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Catalytic asymmetric synthesis of 1,2-diamines

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The asymmetric catalytic synthesis of 1,2-diamines has received considerable interest, especially in the last ten years, due to their presence in biologically active compounds and their applications for the development of synthetic building blocks, chiral ligands and organocatalysts. Synthetic strategies based on C–N bond-forming reactions involve mainly (a) ring opening of aziridines and azabenzonorbornadienes, (b) hydroamination of allylic amines, (c) hydroamination of enamines and (d) diamination of olefins. In the case of C–C bond-forming reactions are included (a) the aza-Mannich reaction of imino esters, imino nitriles, azlactones, isocyano acetates, and isothiocyanates with imines, (b) the aza-Henry reaction of nitroalkanes with imines, (c) imine–imine coupling reactions, and (d) reductive coupling of enamines with imines, and (e) [3+2] cycloaddition with imines. C–H bond forming reactions include hydrogenation of C=N bonds and C–H amination reactions. Other catalytic methods include desymmetrization reactions of *meso*-diamines.

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1. Introduction

Chiral 1,2-diamines are ubiquitous in biologically active compounds, not only in natural products but also synthetic ones including commercial drugs.[1] These compounds are widely used in asymmetric synthesis of chiral auxiliaries, ligands and organocatalysts (Table 1).[2–14] For these reasons, there is broad interest in the development of catalytic methods for the synthesis of enantioenriched 1,2-diamines mainly based on asymmetric metal catalysis and organocatalysis. Among them are C–N, C–C and C–H bond forming reactions (Scheme 1).

In this review article, methods developed mainly in the last 15 years will be considered. For the C–N bond forming reactions, ring-opening of *meso*-aziridines and azabenzonorbornadienes, amination of allylic amines or enamines, ring opening of azabenzonorbornadienes and diamination of alkenes[7–14] will be considered. Classical C–C bond forming reactions such as

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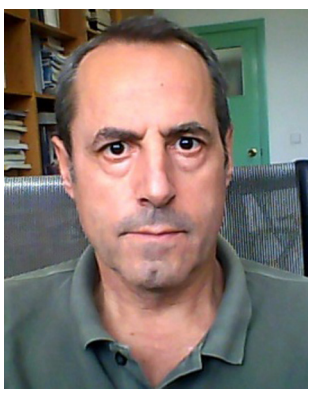

Francisco Foubelo

Francisco Foubelo was born in 1961 and studied Chemistry at the University of Oviedo where he received BS (1984), MS (1986) and PhD (1989) degrees, under the direction of Professors J. Barluenga, M. Yus and F. J. Fañanás. He then joined the laboratory of Professor M. F. Semmelhack at Princeton University as a Fulbright postdoctoral fellow, and, in 1991, the group of Professor M. Yus at the University of Alicante, where he became an associate professor in 1995, and a full professor in 2002. His current research interests are focused on the development of new synthetic methodologies involving chiral sulfinyl imines, and on metal-promoted functionalization of alkenes and alkynes.

Carmen Nájera

Carmen Nájera was born in Nájera (La Rioja, 1951) and received BS (1973) and MS from the University of Zaragoza and PhD (1979) form the University of Oviedo. After postdoctoral stays at the ETH, Oxford, Harvard and Uppsala Universities, she became an associate professor (1985) at the University of Oviedo and a full professor (1993) at the University of Alicante. She is a coauthor of more than 430 papers and supervised 50 PhD students. She has been awarded with several national and international prizes, and in 2012 she was elected as a full member of the Spanish RAC and in 2016–2017 ChemPubSoc Europe Fellow.

aza-Mannich-type reactions, aza-Henry reactions followed by the reduction of the nitro group, aza-pinacol reactions, addition of azaallyl anions to imines and 1,3-dipolar cycloaddition of azomethine ylides to imines will be presented. However, due to space limitations, the Strecker reaction, which is mainly applied to the synthesis of α-amino acids, is not included. In the case of C–H forming approaches, reduction of C=N bonds by hydrogenation reactions and intramolecular nitrene C–H insertion will be considered. Other catalytic methods will be included in Section 6, such as desymmetrization of *meso*-diaminocyclopropanes or kinetic resolution of racemic 1,2-diamines. In this catalytic asymmetric methods, metals, organocatalysts and enzymes are extensively used.

M Gracia Retamosa

Maria de Gracia Retamosa is a Senior Researcher of the University of Alicante (CIDEGENT program of the G. Valenciana) and received her PhD in 2008 from the University of Alicante (Spain) under the guidance of Prof. Carmen Nájera and José Miguel Sansano. She is a coauthor of 45 articles and 5 patents. She completed several postdoctoral stays [with Prof. Michael Greaney at the University of Edinburgh (UK, 2009), Prof. Jesús M. Sanz at the University Miguel Hernández (Elche, Spain, 2009–2011) and Prof. Fernando P. Cossío at the University of the Basque Country and Donostia International Physics Center (Spain, 2012–2016)]. Recently, she has joined the group of Prof. Rosario Fernández and José M. Lassaletta as a postdoctoral researcher [CSIC (Sevilla, Spain)]. Her current research interests include asymmetric metal, and organocatalysis and synthesis of compounds with pharmacological interest.

2. C–N bond-forming reactions

2.1. Ring-opening of aziridines

The catalytic aminolysis of *meso*-aziridines **1** is a very efficient strategy to obtain chiral 1,2-diamines with two differently substituted amino groups. This desymmetrization[15] methodology can be carried out under chiral Lewis or Brønsted acid catalysis. When trimethylsilyl azide was allowed to react with *meso*-aziridines **1**, the corresponding β-azido amino derivatives **2** were isolated (Scheme 2). Initial pioneering work of Jacobsen and co-workers[16] was carried out using a tridentate Schiff base chromium(III) complex **3** derived from 1-amino-2-indanol as a catalyst (Fig. 1). The azido *N*-2,4-1 products **2** were obtained in 73–95% yields and 83–94% ee and they can be easily transformed into chiral 1,2-diamines (Table 2).

Kanai, Shibasaki and co-workers[17] used a yttrium complex formed by a chiral phosphine oxide **4** and $Y(OiPr)_3$ as a catalyst (Fig. 1) for the synthesis of compounds **2** with high yields (94 to >99%) and good enantioselectivities (83–96% ee) (Table 2). Compound **2** [R^1–R^1=$(CH_2)_4$] was transformed in 3 steps into *trans*-1,2-cyclohexanediamine in 96% yield. This reaction was applied to the asymmetric synthesis of Tamiflu starting from aziridine **5**, which was transformed into diamine **6** in four steps (Scheme 3).

Brønsted acid organocatalysis was performed by Antila and co-workers[18] by means of a chiral phosphoric acid (CPA) (*S*)-Vapol (**7**) as a catalyst (Fig. 1). This general method was carried out with cyclic and acyclic aziridines **1** to obtain products **2** in good yields and enantioselectivities (Table 2). In the proposed mechanism, the silylation of the CPA firstly took place, which activates the aziridine followed by subsequent nucleophilic

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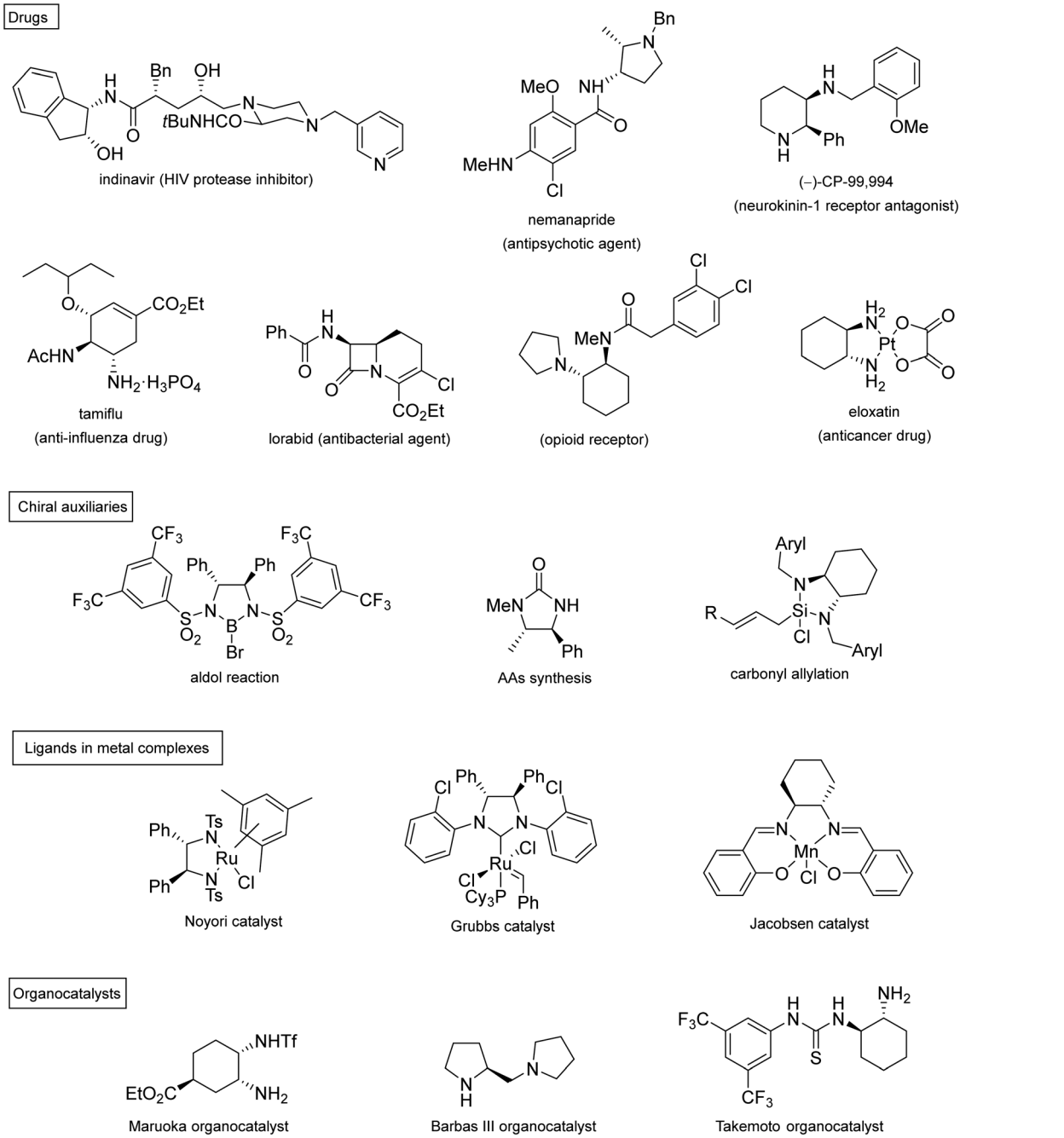
Professor José Miguel Sansano was born in Rojales (Alicante), studied chemistry at the University of Alicante, where he obtained his BSc and PhD degrees in 1988 and 1994, respectively. His thesis was supervised by Prof. C. Nájera and dealt about sulfone chemistry. After spending a two-year postdoctoral stay at the University of Leeds (U.K.) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed as an Associate Professor in 2001. In 2010, he was promoted to a Full Professor in the same University. He was invited as a visiting Professor at Chuo University in 2014 and in the UFRJ (Brazil). He is a coauthor of more than 140 articles and he has supervised 13 PhD students.

