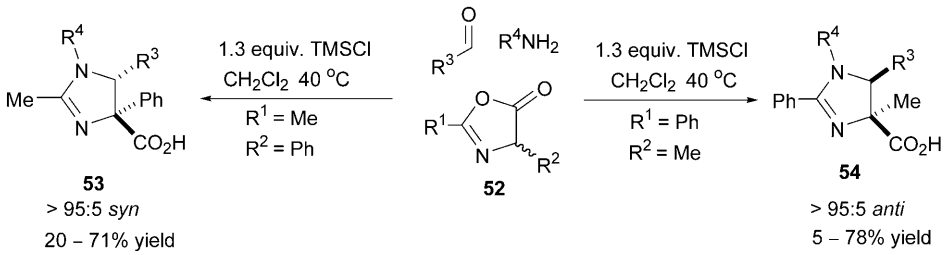
Scheme 13. Synthesis of 2-imidazolines through three-component condensation (Method E).

When $Zn(OTf)_2$ was used as catalyst, the reaction was conducted under solvent-free conditions to achieve high yields.[51]

In 2008, Liang et al. reported a different reaction behaviour of aziridines towards 2-imidazolines (Scheme 13).[52] From *trans*-*N*-unsubstituted aziridines **47** derived from chalcones, terminal alkynes **48**, and tosyl azide **49**, the *N*-tosylamidines **50** with the *trans* configuration were obtained by the catalysis of CuI in moderate to good yields. These intermediates were transformed to *trans*-4,5-disubstituted-2-imidazolines **51** through NaI-mediated ring expansion with full retention of the configuration.

2.7 Synthesis of 2-Imidazolines from Azlactones and Imines (Method F)

From 2002 to 2005, Tepe et al. developed a TMSCl-mediated cycloaddition of azlactones **52** (münchnones) with *in situ* generated imines.[53–55] The mechanism of the reaction was proposed as a TMSCl-mediated 1,3-dipole formation followed by [3+2] cycloaddition and elimination. The possibility of a stepwise mechanism was excluded by experiments. Heating the mixture of azlactones, aldehdyes and amines without

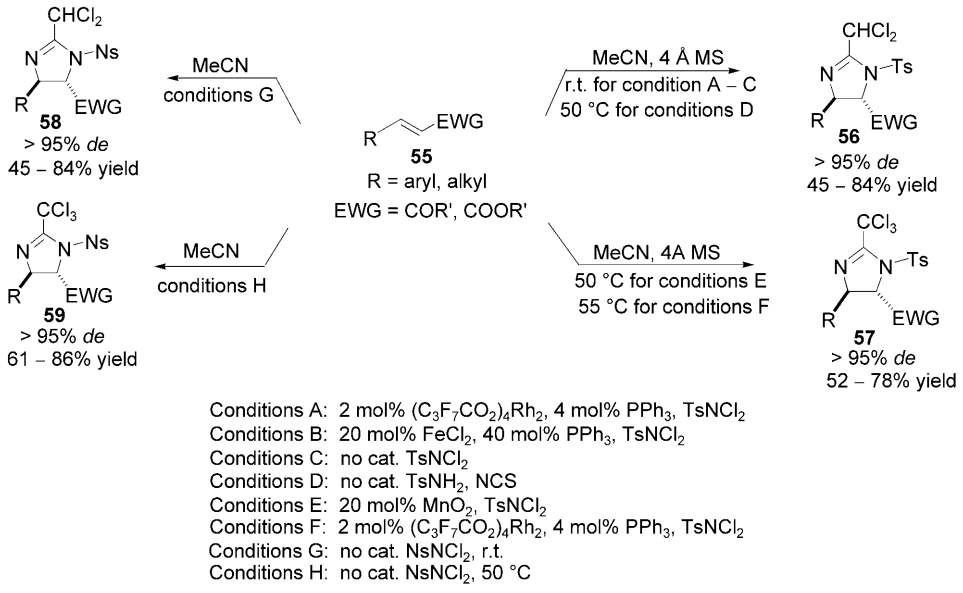


Scheme 14. Synthesis of 2-imidazolines from azlactones and imines (Method F).

TMSCl led to undesired products formed *via* ketene formation. The diastereoselectivity of this reaction can be inverted by using different substrates, as illustrated in Scheme 14. If R^1 and R^2 were changed to other groups, the diastereoselectivity decreased significantly. The chiral induction using (*R*)-1-phenylethylamine as amine component was also tested. However, no product was formed in this case.

2.8 Synthesis of 2-Imidazolines from Alkenes (Method G)

From 2001 to 2005, Li et al. developed a diastereoselective synthesis of 2-imidazolines from alkenes (Scheme 15).[56–62] In their first report,[56] the electron-deficient alkenes **55** (enones and unsaturated esters) were transformed to 2-dichloromethyl-2-imidazolines **56** by the catalysis of 4 mol% Rh(II)-PPh_3 complex generated from $(C_3F_7CO_2)_4Rh_2$ *in situ*, using excess acetonitrile as solvent. The addition of molecular sieve was crucial for achieving good results. The *anti* products were obtained in moderate yields with excellent diastereoselectivities at room temperature. In the proposed mechanism,[57] the imidazoline ring was formed through aziridinium formation, ring-opening by acetonitrile, and nucleophilic ring-closing. The two chlorine atoms were introduced through chlorination with $TsNCl_2$. This mechanism suggests that it is possible to form 2-trichloromethyl-2-imidazolines **57**. However, only dichloromethyl-substituted products **56** were obtained using this catalyst at room temperature, as well as when using $FeCl_2/PPh_3$[58] or even without catalyst.[59] The reaction can also be extended to $NsNCl_2$ instead of $TsNCl_2$ with higher reactivity under catalyst-free conditions at room temperature.[60] The trichloromethyl-substituted products **57**/**59** were successfully formed at elevated temperature, for example, using Rh(II)-PPh_3 catalyst at 55 °C[57] or using MnO_2 catalyst at 50 °C,[62] or using more active $NsNCl_2$ at 50 °C without catalyst.[60] The authors also investigated the use of $TsNH_2$/NCS as reagent instead of $TsNCl_2$ in this reaction.[61] The 2-dichloromethyl-2-imidazolines **56** were obtained at 50 °C.



Scheme 15. Synthesis of 2-trichloromethyl- and dichloromethyl-2-imidazolines (Method G).

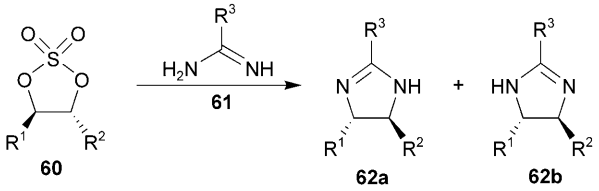
2.9 Miscellaneous (Method H)

In 1983, Tsuji et al. reported the formation of 2,4,5-triphenyl-substituted imidazoline derivatives through Fe- or Cu-catalyzed reaction of benzylamine with CCl_4.[63] The imidazoline products were obtained as a mixture of *N*-H and *N*-Bn isomers, together with many by-products such as imidazoles and benzaldehyde.

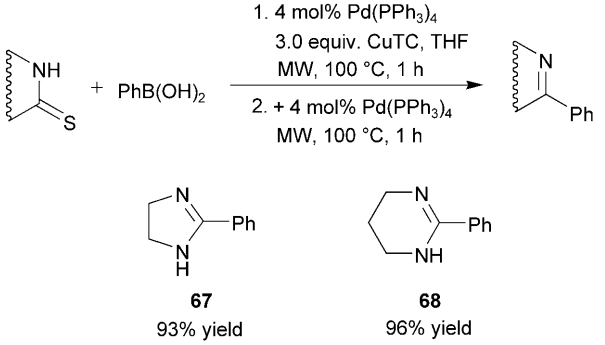
In 1991, Sharpless et al. reported the synthesis of chiral 2-imidazolines **62** from chiral 1,2-cyclic sulfates **60** and non-cyclic amidines **61** through double S_N2 reaction (Scheme 16).[64] The chiral material can be easily prepared from alkenes *via* asymmetric dihydroxylation and condensation with SO_2Cl_2. Both of the two regioisomers were obtained for C_1-symmetrical sulfates, while only racemic imidazolines were obtained for C_2-symmetrical sulfates.

In 1998, Walsh et al. reported the synthesis of 2,4,5-tri-2-pyridyl-2-imidazoline **66** from ammonium hydroxide and pyridine-2-carboxaldehyde **63** (Scheme 17).[65] The *cis*-**66** was formed *via* 6π-electrocyclization of the anion **65** in 84% overall yield. The *cis*-**66** can be epimerized to the thermodynamically favoured *trans*-**66** by treatment with *t*-BuOK in THF in 92% yield.

In 2007, Kappe et al. developed a Pd(0)-catalyzed Cu(I)-mediated coupling of cyclic thioamides or analogues with arylboronic acids (Scheme 18).[66] As analogues of thioamides, five- and six-membered thioureas were coupled with phenylboronic acid in excellent yields, providing 2-imidazoline **67** and tetrahydropyrimidine **68**, respectively. CuTC was used to facilitate the thioimidate formation and the oxidative addition of the C–S bond to Pd(0) for the high affinity of Cu(I) to sulfur.



Scheme 16. Synthesis of 2-imidazolines through double S_N2 reaction (Method H).



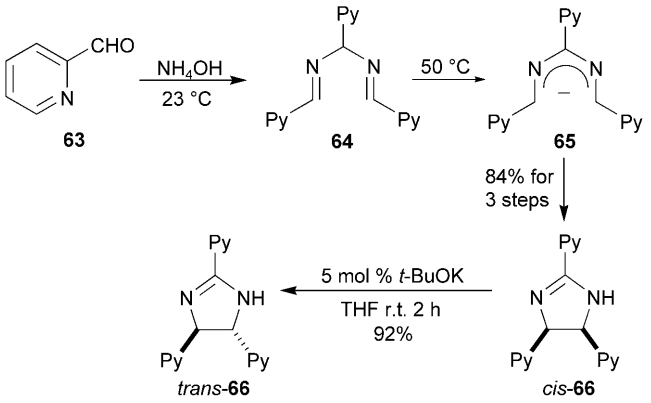
Scheme 18. Synthesis of 2-phenyl-2-imidazoline through cross coupling (Method H).

3 Applications of 2-Imidazolines in Homogeneous Catalysis

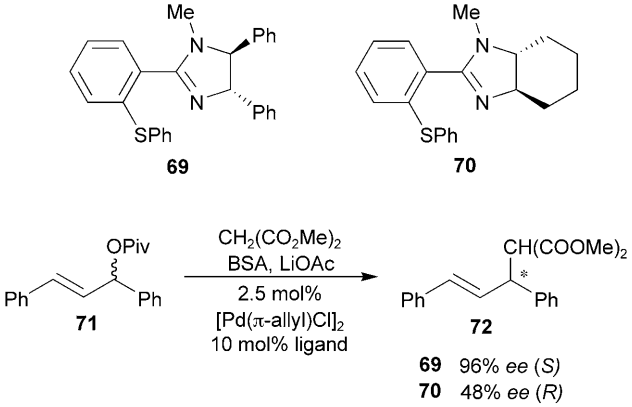
3.1 Applications in Palladium-Catalyzed Reactions

3.1.1 Asymmetric Allylic Alkylation

In 1997, Morimoto et al. reported the Pd-catalyzed asymmetric allylic alkylation reaction (Scheme 19).[67] The authors hoped that the enantioselectivity and reactivity would be improved considering the higher electron-donating ability of imidazoline compared with oxazoline. Ligands **69** and **70** were synthesized from 2-bromobenzonitrile and corresponding 1,2-diamines *via* imidate formation and condensation (Method A3). After the *N*-methylation, the imidazo-



Scheme 17. Synthesis of 2,4,5-tripyridinyl-2-imidazoline (Method H).



Scheme 19. Application of mono-2-imidazoline ligands in allylic alkylation.

lines were treated with *t*-BuLi and then PhSSPh to introduce the sulfide structure. Under the optimized conditions, 1,3-diphenyl-2-propenyl pivalate **71** was transformed to product **72** in 78% yield with 96% *ee* by using 5 mol% Pd and 10 mol% **69**. Reducing the catalyst loading led to a significant decrease of yield and reaction rate, while the enantioselectivity was not affected. Ligand **70** gave lower *ee* than **69** for its smaller steric repulsion of the six-membered ring.

In 2004, Casey et al. reported ligands **73–77** with 5,6,5 or 5,7,5 tricyclic skeletons (Figure 9).[68] The ligands were synthesized from the bis(β-hydroxyamide)s of oxalic acid by sequential treatment with $SOCl_2$, PCl_5, and tethered amines (Method B). When racemic 1,2-diphenylamine was used, **76** and **77** were obtained as 1:1 mixtures of diastereomers, which can be separated by chromatography and characterized by NOE experiments.

The authors prepared the $PdCl_2$ complexes of **73** and **75** (R = *i*-Pr). In the X-ray diffraction (XRD) structures, the two complexes show different torsion angles and Ψ, whose definition is illustrated in Figure 10. In complex **73**-$PdCl_2$, the stronger strain of the 5,6,5 ring system leads to smaller torsion and larger Ψ, while the weaker strain of the 5,7,5 ring system in complex **75**-$PdCl_2$ leads to larger torsion and smaller Ψ.

In the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, ligands **74** and **75** with a 5,7,5 ring system gave better *ee* (R = *i*-Pr, 76% for **74** and 72% for **75**) than **73** with a 5,6,5 ring system. For comparison, bis(oxazoline) ligand **79** was also tested (Figure 10). Lower yield (86% *vs.* 97%) and *ee* (77% *vs.* 80%) were obtained than with **75** (R = *i*-Bu). Chirality in the tether had no effect on enantioselectivity, while the yield was higher with the matched ligand **77**. According to the author, the improved selectivity with the 5,7,5 ring system can be attributed to the decrease in the Pd–N bond lengths and the Ψ angles, which moves the R groups at the chiral centers slightly closer to the metal and provides a better chiral environment. In the allylic alkylation of 1,3-dimethyl-2-propenyl acetate, the differences in *ee* values were negligible.

3.1.2 Asymmetric Overman Rearrangement

In 2006, Peters et al. reported the ferrocene-derived mono-imidazoline ligands **80/83**, and corresponding palladacycles **82/84** (Scheme 20 and Scheme 21).[69] The imidazoline moieties were prepared from imidates formed *in situ* from amide by treatment with Meerwein's salt (Method A3). The palladacycle **82** was prepared through an imidazoline-directed diastereoselective *ortho*-lithiation[70] followed by quenching with 1,2-diiodoethane, and oxidative addition to Pd(0) species. The >19:1 *dr* was determined by NMR analysis of the monomeric complex. On the contrary, **84** was prepared through direct diastereoselective C–H palladation because that all attempts to *ortho*-lithiate

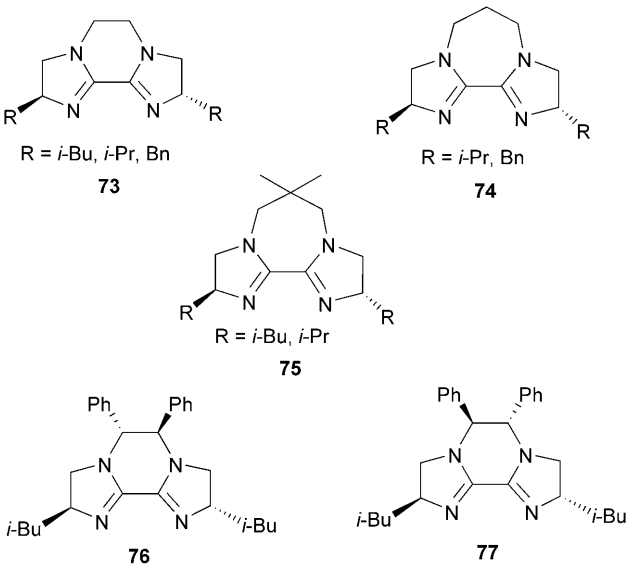


Figure 9. C_2-Symmetrical bis(imidazoline) ligands.

