ChemComm

FEATURE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Commun.*, 2021, **57**, 12741

Asymmetric hydrogenation of O-/N-functional group substituted arenes

Bing-Ru Shao,[a] Lei Shi *[a] and Yong-Gui Zhou *[b]

Received 25th August 2021,
Accepted 14th October 2021

DOI: 10.1039/d1cc04722a

rsc.li/chemcomm

Asymmetric hydrogenation of aromatic compounds represents one of the most straightforward synthetic methods to construct important chiral cyclic skeletons that are often found in biologically active agents and natural products. So far, the most successful examples in this field are largely limited to aromatics containing alkyl and aryl substituted groups due to the poor functional-group tolerance of hydrogenation. Direct asymmetric hydrogenation of functionalized aromatics provides enormous potential for expanding the structural diversity of reductive products of planar aromatic compounds, which is highly desirable and has not been well studied. This feature article focuses on the progress in catalytic asymmetric hydrogenation and transfer hydrogenation of O/N substituted arenes.

1 Introduction

The asymmetric hydrogenation of planar aromatic compounds provides straightforward access to complex chiral three-dimensional cyclic structures that are found as common motifs in many important biologically active agents and natural products. Organic chemists have been enthusiastic about this charming synthetic concept owing to excellent atom- and step-economy, as well as abundance, easy availability and structural diversity of aromatic materials. Moreover, significant progress has been made in highly efficiently introduction of different substituents onto aromatic rings. So, in theory, a wide variety of functionalized aromatic systems can be employed as the starting materials of asymmetric hydrogenation, which provides enormous application potentiality in the field of organic synthesis. However, the major issues that have to be addressed are apparent: (i) this reaction is often a kinetically and/or thermodynamically unfavourable process because of the stable resonance system of the aromatic core. (ii) heteroaromatic compounds will poison the chiral metal catalyst due to the

[a] *State Key Lab of Fine Chemicals, School of Chemical Engineering, Dalian University of Technology, Dalian, 116024, P. R. China. E-mail: shileichem@dlut.edu.cn*

[b] *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, P. R. China. E-mail: ygzhou@dicp.ac.cn*

Bing-Ru Shao

Bingru Shao obtained her BS degree from Beihua University, China. In 2019, she joined Prof. Lei Shi's group at the Dalian University of Technology (DLUT) to pursue a PhD degree, and her current research interest is on asymmetric catalysis.

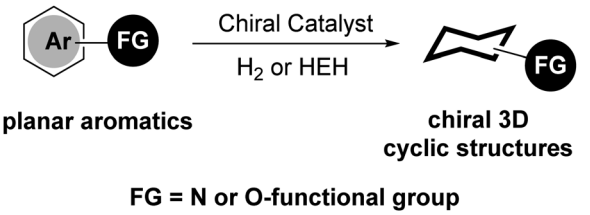
Lei Shi

Lei Shi obtained his PhD degree from DLUT in 2007 under the supervision of Prof. Xiao-Bing Lu. After one year of working in Prof. Wei-Min Dai's group at the Hong Kong University of Science and Technology, he worked with Prof. Andreas Gansäuer at Bonn University as a post-doctoral fellow supported by the Alexander von Humboldt Foundation. In 2010, he joined Prof. Yong-Gui Zhou's group at the Dalian Institute of Chemical Physics (DICP), Chinese Academy of Sciences (CAS). Since 2018, he has been a full professor of organic chemistry at DLUT. His research interest is on developing new catalytic methodology for asymmetric chemical transformations.

strong coordination effects endowed by heteroatoms (N, O or S). (iii) Multi-substitution and different types of double-bonds existing in one aromatic substrate results in the difficulty of controlling the stereoselectivity. (iv) Hydrogenation often suffers from poor functional-group tolerance for aromatic compounds containing hydroxyl, amino, or other functional groups, which limits the applicability of this methodology.

Although it seems an impossible task,[1] the past decades have witnessed significant advances in the development of asymmetric hydrogenation of aromatic compounds since a milestone work reported in 2003 by our group.[2] The first highly enantioselective hydrogenation of quinolines was realized with an iridium catalyst generated *in situ* from $[Ir(COD)Cl]_2$ and axially chiral bisphosphine ligand MeO-BiPhep with the addition of iodine as the activator. After this successful example, much attention has been paid to asymmetric hydrogenation of aromatics. Most of the studies focused on developing a new catalyst system and activation mode of inert aromatic structures to overcome those challenging substrates with high stability. Strategies for efficient asymmetric hydrogenation of aromatics, including catalyst activation, substrate activation, and relay catalysis, have been discussed in detail in several specific reviews and personal accounts by Glorius, Zhou and Kuwano *et al.*[3] Catalyst activation often involves choosing appropriate additives[2] or design of chiral ligands by the fine-tuning of steric and electronic effects,[4,5] forming highly active catalyst species that can hydrogenate aromatic substrates. For *N*-hetero aromatic compounds, especially pyridine, isoquinolines, *etc.*, substrate activation is normally regarded as a more powerful tool to achieve asymmetric hydrogenation under mild conditions. Stoichiometric amounts of electrophiles introduced as the activator interact with the substrate to form iminium ion salts, which are more easily hydrogenated owing to their enhanced electrophilicity and partially destroyed aromaticity.

Based on these above strategies, various heteroarenes such as quinolines,[6] isoquinolines,[7] quinoxalines,[8] pyridines,[9] indoles,[10] pyrroles,[11] imidazoles,[12] oxazoles[13] and furans[13] can be smoothly hydrogenated with good to excellent enantioselectivities and increased turnover numbers, using chiral metallic complexes or organocatalysts. Very recently, frustrated Lewis pair (FLP) chemistry has opened up a viable, metal-free option to asymmetric hydrogenation.[14] Chiral boranes *in situ* prepared using bis(pentafluorophenyl)borane ($HB(C_6F_5)_2$) have shown unique advantages for asymmetric hydrogenation



Scheme 1 Asymmetric hydrogenation of O-/N-functional group substituted arenes.

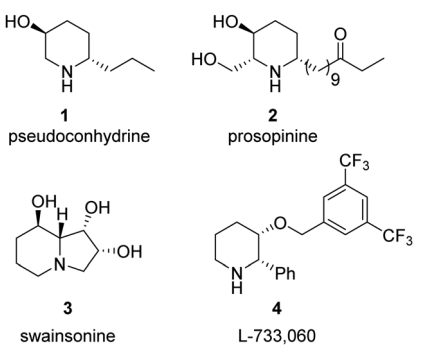
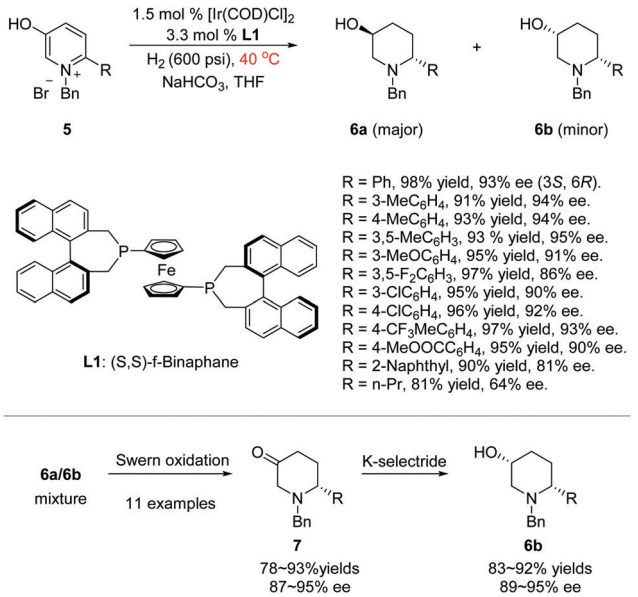


Fig. 1 Representative natural products and pharmaceutical agents containing chiral hydroxyl piperidine motifs.



Scheme 2 Direct synthesis of chiral piperidin-3-ols *via* Ir-catalyzed asymmetric hydrogenation.

Yong-Gui Zhou

Yong-Gui Zhou obtained his PhD degree from the Shanghai Institute of Organic Chemistry of CAS in 1999 under the supervision of Prof. Li-Xin Dai and Prof. Xue-Long Hou. Then he joined Xumu Zhang's group at the Pennsylvania State University as a post-doctoral fellow to work on asymmetric hydrogenation of N-heterocyclic compounds. In 2002, he began his independent academic career at DICP of CAS, where currently he is a professor of organic chemistry. His research interests include the development of catalytic asymmetric reactions, mechanistic elucidation, and asymmetric synthesis.

of polysubstituted quinoline substrates with a high level of diastereoselectivities and enantioselectivities.

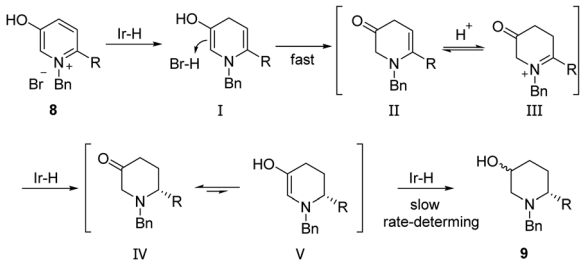
Despite the plethora of efficient asymmetric hydrogenation reactions of different types of aromatic compounds reported so far, the most successful examples in this field are largely limited to aromatic structures containing alkyl and aryl substituted groups. Considering the popularity and significance of O/N functionalized chiral cyclic motifs in bioactive molecules and natural products, direct asymmetric hydrogenation of functionalized aromatics is highly desirable to synthesize these compounds more efficiently (Scheme 1). However, a functional group, such as hydroxyl, amino, halogen atom, *etc.*, will change the reactive characteristics of the parent aromatic ring to a large extent, which could unpredictably affect the result of the hydrogenation reaction. So, this topic has not been well studied in this field. In this feature article, we focus on the discussion of the current status of the catalytic asymmetric hydrogenation and transfer hydrogenation of O-/N-functional group substituted arenes.