Miguel Yus

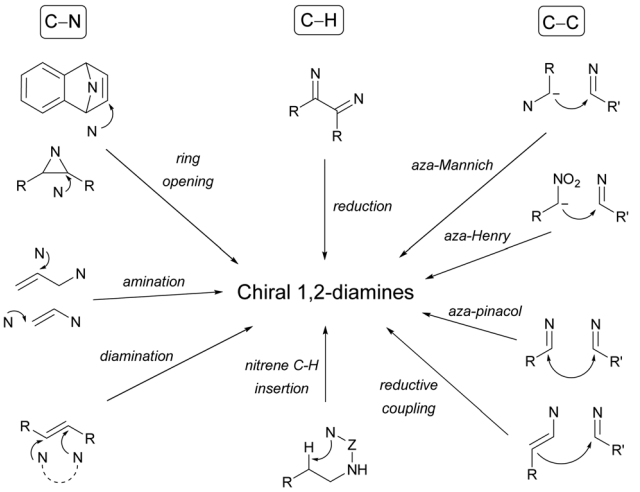
Miguel Yus was born in Zaragoza (Spain, 1947), and received his BSc (1969), MSc (1971) and PhD (1973) degrees from the University of Zaragoza. After two years as a postdoctoral fellow at Max Planck Institut für Kohlenforschung in Mülheim/Ruhr, he returned to the University of Oviedo, Spain where he became an associate professor (1977) and a full professor (1987). In 1988, he moved to the University of Alicante. He is a co-author of 600+ papers, having 33.000+ citations and h-index 83. Professor Yus has been in the Advisory Board of more than 30 international journals and founded in 2002 the company MEDALCHEMY S.L.

Table 1 Drugs, chiral auxiliaries, ligands and organocatalysts containing chiral 1,2-diamines

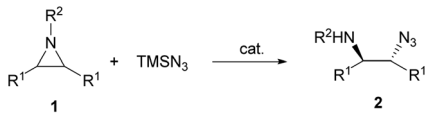


attack by the azide. Parquete, RajanBabu and co-workers[19–21] employed a dimeric yttrium–salen complex **8** as a chiral catalyst (Fig. 1) for the ring-opening of *meso*-aziridines **1** with $TMSN_3$. This reaction took place at room temperature to afford products **2** in high yields and enantioselectivities (Table 2). However, monosubstituted aziridines provided a mixture of regioisomeric products.[21] Nakamura and co-workers[22] used for the first time *meso*-*N*-(2-pyridinesulfonyl)aziridines **1** (R^2 = 6-Me-2-$PySO_2$), which by reaction with trimethylsilyl azide under $Mg(NTf)_2$/bisoxazoline **9** (Fig. 1) catalysis provided products **2** in good yields and moderate enantioselectivities (Table 2). This procedure was applied to the synthesis of U-50488, which is a highly selective K-opioid agonist, starting from compound **10** which was obtained in 99% ee after recrystallization (Scheme 4).

Desymmetrization of *meso*-aziridines with amines was firstly performed under binol derived metal complexes by Kobayashi and co-workers.[23–25] *N*-(2-Methoxyphenyl)aziridines **11** were reacted with anilines in the presence of $Nb(OiPr)_3$ and tetradentate binol (*R*)-**12** (Fig. 2) to furnish diamines **13** in good yields and high enantioselectivities (Scheme 5).[23]



Scheme 1 Catalytic methods for the asymmetric synthesis of 1,2-diamines.



Scheme 2 Catalytic ring-opening of *meso*-aziridines **1** with trimethylsilyl azide.

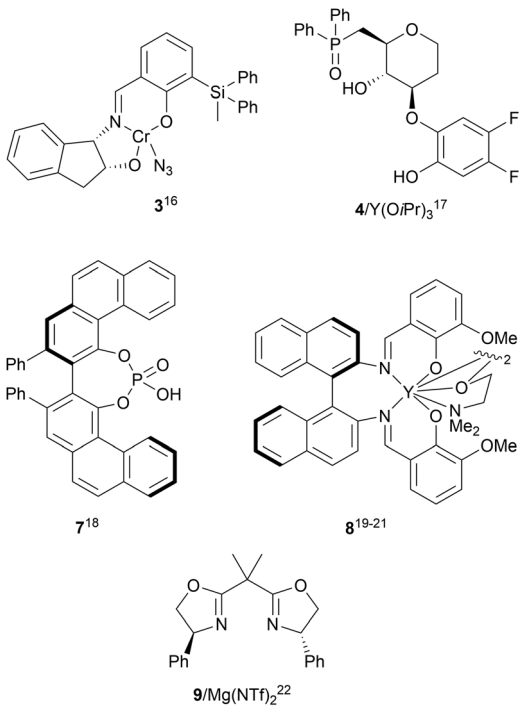


Fig. 1 Catalysts for the ring-opening of *meso*-aziridines with trimethylsilyl azide.

The ring-opening of aziridines **11** with aniline was also studied by the same group[24] using $Ti(OiPr)_4$ and tridentate binol derivatives **14** and **15** (Fig. 2) as catalysts. Cyclic *meso*-aziridines **11** were efficiently transformed into the corresponding *N*,*N*′-diaryl 1,2-diamines **13** in good yields (74–94%) and enantioselectivities (61–95%). Ligand **14** and $Zr(OtBu)_4$ were employed as catalysts for the aminolysis of cyclic and acyclic *N*-benzhydryl aziridines **16** with anilines obtaining products **17** in high yields and enantioselectivities (Scheme 6).[25] For the cleavage of the benzhydryl group, hydrogenation on incarcerated Pd[26] in EtOH at 70 °C was efficiently performed giving quantitatively the monoamine-free diamine.

Schneider and co-workers[27,28] used $Ti(OtBu)_4$ and (*R*)-binol (**18**, Fig. 2) in the aminolysis of cyclic and acyclic *N*-arylaziridines **11** for the direct preparation of *N*,*N*′-diarylated enantioenriched 1,2-diamines **13** (Scheme 7). The chiral catalyst with an oligomeric structure (from ESI-MS experiments) showed, as in the case of Kobayashi's catalyst[24] **15**/$Ti(OiPr)_4$, a positive nonlinear effect (NLE). This method is the simplest and in general efficient for the synthesis of these types of diamines.

In the studies of *meso*-aziridines' ring-opening with primary alcohols, Feng and co-workers[29] reported a single example with aniline. Chiral $Mg(OTf)_2$/*N*,*N*′-dioxide **19** (Fig. 2) acted as a catalyst in the reaction of *N*-(2-picolinoyl)aziridine **20** with aniline to afford diamine **21** in 97% yield and 95% ee (Scheme 8).