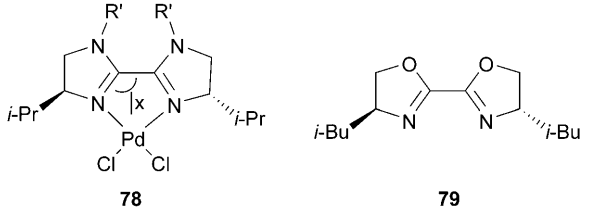
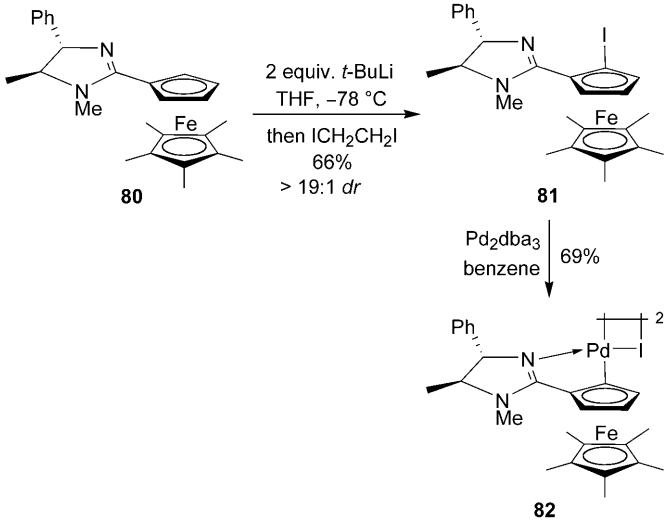
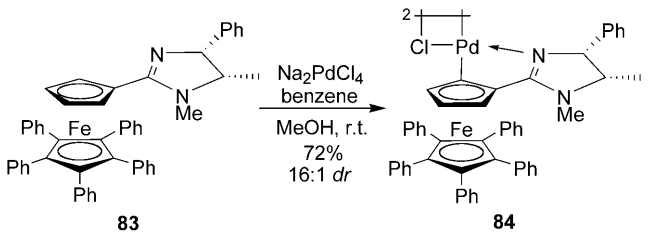


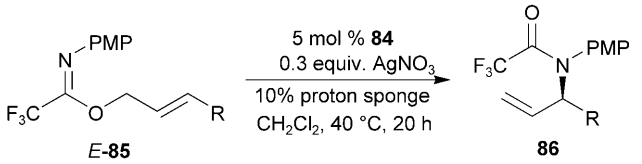
Figure 10. Bis(imidazoline)-Pd complex and bis(oxazoline) analogue.



Scheme 20. Synthesis of pentamethylferrocene-derived 2-imidazoline palladacycle.



Scheme 21. Synthesis of pentaphenylferrocene-derived 2-imidazoline palladacycle.



	yileld	*ee*
R = *n*-Pr	96%	88%
R = $(CH_2)_2$Ph	98%	84%
R = Me	93%	88%

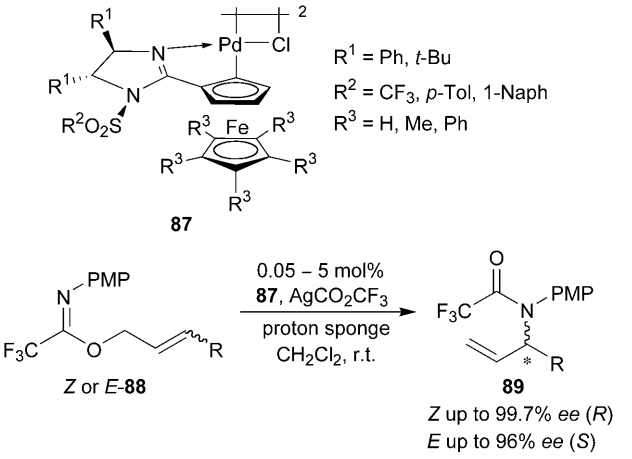
Scheme 22. Asymmetric Overman rearrangement.

C_5Ph_5 derivative **83** failed. The product **84** was further treated with Na(acac) to form the monomeric complex in order to determine the *dr* value.

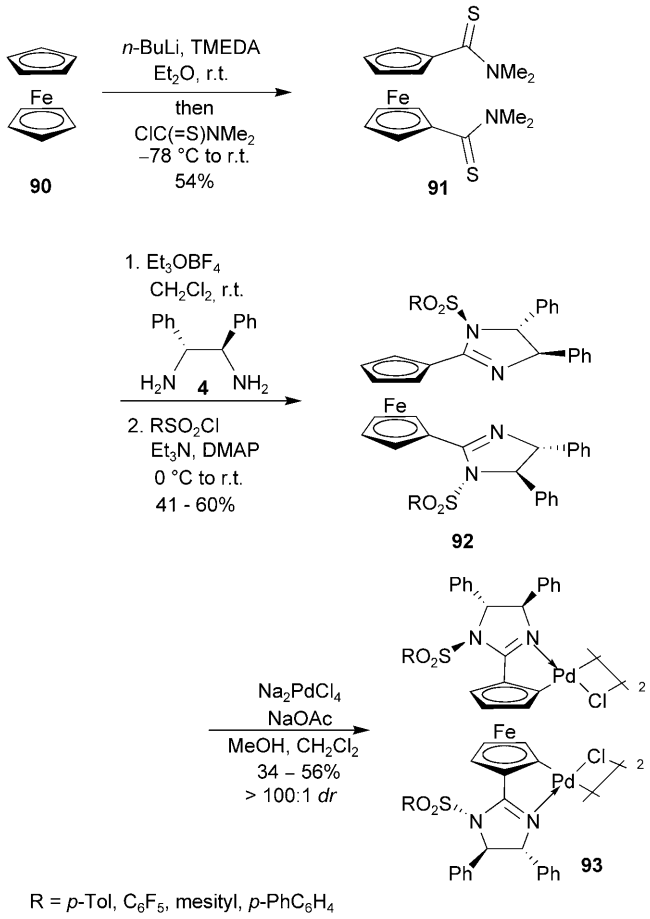
Complex **84** was tested in the Overman rearrangement of trifluoroacetimidates **85** with *E* double bonds (Scheme 22). The cationic catalytic active species was generated *in situ* by treatment with $AgNO_3$. Up to 98% yield and 88% *ee* were obtained with three substrates **86**.

In the same year, Peters et al. reported a series modified imidazoline-containing palladacycles **87** (named as FIP-Cl by the authors), which were also prepared from amide through Method A3 (Scheme 23).[71] Direct C–H palladation gave 9:1 to 83:1 *dr* values and 50–93% yields. All of the precursors showed good activities in the Overman rearrangement of model substrates **88**. The optimized R^1 and R^2 were phenyl and *p*-tolyl, respectively. In the case of *Z*-**88**, palladacycles derived from C_5H_5 and C_5Me_5 gave comparable *ee* values, while the precursor derived from C_5Ph_5 gave the best result in the case of *E*-**88**. In the screening of AgX as activating reagent, $AgCO_2CF_3$ gave good results in most cases and sometimes AgOTf was better. The possible oxidation of ferrocene by Ag(I) was excluded in the rearrangement by NMR experiment. Under the optimized condition, up to 99.7% *ee* were achieved with *Z*-**88**, and up to 96% *ee* with *E*-**88**, with opposite absolute configurations.

In 2007, Peters et al. reported the ferrocene-derived bis(imidazoline) ligands **92** (Scheme 24).[72] The bis(thioamide) intermediate was prepared through dilithiation followed by quenching with $ClC(=S)NMe_2$. The thioimidate generated by treatment with Meerwein's salts was condensed with 1,2-diphenylethylenediamine followed by *N*-sulfonylation to give **92** in moderate yields (Method A5). Direct C–H palladation formed complexes **93** as single diastereomers.



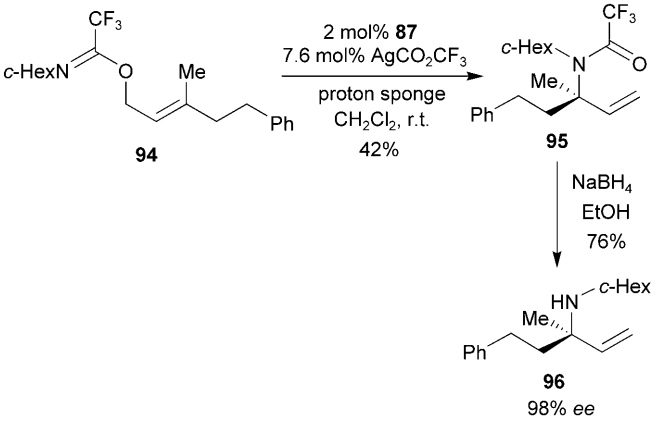
Scheme 23. Asymmetric Overman rearrangement.



Scheme 24. Synthesis of ferrocene derived bis(imidazoline) ligands and palladacycles.

After fine optimization, **93** (R = *p*-Tol) and AgOTs were chosen as the best precursor and activator, respectively. In the asymmetric Overman rearrangement of *Z*-**88**, 93–98% enantioselectivities were achieved by the catalysis of even 0.1 mol% **93**. Other catalysts gave comparable *ee* values but significantly lower yields.

In 2008, the same group extended the application of **93**.[73] In the rearrangement of *E*-configured substrates, the *ee* values decreased to 62–78%. The authors synthesized several functionalized *Z*-configured substrates containing protected hydroxy and amino groups. In all tested cases, 94–100% yields and 96–98% *ee* values were obtained, illustrating the high applicability of this catalytic system. The newly synthesized (1*S*,2*S*)-cyclohexane-1,2-diamine-derived imidazoline-containing palladacycle gave lower *ee* with the opposite configuration. Considering the easily removable trifluoroacetyl group, this rearrangement was developed to an efficient route for the synthesis of chiral allylic amines.[74] The amines were deprotected by treatment with $NaBH_4$ in ethanol. Good yields (75–89%) and no loss in enantioselectivity were achieved. The authors also tested the efficiency of this methodology using the terminally disubstituted allylic trifluoroacetimidate **94** (Scheme 25). The desired allylic amine **96** was obtained in 32% overall yield with 98% *ee*.

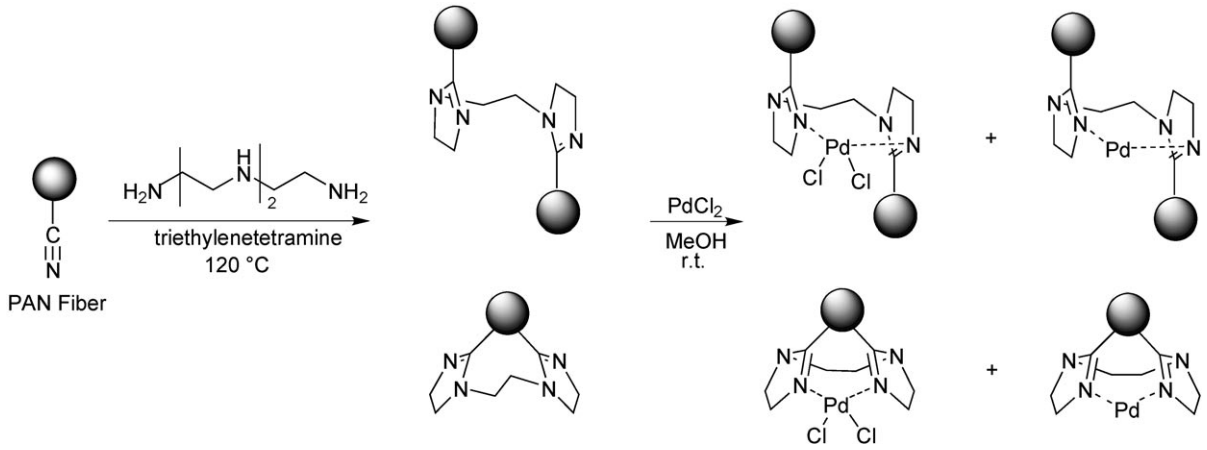


Scheme 25. Synthesis of chiral quaternary allylic amine *via* Overman rearrangement.

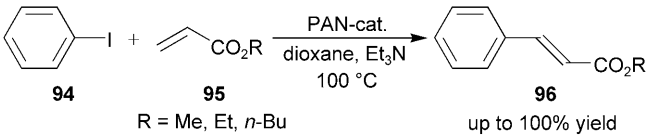
3.1.3 Mizoroki–Heck and Suzuki–Miyaura Reactions

In 2003, Song and Wu et al. developed the polyacrylonitrile (PAN) fiber-immobilized imidazoline ligands (Scheme 26).[75] The PAN fiber was treated with triethylenetetramine at 120 °C to generate a mixture of inter-chain and intra-chain cross-linking products. After coordination with $PdCl_2$, XPS analysis indicated the co-existence of Pd(II) and Pd(0) species. This polymer-immobilized Pd complex showed good activity in Mizoroki–Heck reactions of aryl iodides **94** with acrylates **95** (Scheme 27). Excellent yields could be obtained at 100 °C in dioxane using 0.01 mol% catalyst and Et_3N as base. In the case of ethyl acrylate, the TON value can be raised to 31,500, although the reaction time had to be prolonged to 130 h. Aryl bromides were less reactive in this system, while aryl chlorides were totally unreactive. The immobilized catalyst can be recycled for at least 20 times without any loss of activity.

In the same year, Busacca et al. reported an investigation of ligand electronic effects in the asymmetric intramolecular Mizoroki–Heck reaction (Scheme 28).[76] The tunable modular ligand **97** (also named as BIPI) was synthesized from 1,2-diamine and *o*-fluoro- or *o*-iodobenzonitrile through Method A3. The diarylphosphinyl group was introduced by an S_NAr reaction or Pd-catalyzed C–P coupling. The substituents on the diarylphosphinyl group and imidazoline ring were screened comprehensively. According



Scheme 26. Synthesis of PAN immobilized imidazoline-Pd complexes.