2 Asymmetric hydrogenation of hydroxyl substituted arenes

2.1 Hydroxyl pyridines

Chiral piperidine rings with hydroxyl groups are common motifs widely embedded in many natural products and pharmaceutical agents (Fig. 1).[15] The first common synthetic methodologies involve intramolecular nucleophilic attack cyclization of the acyclic precursor, such as reductive amination, conjugate addition and nucleophilic displacement. Cycloaddition reactions and RCM reactions also can rapidly construct chiral functionalized piperidine in a stereo-controlled manner.[16] Though being widely used, the existing methods suffer from drawbacks such as chiral starting materials, long synthetic steps, and low overall yields. Asymmetric hydrogenation of pyridin-3-ols is one of the most straightforward approaches to achieve chiral piperidin-3-ols.

In 2016, our group reported a rare example of asymmetric hydrogenation of hydroxyl pyridine (Scheme 2).[17] Chiral piperidin-3-ols were directly synthesized *via* asymmetric hydrogenation of 6-substituted 3-hydroxypyridinium salts. Previously, we have chosen *N*-benzyl 2-substituted 3-hydroxypyridinium salts as substrates to carry out asymmetric hydrogenation. Unfortunately, only racemic piperidin-3-ones were obtained even by using a chiral Ir catalyst due to the fast enol/ketone isomerization.[18] And then, 6-substituted 3-hydroxypyridinium salts were designed in order to avoid this problem. In the presence of 3 mol% of catalyst generated *in situ* by $[Ir(COD)Cl]_2$/(*S*, *S*)-*f*-Binaphane and 600 psi of hydrogen gas, a variety of 6-substituted 3-hydroxy-pyridinium salts were smoothly reduced to the corresponding chiral piperidines. The *trans* 6-substituted piperidin-3-ols were obtained as the main products with excellent enantioselectivities (dr up to 9 : 1, ee of *trans* isomer up to 95%). Direct Swern oxidation of the hydrogenation products without separation of the *trans* and *cis* isomers afforded piperidin-3-ones with high ee values, which



Scheme 3 Proposed mechanism of hydrogenation of pyridin-3-ols.

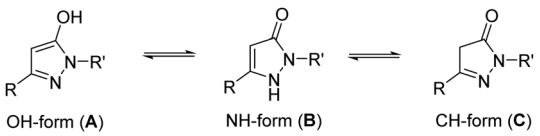
were subsequently reduced to the *cis* 6-substituted piperidin-3-ols using K-selectride. Thus, three chiral piperidine products, 6-substituted piperidin-3-ones, and *trans* and *cis* 6-substituted piperidin-3-ols, can be easily accessed from the same starting materials. Moreover, using piperidin-3-ols as a versatile building block, chiral 3-amino piperidine and 3-fluoropiperidine were efficiently prepared in excellent optical purity by one or several steps of simple treatment.

A possible reaction pathway is proposed in Scheme 3. First, 1,4-reduction of 3-hydroxypyridinium salt gives a 1,4-dihydropyridine intermediate containing an enol structure, which is transformed into piperidin-3-one *via* fast protonation. Then, enamine–iminium tautomerization takes place; subsequent hydrogenation of more active iminium salt delivers chiral piperidin-3-one with high ee. The resulting piperidin-3-one is further reduced into saturated 6-substituted piperidin-3-ol through the substrate-controlled manner and leads to a moderate d.r. value, which has been confirmed from experimental studies.

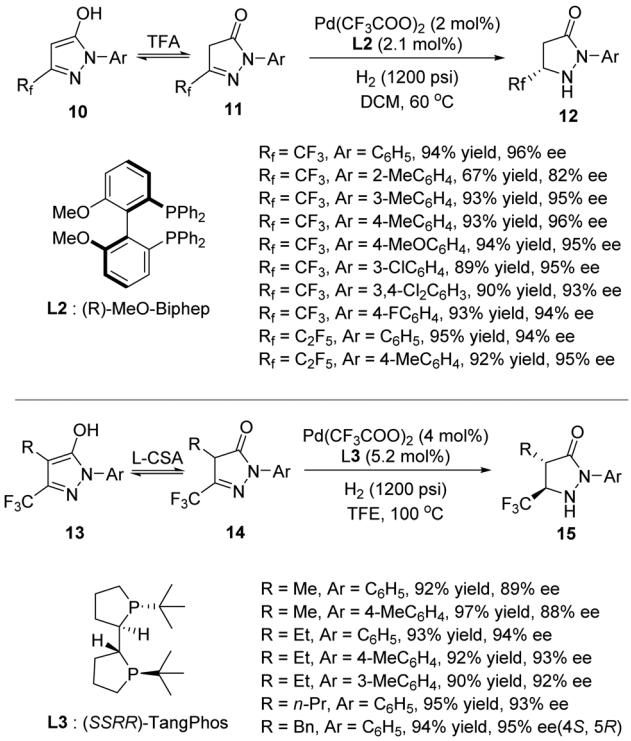
2.2 Hydroxyl pyrazoles

In principle, pyrazol-5-ols exist in three tautomeric forms, *i.e.* the OH– (form A), the NH– (form B) and the CH–isomer (form C) (Scheme 4), which dramatically affects the stability and reactivity of pyrazoles. Literature research and experimental data including X-ray crystal structure analysis reveal that form **A** with higher aromatic stability is dominant in the tautomeric equilibrium.[19] However, appropriate conditions would promote the tautomerization of the highly aromatic tautomer **A** to other tautomers. The inseparable active tautomer might be captured under a specific reaction condition to give the corresponding product. As a result, pyrazol-5-ols possess multiple reactive centers and can be manipulated into many valuable bioactive enantiopure pyrazolone and pyrazole derivatives.[20]

Previous results have demonstrated that a Brønsted acid could shift the tautomeric equilibrium[21] and accelerate iminium–enamine isomerization to facilitate asymmetric hydrogenation.[22]



Scheme 4 The tautomeric forms of pyrazol-5-ols.

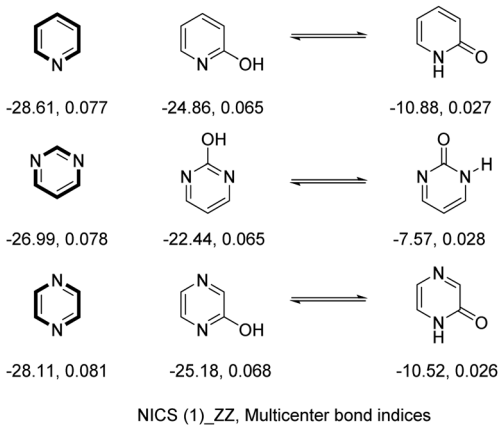


Scheme 5 Pd-catalyzed asymmetric hydrogenation of pyrazol-5-ols.

Inspired by these studies, we envisioned that asymmetric hydrogenation of pyrazol-5-ols might be feasible in the presence of a Brønsted acid. The excellent tolerance of the chiral palladium complex with a strong Brønsted acid led us to speculate that a Pd-catalyzed asymmetric hydrogenation of pyrazol-5-ols had occurred.[23] The combination of $Pd(OCOCF_3)_2$ and chiral axial bisphosphine ligands and TFA furnished a wide variety of 2,5-disubstituted and 2,4,5-trisubstituted pyrazolidinone derivatives with excellent enantioselectivities (up to 96%), diastereoselectivities and yields (up to 95%) (Scheme 5). Although only fluorinated aromatic pyrazol-5-ols smoothly gave the corresponding products, this study provides some enlightenment on the application of asymmetric hydrogenation of the aromatic structure containing a tautomeric group.

2.3 Hydroxyl pyrimidines

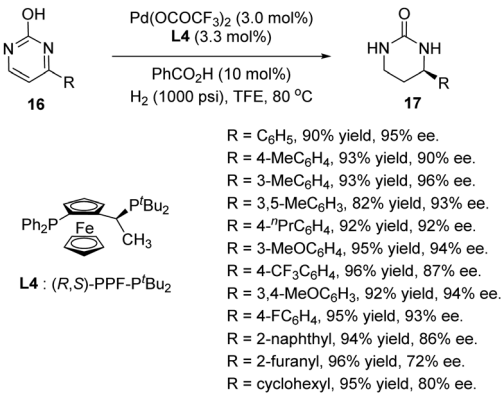
Six-membered aromatics, such as benzene, pyridine, pyrimidine, pyrazine, and so on, represent the most stable aromatic structure. Thus, asymmetric hydrogenation of these types of aromatics is the most challenging project in this research field. Tautomerism of *N*-heteroarenes containing the potential tautomeric functional group (OH, SH, NHR, acylmethyl, *etc.*) is intimately related to the aromaticity, chemical reactivity and biological activity. The aromaticity of six-membered *N*-heteroarenes and their 2-hydroxyl substituted derivatives can be evaluated by the calculation of NICS(1) ZZ and multicentre bond indices (Scheme 6). The results demonstrate that a hydroxyl group substituted at the *ortho*-position would dramatically reduce the aromaticity of the resonance system of the



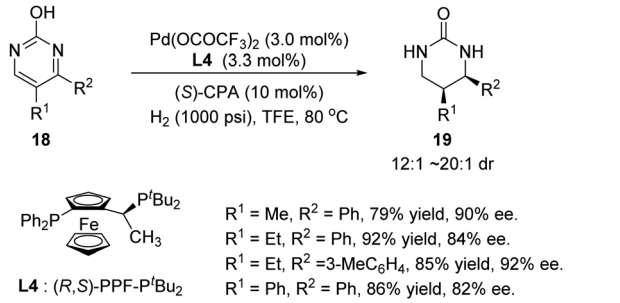
Scheme 6 Evaluation of the aromaticity of six-membered aromatic compounds.

six-membered aromatic core and the corresponding oxo-tautomers show much lower stabilities than the parent compounds.