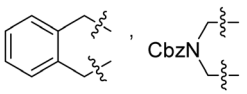
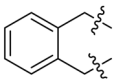
Chai and co-workers[30] have reported an Ag(I)-catalyzed enantioselective ring-opening of *N*-tosylaziridines **22** using (*S*)-DTBM-Segphos (**23**) as a chiral bisphosphine (Fig. 2). This desymmetrization was performed with aromatic and aliphatic amines to obtain the corresponding diamines **24** in general with very good yields and enantioselectivities (Scheme 9a). In addition, these reaction conditions have been applied to the kinetic resolution of 2-aryl-*N*-tosylaziridines **25** with amines to obtain regioselectively diamines **26** with excellent results (Scheme 9b). Gram-scale experiments were performed with *meso*-cyclohexane aziridine and 4-methoxyaniline, and the reaction of 2-phenyl-1-tosylaziridine with 4-methoxyaniline on 4 and 3 mmol scales, respectively.

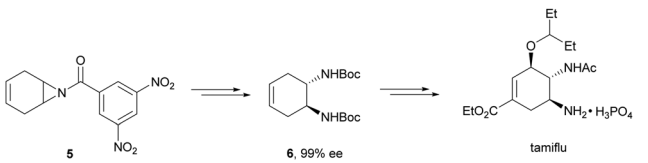
Other nitrogenated compounds such as substituted hydroxylamines,[31] tetrazoles[32] and pyrazoles[33] have been employed as nucleophiles for desymmetrization of *meso*-aziridines using Mg(II) complexes as catalysts. Wang and co-workers[31] performed the ring-opening of *N*-(2-picolinoyl)aziridines **20** with different carbonyl protected hydroxylamines **27** to obtain compounds **29** in good yields and enantioselectivities employing *n*-Bu_2Mg and oxazoline **28** as a catalyst (Scheme 10). This Mg-catalyzed desymmetrization can also be carried out on a gram-scale.

In the case of monosubstituted tetrazoles **30**, aziridines **20** underwent ring-opening under *n*Bu_2Mg and a binolam[32] derivative **31** to afford products **32** (Scheme 11).[33] These compounds **32** were monodeprotected to the corresponding primary amines with NaOH in EtOH at 90 °C. As a possible mechanism, it has been proposed the formation of chiral catalyst **I**, which after coordination with the aziridine **20** forms intermediate **II**. Subsequent coordination of the tetrazole gives intermediate **III**, which evolves by ring-opening of the aziridine to provide the product and regenerates the catalyst.

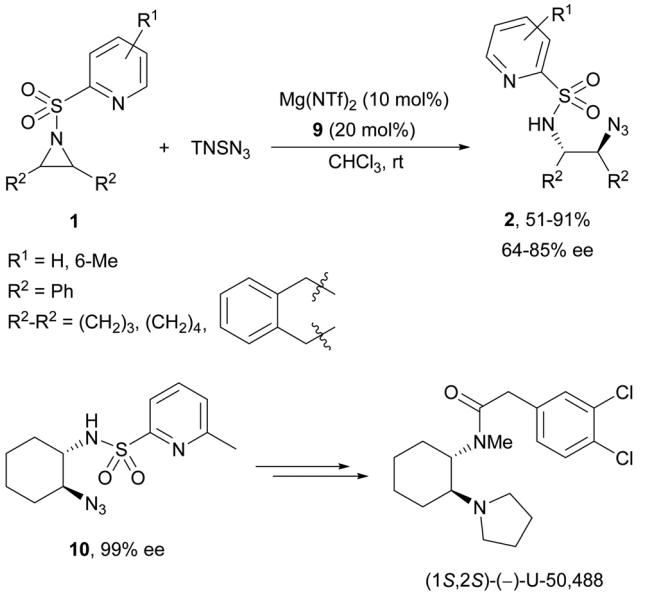
Feng and co-workers[34] applied a similar catalyst employed in the ring opening of aziridines **20** with aniline (see Scheme 8) for pyrazoles **33** (Scheme 12). In this case, $Mg(OTf)_2$ and

Table 2 Enantioselective ring-opening of *meso*-aziridines **1** with trimethylsilyl azide

R^1	R^2	Catalyst	Yield (%)	ee (%)	Ref.
Me, $(CH_2)_2$, $(CH_2)_4$, CH_2OCH_2, 3,5-$(NO_2)_2C_6H_3CH_2$, (*Z*)-$CH_2CH{=}CHCH_2$	2,4-$(NO_2)_2C_6H_3CH_2$	**3**	73–95	83–94	16
Me, Ph, $(CH_2)_3$, $(CH_2)_4$, (*Z*)-$CH_2CH{=}CHCH_2$, 3,5-$(NO_2)_2C_6H_3CO$, CH_2OCH_2	3,5-$(NO_2)_2C_6H_3CO$	**4**	94–>99	83–96	17
Me, Ph, $(CH_2)_3$, $(CH_2)_4$, (*Z*)-$CH_2CH{=}CHCH_2$, 3,5-$(NO_2)_2C_6H_3CO$, CH_2OCH_2	3,5-$(NO_2)_2C_6H_3CO$	**8**	49–97	69–95	17
					
*n*Pr, Ph, $(CH_2)_3$, $(CH_2)_4$, (*Z*)-$CH_2CH{=}CHCH_2$	4-$NO_2C_6H_4CO$	**11**	47–99	90–99	19–21
Ph, $(CH_2)_3$, $(CH_2)_4$, 	2-$PySO_2$, 6-Me, 2-$PySO_2$	**14**	51–91	64–85	22



Scheme 3 Synthesis of tamiflu by ring-opening of aziridine **5** with trimethylsilyl azide as the key step.



Scheme 4 Ring-opening of *meso*-*N*-(2-pyridinesulfonyl)aziridines **1** with trimethylsilyl azide under $Mg(NTf)_2$/bisoxazoline **9** catalysis.

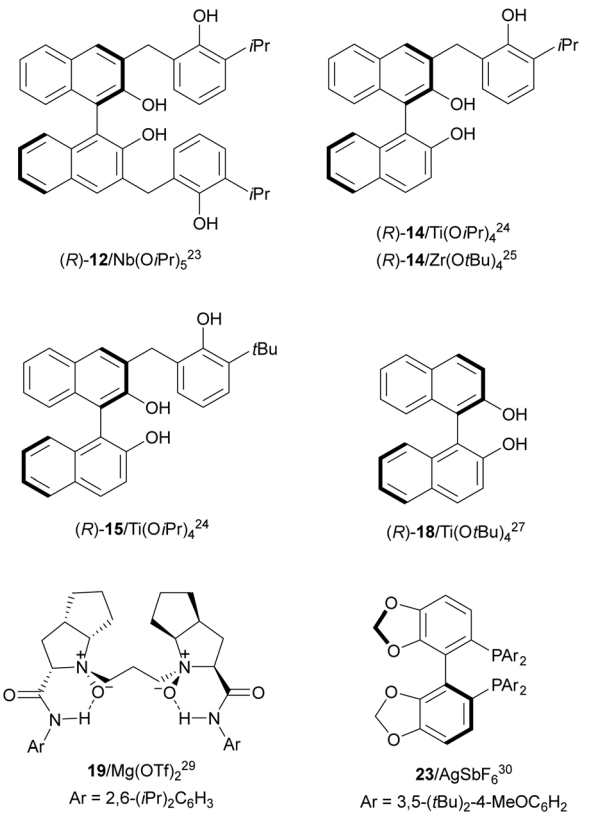


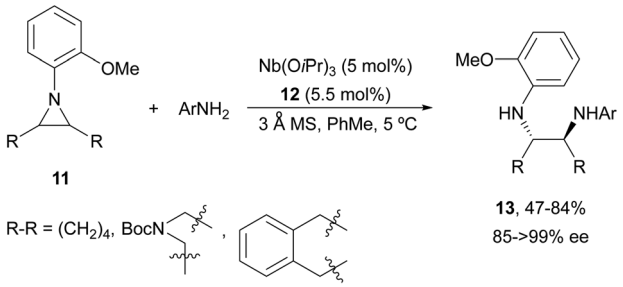
Fig. 2 Chiral catalysts for the aminolysis of *meso*-aziridines.

N,*N*′-dioxide **34** were used as catalysts for the desymmetrization of differently substituted *N*-(2-picolinoyl)aziridines **20** with pyrazoles **33** to furnish products **35** in good yields (up to 99%) and enantioselectivities (up to 94% ee). Strong positive NLE was observed for this type of desymmetrization. Besides, benzotriazole, 3-phenyltetrazole and trimethylsilyl azide were also applied to this ring-opening of cyclohexane-derived aziridine although with lower enantioselectivities.

According to the procedures for the asymmetric ring-opening of aziridines, the initial use of trimethylsilyl azide under metal-catalysis and CPA as an organocatalyst has evolved to aromatic and aliphatic amines under silver catalysis. The nitrogenated nucleophiles such as substituted hydroxylamines, tetrazoles and pyrazoles can be employed under magnesium catalysis.