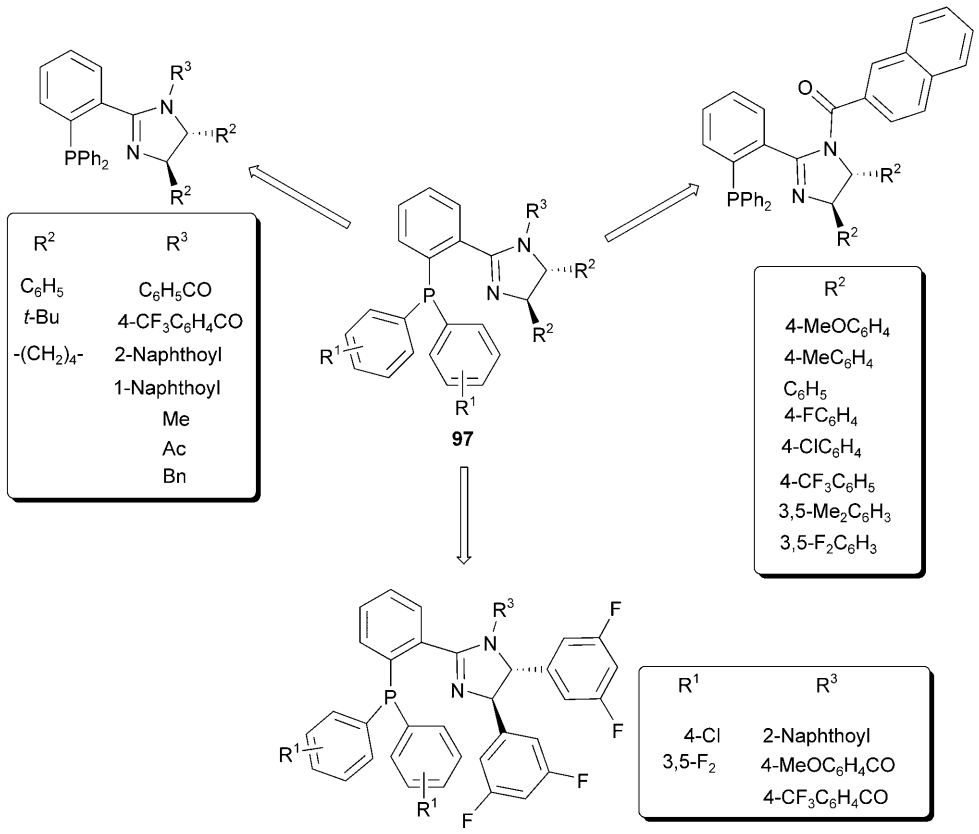
Scheme 27. Mizoroki–Heck reaction of aryl iodides.

to the experimental results, a 2-naphthoyl group was the best choice for R^3. The ligands with electron-withdrawing groups at R^2 and R^3 positions gave better enantioselectivities, although the yields decreased. Up to 88% *ee* was achieved using 11 mol% of the optimized ligand ($R^1=R^2=3,5\text{-}F_2C_6H_3$, $R^3=$2-naphthoyl) combined with 5 mol% Pd_2dba_3 (Scheme 29), which was higher than using the unmodified BINAP as ligand. This work demonstrates the importance of tuning the electronic effect of ligands in asymmetric catalysis.

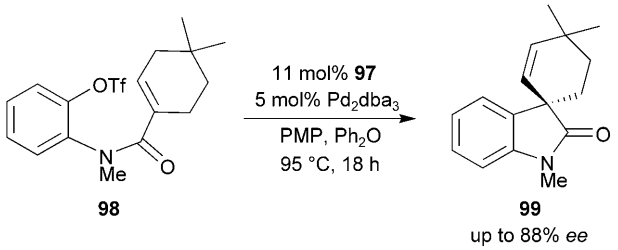
In 2004, Özdemir et al. reported two Pd complexes **100** and **101** containing mono-imidazoline ligands **108/109** and Me_2PPh (Figure 11).[77] The imidazoline ligands were prepared from *N*-substituted ethylenediamine and DMF-DMA (Method A3). For comparison, the authors also synthesized *N*-alkylated benzimidazole-containing complexes. In both Mizoroki–Heck reaction and Suzuki–Miyaura reaction, imidazoline complexes and benzimidazole complexes showed similar reactivities (Scheme 30). Not only aryl bromides **102** but also aryl chlorides **103** can be transformed to products in >90% yields. Especially, this catalytic system was active for deactivated aryl chlorides, such as *p*-chlorotoluene and *p*-chloroanisole. Up to 90% yield can be achieved at 80 °C in 2–4 h using 1.5 mol% catalyst. The high reactivity was ascribed to the strong electron-donating ability of imidazolines and Me_2PPh which accelerate the oxidative addition of the C–Cl bond to the Pd(0) species.

In 2005, the same group synthesized five mono-imidazoline ligands **108–112** with different substitutions on the N atom from DMF-DMA (Method A3) (Figure 12).[78] All of the ligands were tested in the Suzuki–Miyaura coupling of aryl chlorides **103** with phenylboronic acid **104**. The active complexes were generated *in situ* by mixing $PdCl_2(MeCN)_2$ with 2 equivalents of ligands. Compared with the former work, no phosphine ligand was used in this case. Ligand **108** gave excellent yields for both activated and deactivated aryl chlorides. The short reaction time (2–4 h) and mild conditions indicate the high reactivity of the catalyst.

In 2007, Cui and Wu et al. synthesized ferrocene-derived mono-imidazoline palladacycles **113** from cyanoferrocene through an imidate intermediate



Scheme 28. Tuning of the ligand electronic effect.



Scheme 29. Asymmetric intramolecular Mizoroki–Heck reaction.

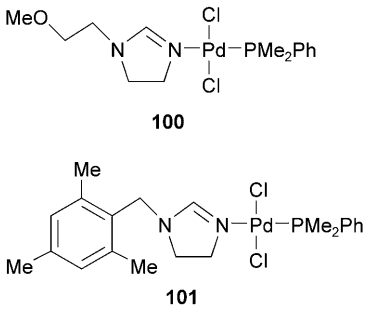


Figure 11. Mono-imidazoline-Pd complexes.

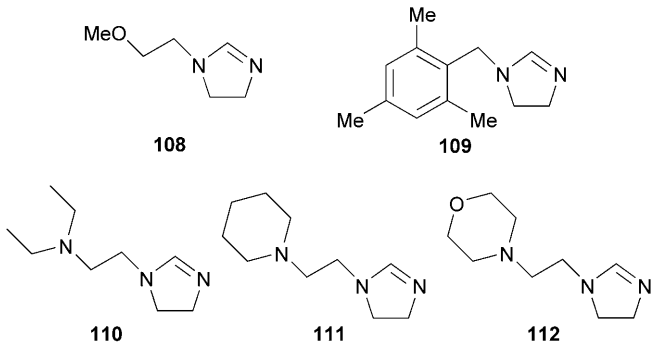


Figure 12. Mono-imidazoline ligands for coupling reactions.

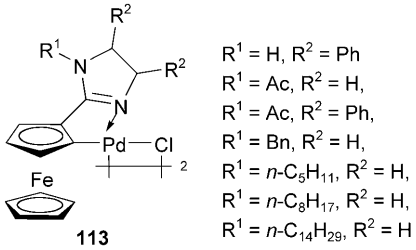
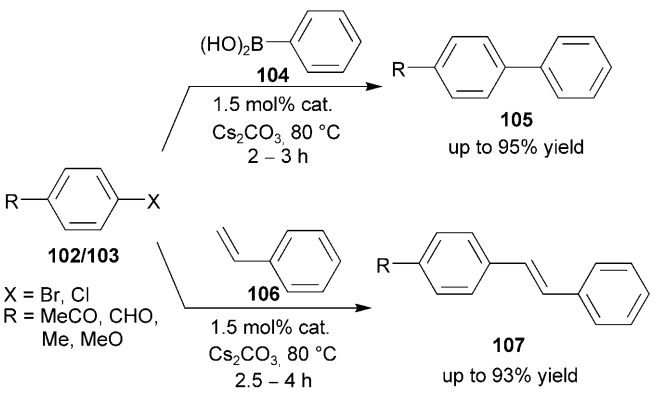


Figure 13. Ferrocene-derived mono-imidazoline palladacycles.

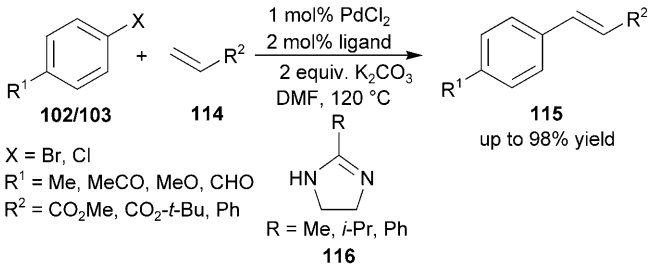
(Method A3) (Figure 13).[79] The direct C–H palladation by Li_2PdCl_4 in methanol at room temperature gave the corresponding palladacycles as single diastereomers. Their catalytic activity in the Suzuki–Miyaura coupling of aryl bromides **102** with phenylboronic acid **104** was evaluated using 0.1 mol% catalysts and $K_3PO_4 \cdot 7H_2O$ as base in toluene at 110 °C. The ethylenediamine-derived catalyst (R^1 = Bn, R^2 = H) gave much better results (96% *vs.* 56%) in the coupling of 2-bromothiophene than the other palladacycles, while comparable good yields were obtained in the coupling of 2-bromonaphthalene and 4-bromotoluene. This catalyst was also used successfully in the coupling of diverse aryl bromides with arylboronic acids (81–99% yields).



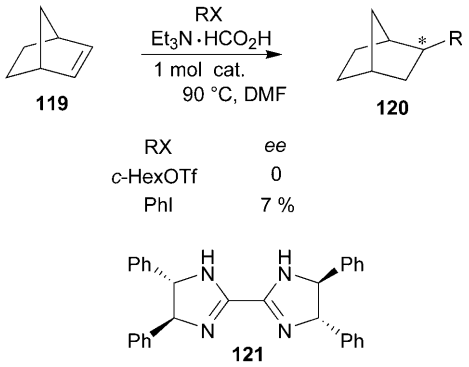
Scheme 30. Suzuki–Miyaura and Mizoroki–Heck reactions.

In the same year, Hayashi et al. reported the application of mono-imidazoline ligands **116** in the Pd-catalyzed Mizoroki–Heck reaction (Scheme 31).[80] The ligands with no substitution on the N atom, which are different from **108–112**, were commercially available. Generally, 2-imidazoline ligands gave better results than 1- and 2-substituted imidazoles, due to their stronger electron-donating ability. 2-Methylimidazoline was the most efficient ligand, giving up to 98% yield for aryl bromides. In the reaction of *p*-chlorobenzaldehyde, the addition of 2 equivalents of *n*-Bu_4NBr was critical for obtaining 85% yield, while only 18% yield was obtained without the additive. Both the preformed 1:2 complex and the *in situ* generated catalyst gave the same result. Although *n*-Bu_4NBr has been used to stabilize Pd nanoparticles in coupling reactions, the authors did not make any comment on the nature of active species.

In 2008, the same group reported the single crystal structures of the Pd complexes with 2-phenylimidazole and 2-phenylimidazoline (Scheme 32).[81] The authors discovered that different complexes can be obtained as single crystals when the mixture of 2-phenylimidazoline and $PdCl_2$ was crystallized under different conditions. When toluene was diffused slowly to a DMF solution of the complex, **117** with the two phenyl groups *trans* to each other crystallized as a single crystal. When the DMF solution was evaporated slowly in vacuum, **118** crystallized as a single crystal instead, while the powder XRD study indicated



Scheme 31. N–H imidazoline ligands in Mizoroki–Heck reaction.



Scheme 33. Pd-catalyzed asymmetric hydroarylation and hydrovinylation.

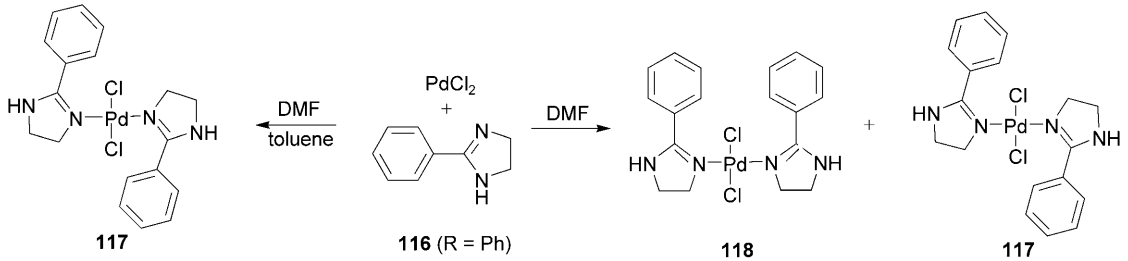
the co-existence of **117**. In the case of the 2-phenylimidazole complex, only the *trans* complex was obtained under both conditions. Further NMR analysis of **117** and **118** indicated that the two complexes tautomerize rapidly and have no difference in solution. In the Mizoroki-Heck reaction of *p*-bromotoluene with *tert*-butyl acrylate, the imidazoline complexes showed higher reactivity and shorter induction period than imidazole complex. In the former system, deposition of Pd black was observed during the reaction, indicating the easier dissociation of imidazoline ligand. The possible reactivity of Pd black was denied by the authors. A similar result was also observed in the Suzuki–Miyaura coupling of *p*-bromotoluene with phenylboronic acid.

3.1.4 Asymmetric Hydroarylation and Hydrovinylation

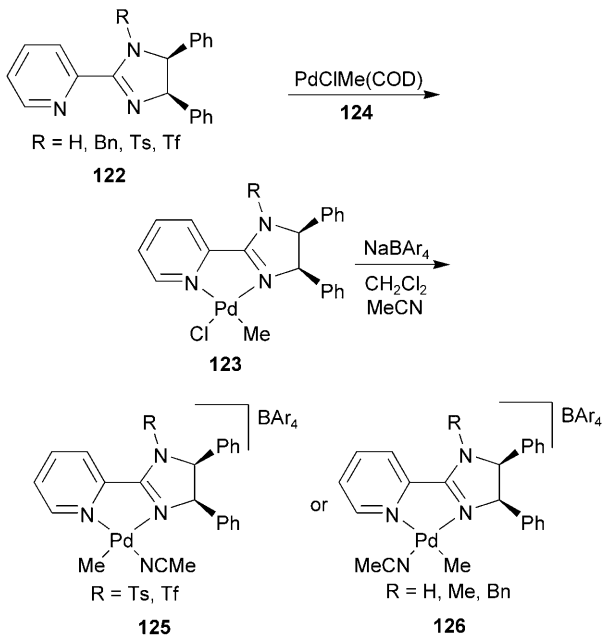
In 2001, Dupont et al. reported the synthesis of ligand **121** (Method A3) and the application of its complex with $PdCl_2$ in the asymmetric hydroarylation and hydrovinylation of norbornene **119** (Scheme 33).[82] The complex was prepared from **121** and Na_2PdCl_4 in methanol. Through XRD analysis of the complex, the intramolecular H···Cl hydrogen bond and its effect on the packing mode were revealed. In the hydroarylation of norbornene **119**, 100% yield was obtained at 90 °C using 1 mol% catalyst, while 42% yield was obtained in the hydrovinylation. However, the two reactions only gave 0–7% *ee*. No information on the absolute configuration was reported.

3.1.5 Copolymerization of CO with Styrene

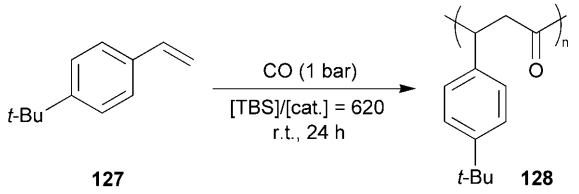
In 2001, Claver et al. reported the application of ligand **122** in the Pd-catalyzed copolymerization of CO with styrene.[83] Ligand **122** was synthesized from 2-cyanopyridine and *cis*-1,2-diphenylethylenediamine by the catalysis of $Yb(OTf)_3$ (Method A2). The neutral complexes **123** were formed from **122** and [PdClMe(COD)] **124** in anhydrous toluene. After being treated with $NaBAr_4$ in the mixture of CH_2Cl_2 and MeCN, two kinds of cationic complexes **125** and **126** were formed (Scheme 34). When R is electron-withdrawing group, the methyl group coordinates *trans* to the less basic imidazoline ring, while it coordinates *cis* to the imidazoline ring when R is H or an electron-donating group. The isolatable mixture of cationic complexes were tested in the copolymerization of CO with 4-*tert*-butylstyrene **127** (Scheme 35). Introducing electron-withdrawing groups into **122** leads to a greater proportion of *u* diads giving highly syndiotactic copolymers. The stereoregularity is attributed to a chain-end control due to the interaction of the growing chain with the incoming styrene unit, which inserts exclusively in a 2,1-fashion. A relation-



Scheme 32. Different configurations of Pd complexes from different solvents.



Scheme 34. Synthesis of neutral and cationic Pd complexes.