This property might supply a possible solution for asymmetric hydrogenation of those heteroarenes with high stability. Tautomeric equilibria for 2- and 4-hydroxypyrimidines in gas or solution phase has been well studied in detail.[24] The lactam–lactim equilibrium of 2-hydroxypyrimidine is more toward the oxo form with relatively lower aromaticity in most solvents, which might be amenable to asymmetric hydrogenation conditions, giving the chiral cyclic ureas. In 2018, based on the above-mentioned analysis, our group realized an efficient Pd-catalyzed asymmetric hydrogenation of 2-hydroxypyrimidine, delivering an array of chiral cyclic ureas with up to 99% ee.[25] Initial investigations on reaction conditions revealed a strong dependency of solvent effects and only trifluoroethanol (TFE) gave satisfactory yields. The role of TFE has been studied theoretically.[26,27] TFE can stabilize some key ionic intermediates or transition states during the catalytic hydrogenation reaction due to its high polarity (ε = 26.5). Further detailed research established the optimized hydrogenation conditions as follows: $Pd(OCOCF_3)_2$ (3.0 mol%)/(*R*,*S*)-PPF-P^{t}Bu$_2$ (3.3 mol%), $PhCO_2H$



Scheme 7 Pd-catalyzed asymmetric hydrogenation of monosubstituted 2-hydroxy pyrimidines.



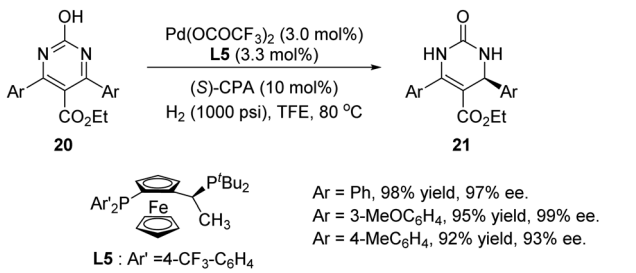
Scheme 8 Pd-catalyzed asymmetric hydrogenation of disubstituted 2-hydroxy pyrimidines.

(10 mol%), TFE, H_2 (1000 psi), 80 °C. A series of 4-aryl substituted 2-hydroxypyrimidines could be hydrogenated smoothly under these standard conditions, giving the corresponding chiral cyclic ureas with excellent yields and excellent enantioselectivities (Scheme 7). Compared with other classical routes that rely on the use of toxic phosgene or isocyanates, this method provides a conceptually simple approach to obtain chiral cyclic ureas through the asymmetric hydrogenation of pyrimidinones.

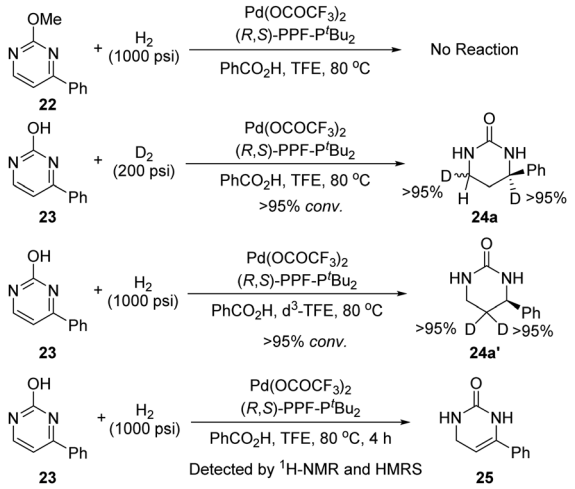
For more complex di- and tri-substituted 2-hydroxypyrimidines, this method also turned out to be successful after modification, using BINOL-derived chiral phosphoric acid instead of benzoic acid (Schemes 8 and 9). 4,5-Disubstituted cyclic ureas were furnished with high diastereoselectivities and 82–92% enantioselectivities. Notably, partial hydrogenation of trisubstituted 2-hydroxypyrimidines gave 3,4-dihydro-pyrimidinones with 93–99% ee, which provides new accessible chiral DHPM derivatives with important application in medicinal chemistry. Control experiments showed that the configuration of BINOL-derived chiral phosphoric acid would not affect the enantioselectivity and absolute configuration.

The control experiment and isotopic labelling experiment were carried out to gain insight into the mechanism (Scheme 10). Based on these results, this reaction is tentatively assigned as a stepwise hydrogenation process (Scheme 11). In the reaction system, 4-phenyl 2-hydroxypyrimidine exists in two tautomeric oxo forms. First, the less bulky N1–C6 double bond is hydrogenated to give the partially hydrogenated intermediate dihydropyrimidin-2(1*H*)-one, which had been identified by ^{1}H-NMR and HRMS. Second, the resulting enamine intermediate tautomerizes to a imine form, followed by the Pd-catalyzed asymmetric hydrogenation of the imine to give the final chiral cyclic urea.

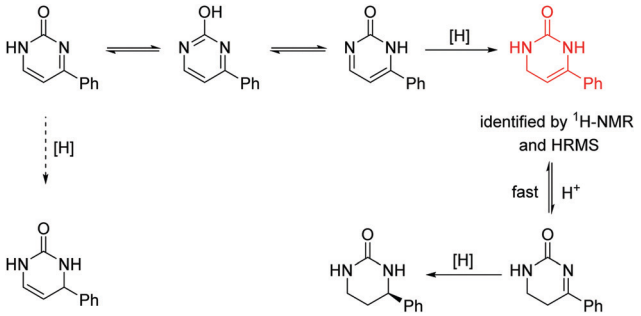
Although Pd-catalyzed asymmetric hydrogenation conditions exhibit an impressive broad substrate scope, for some bulky substrates, such as 4,6-disubstituted 2-hydroxypyrimidines, harsh conditions and high loading of palladium catalyst (5 mol%) are necessary in order to obtain satisfactory yields and enantioselectivities. This phenomenon is easy to be explained because hydrogenation of N–C double bonds in the



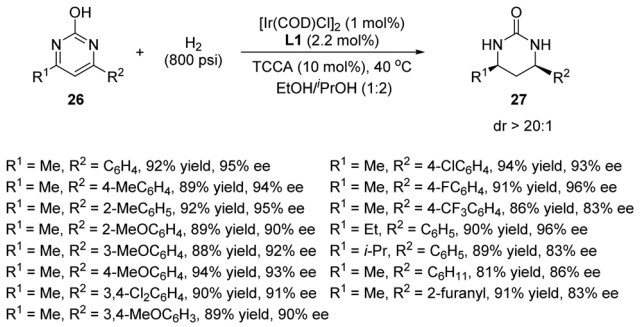
Scheme 9 Pd-catalyzed asymmetric hydrogenation of trisubstituted 2-hydroxy pyrimidines.



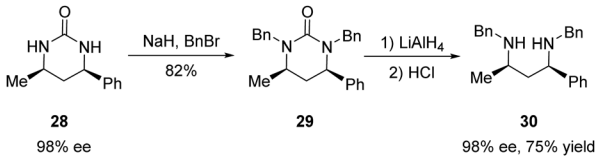
Scheme 10 Mechanistic investigation.



Scheme 11 Proposed stepwise hydrogenation process.



Scheme 12 Ir-catalyzed asymmetric hydrogenation of 4,6-disubstituted 2-hydroxypyrimidines.



Scheme 13 Synthesis of chiral 1,3-diamine from cyclic ureas.

first step became more difficult (see Scheme 11). Thus, a more efficient catalytic system to overcome this kind of bulky substrate is highly imperative (Scheme 12). The chiral iridium complex has been frequently used as an efficient catalyst for asymmetric hydrogenation of heteroaromatics.[2,3] The addition of the halogenide additive can extraordinarily improve the reactivity by oxidizing iridium(I) to iridium(III) and meanwhile *in situ* generate a Brønsted acid as the substrate activator. Subsequently, we set out to develop an efficient Ir catalyst aimed at achieving those bulky 4,6-disubstituted 2-hydroxypyrimidines.[28] Under the iridium-catalyzed hydrogenation conditions, the acid generated *in situ* would shift the equilibrium of the lactame–lactime tautomerism of 2-hydroxyl-pyrimidine more toward the oxo form, which effectively improved the reactivity to facilitate the hydrogenation. With the optimal reaction conditions ($[Ir(COD)Cl]_2$/(*S*, *S*)-*f*-Binaphane (1 : 2.2), TCCA (10 mol%), ethanol: isopropanol (1 : 2), and H_2 (800 psi), at 40 °C), a variety of 4,6-disubstituted 2-hydroxypyrimidine derivatives could be converted into chiral cyclic ureas in excellent diastereoselectivities and up to 96% ee of enantioselectivities. This work is complementary to the previous Pd-catalyzed asymmetric hydrogenation of 2-hydroxypyrimidines.

Moreover, this approach gave new access to chiral 1,3-diamines, an important chiral building block applied in organic synthesis, medicinal chemistry, and asymmetric synthesis. This useful transformation is depicted in Scheme 13. The chiral cyclic urea with 98% ee can be easily protected with benzyl bromide, followed by $LiAlH_4$ reduction and hydrolysis to provide the desired chiral 1,3-diamine without any loss of optical purity.