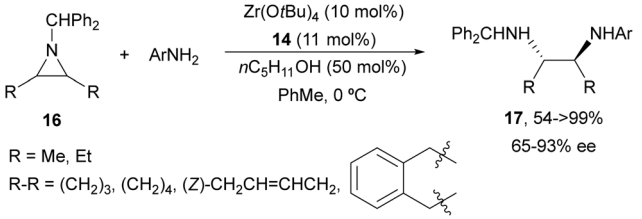
2.2. Ring-opening of azabenzonorbornadienes

Transition-metal-catalyzed asymmetric ring-opening reaction of azabenzonorbornadienes **36** with amines is a desymmetrization[15] strategy for the synthesis of diaminotetralines **37** (Scheme 13). Lautens and co-workers[35–37] reported the first example[35,36] using the rhodium complex of C_2-ferriphos **38** (Fig. 3) and aromatic or



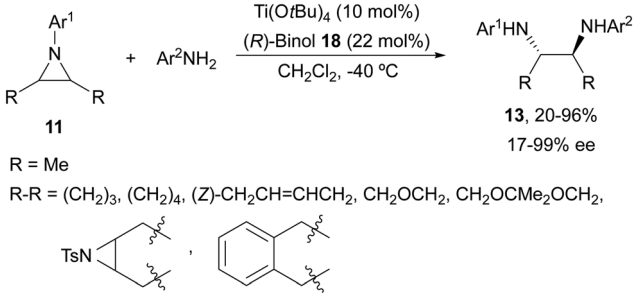
Ar = Ph, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$

Scheme 5 Ring-opening of *meso*-aziridines **11** with anilines under Nb–binol complex **12** catalysis.



Ar = Ph, 3-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 3-IC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 3-NCC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 3-EtO$_2$CC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 3,5-(CF$_3$)$_2$C$_6$H$_3$

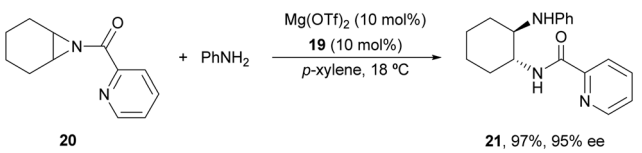
Scheme 6 Ring-opening of *meso*-aziridines **16** with anilines under Zr–binol complex **14** catalysis.



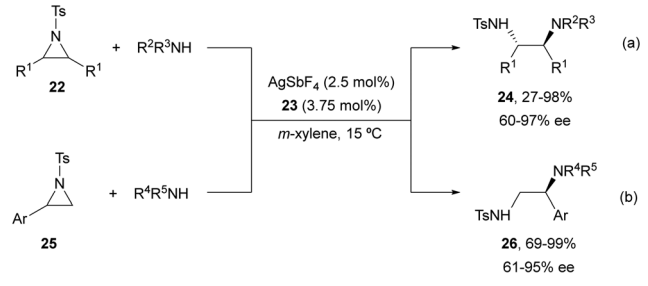
Ar^1 = Ph, 4-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$

Ar^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-HSC$_6$H$_4$

Scheme 7 Ring-opening of *meso*-aziridines **11** with anilines under Ti(O*t*Bu)$_4$/(*R*)-binol (**18**) catalysis.



Scheme 8 Ring-opening of *meso*-aziridine **20** with aniline under Mg(OTf)$_2$/*N*,*N*′-dioxide **19**.



R^1 = Et

R^1-R^1 = (CH$_2$)$_3$, (CH$_2$)$_4$, (CH$_2$)$_5$, (*Z*)-CH$_2$CH=CHCH$_2$

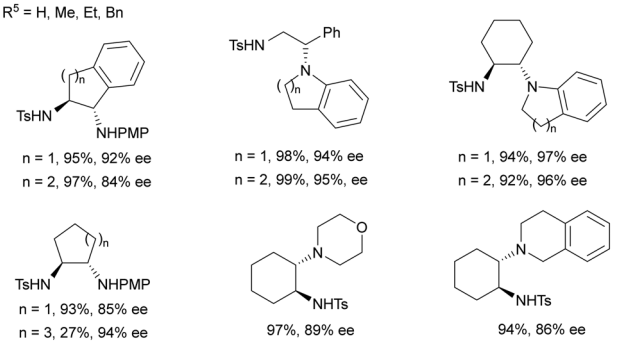
R^2 = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, mesityl, Bn, Ph$_2$CH

R^3 = H, Me

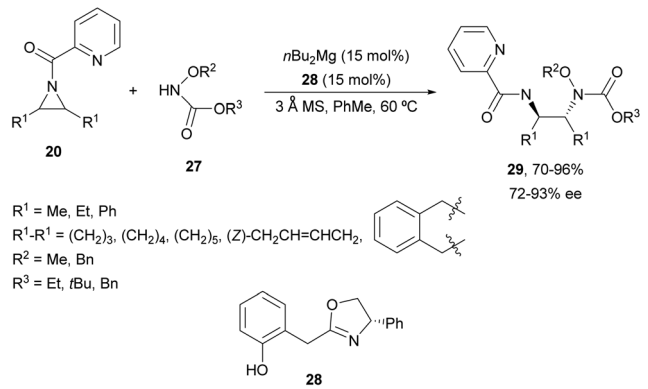
Ar = Ph, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-*t*BuC$_6$H$_4$, 4-MeOC$_6$H$_4$

R^4 = Ph, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, mesityl, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-IC$_6$H$_4$, 2-BrC$_6$H$_4$, Bn, Et, Ph$_2$CH, EtO$_2$CCH$_2$

R^5 = H, Me, Et, Bn



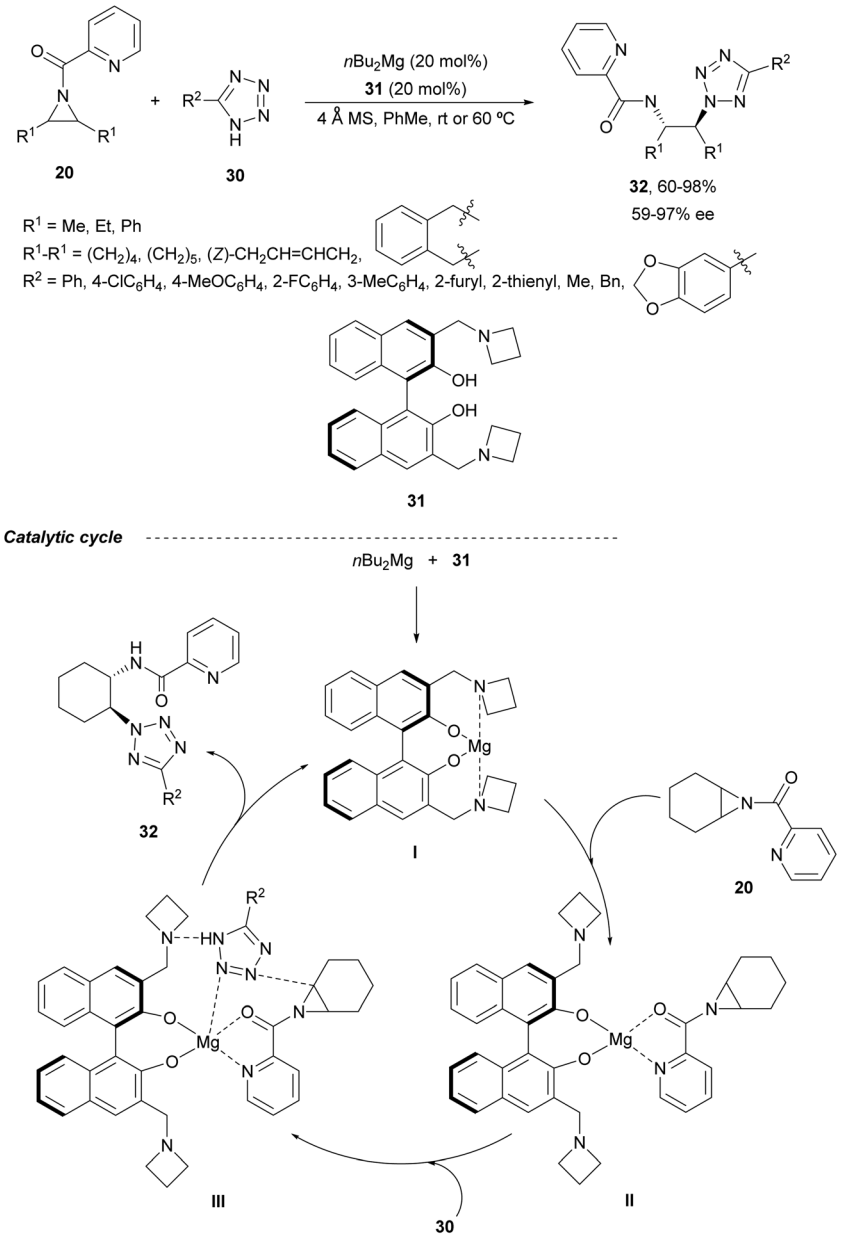
Scheme 9 Ring-opening of aziridines **22** and **25** with aromatic and aliphatic amines under AgSbF$_6$/(*S*)-DTBM-Segphos (**23**) catalysis.



Scheme 10 Ring-opening of aziridines **20** with carbonyl-protected hydroxylamines **27** under *n*Bu$_2$Mg/oxazoline **28** catalysis.

aliphatic amines to provide regioselectively diamines **37** in 50–98% yield and 89 to >99% ee. This process was applied to the total synthesis of an analgesic compound **39**, a highly selective K-opioid agonist,[38] starting from *N*-Boc-pyrrole. Experimental results[36] support the formation of a dimer **I**, which after *exo*-binding at the C–C double bond and to the nitrogen atom forms intermediate **II**. Oxidative insertion of a Rh catalyst to C–N bond gives **III** and subsequent S_N2' displacement by the amine provides product **37** regenerating the catalyst (Scheme 13).