Scheme 35. Copolymerization of CO with 4-*tert*-butylstyrene.

ship between the nature of the R substituent and the activity of the catalytic system was not found.

In 2002, the same group reported their investigation on the influence of pyridine-imidazoline ligands on the reactivity of Pd-methyl complexes with CO.[84] All the reaction steps and intermediates were extensively revealed by NMR analysis. As illustrated in Figure 14, when R = H or Bn, the complexes **129** in which CO coordinates *trans* to the pyridine ring were formed specifically. When R = Ts or Tf, mixtures of *cis* and *trans* complexes **130** were observed because of the equilibrium between *cis* and *trans* isomers. Less observable intermediate types in the latter case indicates that the electron-deficient complexes reacted faster with CO than the electron-rich ones. Considering the reactivity and stereoregularity data in the former work, the author concluded that the Pd-acyl fragment *cis* to imidazoline may be more reactive than the *trans* one.

In 2004, a further investigation was reported.[85] Chiral ligands **131** with different R groups were synthesized from (1*R*,2*R*)-1,2-diphenylethylenediamine (Figure 15). Compared with the cationic complexes

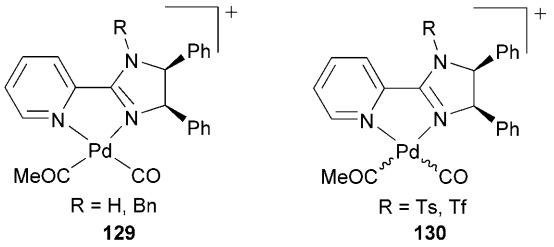


Figure 14. Complexes formed through CO insertion.

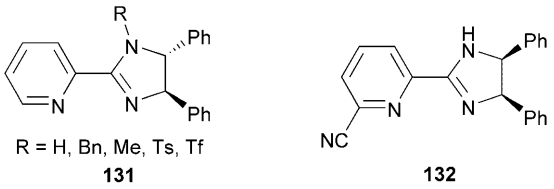


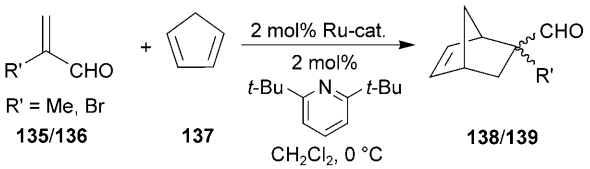
Figure 15. Pyridine derived mono-imidazoline ligands.

derived from **122**, the methyl group coordinates *cis* to the electron-rich imidazoline ring, while the mixture of *trans* and *cis* isomers is formed with the electron-deficient imidazoline ring. According to density functional theory (DFT) calculations, both the isomers are formed through dissociation of one Pd–N bond (pyridine side or imidazoline side) followed by MeCN coordination. The equilibrium between the isomers is disfavoured in energy. In the copolymerization reaction, complexes derived from **131** showed higher reactivity than those derived from **122**. The complex derived from **132** has no reactivity for the disfavoured steric repulsion between the CN group and the growing chain. The electronic effect of **131** is weaker than that of **122**. The content of *l* diads of the polyketones ranged between 23% and 37%, while the content varied from 15% to 65% in the latter case. A prevailing syndiotactic microstructure was obtained just similar to the case of the corresponding oxazoline ligands, which was attributed to the chain-end control that overcomes the enantiosite control created by the chiral ligands. No chiral induction was observed.

3.2 Applications in Ruthenium-Catalyzed Reactions

3.2.1 Asymmetric Diels–Alder Reaction

In 2001, Davies et al. reported the application of **131** in the Ru-catalyzed asymmetric Diels–Alder reaction (Scheme 36).[86] In this work, compounds **131** with an Me- and H-substituted imidazoline ring were synthesized through Method A3. Complexes **133** (Figure 16) were prepared by treating **131** with $[RuCl_2(mesitylene)]_2$ in refluxing methanol in the presence of $NaSbF_6$. Two stereomers can be observed



Scheme 36. Ru-catalzyed asymmetric Diels–Alder reaction.

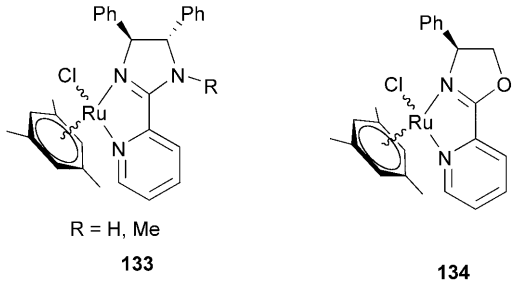


Figure 16. Ru complexes for asymmetric Diels–Alder reaction.

in the crude product solution by NMR, while in the single crystal the phenyl substituent adjacent to the imine nitrogen on the imidazoline ring is on the same side as the chloride rather than the mesitylene. The complexes undergo isomerization in CH_2Cl_2 at room temperature, faster than complex **134**. The reactive dication catalysts for the Diels–Alder reaction were generated by treating **133** or **134** with $AgSbF_6$. In the reaction of methacrolein **135** with cyclopentadiene **137**, the desired product **138** was formed smoothly. The *N*-Me catalyst gave lower yields than the *N*-H catalyst (35% *vs.* 90%), while the *exo*/*endo* ratio was similar (93:7 *vs.* 94:6). Unfortunately, only 31% and 45% *ee* were obtained for *N*-Me and *N*-H catalysts, respectively. Both imidazoline catalysts were inferior to the oxazoline catalyst derived from complex **134** (58% *ee*). In the reaction of 2-bromoacrolein **136**, both imidazoline catalysts gave comparable yields and *exo*/*endo* ratios, together with up to 26% *ee*.

In 2006, the same group developed imidazoline complexes **140** with one chiral center on the imidazoline ring (Figure 17), from unsymmetrical chiral 1,2-diamines and pyridine-2-methoxyimidate (Method A3).[87] The catalytic activity of the dication complexes was evaluated in the same reaction as their former report. Generally, the improvement was not significant in the reaction of 2-methacrolein. The highest 58% *ee* was obtained using the valinol derived *N*-*n*-Bu catalyst, which is still lower than the result of **141** (75% *ee*). In the reaction of 2-bromoacrolein, the *ee* was improved to 50% by the same catalyst, while **141** showed no reactivity in this reaction.

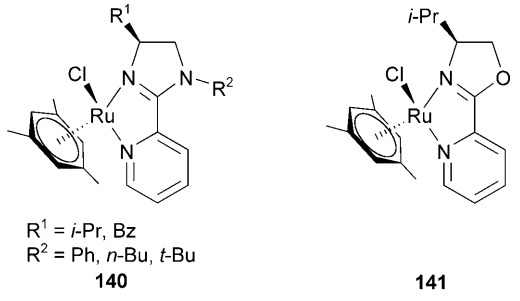


Figure 17. Ru complexes for asymmetric Diels–Alder reaction.

3.2.2 Asymmetric Epoxidation

In 2005, Beller et al. reported the combinatorial synthesis of PyBox-type bis(imidazoline) ligands **142** from pyridine-2,6-dimethoxyimidate, (1*R*,2*R*)-1,2-diphenylethylenediamine or (1*R*,2*R*)-1,2-diaminocyclohexane, and different electrophiles R^2X (Method A3).[88,89] On the basis of their work on the PyBox-Ru complexes-catalyzed asymmetric epoxidation of olefins,[90] the authors wanted to improve the results by using bis(imidazoline) as a more flexible scaffold for modification. As illustrated in Figure 18, 28 different electrophiles were used in the modification. Because mono-modification was observed in some cases, the authors also synthesized some ligands with unsymmetrical *N*-substitutions.

All of the 36 novel ligands were tested in the Ru-catalyzed asymmetric epoxidation of styrene and *trans*-stilbene using H_2O_2 (30% in water) as oxidant in *tert*-amyl alcohol. The active catalysts were generated before use by treating the ligands with $[RuCl_2(p\text{-cymene})]_2$ and sodium pyridine-2,6-dicarboxylate in moderate to good yields. Through fine screening, catalysts **143** modified with two (+)-menthyl chloroformates and **144** modified with one (+)-menthyl chloroformate and one 2,4,6-trimethylbenzoyl chloride gave better *ee* values than the other complexes (Figure 19). Up to 43% *ee* for styrene and 71% *ee* for *trans*-stilbene were comparable to the best enantioselectivity reported before using H_2O_2 as oxidant.[90] For the easier preparation of catalyst **143**, it was further applied in the epoxidation of other olefins with moderate *ee* values.

3.2.3 Asymmetric Transfer Hydrogenation

In 2007, Beller et al. reported the application of *N*,*N*,*N*-pyridinebis(imidazoline) ligands in Ru-catalyzed asymmetric transfer hydrogenation of prochiral ketones.[91] Some of theses ligands were developed by the same group for Ru-catalyzed asymmetric epoxidation (*vide supra*). After fine screening of different Ru sources and amount of base, two optimized catalytic systems were selected for further application. In the

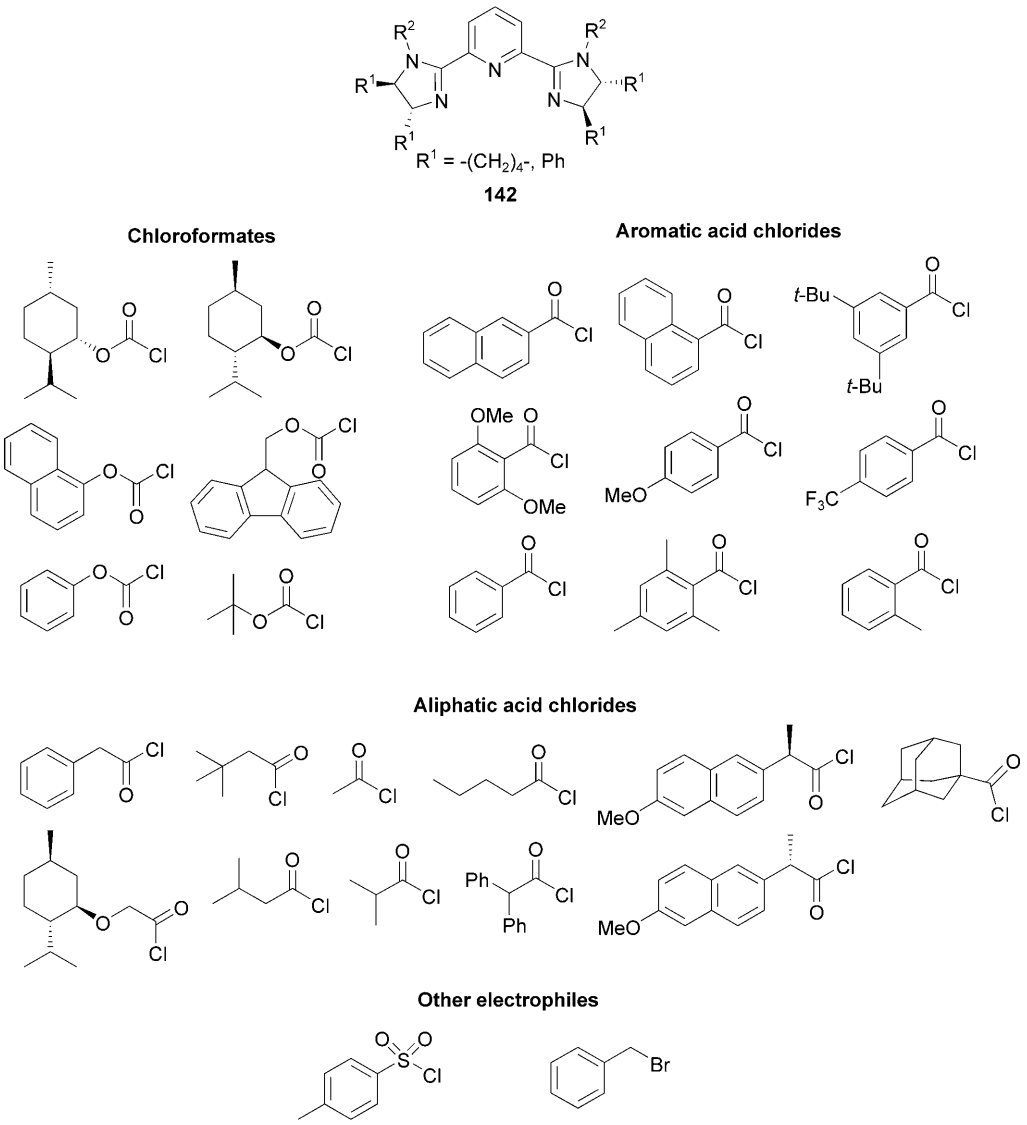
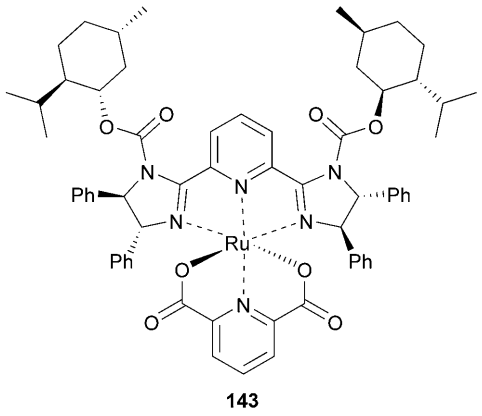


Figure 18. Different electrophiles used in the modification of bis(imidazoline) ligand.

kinetic experiment, catalyst A generated *in situ* from **142** (R^1 = Ph, R^2 = H), $[RuCl_2(C_6H_6)]_2$, and PPh_3 showed lower reactivity and selectivity than catalyst B, which was generated *in situ* from the same ligand and $RuCl_2(PPh_3)_3$. Chiral (*S*)-2-phenylethanol was obtained in excellent yield with 94% and 98% *ee*, respectively. Generally, bis(imidazoline) ligands gave better results than the corresponding bis(oxazoline) ligands. The superiority of *N*-H substituted **142** was dramatic. In the asymmetric transfer hydrogenation of other prochiral ketones, the *ee* values ranged from 72% to 98% for catalyst A, compared with from 12% to 89% for catalyst B (Scheme 37). The two catalytic systems can be good supplements to each other for different substrates.

3.2.4 Cycloisomerizations

In 1999, Özdemir and Dixneuf et al. reported the synthesis of Ru complexes **147**/**148** with mono-imidazoline ligands, as well as complexes with mono-tetrahydropyrimidine ligands (Figure 20).[92] The catalytic activity of the complexes was tested in the Ru-catalyzed cycloisomerzation of (*Z*)-3-methyl-2-en-4-yn-1-ol **149** to 2,3-dimethylfuran **150** (Scheme 38). According to the experimental data, complexes **148** derived from hexamethylbenzene gave better results than **147** derived from *p*-cymene. Complexes with mono-tetrahydropyrimidine ligands showed higher reactivity, and the *N*-Bn substituted complex gave 99% conversion within 22 h. The desired product can be purified by simple distillation in 84% yield. The different reactivity was attributed to the electron-richness of the



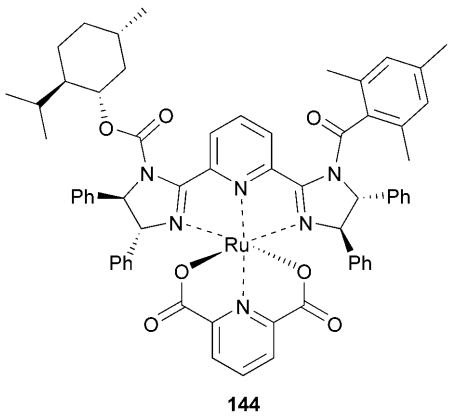
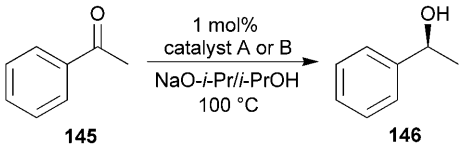


Figure 19. Optimized Ru complexes for asymmetric epoxidation.