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) possess a wide range of pharmacological properties, including anticancer activity, calcium channel inhibition, anti-inflammatory activity, antibacterial activity, *etc*. (Fig. 2).[29] Intensive research suggested that both enantioisomers of DHPMs often show very different or even opposite biological activities.[30] Although the asymmetric Biginelli reaction has proved a conceptually straightforward pathway to achieve chiral DHPMs,[31] new approaches are still of great value for building a giant molecule library of chiral DHPMs in order to meet the growing demand

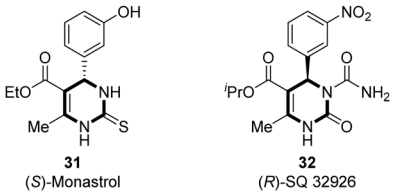
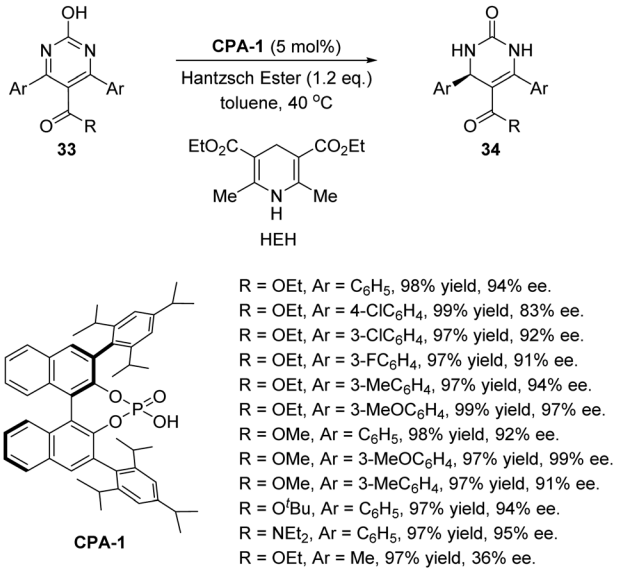


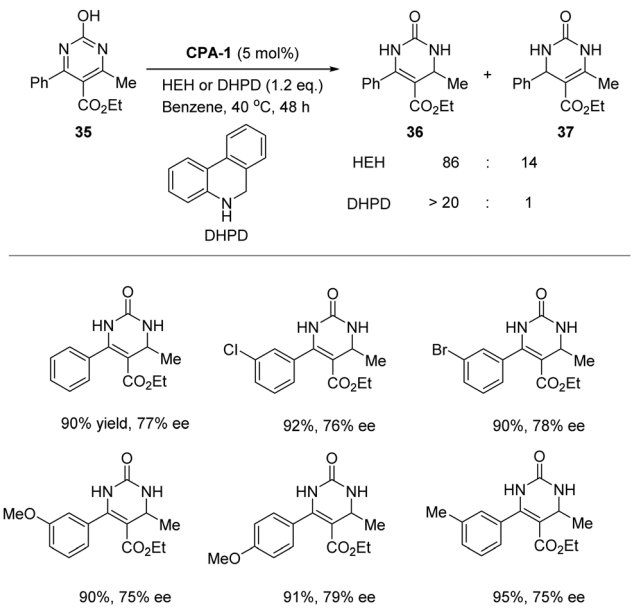
Fig. 2 Chiral DHPMs with pharmacological activities.



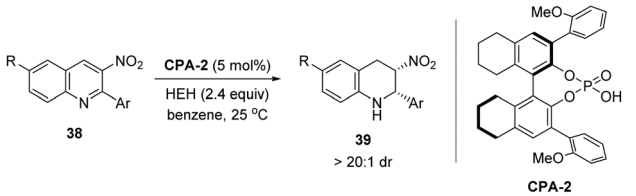
Scheme 14 CPA-catalyzed asymmetric partial transfer hydrogenation of multisubstituted 2-hydroxypyrimidines.

for further drug development. Previous work on Ir- or Pd-catalysed asymmetric partial hydrogenation of 2-hydroxypyrimidines has demonstrated the good practical utility for efficient construction of the chiral DHPMs.

Alongside these achievements, our group disclosed asymmetric biomimetic transfer hydrogenation of pyrimidines catalyzed by chiral phosphoric acid with Hantzsch ester as a hydride donor, furnishing chiral DHPMs with excellent enantioselectivities (Scheme 14).[32] In general, a variety of 2-hydroxy-4,6-diarylpyrimidine-5-carboxylate derivatives were converted into chiral DHPMs with good enantioselectivities



Scheme 15 Asymmetric transfer hydrogenation of unsymmetrical multisubstituted 2-hydroxypyrimidines.



R = H, Ar = C_6H_5, 97% yield, 94% ee (*S*,*S*).
R = H, Ar = 3-MeC_6H_4, 99% yield, 97% ee.
R = H, Ar = 4-MeC_6H_4, 99% yield, 98% ee.
R = H, Ar = 4-$MeOC_6H_4$, 97% yield, 88% ee.
R = H, Ar = 4-ClC_6H_4, 97% yield, 96% ee.
R = H, Ar = 4-BrC_6H_4, 99% yield, 96% ee.
R = H, Ar = 4-FC_6H_4, 97% yield, 95% ee.
R = H, Ar = 4-$CF_3C_6H_5$, 95% yield, 99% ee.
R = H, Ar = 2-furanyl, 99% yield, 80% ee.
R = H, Ar = 2-naphthyl, 99% yield, 98% ee.
R = F, Ar = C_6H_5, 97% yield, 92% ee.
R = MeO, Ar = C_6H_5, 91% yield, 92% ee.
R = H, Ar = (*E*)-styryl, 61% yield, 96% ee.
R = H, Ar =(*E*)-4-fluorostyryl, 51% yield, 94% ee.
R = H, Ar =(*E*)-4-chlorostyryl, 59% yield, 91% ee.

Scheme 16 Asymmetric transfer hydrogenation of 3-nitroquinolines.

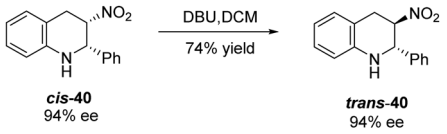
(up to 99% ee) and yields with an optimal reaction protocol. The multisubstituted 2-hydroxypyrimidines with an unsymmetrical structure gave an inseparable mixture of two kinds of partially reduced products (**36** and **37**) under the same reaction conditions, which may lead to the more classic Biginelli products. After careful reoptimization of conditions, excellent chemoselectivity can be achieved with dihydrophenanthridine (DHPD) used as an alternative hydride donor. It is interesting that partially reduced products with an alkyl substituted chiral centre were detected exclusively in the crude reaction mixture in moderate enantioselectivity. To the best of our knowledge, effective synthesis of DHPMs with an alkyl substituted chiral center is still very rare. Some novel chiral DHPMs with methyl substituted chiral carbon atom at the C-4 position were prepared with good yields and moderate values of ee (Scheme 15).

3 Asymmetric hydrogenation of *N*-functional group substituted arenes

3.1 Nitro quinolines

Optically active nitro alkanes are valuable building blocks in organic synthesis because they can be easily converted to a wide range of other versatile organics, such as amines, aldehydes, carboxylic acids, nitrile oxides, and denitrated compounds.[33] In view of the ready availability and easy preparation of the aromatic nitro compounds, the asymmetric reduction of this kind of substrate is of great value for the facile construction of chiral cyclic nitro compounds. Despite the fact that many elegant catalytic methods for the synthesis of enantiopure nitro compounds have been well developed,[34] there is still little information available on the asymmetric catalytic synthesis of chiral cyclic nitro compounds due to their easy racemization of chiral secondary nitro compounds.

A preliminary attempt in our lab to explore the iridium catalysed asymmetric hydrogenation of a readily available 2-phenyl-3-nitroquinoline revealed a poor nitro group tolerance. Subsequently, employing chiral phosphoric acid as the catalyst with Hantzsch ester as the hydrogen source, the first organocatalyzed asymmetric transfer hydrogenation of 3-nitroquinolines was successfully realized (Scheme 16).[35] High diastereo and enantioselectivities (>20 : 1 dr, up to 99% ee) were observed for



Scheme 17 DBU-promoted epimerization of *cis* 2-pheyl 3-nitro quinolines to the *trans* isomer.

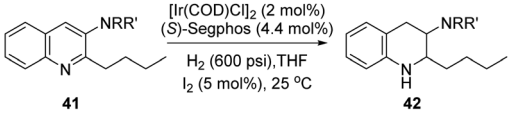
all the 2-aryl 3-nitro quinoline substrates. This new methodology provides a direct and facile access to a series of valuable enantiopure cyclic nitro compounds with two contiguous stereocenters. Moreover, the chiral *cis* product could be transformed to the *trans* isomer *via* epimerization promoted by DBU and the latter is generally difficult to prepare through direct asymmetric hydrogenation (Scheme 17).

3.2 Amido quinolines

Despite the plethora of efficient chiral catalyst systems for asymmetric hydrogenation of quinolines reported so far,[6] the amino substituted quinoline is still highly challenging due to the strong coordinating ability of the free amino group. In order to overcome this issue, a "Mask" strategy has been successfully developed to realize this transformation in our group.[36]

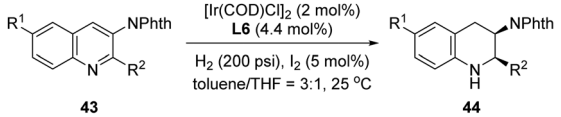
Initially, a series of *N*-protected 2-butylquinolin-3-amines as model substrates were surveyed with the chiral Ir complex as the catalyst (Scheme 18). To our delight, these quinolines could be smoothly hydrogenated with full conversion but only 3-phthalimido substituted quinolines gave a satisfactory diastereoselectivity. The poor diastereoselectivity may be attributed to the unexpected isomerization pathway to the exocyclic imine caused by active N–H bonds of the amido group during the whole hydrogenating process.