Another synthetic application of this Rh-catalyzed ring-opening of azabenzonorbornadienes was the preparation of new chiral ligands.[37] In this case, the ring-opening of **36** was carried out with dibenzylamine in the presence of (*S*,*S*′)-(*R*,*R*′)-C$_2$-ferriphos-tolyl **40** (Fig. 3) at 80 °C to give diamines **37** in

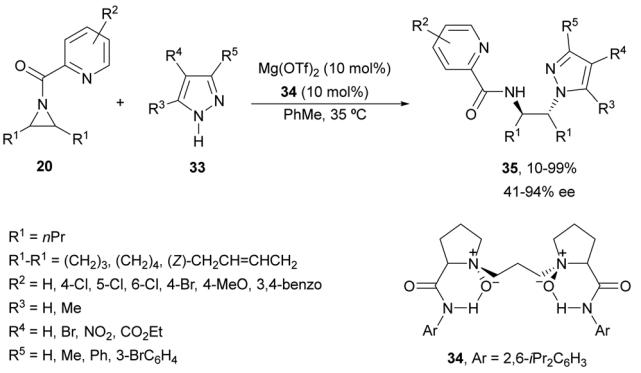


Scheme 11 Ring-opening of *meso*-aziridines **20** with tetrazoles **30** under nBu$_2$Mg/binolam **31** catalysis.

70–99% yield and 97–99% ee. After deprotection of diaminotetralins **37** resulted the corresponding tartrate salts of primary amines **41**, and these diamines were transformed into salen-type ligands **42** (Scheme 14).

Yang and co-workers[39,40] reported the Rh-catalyzed ring opening of *N*-Boc-azabenzonorbornadienes **36** with piperazine nucleophiles **43** using (*R*,*S*)-PPF-P(tBu)$_2$ **44** as a chiral ligand (Fig. 3). The resulting diaminotetralines **45** were obtained in the presence of ammonium iodide as an additive in tetrahydropyran (THP) at 100 °C with good yields and moderate enantioselectivities (Scheme 15).[40]

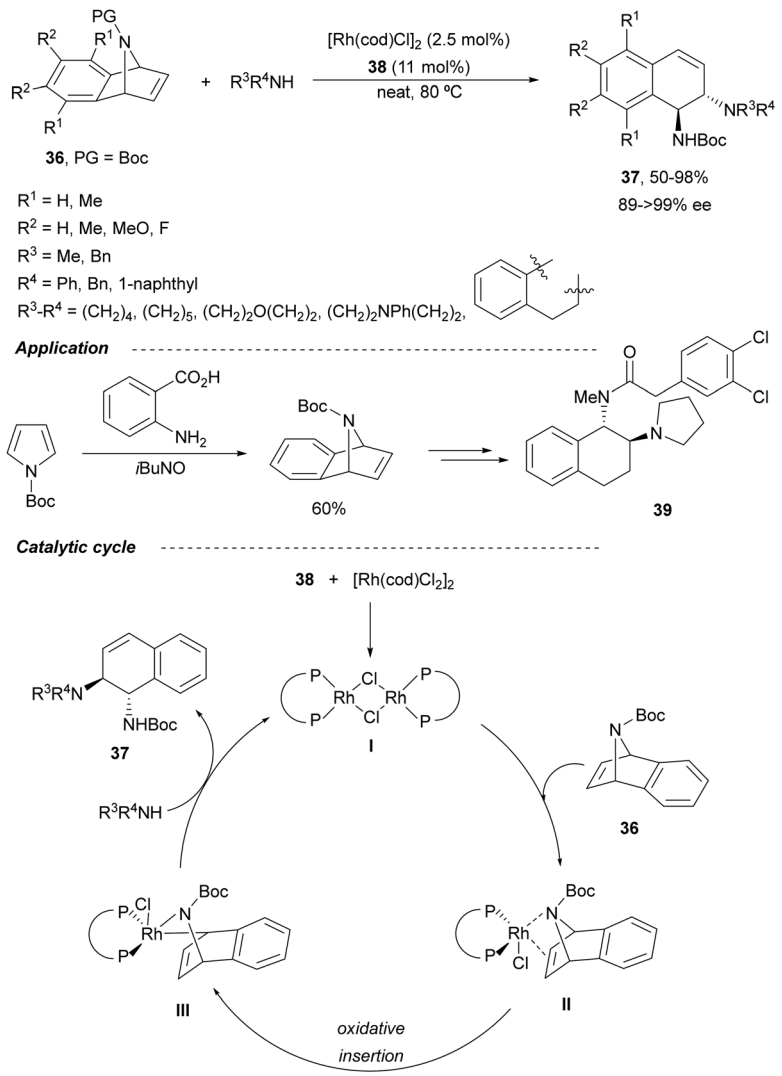
Iridium-catalyzed desymmetrization of *N*-Boc-azabenzonorbornadienes **36** with different amines has been described by Yang and co-workers.[41–43] Secondary amines[41,42] were employed as nucleophiles in the presence of [Ir(cod)Cl]$_2$ and (*S*)-Binap **46** (Fig. 3) as catalysts in THP at 100 °C. *N*-Substituted piperazines **43** gave the corresponding diamines with good yields (55–86%) and enantioselectivities (61–87% ee), whereas *N*-methylanilines provided lower results (24–59% yields and 42–85% ee). The authors proposed the same mechanism as depicted in Scheme 13 for the Rh-catalyzed ring opening of *N*-Boc-azabenzonorbornadienes. Higher yields and enantioselectivities were obtained in the reaction of different *N*-substituted azabenzonorbornadienes **36** with primary aromatic amines working on THP at 100 °C (bath temperature) with a lower catalyst loading to furnish diamines **37** in up to 97% yield and up to 97% ee (Scheme 16).[43] The best results were obtained with *N*-tosyl-azabenzonorbornadiene.



Scheme 12 Ring-opening of *meso*-aziridines **20** with pyrazoles **33** under $Mg(OTf)_2$/*N*,*N*′-oxide **34** catalysis.

A chiral monophosphine **47** (Fig. 3) has been employed by Luo and co-workers[44,45] as a ligand for the Ir-catalyzed desymmetrization of oxa- and azabenzonorbornadienes. However, in the case of *N*-Boc protected compound **36,** the reaction with *N*-phenylpiperazine (**43**) afforded the corresponding diamine **45** in only 19% yield and 35% ee.[44] Lately, they found that $[Ir(coe)_2Cl]_2$ and ligand **48** (Fig. 3) were better catalysts for the ring-opening of *N*-Boc-azabenzonorbornadienes **36** with secondary aliphatic amines in the presence of NaI as an additive (Scheme 17).[45] The resulting diamines **45** were obtained in good yields and enantioselectivities and one example was scaled up to *ca.* 2 g scale.

A combination of Ir/Cu co-catalyzed asymmetric ring-opening of *N*-substituted azabenzonorbornadienes **36** with amines was reported by Wang, Fan and co-workers.[46] Besides $[Ir(cod)Cl]_2$ and (*R*)-difluorphos **49** (Fig. 3), CuBr (20 mol%) was the best Lewis acid for the desymmetrization affording diamines **37** in very good yields and enantioselectivities (Scheme 18). In this case, for *N*-Boc derivatives primary and secondary aromatic amines, as well as Bn_2NH, worked efficiently. When electro-withdrawing groups at the nitrogen atom of azabenzonorbornadiene were used such as Ts, Ns or CO_2Me, instead of a Boc group, the yield decreased, though the



Scheme 13 Ring-opening of *N*-Boc-azabenzonorbornadienes **36** with amines under Rh(I)/C_2-ferriphos **38**.

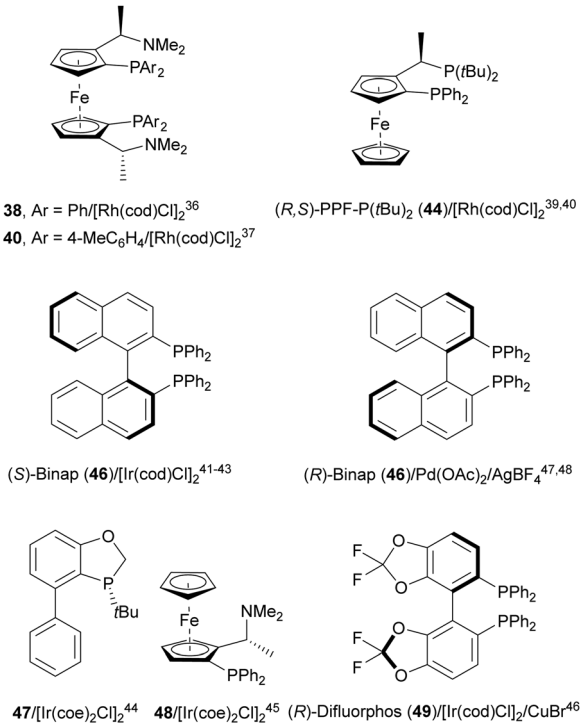
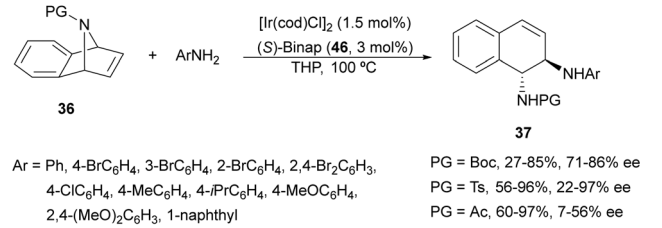


Fig. 3 Catalysts for the ring-opening of azabenzonorbornadienes with amines.