Scheme 37. Asymmetric hydrogenation of ketones.

Ru(II) center as indicated by the redox potentials. The authors postulated that the Ru(II) provides a catalytic electrophilic activation of the alkyne bond only in a short range of redox potentials, for example, not with very electrophilic or electron-rich Ru(II) complexes.

In 2004, Ru complexes **151** and **152** were applied to the cycloisomerization of 1,6-dienes by the same group (Figure 21).[93] Through screening, the complex **151** derived from *p*-cymene and *N*-2,4,6-trimethylbenzylimidazoline gave the best yield. The mechanism of the reaction was postulated by the authors. After being treated with AgOTf, the complex $RuCl_2$(arene)L was transformed to a monocation, which reacts rapidly with 1,1-diphenyl-2-propyn-1-ol **153** and generates a purple complex **154**, as illustrated in Scheme 39. Complex **154** was hypothesized as the catalytically active species. *N*-Tosyldiallylamine **155** can

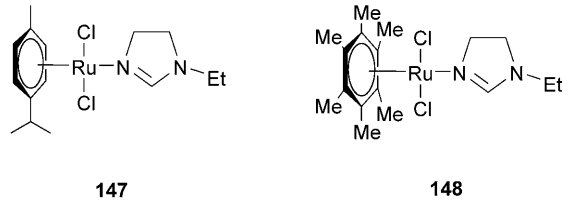
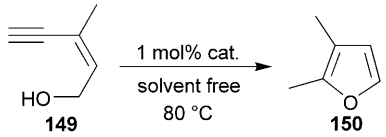


Figure 20. Ru complexes for cycloisomerization of (*Z*)-3-methyl-2-en-4-yn-1-ol.



Scheme 38. Ru-catalyzed cycloisomerization of (*Z*)-3-methyl-2-en-4-yn-1-ol.

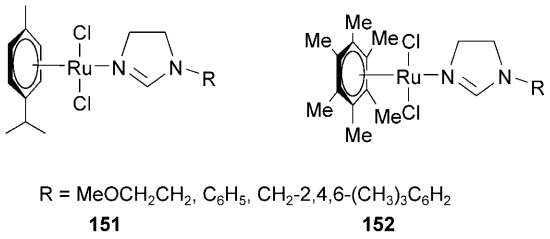


Figure 21. Ru complexes for cycloisomerization of 1,6-diene.

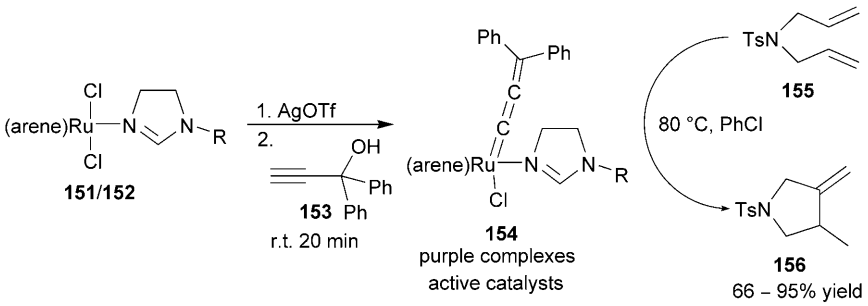
be transformed to desired methylenepyrrolidine product **156** in up to 95% yield.

3.3. Applications in Copper-Catalyzed Reactions

3.3.1 Asymmetric Benzoylation of Diol

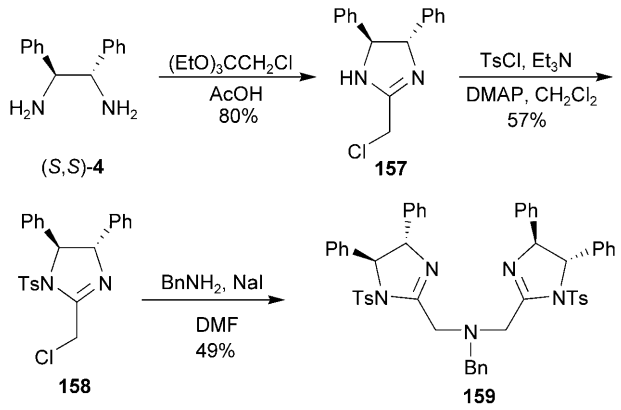
In 2005, Arai et al. reported the modular synthesis of *N*,*N*,*N*-tridentate bis(imidazoline) ligands from triethyl 2-chloroorthoacetate (Method A3) (Scheme 40).[94] The two mono-imidazoline units **157** were linked to $BnNH_2$ by the catalysis of NaI in DMF. This single ligand **159** was tested in the Cu-catalyzed asymmetric desymmetrization of racemic *trans*-1,2-diphenylethylenediol **160**. The (*S*,*S*) isomer was selectively monobenzoylated by PhCOCl, **161**, by the catalysis of 5 mol% of the chiral complex in CH_2Cl_2. Unfortunately, a 28% yield (with 50% maximum yield) and 48% *ee* were obtained together with 67% recovered diol (Scheme 41).

In 2007, the same group reported the application of high-throughput screening technology in the optimization of the reaction conditions.[95] The modular ligand **159** was selected as the initial structure for the feasibility of synthesis on solid phase. The 2-chloromethylimidazoline was immobilized on functionalized

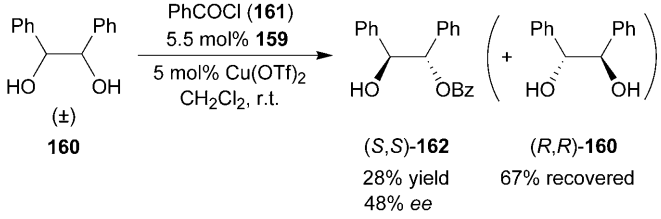


Scheme 39. Mechanism of Ru-catalyzed cycloisomerization.

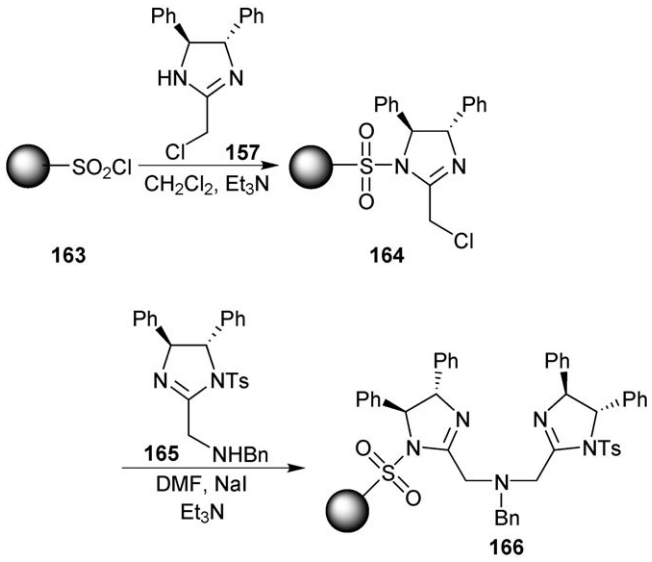
polystyrene through a sulfonamide bond. The immobilized ligand **166** was prepared through nucleophilic substitution similar to the former procedure (Scheme 42). In this work, the asymmetric benzoylation of *meso*-2,3-butanediol **167** was chosen as the model reaction (Scheme 43). The efficiency of asymmetric induction can be monitored conveniently by CD (circular dichroism) spectroscopy.[96] The optimized conditions were obtained after the rapid screening of metal salts, solvents, amines, and temperature. The immobilized ligand **166** was only used in the high-throughput screening, while the free **159** was used in normal asymmetric catalysis. Up to 97% yield and 95% *ee* were achieved by the catalysis of 5 mol% CuCl-**159** complex in CH_2Cl_2 at −40 °C in the presence of DIPEA. Good results can also be achieved with other linear and cyclic 1,2-diols.



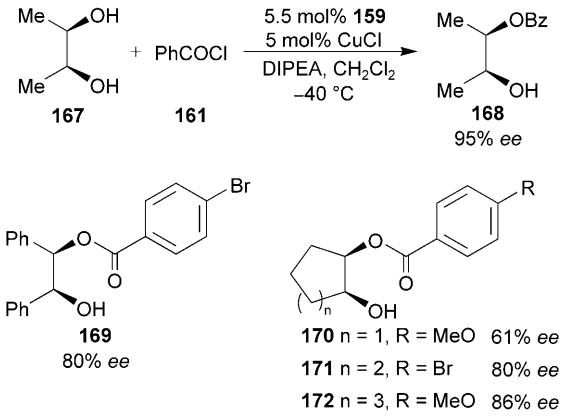
Scheme 40. Synthesis of tridentate bis(imidazoline) ligand.



Scheme 41. Cu-catalyzed asymmetric benzoylation of diols.



Scheme 42. Synthesis of immobilized bis(imidazoline) ligand.



Scheme 43. Cu-catalyzed asymmetric benzoylation of *cis*-diols.

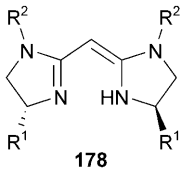
3.3.2 Asymmetric Cyclopropanation

The modular bis(imidazoline) ligand **159** was also tested in the Cu-catalyzed asymmetric cyclopropana-

tion by Arai et al. in 2005 (Scheme 44).[94] Under the catalysis of 5 mol% catalyst, the yield and diastereoselectivity varied drastically with different substrates. In the case of styrene **106**, the *trans* isomer was formed preferentially in excellent yield with 75% *ee*. On the contrary, nearly no diastereoselectivity was observed in the case of 1-methylstyrene **173**. The combined yield decreased to 42%, although 80% and 70% *ee* were obtained for the two isomers, respectively. When the R group was changed to phenyl, **174**, the desired cyclopropane was obtained in 39% yield with 75% *ee*.

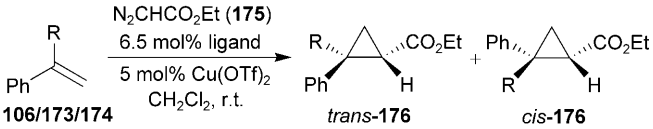
Another bis(imidazoline) system for asymmetric cyclopropanation was developed by Pfaltz et al. in 2007.[97] As part of their study on boron-bridged C_2-symmetrical chiral ligands,[98–100] they synthesized a series of boron-bridged bis(imidazoline) ligands **177** from different mono-imidazoline units (Scheme 45). Some of the compounds **175** were prepared from β-hydroxy amides **176** and primary amines in moderate yields (Method B), while the other ones were prepared from unsymmetrical substituted 1,2-diamines **173** and imidate **174** (Method A3).

The desired boron-bridged ligands **177** were synthesized through 2-lithiation of mono-imidazoline units and reaction with $(R^3)_2BX$ (X = Cl or Br). The carbon-bridged bis(imidazoline) ligands **178** were also synthesized for comparison from diethyl malonimidate with chiral diamines **173** (Figure 22). All the ligands were tested in the asymmetric cyclopropanation of styrene **106** with diazoacetate **175**. The best result was obtained by using **178** (R^1 = *t*-Bu, R_2 = 4-MeC_6H_4 or 4-$MeOC_6H_4$). The *trans*-**180** was obtained in up to 88% yield with >99:1 *de*, and 85% *ee*, for which the steric effect of **179** was crucial (Figure 23). The results obtained from boron-bridged ligands **177** were much inferior.



R^1 = *i*-Pr, *t*-Bu, Ph
R^2 = 4-MeC_6H_4, 4-$MeOC_6H_4$, Bn

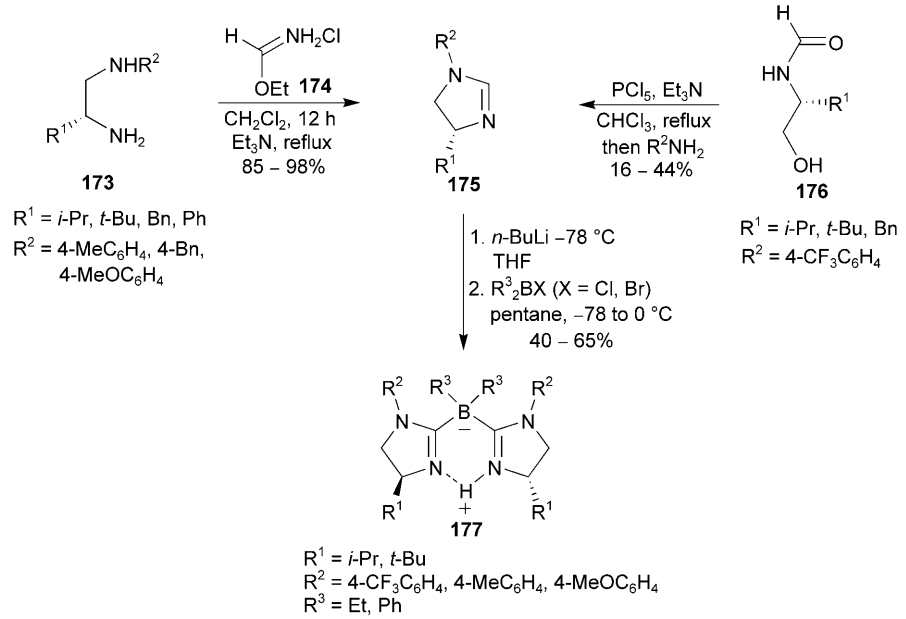
Figure 22. *C*-Tethered bis(imidazoline) ligands.



Scheme 44. Cu-catalyzed asymmetric cyclopropanation.

3.3.3 Asymmetric Henry Reaction

In 2007, You et al. reported the application of ligands **181** and **182** in the Cu-catalyzed asymmetric Henry reaction (Figure 24).[101] Ligands **181**/**182** were synthesized from pyridine-2,6-dicarboxylic acid/isophthalic acid and amino alcohols (Method B), which was different from the synthesis of **142**. In addition, there was only one substitution on the 4-position of the imi-



Scheme 45. Synthesis of *B*-tethered bis(imidazoline) ligands.

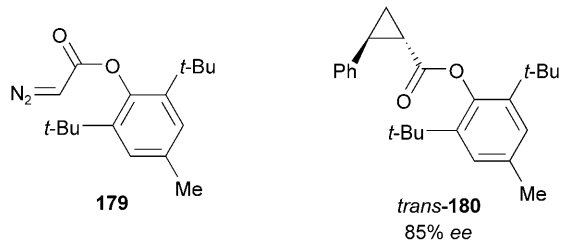


Figure 23. Product of cyclopropanation and the diazoacetate used.