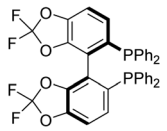
With 3-phthalimido substituted quinolones as the substrate, a variety of different parameters, including chiral ligands, additives, solvents, pressure of hydrogen, reaction temperatures, *etc.*, are included to establish the optimized conditions: $[\{Ir(cod)Cl\}_2]$/(*R*)-difluorPhos, I_2 (5.0 mol%), H_2 (200 psi), toluene/THF (3 : 1), 25 °C. Iodine as an additive played a pivotal role and no product was observed in the absence of iodine. The Ir(I) catalyst precursor was oxidized to Ir(III) *in situ* by iodine and the latter can exhibit a higher catalytic activity.[37] All the substrates bearing an alkyl group at the 2-position of the quinoline motif gave good enantioselectivities (81–94%) and excellent yields (94–99%) (Scheme 19). The 2-phenyl-substituted substrate



NRR'	NH_2	NHTs	NHBz	$NHCO_2Ph$	NPhth
Conv. (%)	< 5	> 95	> 95	> 95	> 95
d.r.	N/A	5:1	8:1	8:1	>20:1
ee (%)	N/A	62	84	63	37

Scheme 18 Asymmetric hydrogenation of *N*-protected 2-butylquinolin-3-amine.



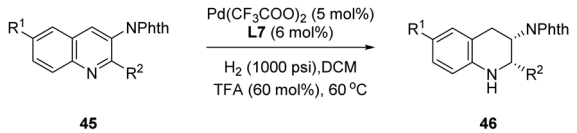


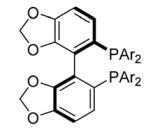
R^1 = H, R^2 = *n*-Bu, 99% yield, 93% ee(*R*, *R*).
R^1 = H, R^2 = Me, 97% yield, 81% ee.
R^1 = H, R^2 = Et, 97% yield, 90% ee.
R^1 = H, R^2 = *n*-Pr, 94% yield, 92% ee.
R^1 = H, R^2 = *i*-Bu, 99% yield, 94% ee.
R^1 = H, R^2 = *i*-Pentyl, 97% yield, 88% ee.
R^1 = H, R^2 = *n*-Hexyl, 97% yield, 92% ee.
R^1 = H, R^2 = Phenethyl, 99% yield, 93% ee.
R^1 = H, R^2 = (*E*)-Styryl[a], 97% yield, 90% ee.
R^1 = H, R^2 = C_6H_5, 97% yield, 40% ee.
R^1 = MeO, R^2 = *n*-Bu, 97% yield, 87% ee.
[a]The conjugated double bond was also hydrogenated.

Scheme 19 Ir-catalyzed asymmetric hydrogenation of 3-phthalimido quinolones.

could also be transformed with moderate enantioselectivity (97% yield, 40% ee). More importantly, the phthaloyl group could be easily removed by using hydrazine hydrate without any loss of optical purity. The key to the success of the Mask strategy lies in the following facts: (1) suppression of the strong coordination and poisoning ability of the substrate and the corresponding reduced product towards the catalyst. (2) Activation of the substrate by decreasing the electron density at the aromatic rings. (3) Improving the diastereoselectivity by inhibition of side-reaction pathways. (4) This group can be easily introduced and removed.

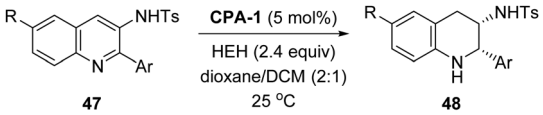
Soon after this work, Pd-catalyzed asymmetric hydrogenation conditions for the same type of 3-phthalimido substituted quinolone were also revealed by our group, which further broadened the substrate scope of homogeneous Pd-catalyzed asymmetric hydrogenation (Scheme 20).[38] Under the optimized conditions ($Pd(OCOCF_3)_2$/L7, TFA (60 mol%), H_2 (1000 psi), CH_2Cl_2, and 70 °C.), a variety of 3-phthalimido 2-alkyl substituted quinolines were hydrogenated smoothly with high yields and 79–90% ee, regardless of the length of the side chain. It is noted that this methodology cannot be well suitable for





R^1 = H, R^2 = *n*-Bu, 91% yield, 90% ee(*S*, *S*).
R^1 = H, R^2 = Me, 86% yield, 81% ee.
R^1 = H, R^2 = Et, 93% yield, 85% ee.
R^1 = H, R^2 = *n*-Pr, 97% yield, 87% ee.
R^1 = H, R^2 = *i*-Bu, 94% yield, 90% ee.
R^1 = H, R^2= *i*-Pentyl, 91% yield, 90% ee.
R^1 = H, R^2 = *n*-Hexyl, 86% yield, 90% ee.
R^1 = H, R^2 = Phenethyl, 95% yield, 90% ee.
R^1 = H, R^2 = (*E*)-Styryl, 99% yield, 90% ee.
R^1 = H, R^2 = *c*-Pr, 72% yield, 80% ee.
R^1 = F, R^2 = *n*-Bu, 97% yield, 79% ee.
R^1 = H, R^2 = C_6H_5, 83% yield, 14% ee.
R^1 = H, R^2 = (*E*)-4-fluorostyryl, 86% yield, 88% ee.

Scheme 20 Pd-catalyzed asymmetric hydrogenation of 3-phthalimido quinolones.

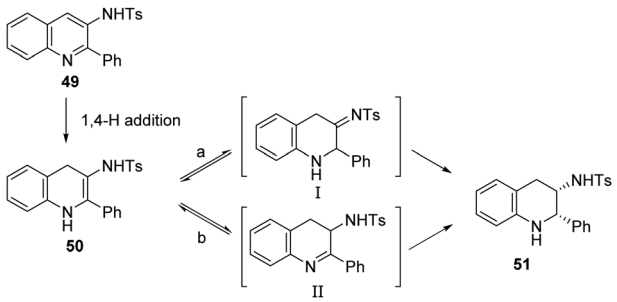


R = H, Ar = C_6H_5, 94% yield, 95% ee(*S*, *S*)
R = H, Ar = 3-MeC_6H_4, 96% yield, 97% ee
R = H, Ar = 4-MeC_6H_4, 98% yield, 91% ee
R = H, Ar = 4-$MeOC_6H_4$, 96% yield, 99% ee
R = H, Ar = 4-ClC_6H_4, 97% yield, 95% ee
R = H, Ar = 4-BrC_6H_4, 99% yield, 96% ee
R = H, Ar = 4-FC_6H_4, 93% yield, 98% ee
R = H, Ar = 4-$CF_3C_6H_4$, 99% yield, 98% ee
R = H, Ar = 4-^{t}BuC_6H_4, 93% yield, 94% ee
R = H, Ar = 2-naphthyl, 91% yield, 83% ee
R = F, Ar = C_6H_5, 94% yield, 73% ee
R = H, Ar = 3-Pyridinyl, 70% yield, 97% ee

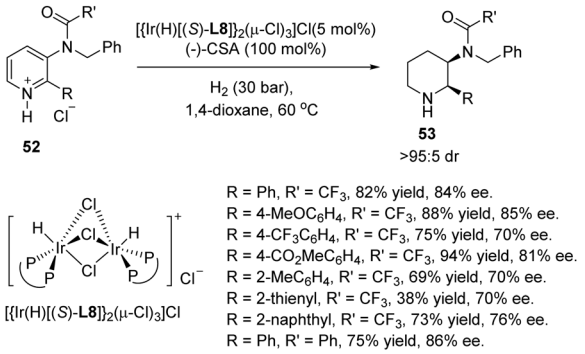
Scheme 21 CPA-catalyzed asymmetric hydrogenation of 3-tosylamido quinolones.

other substituted quinolines, such as 2-methylquinoline, 3-carbalkoxy substituted and 3-*p*-toluenesulfonamido substituted quinolone. Tentatively it can be suggested that the electron-withdrawing phthalimido group at the C3 position could activate the substrates through decreasing the electron density of the aromatic ring.

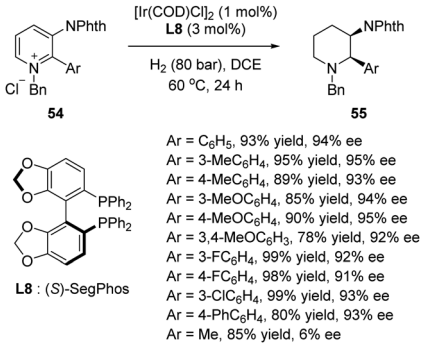
However, for the 2-aryl substituted substrate, only a moderate ee value was obtained irrespective of the metal (Ir, Pd) complex used as the catalyst for asymmetric hydrogenation. As a part of our sustained efforts in extending the application of asymmetric hydrogenation of aromatic compounds, we started to consider the possibility of asymmetric reduction of 2-aryl substituted quinolin-3-amine with CPA-catalyzed transfer hydrogenation.[39] Initial attempts focused on evaluation of protecting groups of quinolin-3-amines. In sharp contrast to the previous results of Ir or Pd catalysed hydrogenation, the Ts group protected substrate gave better yield and enantioselectivity. A series of 2-aryl substituted quinolin-3-amines were smoothly converted to *cis* isomers of the corresponding products in high yields with high ee values (73–99% ee), using the TRIP catalyst and Hanztsch ester as the hydride donor (Scheme 21). Preliminary mechanistic studies indicate that hydrogenation mainly proceeded *via* the endocyclic imine intermediate (path b), and a dynamic kinetic resolution process was involved during the hydrogenation, which also reveal the reason for excellent diastereoselectivity



Scheme 22 Two possible paths for CPA-catalyzed asymmetric transfer hydrogenation.



Scheme 23 Ir-catalyzed asymmetric hydrogenation of protected 3-amido-2-arylpyridinium salt.