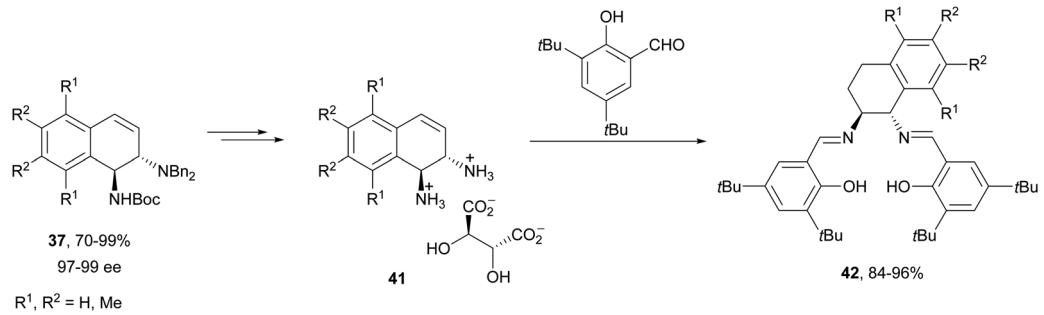


Scheme 16 Ring-opening of *N*-substituted azabenzonorbornadienes **36** with primary aromatic amines under Ir/(*S*)-Binap **46** catalysis.

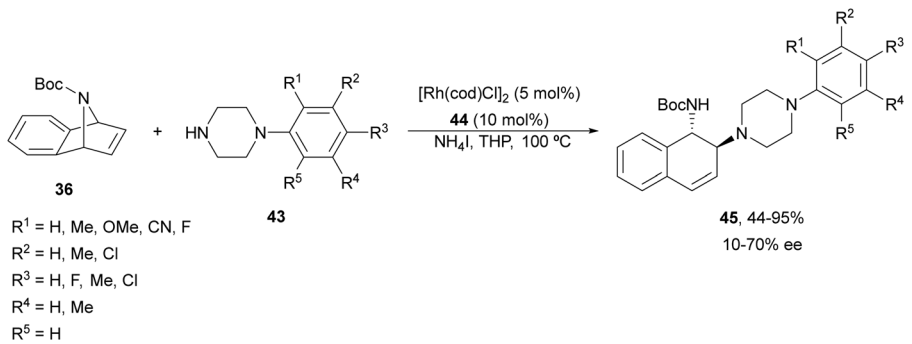
enantioselectivity could be maintained. In the proposed mechanism, the catalytic cycle is initiated by coordination of $[Ir(cod)Cl]_2$ with the chiral ligand **49** forming catalyst **I**. Subsequent coordination with **36**, Cu^+ and aniline gives intermediate **II**, which after intramolecular addition reaction generates intermediate **III**. Final β-elimination reaction provides the copper complex **IV**, which by cation exchange forms the product **37**.

The same group[47] employed for the first time $Pd(OAc)_2$, $AgBF_4$ and (*R*)-Binap (**46**) (Fig. 3) as catalysts for the ring-opening of *N*-Boc-azabenzonorbornadienes **36** with primary and secondary aromatic amines (Scheme 19). Resulting diamines **37** were obtained up to 97% yield and up to >99% ee working in toluene at 90 °C.

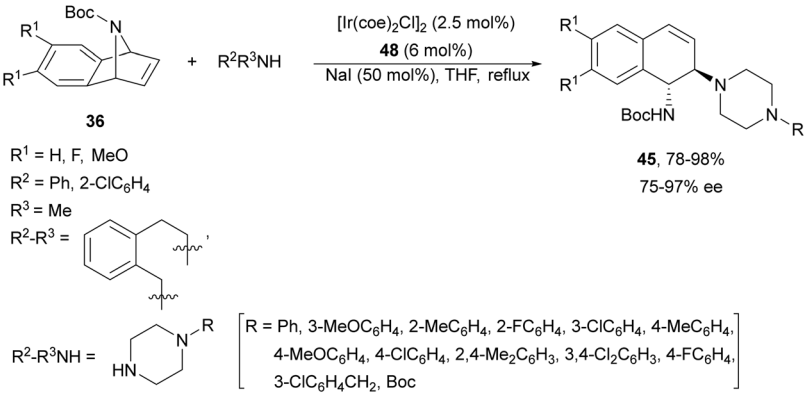
Under these reaction conditions, *N*-Boc-azabenzonorbornadienes **36** were reacted with different amides such as sulfonamides, carbamates, carboxamides and phosphoramides to obtain *syn*-1,2-diamine derivatives **50** (Scheme 20).[48] This is the first example of *syn*-stereoselective ring-opening of compounds **36**. Products **50** were obtained in good to high yields (up to 96%) and enantioselectivities (up to 98% ee). In the proposed reaction pathway, the catalytic cycle commenced with the chiral Pd



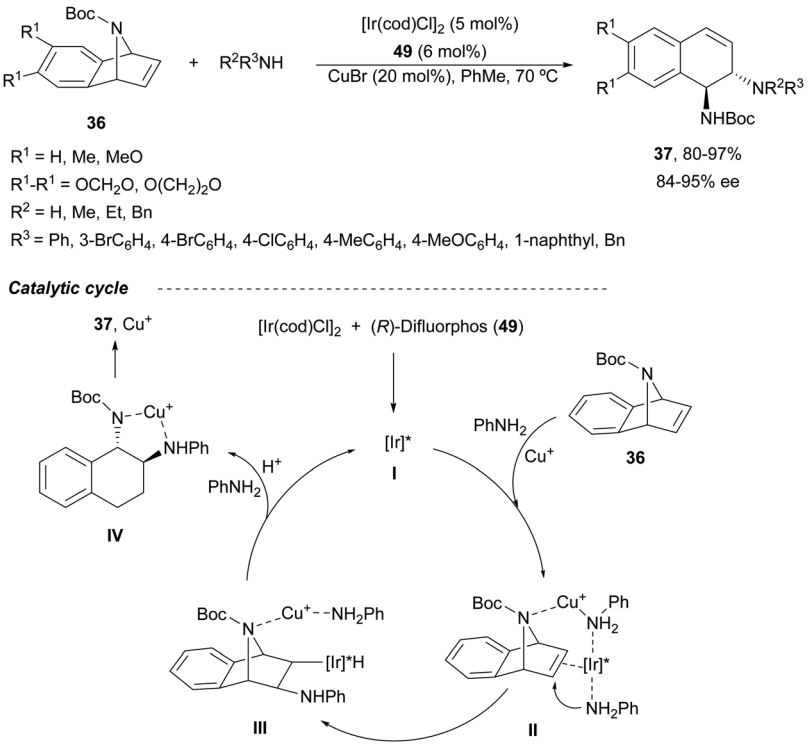
Scheme 14 Synthesis of chiral salen-type ligands **42** from diaminotetralins **37**.



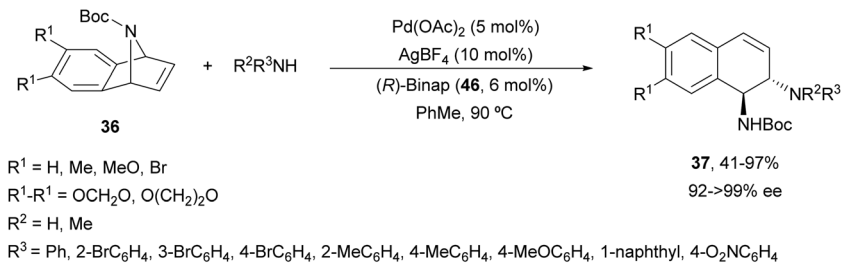
Scheme 15 Ring-opening of *N*-Boc-azabenzonorbornadiene **36** with piperazines **43** under Rh/(*R*,*S*)-PPF-P(*t*Bu)$_2$ (**44**) catalysis.