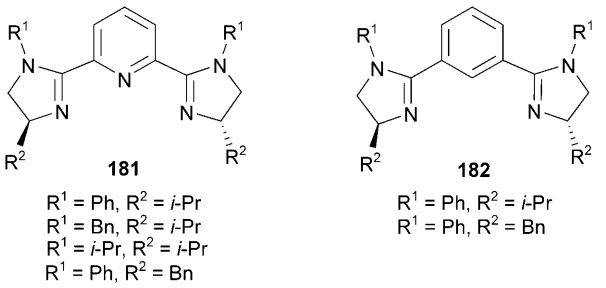
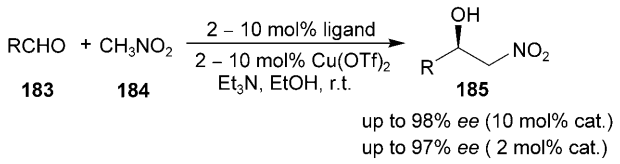


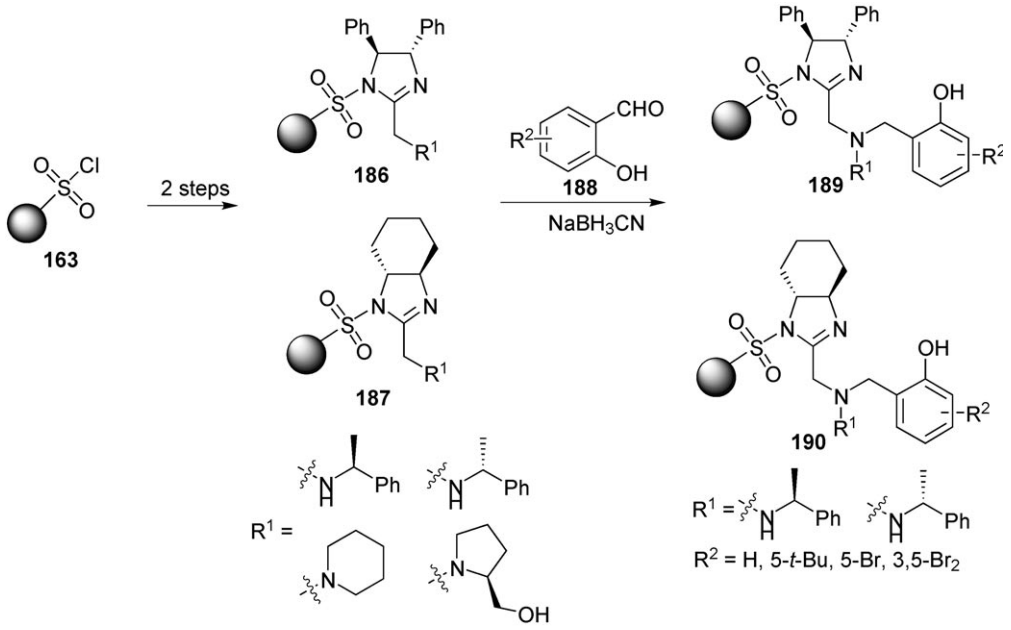
Figure 24. Pyridine- and benzene-derived bis(imidazoline) ligands.



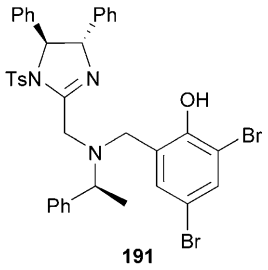
Scheme 46. Cu-catalyzed asymmetric Henry reaction.

dazoline ring. The small library of ligands was tested in the Henry reaction. The combination of 10 mol% $Cu(OTf)_2$ and 10.5 mol% **181** (R^1 = Ph, R^2 = *i*-Pr) showed the best result in ethanol, using 10 mol% Et_3N as base. Raising the amount of Et_3N led to lower enantioselectivity, while reducing its amount led to lower yield. The incomparable results from **182**-$Cu(OTf)_2$ complexes indicate the importance of the tridentate coordination mode. In the proposed transition state, the Cu(II) center has an octahedral structure in which the ligand, aldehyde, deprotonated nitromethane, and one OTf anion coordinate to the cation. This optimized catalyst can be successively used in the Henry reaction of both aromatic and aliphatic aldehydes **183** (Scheme 46). The chiral 2-nitro alcohols **185** were obtained with 93–98% *ee*. The catalyst loading can be further reduced from 10 mol% to 2 mol% without a significant effect on the enantioselectivity. The high stability of the catalyst can be proved by the good results of the reactions under air.

In 2008, another library of ligands was developed by Arai et al. for the Cu-catalyzed asymmetric Henry reaction.[102] On the basis of their former work,[95] they designed a series of immobilized mono-imidazoline ligands with a tertiary amine unit, or together with a phenol unit (Scheme 47). The diverse structures were synthesized in two or three steps in high efficiency from commercially available materials. Through high-throughput screening using the Cu-catalyzed Henry reaction of 2-nitrobenzaldehyde as model reaction, the ligands with both phenol and tertiary amine units gave better results. In the further optimization of the substitution on the phenol unit, the introduction of electron-withdrawing bromine atoms was found to be



Scheme 47. Synthesis of an immobilized mono-imidazoline ligand library.



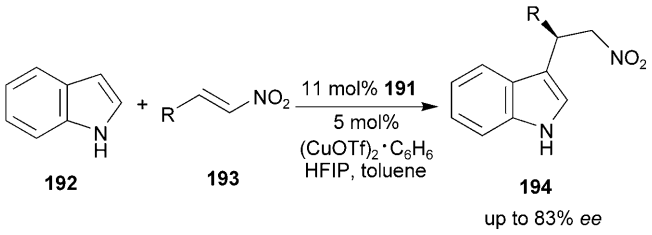
191

Figure 25. Optimized structure of mono-imidazoline ligand.

fruitful for the reaction. The source of Cu(II) was also critical in that $Cu(OAc)_2 \cdot H_2O$ was found to be the best one. With the optimized ligand structure and metal salt, the free ligand **191** (Figure 25) was synthesized to test the efficiency of the catalyst in the reaction of more substrates. Up to 94% and 91% *ee* were achieved for aromatic and aliphatic aldehydes, respectively.

3.3.4 Asymmetric Friedel–Crafts Alkylation

The effect of **191** in Cu(I)-catalyzed asymmetric Friedel–Crafts alkylation of indole **192** with nitroalkenes **193** were also tested by Arai et al. in 2008 (Scheme 48).[102] The desired product **194** was obtained in quantitative yield with up to 83% *ee*, in the presence of 2 equivalents of hexafluoroisopropyl alcohol as additive.



192 193 194

up to 83% *ee*

Scheme 48. Cu-catalyzed asymmetric Friedel–Crafts alkylation.

In the same year, Toru et al. reported the asymmetric Friedel–Crafts alkylation of indole **192** with ethyl 3,3,3-trifluoropyruvate **196** by the catalysis of **195**-Cu(OTf)$_2$ or **195**-Cu(NTf$_2$)$_2$ (Scheme 49).[103] The ligands (Figure 26) were synthesized from 1,3-diformylbenzene and 1,2-diamine through Method A4. In their experiments, they found that opposite absolute configurations were obtained using the same ligands but different Cu(II) sources. More interesting, good enantioselectivities with opposite configurations can even be achieved using TfOH and HNTf$_2$, instead of Cu(OTf)$_2$ and Cu(NTf$_2$)$_2$, respectively. Considering the structural feature of **195** that the C–H bond between the two imidazoline units occupies the position of the metal cation, it is impossible for **195** to chelate a metal cation. To interpret the origin of the unique phenomena, the authors postulated a putative transition state. The **195**-Cu(II) complex works in a bifunctional form, in that one imidazoline unit coordinates to Cu(II) and the other one fixes the position of indole through hydrogen bonding. The non-C_2 symmetrical structure and the coordination of the anion provide us with a way to realize the dramatic effect of the anion on the absolute configuration. The structure of the transition state may be affected significantly by the different coordination abilities and steric effects of OTf and NTf$_2$.

3.3.5 Miscellaneous

The carbon-bridged ligands **178** were also used in the Cu(I)-catalyzed asymmetric allylic oxidation of cyclopentene **198** and cyclohexene **199**, using *tert*-butyl perbenzoate **200** as oxidant (Scheme 50).[97] Good yields were obtained using 5 mol% catalyst, while only 59% and 44% *ee* were achieved for cyclopentene and cyclohexene, respectively, at room temperature.

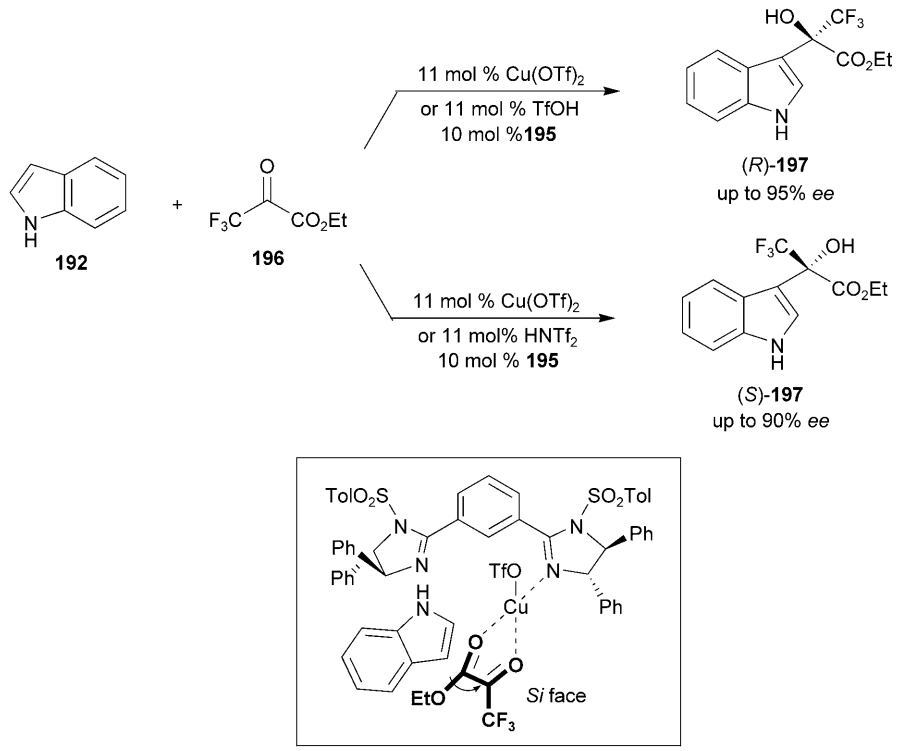
As a natural extension of their former work,[102] the mono-imidazoline ligand **191** optimized for asymmetric Henry reaction and Friedel–Crafts alkylation was applied to the tandem Friedel–Crafts/Henry reaction by Arai et al. in 2008 (Scheme 51).[104] The three materials were added together to the solution of catalyst and additive in toluene. As proposed by the authors, a Cu(I) coordinated deprotonated nitroalkane intermediate would be generated through the alkylation of indole, and react with aldehyde rapidly *via* a chair-like transition state before the protonation of the intermediate. The isolated Friedel–Crafts product cannot reacted with aldehyde using this catalytic system.

3.4 Applications in Other Metal-Catalyzed Reactions

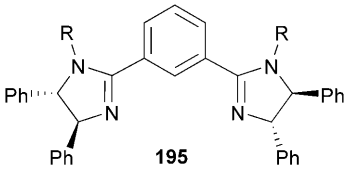
3.4.1 Rhodium-Catalyzed Reactions

In 1989, Botteghi et al. reported the synthesis and application of bidentate mono-imidazoline ligands **131** (R = H) and **208**/**209** in the asymmetric hydrosilylation of acetophenone (Figure 27).[105] This is the first application of chiral imidazoline ligands in asymmetric catalysis in the literature. In this pioneering work, the ligands were prepared through Method A3. The 2-phenylethanol was obtained with moderate yield but only up to 5.2% *ee*.

In 1997, Özdemir et al. reported the application of Rh(I) complexes **210** in the cyclopropanation of sty-

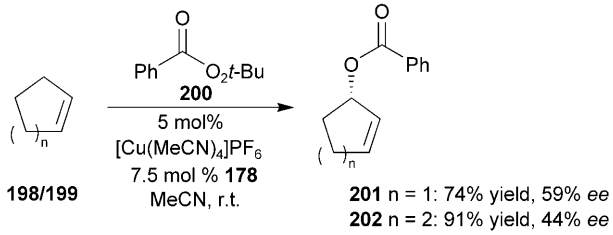


Scheme 49. Cu-catalyzed asymmetric Friedel–Crafts alkylation.



R = Ts, Bs, Tf, Bz, Ms, Ac
4-$NO_2C_6H_4CO$, 4-$MeOC_6H_4CO$
4-$NO_2C_6H_4SO_2$, 4-$CF_3C_6H_4SO_2$
4-$CF_3C_6H_4CO$, 4-$MeOC_6H_4SO_2$
3,5-$(CF_3)_2C_6H_3SO_2$,
2,4,6-$Me_3C_6H_2SO_2$

Figure 26. Benzene-derived bis(imidazoline) ligands.



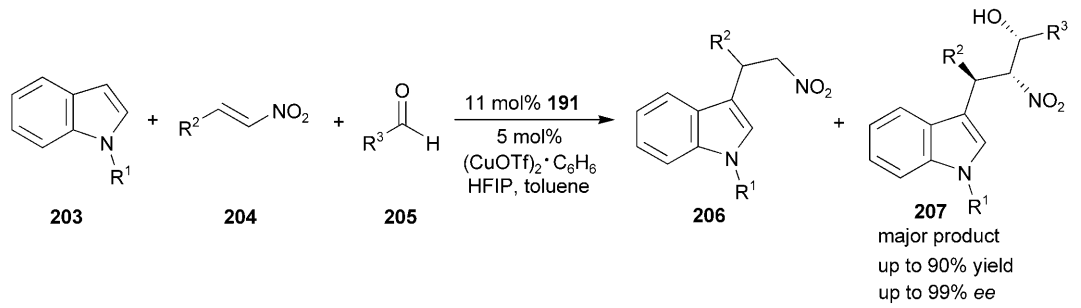
Scheme 50. Cu-catalyzed asymmetric allylic oxidation.

rene (Scheme 52).[106] If an excess amount of styrene was used as solvent, a 95% yield can be achieved by the catalysis of 0.9 mol% catalyst. No comment on the diastereoselectivity was given in the report.

3.4.2 Iridium-Catalyzed Reactions

In 2002, Pfaltz et al. reported the application of Ir(I) complexes **211** in the asymmetric hydrogenation of olefins (Figure 28, Scheme 53).[107] The optimized catalyst ($R^1 = t$-Bu, $R^2 = o$-Tol, $R^3 =$ Ph) showed high reactivity and 94% *ee* in the hydrogenation of *trans*-α-methylstilbene **213**. For comparison, 97% *ee* was obtained using **212** as catalyst. The enantioselectivity varied significantly with the structures of the substrates. Complexes **211** gave better results in some cases, while **212** gave high *ee* values in other cases. The difference between **211** and **212** can also be observed in their XRD structures. The dihedral angle indicated by a black line in **211** was much larger than that in **212**.

In 2004, another type of Ir(I) complexes **215** was reported by Claver et al. as catalyst in the asymmetric hydrogenation of imines (Figure 29).[108] The ligand was synthesized from dithioester and 1,2-diamine through Method A5. Under the action of 1 mol% catalysts, low to moderate enantioselectivities were obtained with different substrates. In the cases of the non-cyclic imines, the complex with an electron-withdrawing CF_3 group gave better results.



Scheme 51. Cu-catalyzed asymmetric tandem Friedel–Crafts/ Henry reaction.

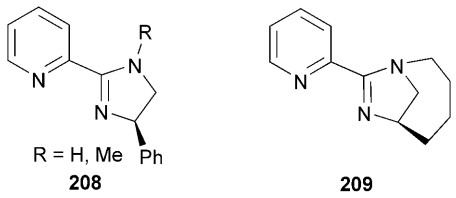


Figure 27. Pyridine-derived mono-imidazoline ligands.