Scheme 24 Ir-catalyzed asymmetric hydrogenation of 3-phthalimido-2-aryl pyridinium salts.

(Scheme 22). Anyway, this method efficiently supplements previous work to further show the practicability.

3.3 Amido pyridines

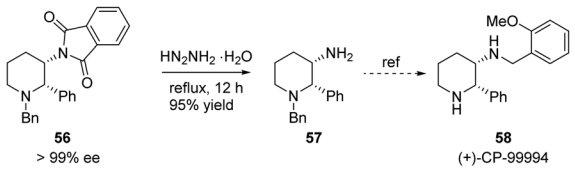
Chiral amino substituted piperidines is one ubiquitous skeleton in biologically active molecules and drugs. For example, 3-amino-2-piperidine derivatives have attracted special interest due to their strong biological relevance as non-peptide antagonists of neurokinin-1 (NK-1) substance P receptors, including (+)-(2*S*,3*S*)-CP-99,994, (+)-(2S,3S)-GR-205,171, (+)-(2S,3S)-T-2,328, *etc.*[40] Traditional asymmetric synthetic methods, such as chiral pool synthesis and diastereoselective reactions, to construct chiral piperidines normally require tedious and complex multistep synthesis.[41] Asymmetric hydrogenation of amino group substituted arenes provides a rational synthetic tool for constructing this kind of chiral compound. However, few successful examples were reported so far using masked amino substrates because the free amino group will deactivate the catalyst through a strong coordination tendency.

Mashima and his co-workers designed a trifluoroacetyl and benzyl protected 3-amido-2-arylpyridinium salt for enantiopure dinuclear iridium complex catalysed asymmetric hydrogenation (Scheme 23).[42] The corresponding 3-amido-2-arylpyidines were afforded in high diastereoselectivity and moderately high enantioselectivity under the optimized reaction conditions. Although pyridinium chloride was tested as the substrate, one equivalent of additional organic acid, such as (−)-CSA, was still needed to achieve satisfactory yields and ees. After a basic work-up and further deprotection of the trifluoroacetyl group and benzyl group, an *o*-methoxybenzyl group was attached to the 3-amino group without loss of enantiomeric purity.

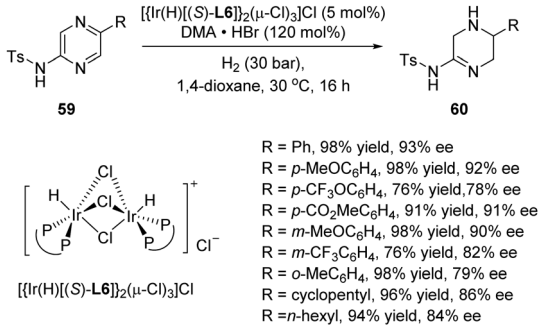
Normally, *N*-alkyl pyridinium salts is more active than Brønsted acid activated pyridines under Ir-catalyzed hydrogenation conditions. Very recently, Zhang's group developed a facile approach to furnish chiral 3-amino 2-aryl piperidine derivatives with up to >99:1 dr and 95% ee through Ir-catalyzed asymmetric hydrogenation of 3-phthalimido-2-aryl pyridinium salts (Scheme 24).[43] More importantly, scalable preparation and easy removal of amino protected groups convincingly demonstrated the practical utility of this protocol. A gram scale hydrogenation catalyzed by Ir/(*R*)-SegPhos was able to produce one gram of chiral (*S*, *S*)-*N*-benzyl 3-phthalimido-2-phenyl piperidine with 92% ee. After single crystallization and deprotection of the phthaloyl group using hydrazine hydrate, the key intermediate for (+)-CP-99994[44] was afforded with good yield and high optical purity, demonstrating the advantage of this protocol (Scheme 25).

3.4 Amido-pyrazines

Asymmetric hydrogenation of pyrazines provides a rational and direct synthetic method to prepare chiral piperazines, the most common chiral six-membered cyclic amines in natural products and bioactive compounds. Owing to not only the aromatic stabilization of pyrazines but also to the stronger coordination ability of pyrazines and piperazines with two *N*-atoms, asymmetric hydrogenation of pyrazines is considered more difficult than hydrogenation of the aforementioned *N*-heteroaromatics.[45] Mashima *et al.* successfully realized asymmetric hydrogenation of 2-tosylamido-5-substituted pyrazines with a combination of dinuclear chloride-bridged iridium(III) complexes as catalysts and stoichiometric amounts of the HBr salt of *N*,*N*-dimethylaniline as an additive, producing the corresponding chiral amidinated tetrahydropyrazines in high yield and high enantioselectivity (Scheme 26).[46] Both the yield and enantioselectivity were dramatically improved by using Brønsted acids salts as additive in comparison with those of the reaction without any additive. Additive effects were discussed in detail during their research. On the one hand, salts were to trap the stronger basic amine products to avoid the deactivation of the catalyst. On the other hand, a probable interaction of the released amines with iridium metal centers occurred to improve both the reaction rate and enantioselectivity. Scheme 27 shows the rational derivatization of chiral product, 5-phenyl-2-tosylamido tetrahydropyrazines. Simple hydration and



Scheme 25 Synthetic application for NK1 receptor (+)-CP-99994.



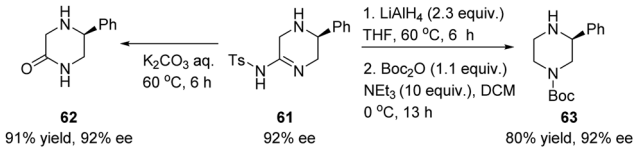
Scheme 26 Ir-catalyzed asymmetric hydrogenation of 2-tosylamido pyrazines.

reduction work-up afforded (*S*)-5-phenylpiperazin-2-one and (*S*)-3-phenylpiperazine without any loss of optical purity, respectively.

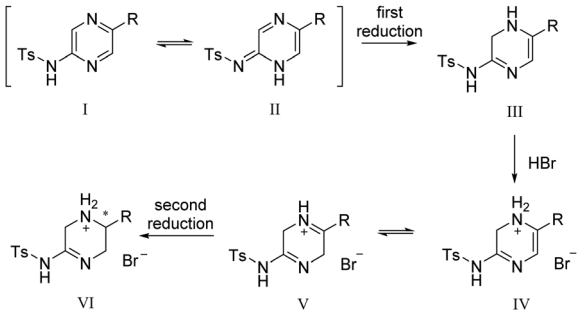
Based on the investigation of the mechanism, a plausible reaction pathway is proposed in Scheme 28. 2-Tosylamido, a potential tautomeric functional group, possibly results in a tautomerization between sulfonamide I and sulfonimide II and the latter was considered as a dearomatizing product of the starting material to facilitate the following hydrogenation. After an initial reduction at the C-3═N-4 bond, the resulting intermediate enamine III was trapped by *N*,*N*-dimethylanilinium bromide and subsequently tautomerized to iminium V, following the second reduction of the N-4═C-5 bond to afford the final product.

3.5 Amido phenanthrenes

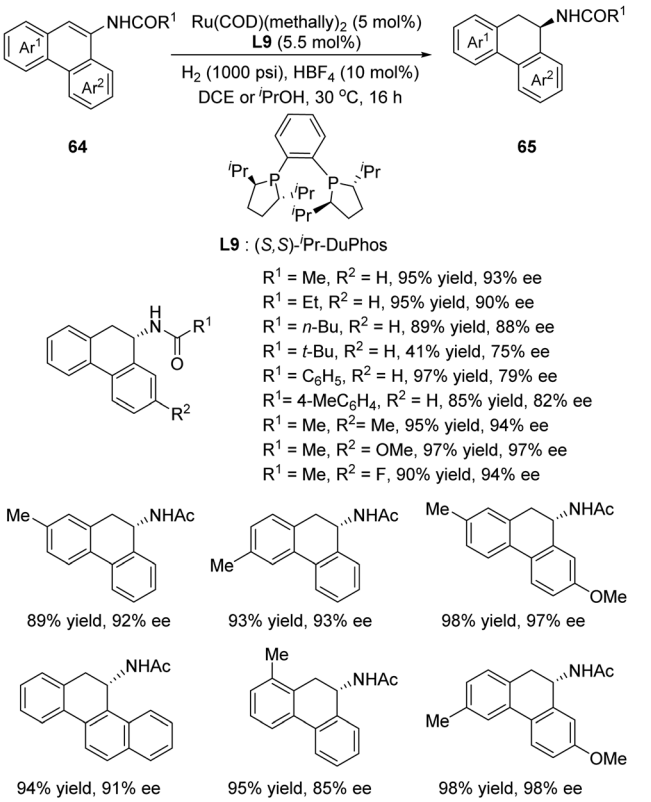
Asymmetric hydrogenation of carbocyclic aromatics remains much less explored mostly because of the inherent aromatic resulting from aromaticity and the lack of a coordinating group that makes stereoselectivity difficult to control. The first example of highly enantioselective hydrogenation of carbocyclic aromatic amines was reported by our group recently (Schemes 29 and 30).[47] We reasoned that polycyclic aromatics, such as phenanthrene and chrysene, might be suitable substrates for asymmetric hydrogenation since the aromatic stabilization of the middle aromatic ring is somewhat lower. To test this hypothesis, *N*-(phenanthren-9-yl)acetamide was chosen as the



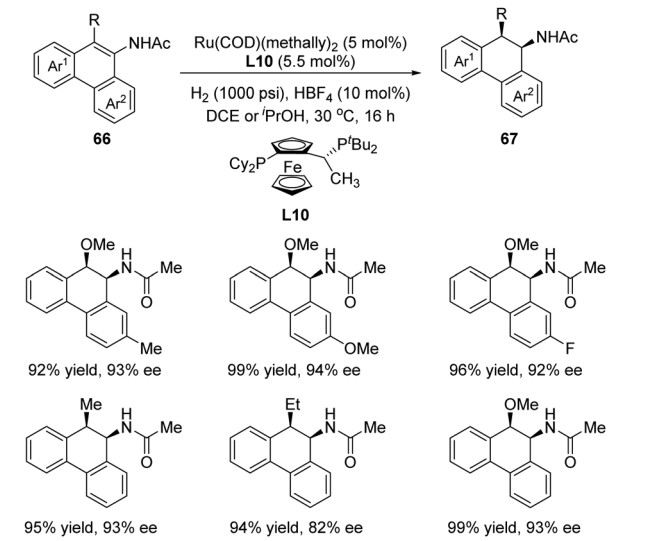
Scheme 27 Derivatization of 5-phenyl-2-tosylamido tetrahydropyrazines.