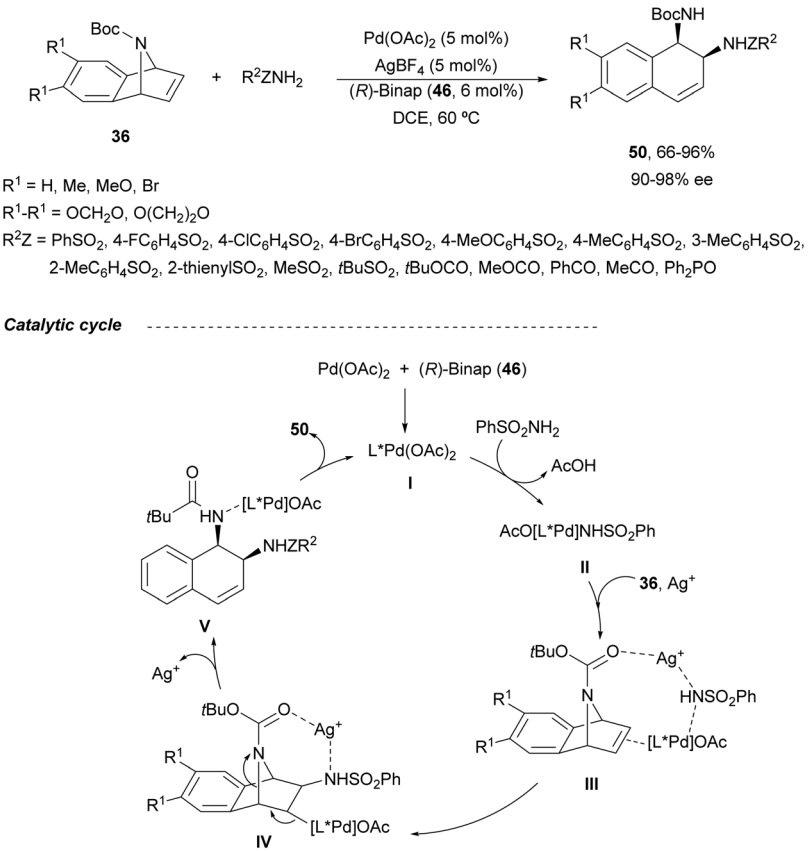
Scheme 17 Ring-opening of *N*-Boc-azabenzonorbornadienes **36** with secondary amines under Ir/**48** catalysis.



Scheme 18 Ring-opening of *N*-Boc-azabenzonorbornadienes **36** with amines under Ir/**49** and CuBr catalysis.



Scheme 19 Ring-opening of *N*-Boc-azabenzonorbornadienes **36** with aromatic amines under Pd/(*R*)-Binap (**46**) catalysis.



Scheme 20 Ring-opening of *N*-Boc-azabenzonorbornadienes **36** with amides under Pd/(*R*)-Binap (**46**) catalysis.

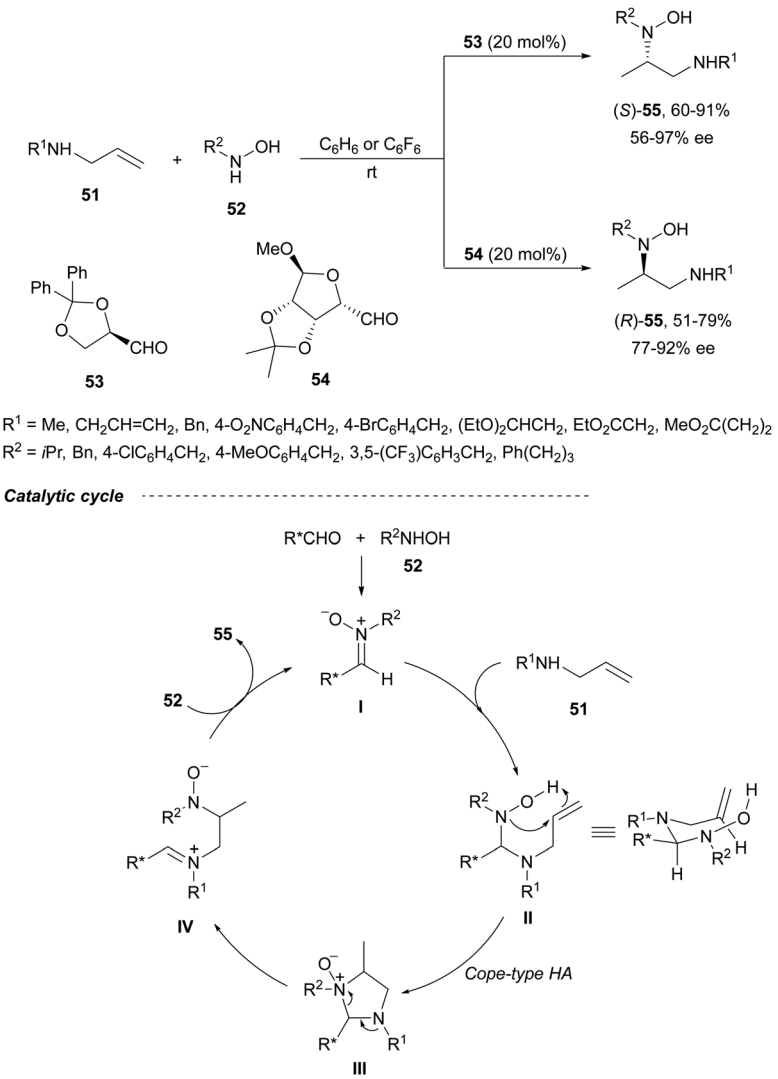
complex **I**. Subsequent coordination of the catalyst **I** with benzenesulfonamide forms complex **II**, which coordinates the silver cation and the azabenzonorbornadiene **36** to provide intermediate **III**. After nucleophilic addition, intermediate **IV** is formed, which evolves to give the ring-opening complex **V** through a β-elimination reaction. Finally, product **50** is formed regenerating the Pd catalyst.

From the results included in this section, it can be concluded that for the asymmetric ring-opening of *N*-Boc-azabenzonorbornadienes Rh/ferriphos is the best catalyst for both secondary aliphatic and aromatic amines. Besides, Pd/Binap (**46**) is the simplest catalyst for primary and secondary aromatic amines. *anti*-Selectivity was observed in all cases except in the case of using amides as nucleophiles, which gave *syn*-diamine derivatives. The resulting enantioenriched 1,2-diaminotetralines are valuable intermediates for the synthesis of biologically active compounds[35] and chiral ligands.[37]

2.3. Amination of allylic amines

Direct hydroamination of allylamines is an attractive route to 1,2-diamines with 100% atom economy. Intermolecular enantioselective hydroamination (HA) of allylic amines was developed by Beauchemin and co-workers[49] with chiral aldehydes as tethering catalysts. Based on previous studies with racemic aldehydes,[50,51] they used chiral aldehydes **53** and **54** (20 mol%) for the HA of allylic amines **51** with hydroxylamines **52** (Scheme 21).[49] This intermolecular Cope-type HA took place in benzene or hexafluorobenzene under an argon atmosphere and at room temperature for 1 to 3 days reaction time to provide unsymmetrical 1,2-diamine derivatives **55** in good yields and enantioselectivities. Aldehyde **53** derived from (*R*)-glyceraldehyde gave products (*S*)-**55**, whereas bicyclic aldehyde **54** provided access to the corresponding (*R*)-**55** enantiomers in an enantiodivergent manner.[52] The proposed mechanism is based on racemic reactions[51] involving α-(benzyloxy)acetaldehyde. After condensation of the aldehyde with hydroxylamine **52** a nitrone **I** is formed, which suffers nucleophilic attack by the allylic amine **51** to furnish intermediate **II**. This mixed chiral aminal **II** undergoes, through a bicyclic TS, a Cope-type HA to provide intermediate **III** with efficient transfer of chirality. Subsequent aminal cleavage forms the iminium intermediate **IV**, which after condensation with a second molecule of hydroxylamine **52** releases the product **55** and the nitrone **I**.

The first Rh-catalyzed asymmetric HA of allylic amines **51** was recently described by Hull and co-workers.[53] They employed MeO-Biphep **56** as a chiral ligand and secondary aliphatic amines as nucleophiles resulting diamines **57** in moderate to good yields and up to 95% ee (Scheme 22). Diamine **57a** was transformed into a methylated antidepressant methyl-moclobemide **58** in 47% overall yield by treatment with phenol and phosphoric acid followed by benzoylation with 4-chlorobenzoyl chloride. According to the previously proposed catalytic cycle for allylic imines,[54]



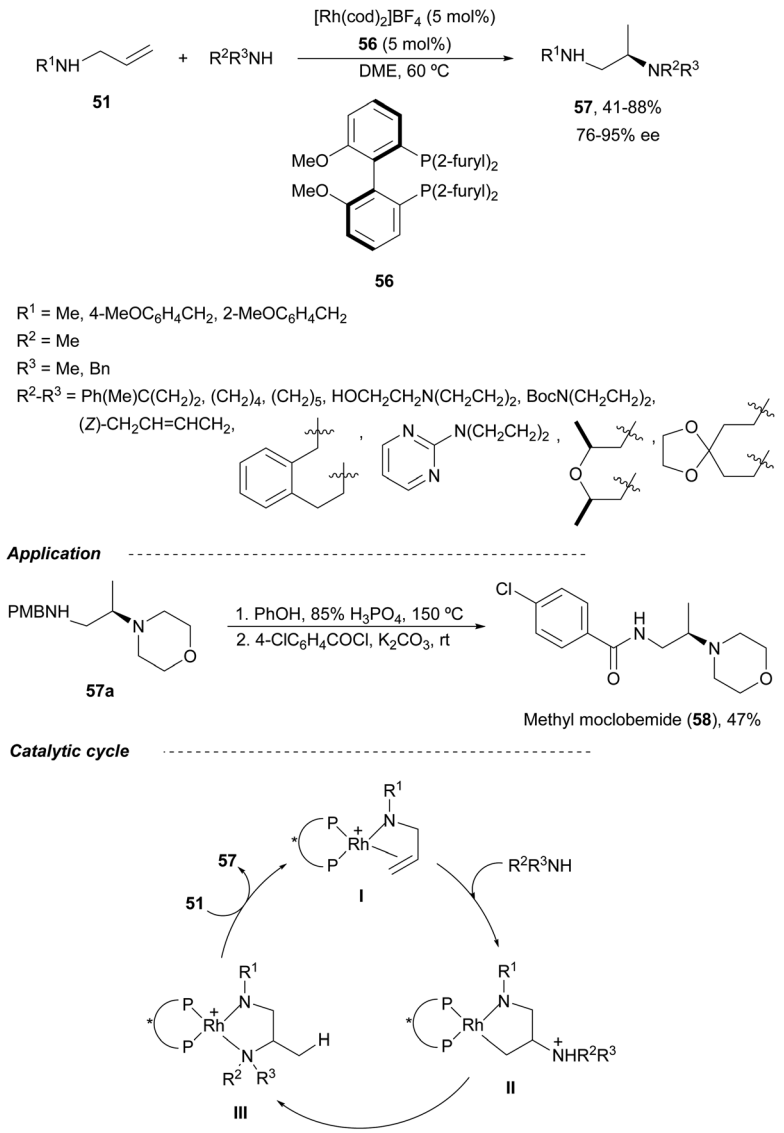
Scheme 21 Enantiodivergent hydroamination of allylic amines **51** with chiral aldehydes **53** or **54** as organocatalysts.