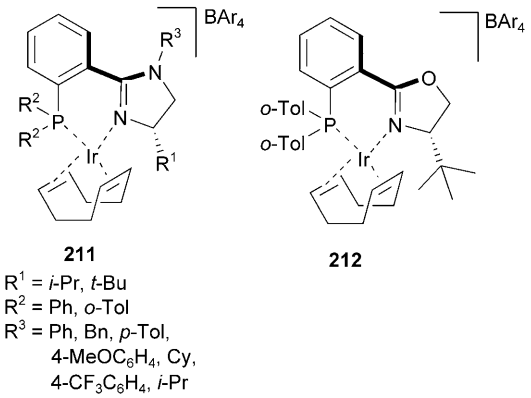
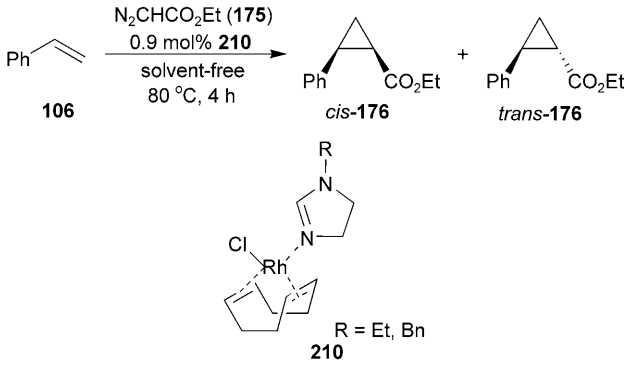
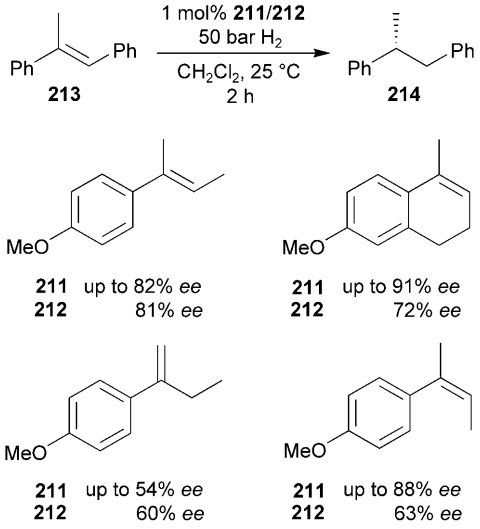


Figure 28. Ir complexes for asymmetric hydrogenation of alkenes.



Scheme 52. Rh-catalyzed cyclopropanation of styrene.



Scheme 53. Ir-catalyzed asymmetric hydrogenation of alkenes.

3.4.3 Nickel-Catalyzed Reactions

In 2004, Iwasawa et al. reported the Ni(0)-catalyzed coupling of CO_2 with alkynes using bis(imidazoline) ligands **216** (Figure 30, Scheme 54).[109] In the screening of ligands, the condition that $R^1 = H$ and $R^2 \neq H$ was important for achieving good yield and regioselectivity. In the reaction of other alkynes **217**, the regioselectivity varied significantly with substrates, which was determined by steric effects. When the reaction was extended to allenes **220**, the unsaturated acids can be obtained in good yields with excellent regioselectivity.

3.4.4 Zinc-Catalyzed Reactions

In 2002, Casey et al. reported the study on ligand electronic effects in asymmetric diethylzinc additions.[110] The hydroxy groups in the ligands **224**/**225** were synthesized through 2-lithiation of mono-imidazolines **223** and addition to pivaldehyde (Scheme 55).

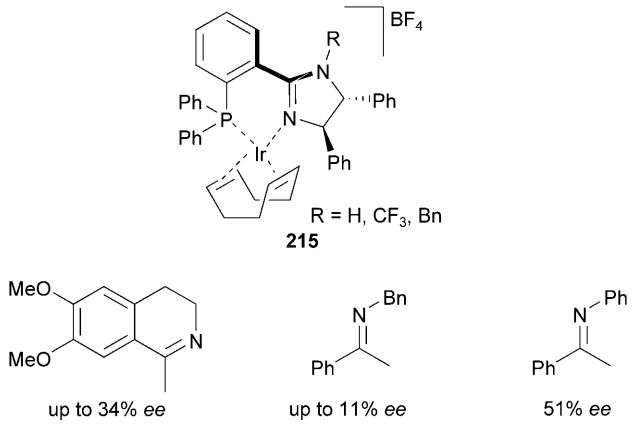


Figure 29. Ir complexes for asymmetric hydrogenation of imines.

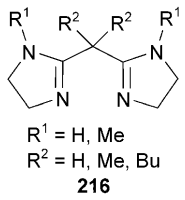
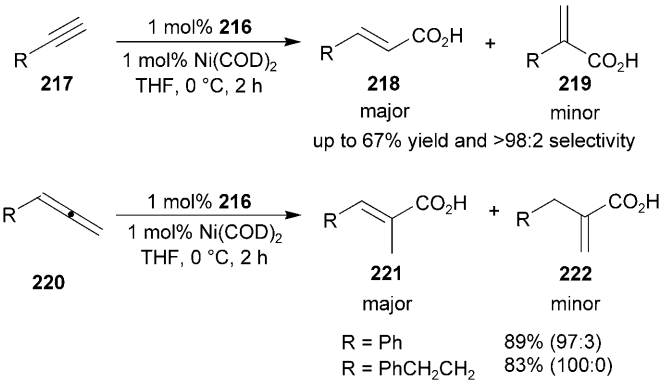
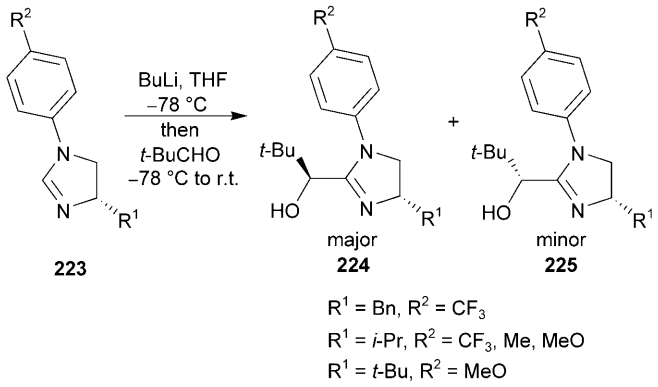


Figure 30. Bis(imidazoline) ligands for Ni-catalyzed reaction.

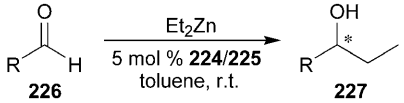
Ligands **224** were obtained in 24–38% yields, while **225** were not available in some cases. The independent tuning of R^1 and R^2 provides a chance for the orthogonal tuning of steric and electronic effects. When R^2 was varied from electron-withdrawing CF_3 to electron-donating MeO, different tendencies of *ee* value variation were observed in the addition of diethylzinc to different aldehydes **226** (Scheme 56). In the case of cyclohexanecarbaldehyde, the *ee* increased from 45% to 89%, while the *ee* decreased from 94% to 84% in the case of 1-naphthaldehyde. In the case of benzaldehyde, the *ee* and even the absolute configuration



Scheme 54. Ni-catalyzed coupling of CO_2 with alkynes.



Scheme 55. Synthesis of novel 2-imidazoline ligands.



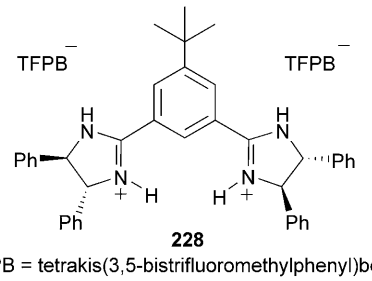
Scheme 56. Asymmetric addition of $ZnEt_2$ to aldehydes.

varied irregularly. The origin of such a dramatic ligand electronic effect is still not clear.

3.5 Imidazolines as Organocatalysts

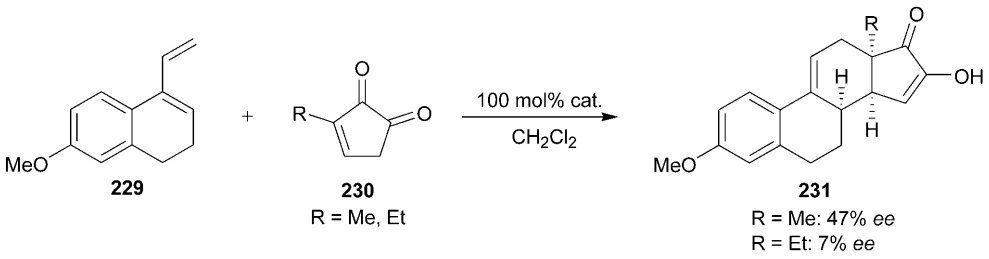
In 2003 Tsogoeva and Göbel et al. synthesized a novel diprotonated bis(imidazoline) compound **228** (Figure 31).[111] The bis(imidazoline) was prepared from the corresponding bis(imidate) and diamine (Method A3), while the two TFPB anions were introduced by treating the hydrochloride salt with NaTFPB. This diprotonated compound was used as chiral Brønsted acid catalyst in the asymmetric Diels–Alder reaction (Scheme 57). A significant acceleration of the reaction can be observed. The desired cycloadducts were obtained with high regioselectivity in up to 80% yield by the catalysis of stoichiometric amount of **228** at −70 °C. However, the enantioselectivities were only low to moderate for the two dienophiles.

In 2005, Lectka et al. developed an ammonium sulfate-containing mono-imidazoline catalyst **232** for dia-



TFPB = tetrakis(3,5-bistrifluoromethylphenyl)borate

Figure 31. Novel diprotonated bis(imidazoline) compound.



Scheme 57. Organocatalytic asymmetric Diels–Alder reaction.

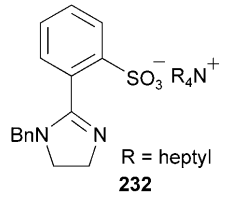


Figure 32. Ammonium sulfate-containing mono-imidazoline catalyst.

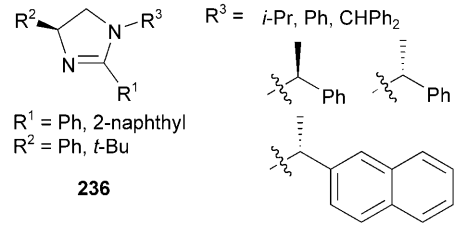
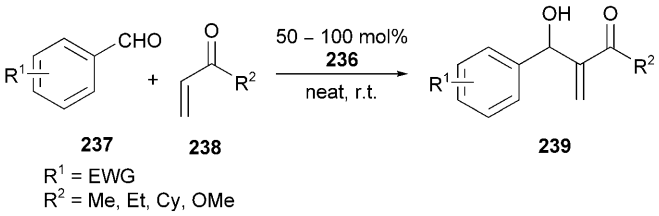


Figure 33. Mono-imidazolines as organocatalysts.

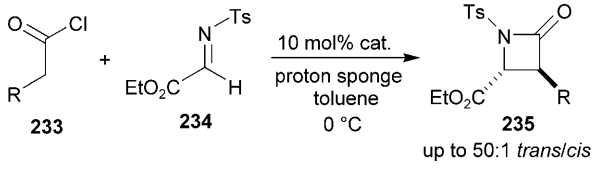
stereoselective Staudinger lactam synthesis (Figure 32, Scheme 58).[112] The imidazoline works as an activator of ketene generated *in situ* through nucleophilic addition. On the contrary to other catalysts, the *trans* products **235** were obtained with excellent diastereoselectivity. After excluding the possibility of epimerization under the reaction conditions, the authors postulated a mechanism to interpret the origin of the *trans* selectivity. In this mechanism, the configuration of the enolate intermediate was different from the cases of other catalysts for the ion pair formation between the enolate and the bulky ammonium unit. This hypothesis was proved by the *cis* selectivity of mono-imidazoline catalyst without an ammonium sulfate unit.

In 2006, Tan et al. reported the application of mono-imidazoline compounds **236** as catalyst in asymmetric Morita–Baylis–Hillman reaction (Figure 33, Scheme 59).[113] Considering the higher basicity and nucleophilicity of imidazoline than oxazoline, the authors hoped that **236** can work as DABCO or Et_3P through nucleophilic addition to the unsaturated carbonyl compounds. As they expected, **236** accelerated the asymmetric Morita–Baylis–Hillman reaction of aromatic aldehydes **237** with acrylates or enones **238**. In the case of acrylates, neat condition and 100 mol% **236** have to be used to achieve good conversion within 14 days, while 50 mol% **236** and toluene solvent can be used in the case of more reactive enones. The aldehydes were restricted to those with electron-withdrawing substituents. Moderate to good enantioselectivities (up to 78%) can be achieved using the optimized catalyst [R^1 = Ph, R^2 = *t*-Bu, R^3 = 1-(2-naphthyl)ethyl].



Scheme 59. Organocatalytic asymmetric Morita–Baylis–Hillman reaction.

In 2007, Göbel et al. reported another two chiral Brønsted acid catalysts **240** and **241** derived from carbon-bridged bis(imidazoline) compounds (Figure 34).[114] Compound **241** was prepared from **240** by treatment with dimethyl acetonedicarboxylate in toluene and then protonated by $[H(OEt_2)_2]^+$



Scheme 58. Organocatalytic diastereoselective β-lactam synthesis.

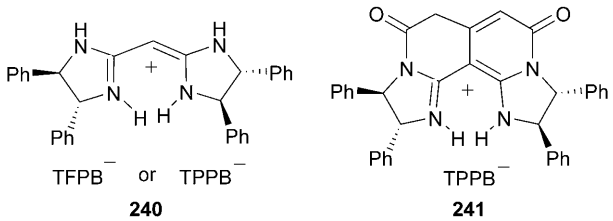


Figure 34. Novel diprotonated bis(imidazoline) compounds.

$[B(C_6F_5)_4]^-$. Both of the two catalysts showed good reactivities in the Diels–Alder reaction of cyclopentadiene with methyl vinyl ketone, the hetero-Diels–Alder reaction of 3-chlorobenzaldehyde with Danishefsky's diene, and the Friedel–Crafts alkylation of 1-methylindole with nitrostyrene. The reactivity was affected significantly by the counterions. The bulky borates with weak basicity and no coordination ability gave better results than triflate and picrate anions. Compared with their former publication,[104] no improvement of enantioselectivity was obtained.

4 Conclusion

As a structural analogue of oxazoline, the imidazoline system is attracting attention from chemists working in the field of natural product chemistry, pharmaceutical chemistry, coordination chemistry, synthetic organic chemistry, and homogeneous catalysis. During the past two decades, many efficient methods have been developed for the construction of chiral imidazoline compounds, as well as modifications of traditional methods. Higher yields and milder conditions provide us with accesses to imidazoline compounds with higher complexity. However, only Methods A and B have been widely used in the synthesis of imidazoline ligands and bioactive compounds. The other methods still need further development, especially the introduction of chiral factors towards enantiopure compounds.

From the first application of imidazoline ligands in homogeneous catalysis in 1989,[105] more than twenty different types of reactions have been catalyzed by metal-imidazoline complexes or imidazoline-derived organocatalysts. In some cases, imidazoline catalysts show better reactivity and selectivity than the corresponding oxazoline catalysts. Considering the high potential of imidazoline ligands for fine-tuning of electronic effects and immobilization, their application in homogeneous catalysis needs more investigation, such as developing novel catalysts, expanding the reaction types, and application of high-throughput screening technology. In addition, the immobilized imidazoline catalysts will also provide opportunities for heterogeneous catalysis. More efficient imidazoline catalysts will be developed in the following years.

Acknowledgements

We thank the support from National Natural Science Foundation of China (Grant Nos: 20572003 and 20772006), the Program for New Century Excellent Talents in University (NCET-07-0011) and the Development Program for Excellent Mid-Youth Teachers of Beijing Institute of Technology.