Scheme 28 Plausible reaction pathway for asymmetric hydrogenation of 2-tosylamido pyrazines.

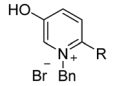
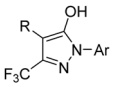
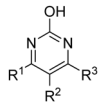
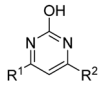
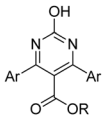


Scheme 29 Ru-catalyzed asymmetric hydrogenation of 9-acetamido phenanthrenes.



Scheme 30 Ru-catalyzed asymmetric hydrogenation of *ortho*-substituted 9-acetamido phenanthrenes.

Table 1 Summary of asymmetric hydrogenation of hydroxyl substituted arenes

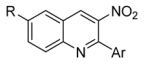
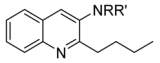
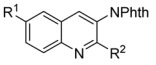
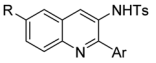
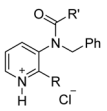
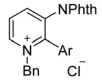
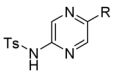
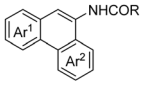
Substrate structure	Reaction conditions	Ref.
	$[Ir(COD)Cl]_2$/(*S*, *S*)-*f*-Binaphane, H_2 (600 psi), 40 °C, $NaHCO_3$, THF	17
	$Pd(CF_3COO)_2$/(*S*,*S*,*R*,*R*,)-TangPhos, H_2 (1200 psi), 100 °C, TFE	23
	$Pd(CF_3COO)_2$/(*R*,*S*)-PPF-P^{t}Bu$_2$, (*S*)-CPA or $PhCO_2H$, H_2 (1000 psi), 80 °C, TFE	25
	$[Ir(COD)Cl]_2$/(*S*, *S*)-*f*-Binaphane, H_2 (800 psi), TCCA, 40 °C, EtOH/^{i}PrOH (1 : 2)	28
	CPA-1, Hantzsch ester or DHPD, 40 °C, toluene	32

substrate for asymmetric hydrogenation employing a chiral Ru catalyst. To our delight, the *in situ*-generated catalyst with Ru(COD)(methallyl)$_2$, chiral electron-rich bisphosphine ligands (DuPhos or JosiPhos) and HBF_4 promoted the asymmetric hydrogenation process, furnishing chiral exocyclic amines with excellent yields and enantioselectivities (up to 98% ee). Isotopic labelling experiments suggested that the hydrogenation pathway is direct hydrogenation of C9–C10 double bonds of enamide moieties and the tautomerization process of enamide to ketamine, a phenomenon often mentioned in previous discussion of this article, is not involved here.

4 Conclusions

Direct asymmetric hydrogenation of O or N-functional group substituted aromatics provides enormous potential for expanding the structural diversity of reductive products of planar aromatic compounds, which is even beyond the traditional hydrogenation. But this topic is far less developed compared to the great achievements on asymmetric hydrogenation of simple aryl or alkyl substituted aromatics. In this feature article, we have summarized recent advances in asymmetric (transfer) hydrogenation of O/N-functionalized aromatics (Tables 1 and 2). For the hydroxyl substituted *N*-heteroaromatic substrates, substrate

Table 2 Summary of asymmetric hydrogenation of N-functional group substituted arenes

Substrate structure	Reaction conditions	Ref.
	CPA-2, Hantzsch ester, benzene, 25 °C	35
	$[Ir(COD)Cl]_2$/(*S*)-Segphos, H_2 (600 psi), I_2, THF, 25 °C	36
	$Pd(CF_3COO)_2$/L7, H_2 (1000 psi), TFE, DCM, 60 °C	33
	CPA-1, Hantzsch ester, dioxane/DCM (2 : 1), 25 °C	34
	[{Ir(H)[(*S*)-L8]}$_2$(μ-Cl)$_3$]Cl, (−)-CSA, H_2 (30 bar), 60 °C, 1,4-dioxane	42
	$[Ir(COD)Cl]_2$/(*S*)-Sephos, H_2 (80 bar), 60 °C, DCE	43
	[{Ir(H)[(*S*)-L6]}$_2$(μ-Cl)$_3$]Cl, DMA·HBr, H_2 (30 bar), 30 °C, 1,4-dioxane	46
	Ru(COD)(methally)$_2$/(*S*, *S*)-^{i}Pr-DuPhos, H_2 (1000 psi), HBF_4, 30 °C, DCE or ^{i}PrOH	47

activation through the addition of stoichiometric amounts of electrophiles is still effective. Introducing a hydroxy substituent α or γ to pyridine-like nitrogen atoms of *N*-heteroarenes leads to hydroxy–oxo tautomerism to weaken aromaticity. This phenomenon supplies an alternative solution for enantioselective hydrogenation of those heteroarenes with high aromaticity. Asymmetric hydrogenation of active tautomers of hydroxyl pyrazoles and hydroxyl pyrimidines gave chiral cyclic amides and ureas as the uncommon reductive products, respectively. Free amino groups will deactivate metal catalysts due to their strong coordination capacity. A "Mask" strategy with suitable protecting groups was successfully applied to realize asymmetric hydrogenation of amino substituted arenes. Notably, the protecting group dramatically affects the stereochemistry of the hydrogenation reaction. With the examples described in this feature article, we are convinced that a reasonable design of ingenious methodologies is possible to find new answers to these important synthetic challenges.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (21772195) and the Fundamental Research Funds for the Central Universities (DUT20RC5030). This article is dedicated to mark the celebration of the 10th Anniversary of the Youth Innovation Promotion Association of the Chinese Academy of Sciences.