References

[1] M. R. Grimmett, in: *Comprehensive Heterocyclic Chemistry*, (Eds.: A. R. Katrizky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, Vol. 3, pp 77–120.
[2] S. Tsujii, K. L. Rinehart, Y. Kashman, S. S. Cross, M. S. Lui, S. A. Pomponi, M. C. Diaz, *J. Org. Chem.* **1988**, *53*, 5446.
[3] P. Bousquet, J. Feldman, J. Schwartz, *J. Pharmacol. Exp. Ther.* **1984**, *230*, 232.
[4] C. Dardonville, I. Rozas, *Med. Res. Rev.* **2004**, *24*, 639.
[5] A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1.
[6] M. Gómez, G. Muller, M. Rocamora, *Coord. Chem. Rev.* **1999**, *193–195*, 769.
[7] H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151.
[8] J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2005**, *34*, 664.
[9] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561.
[10] A. W. Hofmann, *Ber. dtsch. chem. Ges.* **1888**, *21*, 2332.
[11] R. J. Ferm, J. L. Riebsomer, *Chem. Rev.* **1954**, *54*, 593.
[12] G. Neef, U. Eder, G. Sauer, *J. Org. Chem.* **1981**, *46*, 2824.
[13] G. Rousselet, P. Capdevielle, M. Maumy, *Tetrahedron Lett.* **1993**, *34*, 6395.
[14] P. Dash, D. P. Kudav, J. A. Parihar, *J. Chem. Res. (S)* **2004**, 490.
[15] V. Mirkhani, M. Moghadam, S. Tangestaninejad, H. Kargar, *Tetrahedron Lett.* **2006**, *47*, 2129.
[16] V. Mirkhani, I. Mohammadpoor-Baltork, M. Moghadam, S. Tangestaninejad, M. Abdollahi-Alibeik, H. Kargar, *Appl. Catal. A: Gen.* **2007**, *325*, 99.
[17] I. Mahammadpoor-Baltork, V. Mirkhani, M. Moghadam, S. Tangestaninejad, M. A. Zolfigol, M. Abdollahi-Alibeik, A. R. Khosropour, H. Kargar, S. F. Hojati, *Catal. Commun.* **2008**, *9*, 894.
[18] I. Mahammadpoor-Baltork, M. Moghadam, S. Tangestaninejad, V. Mirkhani, S. F. Hojati, *Polyhedron* **2008**, *27*, 750.
[19] C. Dauwe, J. Buddrus, *Synthesis* **1995**, 171.
[20] R. C. F. Jones, K. J. Howard, J. S. Snaith, *Tetrahedron Lett.* **1996**, *37*, 1707.
[21] For examples, see: Y. Hsiao, L. S. Hegedus, *J. Org. Chem.* **1997**, *62*, 3586.
[22] H. Fujioka, K. Murai, Y. Ohba, A. Hiramatsu, Y. Kita, *Tetrahedron Lett.* **2005**, *46*, 2197.
[23] H. Fujioka, K. Murai, O. Kubo, Y. Ohba, Y. Kita, *Tetrahedron* **2007**, *63*, 638.
[24] P. Gogoi, D. Konwar, *Tetrahedron Lett.* **2006**, *47*, 79.
[25] M. Ishihara, H. Togo, *Synlett* **2006**, 227.
[26] M. Ishihara, H. Togo, *Tetrahedron* **2007**, *63*, 1474.
[27] M. Ishihara, H. Togo, *Synthesis* **2007**, 1939.
[28] S. Sayama, *Synlett* **2006**, 1479.
[29] R. Baati, V. Gouverneur, C. Mioskowski, *Synthesis* **1999**, 927.
[30] G. Levesque, J.-C. Gressier, M. Proust, *Synthesis* **1981**, 963.
[31] G. I. Shin, J. I. Lee, J.-H. Kim, *Bull. Korean Chem. Soc.* **1996**, *17*, 29.
[32] N. A. Boland, M. Casey, S. J. Hynes, J. W. Matthews, M. P. Smyth, *J. Org. Chem.* **2002**, *67*, 3919.

[33] R. Meyer, U. Schöllkopt, P. Böhme, *Justus Liebigs Ann. Chem.* **1977**, 1183.
[34] For a review, see: D. van Leusen, A. M. van Leusen, *Org. React.* **2001**, *57*, 417.
[35] T. Hayashi, E. Kishi, V. A. Soloshonok, Y. Uozumi, *Tetrahedron Lett.* **1996**, *37*, 4969.
[36] Y.-R. Lin, X.-T. Zhou, L.-X. Dai, J. Sun, *J. Org. Chem.* **1997**, *62*, 1799.
[37] D. Benito-Garagorri, V. Bocokić, K. Kirchner, *Tetrahedron Lett.* **2006**, *47*, 8641.
[38] J. Aydin, K. S. Kumar, L. Eriksson, K. J. Szabó, *Adv. Synth. Catal.* **2007**, *349*, 2585.
[39] X.-T. Zhou, Y.-R. Lin, L.-X. Dai, J. Sun, L.-J. Xia, M.-H. Tang, *J. Org. Chem.* **1999**, *64*, 1331.
[40] X.-T. Zhou, Y.-R. Lin, L.-X. Xai, *Tetrahedron: Asymmetry* **1999**, *10*, 855.
[41] T. Hayashi, M. Sawamura, Y. Ito, *Tetrahedron* **1992**, *48*, 1999.
[42] J. Aydin, A. Rydén, K. J. Szabó, *Tetrahedron: Asymmetry* **2008**, *19*, 1867.
[43] R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Spek, R. V. A. Orru, *Org. Lett.* **2003**, *5*, 3759.
[44] R. S. Bon, B. van Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. de Kanter, C. V. Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2005**, *70*, 3542.
[45] N. Elders, R. F. Schmitz, F. J. J. de Kanter, E. Ruijter, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2007**, *72*, 6135.
[46] S.-L. You, J. W. Kelly, *Org. Lett.* **2004**, *6*, 1681.
[47] T. Hiyama, H. Koide, S. Fujita, H. Nozaki, *Tetrahedron* **1973**, *29*, 3137.
[48] J. Legters, J. G. H. Willems, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59.
[49] J. M. Concellón, E. Riego, J. R. Suárez, S. García-Granda, M. R. Díaz, *Org. Lett.* **2004**, *6*, 4499.
[50] B. A. B. Prasad, G. Pandey, V. K. Singh, *Tetrahedron Lett.* **2004**, *45*, 1137.
[51] S. Gandhi, A. Bisai, B. A. B. Prasad, V. K. Singh, *J. Org. Chem.* **2007**, *72*, 2133.
[52] Y. Han, Y.-X. Xie, L.-B. Zhao, M.-J. Fan, Y.-M. Liang, *Synthesis* **2008**, 87.
[53] S. Peddibhotla, S. Jayakumar, J. J. Tepe, *Org. Lett.* **2002**, *4*, 3533.
[54] S. Peddibhotla, J. J. Tepe, *Synthesis* **2003**, 1433.
[55] V. Sharma, J. J. Tepe, *Org. Lett.* **2005**, *7*, 5091.
[56] G. Li, H.-X. Wei, S. H. Kim, M. D. Carducci, *Angew. Chem.* **2001**, *113*, 4407; *Angew. Chem. Int. Ed.* **2001**, *40*, 4277.
[57] H.-X. Wei, S. Siruta, G. Li, *Tetrahedron Lett.* **2002**, *43*, 3809.
[58] H.-X. Wei, S. H. Kim, G. Li, *J. Org. Chem.* **2002**, *67*, 4777.
[59] D. Chen, C. Timmons, H.-X. Wei, G. Li, *J. Org. Chem.* **2003**, *68*, 5742.
[60] W. Pei, H.-X. Wei, D. Chen, A. D. Headley, G. Li, *J. Org. Chem.* **2003**, *68*, 8404.
[61] C. Timmons, D. Chen, X. Xu, G. Li, *Eur. J. Org. Chem.* **2003**, 3850.
[62] C. Timmons, L. M. Mcpherson, D. Chen, H.-X. Wei, G. Li, *J. Peptide Res.* **2005**, *66*, 249.
[63] J. Tsuji, K. Sakai, H. Nemoto, H. Nagashima, *J. Mol. Catal.* **1983**, *18*, 169.
[64] R. Oi, K. B. Sharpless, *Tetrahedron Lett.* **1991**, *32*, 999.
[65] M. L. Larter, M. Phillips, F. Ortega, G. Aguirre, R. Somanathan, P. J. Walsh, *Tetrahedron Lett.* **1998**, *39*, 4785.
[66] H. Prokopcová, C. O. Kappe, *J. Org. Chem.* **2007**, *72*, 4440.
[67] T. Morimoto, K. Tachibana, K. Achiwa, *Synlett* **1997**, 783.
[68] N. A. Boland, M. Casey, S. J. Hynes, J. W. Matthews, H. Müller-Bunz, P. Wilkes, *Org. Biomol. Chem.* **2004**, *2*, 1995.
[69] R. Peters, Z.-Q. Xin, D. F. Fischer, W. B. Schweizer, *Organometallics* **2006**, *25*, 2917.
[70] R. Peters, D. F. Fischer, *Org. Lett.* **2005**, *7*, 4137.
[71] M. E. Weiss, D. F. Fischer, Z.-Q. Xin, S. Jautze, W. B. Schweizer, R. Peters, *Angew. Chem.* **2006**, *118*, 5823; *Angew. Chem. Int. Ed.* **2006**, *45*, 5694.
[72] S. Jautze, P. Seiler, R. Peters, *Angew. Chem.* **2007**, *119*, 1282; *Angew. Chem. Int. Ed.* **2007**, *46*, 1260.
[73] S. Jautze, P. Seiler, R. Peters, *Chem. Eur. J.* **2008**, *14*, 1430.
[74] Z.-Q. Xin, D. F. Fischer, R. Peters, *Synlett* **2008**, 1495.
[75] K. Lin, M. Song, D. Cai, X. Hao, Y. Wu, *Tetrahedron Lett.* **2003**, *44*, 3955.
[76] C. A. Busacca, D. Grossbach, R. C. So, E. M. O'Brien, E. M. Spinelli, *Org. Lett.* **2003**, *5*, 595.
[77] İ. Özdemir, B. Çetinkaya, S. Demir, *J. Mol. Catal. A: Chem.* **2004**, *208*, 109.
[78] İ. Özdemir, N. Şahin, N. Gürbüz, S. Demir, Y. Gök, B. Çetinkaya, E. Çetinkaya, *Synth. React. Inorg. Metal-Org. Nano-Met. Chem.* **2005**, *35*, 541.
[79] J. Ma, X. Cui, B. Zhang, M. Song, Y. Wu, *Tetrahedron* **2007**, *63*, 5529.
[80] S. Haneda, C. Ueba, K. Eda, M. Hayashi, *Adv. Synth. Catal.* **2007**, *349*, 833.
[81] K. Kawamura, S. Haneda, Z. Gan, K. Eda, M. Hayashi, *Organometallics* **2008**, *27*, 3748.
[82] J. Dupont, G. Ebeling, M. R. Delgado, C. S. Consorti, R. Burrow, D. H. Farrar, A. J. Lough, *Inorg. Chem. Commun.* **2001**, *4*, 471.
[83] A. Bastero, A. Ruiz, C. Claver, S. Castillón, *Eur. J. Inorg. Chem.* **2001**, 3009.
[84] A. Bastero, A. Ruiz, C. Claver, B. Milani, E. Zangrando, *Organometallics* **2002**, *21*, 5820.
[85] A. Bastero, C. Claver, A. Ruiz, S. Castillón, E. Daura, C. Bo, E. Zangrando, *Chem. Eur. J.* **2004**, *10*, 3747.
[86] A. J. Davenport, D. L. Davies, J. Fawcett, D. R. Russell, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1500.
[87] A. J. Davenport, D. L. Davies, J. Fawcett, D. R. Russell, *J. Organomet. Chem.* **2006**, *691*, 3445.
[88] S. Bhor, G. Anikumar, M. K. Tse, M. Klawonn, C. Döbler, B. Bitterlich, A. Grotevendt, M. Beller, *Org. Lett.* **2005**, *7*, 3393.
[89] G. Anikumar, S. Bhor, M. K. Tse, M. Klawonn, B. Bitterlich, M. Beller, *Tetrahedron: Asymmetry* **2005**, *16*, 3536.
[90] M. K. Tse, C. Döbler, S. Bhor, M. Klawonn, W. Mägerlein, H. Hugl, M. Beller, *Angew. Chem.* **2004**, *116*, 5367; *Angew. Chem. Int. Ed.* **2004**, *43*, 5255, and references cited therein.

[91] S. Enthaler, B. Hagemann, S. Bhor, G. Anilkumar, M. K. Tse, B. Bitterlich, K. Junge, G. Erre, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 853.
[92] B. Çetinkaya, B. Alici, İ. Özdemir, C. Bruneau, P. H. Dixneuf, *J. Organomet. Chem.* **1999**, *575*, 187.
[93] İ. Özdemir, B. Çetinkaya, S. Demir, E. Çetinkaya, N. Gürbüz, M. Çiçek, *Appl. Organomet. Chem.* **2004**, *18*, 15.
[94] T. Arai, T. Mizukami, N. Yokoyama, D. Nakazato, A. Yanagisawa, *Synlett* **2005**, 2670.
[95] T. Arai, T. Mizukami, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 1145.
[96] T. Arai, M. Watanabe, A. Fujiwara, N. Yokoyama, A. Yanagisawa, *Angew. Chem.* **2006**, *118*, 6124; *Angew. Chem. Int. Ed.* **2006**, *45*, 5978.
[97] B. Ramalingam, M. Neuburger, A. Pfaltz, *Synthesis* **2007**, 572.
[98] C. Mazet, V. Köhler, A. Pfaltz, *Angew. Chem.* **2005**, *117*, 4966; *Angew. Chem. Int. Ed.* **2005**, *44*, 4888.
[99] C. Mazet, S. Roseblade, V. Köhler, A. Pfaltz, *Org. Lett.* **2006**, *8*, 1879.
[100] C. Mazet, V. Köhler, S. Roseblade, A. Toussaint, A. Pfaltz, *Chimia* **2006**, *60*, 195.
[101] K. Ma, J. You, *Chem. Eur. J.* **2007**, *13*, 1863.
[102] T. Arai, N. Yokoyama, A. Yanagisawa, *Chem. Eur. J.* **2008**, *14*, 2052.
[103] S. Nakamura, K. Hyodo, Y. Nakamura, N. Shibata, T. Toru, *Adv. Synth. Catal.* **2008**, *350*, 1443.
[104] T. Arai, N. Yokoyama, *Angew. Chem.* **2008**, *120*, 5067; *Angew. Chem. Int. Ed.* **2008**, *47*, 4989.
[105] C. Botteghi, A. Schionato, G. Chelucci, H. Brunner, A. Kürzinger, U. Obermann, *J. Organomet. Chem.* **1989**, *370*, 17.
[106] B. Çetinkaya, E. Çentinkaya, P. B. Hitchcock, M. F. Lappert, İ. Özdemir, *J. Chem. Soc. Dalton Trans.* **1997**, 1359.
[107] F. Menges, M. Neuburger, A. Pfaltz, *Org. Lett.* **2002**, *4*, 4713.
[108] E. Guiu, C. Claver, J. Benet-Buchholz, S. Castillón, *Tetrahedron: Asymmetry* **2004**, 15, 3365.
[109] M. Aoki, M. Kaneko, S. Izumi, K. Ukai, N. Iwasawa, *Chem. Commun.* **2004**, 2568.
[110] M. Casey, M. P. Smyth, *Synlett* **2003**, 102.
[111] S. B. Tsogoeva, G. Dürner, M. Bolte, M. W. Göbel, *Eur. J. Org. Chem.* **2003**, 1661.
[112] A. Weatherwax, C. J. Abraham, T. Lectka, *Org. Lett.* **2005**, *7*, 3461.
[113] J. Xu, Y. Guan, S. Yang, Y. Ng, G. Peh, C.-H. Tan, *Chem. Asian J.* **2006**, *1*, 724.
[114] D. Akalay, G. Dürner, J. W. Bats, M. Bolte, M. W. Göbel, *J. Org. Chem.* **2007**, *72*, 5618.