Notes and references

1 P. J. Dyson, *Dalton Trans.*, 2003, 2964.
2 W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 10536.
3 Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357; R. Kuwano, *Heterocycles*, 2008, **76**, 909; D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557; Z. Yu, W. Jin and Q. Jiang, *Angew. Chem., Int. Ed.*, 2012, **51**, 6060; Y.-M. He, F.-T. Song and Q.-H. Fan, *Top. Curr. Chem.*, 2014, **343**, 145; B. Balakrishna, J. L. Núñez-Rico and A. Vidal-Ferran, *Eur. J. Org. Chem.*, 2015, 5293; M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton and F. Glorius, *Angew. Chem., Int. Ed.*, 2019, **58**, 10460; A. N. Kim and B. M. Stoltz, *ACS Catal.*, 2020, **10**, 13834.
4 J.-W. Zhang, F. Chen, Y.-M. He and Q.-H. Fan, *Angew. Chem., Int. Ed.*, 2015, **54**, 4622.
5 T.-L. Wang, L.-G. Zhuo, Z.-W. Li, F. Chen, Z.-Y. Ding, Y.-M. He, Q.-H. Fan, J.-F. Xiang, Z.-X. Yu and A. S. C. Chan, *J. Am. Chem. Soc.*, 2011, **133**, 9878.
6 M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 3683; Z.-J. Wang, G.-J. Deng, Y. Li, Y.-M. He, W.-J. Tang and Q.-H. Fan, *Org. Lett.*, 2007, **9**, 1243; T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu and A. S. C. Chan, *J. Am. Chem. Soc.*, 2011, **133**, 9878; X.-F. Tu and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2012, **51**, 11346; J. Wen, R. Tan, S. Liu, Q. Zhao and X. Zhang, *Chem. Sci.*, 2016, **7**, 3047.
7 S.-M. Lu, Y.-Q. Wang, X.-W. Han and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2006, **45**, 2260; L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2012, **51**, 8286; Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2013, **52**, 3685; A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita and K. Mashima, *Angew. Chem., Int. Ed.*, 2013, **52**, 2046; M.-W. Chen, Y. Ji, J. Wang, Q.-A. Chen, L. Shi and Y.-G. Zhou, *Org. Lett.*, 2017, **19**, 4988; A. N. Kim, A. Ngamnithiporn, E. R. Welin, M. T. Daiger, C. U. Grünanger, M. D. Bartberger, S. C. Virgil and B. M. Stoltz, *ACS Catal.*, 2020, **10**, 3241.
8 C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti and M. Graziani, *Organometallics*, 1998, **17**, 3308; J. P. Henschke, M. J. Burk, C. G. Malan, D. Herzberg, J. A. Peterson, A. J. Wildsmith, C. J. Cobley and G. Casy, *Adv. Synth. Catal.*, 2003, **345**, 300; W. Tang, L. Xu, Q.-H. Fan, J. Wang, B. Fan, Z. Zhou, K.-H. Lam and A. S. C. Chan, *Angew. Chem., Int. Ed.*, 2009, **48**, 9135; N. Mršić, T. Jerphagnon, A. J. Minnaard, B. L. Feringa and J. G. de Vriesa, *Adv. Synth. Catal.*, 2009, **351**, 2549; M. Rueping, F. Tato and F. R. Schoepke, *Chem. – Eur. J.*, 2010, **16**, 2688; D. Cartigny, T. Nagano, T. Ayad, J.-P. Genet, T. Ohshim, K. Mashima and V. Ratovelomanana-Vidal, *Adv. Synth. Catal.*, 2010, **352**, 1886; J. Qin, F. Chen, Z. Ding, Y.-M. He, L. Xu and Q.-H. Fan, *Org. Lett.*, 2011, **13**, 6568; S. Fleischer, S. Zhou, S. Werkmeister, K. Junge and M. Beller, *Chem. – Eur. J.*, 2013, **19**, 4997; Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang and Z. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 6126.
9 M. Studer, C. Wedemeyer-Exl, F. Spindler and H.-U. Blaser, *Monatsh. Chem.*, 2000, **131**, 1335; C. Y. Legault and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 8966; M. Rueping and A. P. Antonchick, *Angew. Chem., Int. Ed.*, 2007, **46**, 4562; C. Y. Legault, A. B. Charette and P. G. Cozzi, *Hetereocycles*, 2008, **76**, 1271; Y. Kita, A. Iimuro, S. Hida and K. Mashima, *Chem. Lett.*, 2014, **43**, 284; M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 12761; Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2012, **51**, 10181; M.-W. Chen, Z.-S. Ye, Z.-P. Chen, B. Wu and Y.-G. Zhou, *Org. Chem. Front.*, 2015, **2**, 586.
10 R. Kuwano, K. Sato, T. Kurokawa, D. Karube and Y. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 7614; A. Baeza and A. Pfaltz, *Chem. – Eur. J.*, 2010, **16**, 2036; J. L. Núez-Rico, H. Fernández-Pérez and A. Vidal-Ferran, *Green Chem.*, 2014, **16**, 1153; Z. Yang, F. Chen, Y. He, N. Yang and Q.-H. Fan, *Angew. Chem., Int. Ed.*, 2016, **55**, 13863; T. Touge and T. Arai, *J. Am. Chem. Soc.*, 2016, **138**, 11299; D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2010, **132**, 8909; Y. Duan, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2014, **136**, 7688.
11 D.-S. Wang, Z.-S. Ye, Q.-A. Chen, Y.-G. Zhou, C.-B. Yu, H.-J. Fan and Y. Duan, *J. Am. Chem. Soc.*, 2011, **133**, 8866.
12 R. Kuwano, N. Kameyama and R. Ikeda, *J. Am. Chem. Soc.*, 2011, **133**, 7312.
13 S. Kaiser, S. P. Smidt and A. Pfaltz, *Angew. Chem., Int. Ed.*, 2006, **45**, 5194; J. Wysocki, N. Ortega and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 8751; J. Wysocki, N. Ortega and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 8751.
14 Z. Zhang and H. Du, *Org. Lett.*, 2015, **17**, 2816; Z. Zhang and H. Du, *Angew. Chem., Int. Ed.*, 2015, **54**, 623; X. Li, J.-J. Tian, N. Liu, X.-S. Tu, N.-N. Zeng and X.-C. Wang, *Angew. Chem., Int. Ed.*, 2019, **58**, 4664.
15 M. A. Wijdeven, J. Willemsen and F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, 2010, 2831.
16 D. Gomez Pardo and J. Cossy, *Chem. – Eur. J.*, 2014, **20**, 4516; J. Cossy, *Chem. Rec.*, 2005, **5**, 70.
17 W.-X. Huang, C.-B. Yu, Y. Ji, L.-J. Liu and Y.-G. Zhou, *ACS Catal.*, 2016, **6**, 2368.
18 W.-X. Huang, B. Wu, X. Gao, M.-W. Chen, B. Wang and Y.-G. Zhou, *Org. Lett.*, 2015, **17**, 1640.
19 S. Bieringer and W. Holzer, *Heterocycles*, 2006, **68**, 1825.
20 P. Chauhan, S. Mahajan and D. Enders, *Chem. Commun.*, 2015, **51**, 12890; S. Liu, X. Bao and B. Wang, *Chem. Commun.*, 2018, **54**, 11515.
21 E. P. Kündig, A. Enriquez-Garcia, T. Lomberget and G. Bernardinelli, *Angew. Chem., Int. Ed.*, 2006, **45**, 98; E. P. Kündig and A. Enriquez-Garcia, *Beilstein J. Org. Chem.*, 2008, **4**, 37.
22 C.-B. Yu, K. Gao, Q.-A. Chen, M.-W. Chen and Y.-G. Zhou, *Tetrahedron Lett.*, 2012, **53**, 2560; C.-B. Yu, K. Gao, D.-S. Wang, L. Shi and Y.-G. Zhou, *Chem. Commun.*, 2011, **47**, 5052.
23 Z.-P. Chen, M.-W. Chen, L. Shi, C.-B. Yu and Y.-G. Zhou, *Chem. Sci.*, 2015, **6**, 3415.
24 B. Stanovnik, M. Tišler, A. R. Katritzky and O. V. Denisko, *Adv. Heterocycl. Chem.*, 2006, **91**, 1; M. Chevrier, O. Bensaude, J. Guillerez and

J. E. Dubois, *Tetrahedron Lett.*, 1980, **21**, 3359; P. Cieplak and M. Geller, *J. Mol. Struct.: THEOCHEM*, 1985, **124**, 249; C. Kashima, A. Katoh, M. Shimizu and Y. Omote, *Heterocycles*, 1984, **22**, 2591; P. Beak, F. S. J. Fry, J. Lee and F. Steele, *J. Am. Chem. Soc.*, 1976, **98**, 171.
25 G.-S. Feng, M.-W. Chen, L. Shi and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2018, **57**, 5853.
26 Y. Du, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2014, **136**, 7688.
27 I.-A. Shuklov, N.-V. Dubrovinaa and A. Börner, *Synthesis*, 2007, 2925.
28 G.-S. Feng, L. Shi, F.-J. Meng, M.-W. Chen and Y.-G. Zhou, *Org. Lett.*, 2018, **20**, 6415.
29 C. O. Kappe, *Eur. J. Med. Chem.*, 2000, **35**, 1043.
30 S. Debonis, J. P. Simorre, I. Crevel, L. Lebeau, D. A. Skoufias, A. Blangy, C. Ebel, P. Gans, R. Cross, D. D. Hackney, R. H. Wade and F. Kozielski, *Biochemistry*, 2003, **42**, 338; K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806.
31 L.-Z. Gong, X.-H. Chen and X.-Y. Xu, *Chem. – Eur. J.*, 2007, **13**, 8920; H. Rao, Z. Quan, L. Bai and H. Ye, *Chin. J. Org. Chem.*, 2016, **36**, 283.
32 F.-J. Meng, L. Shi, G.-S. Feng, L. Sun and Y.-G. Zhou, *J. Org. Chem.*, 2019, **84**, 4435.
33 N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001; H. Feuer and A. T. Nielsen, *Nitro Compounds: Recent Advances in Synthesis and Chemistry: Organic Nitro Chemistry Series*, VCH, Weinheim, 1990.
34 O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877; S. E. Milner, T. S. Moody and A. R. Maguire, *Eur. J. Org. Chem.*, 2012, 3059.
35 X.-F. Cai, M.-W. Chen, Z.-S. Ye, R.-N. Guo, L. Shi, Y.-Q. Li and Y.-G. Zhou, *Chem. – Asian J.*, 2013, **8**, 1381.
36 X.-F. Cai, R.-N. Guo, M.-W. Chen, L. Shi and Y.-G. Zhou, *Chem. – Eur. J.*, 2014, **20**, 7245.
37 D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou and Y.-X. Li, *J. Org. Chem.*, 2009, **74**, 2780.
38 X.-F. Cai, W.-X. Huang, Z.-P. Chen and Y.-G. Zhou, *Chem. Commun.*, 2014, **50**, 9588.
39 X.-F. Cai, R.-N. Guo, G.-S. Feng, B. Wu and Y.-G. Zhou, *Org. Lett.*, 2014, **16**, 2680.
40 M. C. Desai, S. L. Letkowitz, P. F. Thadeio, K. P. Longo and R. M. Snider, *J. Med. Chem.*, 1992, **35**, 4911; G. J. Boks, J. P. Tollenaere and J. Kroon, *Bioorg. Med. Chem.*, 1997, **5**, 535.
41 P. R. Sultane and R. G. Bhat, *J. Org. Chem.*, 2012, **77**, 11349; E. Semina, F. Colpaert, K. Van Hecke, N. De Kimpe and S. Mangelinckx, *Eur. J. Org. Chem.*, 2015, 4847; R.-H. Liu, K. Fang, B. Wang, M.-H. Xu and G.-Q. Lin, *J. Org. Chem.*, 2008, **73**, 3307; M. Ahari, A. Perez, C. Menant, J.-L. Vasse and J. Szymoniak, *Org. Lett.*, 2008, **10**, 2473.
42 A. Iimuro, K. Higashida, Y. Kita and K. Mashima, *Adv. Synth. Catal.*, 2016, **358**, 1929.
43 L.-S. Zheng, F. Wang, X.-Y. Ye, G.-Q. Chen and X. Zhang, *Org. Lett.*, 2020, **22**, 8882.
44 E. Juaristi, J. Vargas-Caporali and C. Cruz-Hernández, *Heterocycles*, 2012, **86**, 1275.
45 W.-X. Huang, L.-J. Liu, B. Wu, G.-S. Feng, B. Wang and Y.-G. Zhou, *Org. Lett.*, 2016, **18**, 3082.
46 K. Higashida, H. Nagae and K. Mashima, *Adv. Synth. Catal.*, 2016, **358**, 3949.
47 Z. Yan, H.-P. Xie, H.-Q. Shen and Y.-G. Zhou, *Org. Lett.*, 2018, **20**, 1094.