the cationic Rh(I) complex coordinates the N and C–C double bond to give intermediate **I**. This complex **I** undergoes nucleophilic attack by the amine to form intermediate **II**, which suffers direct protonation of the [Rh]–C bond or proton transfer to generate a [Rh]–H complex followed by reductive elimination giving intermediate **III**. Final ligand exchange with the allylic amine provides the product and regenerates the Rh complex **I**.

Copper-catalyzed asymmetric HA of γ-substituted *N*-pivaloyl allylic amines **59** has been described by Buchwald and co-workers.[55] This type of HA requires as electrophilic amines *O*-benzoylated hydroxylamines **60** for the C–N bond forming process. The *N*-pivaloyl group in the allylic amine is essential facilitating the hydrocupration step. Differently protected 1,2-diamine derivatives **61** were obtained using the *in situ* generated catalyst by mixing $Cu(OAc)_2$, (*R*)-DTBM-Segphos **23** (Fig. 2) and triphenylphosphine, a mixture known as CuCat-Mix*[56] (Scheme 23). In general, this process took place with good regioselectivity (3 : 1–> 20 : 1) and enantioselectivity (94–98%) and could be performed on a gram-scale. In the proposed mechanism for the CuH-catalyzed HA,[57] firstly the allylic amine undergoes hydrocupration to form a chiral alkylcopper intermediate **II**, which is trapped by hydroxylamine benzoate **60** to provide the product and copper(I) benzoate **III**. For the generation of the catalyst **I**, a σ-bond metathesis with the hydrosilane $(MeO)_2MeSiH$ occurs. In the undesired β-elimination of intermediate **II**, the protected group at nitrogen of the allylic amine is crucial, which also controls the regioselectivity of the hydrocupration step.

Intramolecular asymmetric carboamination of allylic ureas[58] and sulfamides[59] has been extensively studied by Wolfe and co-workers. These cyclizations were carried out under Pd-catalyzed conditions based on carboheterofunctionalization processes.[60,61] Eventually, the resulting saturated heterocyclic compounds can be transformed into chiral 1,2-diamines.

Imidazolidin-2-ones **64**[58] are obtained under Pd-catalysis by carboamination of *N*-allylureas **62**, which can be prepared by a reaction of allylic amines with isocyanates.[62] In the presence of $Pd_2(dba)_3$ and a chiral phosphoramidite (*S*)-Siphos-PE **63** as a catalyst, the intramolecular hydroamination followed by C–C



Scheme 22 Asymmetric hydroamination of allylic amines **51** with secondary aliphatic amines under Rh/MeO-Biphen (**56**) catalysis.

bond formation with aryl or alkenyl halides took place (Scheme 24). The resulting 4-aryl or alkenyl methylimidazolidin-2-ones **64** were obtained in good yields and enantioselectivities. According to the experimental results, a plausible catalytic cycle is depicted in Scheme 24. Firstly, oxidative addition to Pd(0) of the aryl/alkenyl halide generates intermediate **I**, which by reaction with **62** is converted by aminopalladation into Pd-amino complex **II**. Then, *syn*-insertion of the alkene into the Pd–N bond yields cyclic intermediate **III**, which after reductive elimination forms product **64** and regenerates the catalyst. This last process is the enantiodetermining step of the catalytic cycle.

Cyclic sulfamides **66**[59] have been prepared by asymmetric intramolecular carboamination of *N*-allylsulfamides **65** using similar reaction conditions to those previously described for allylureas.[58] Again, the addition of 2 equivalents of water improved yields and enantioselectivities giving products **66** in up to 96% yield and up to 90% ee (Scheme 25a). Deprotection of the *t*Bu group with TFA at room temperature of **66a** (R = Ph) gave **67** in 98% yield and the same 86% ee. In a second step, **67** was treated with HBr in phenol to obtain diamine **68** in 85% yield and 88% ee (Scheme 25b).

Buchwald and co-workers[63] reported a regioselective intramolecular asymmetric HA of allylic hydroxylamine esters **69** using the same CuCatMix*[56] as it was described for the intermolecular HA (Scheme 23). In this case, enantioenriched aziridines **70** were formed in good to excellent yields (Scheme 26a). The aziridine **70a** underwent regioselective ring-opening with trimethylsilylazide and acetic acid to provide compound **71** in 92% yield, 98% ee and 9.5 : 1 rr (Scheme 26b).

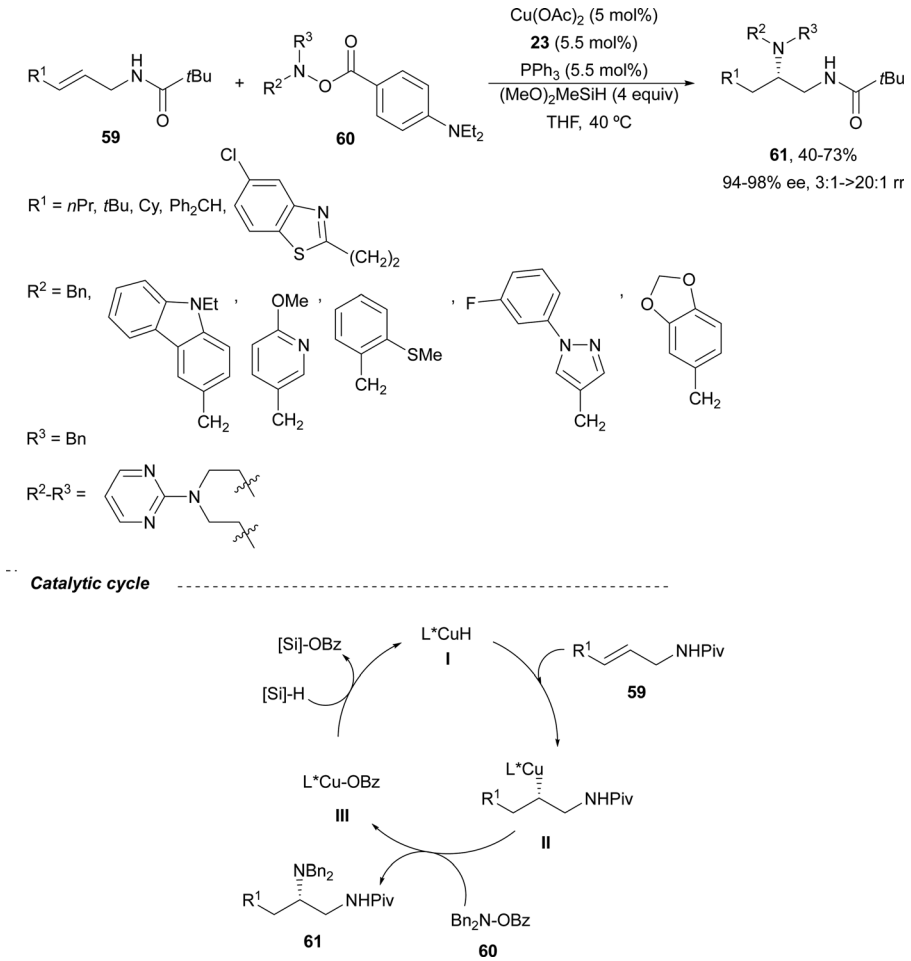
The asymmetric intermolecular HA of allylic amines with nucleophilic nitrogenated compounds gives 1,2-diamines either under aldehyde organocatalyzed conditions or under Rh or Cu catalysis. This methodology allows the preparation of propylene diamines, which increases in potency for some drugs called

'magic methyl effects'.[64] Hydrocupration of γ-substituted *N*-protected allylic amines has to be performed with electrophilic *O*-benzoylated hydroxylamines. An intramolecular HA of allylic hydroxylamine esters under Cu-catalysis gave enantioenriched aziridines. Besides, asymmetric intramolecular HA of allylic derivatives has been achieved under Pd-catalysis with concomitant coupling with aryl or alkenyl halides to obtain imidazolidinones or cyclic sulfamides precursors of 1,2-diamines.

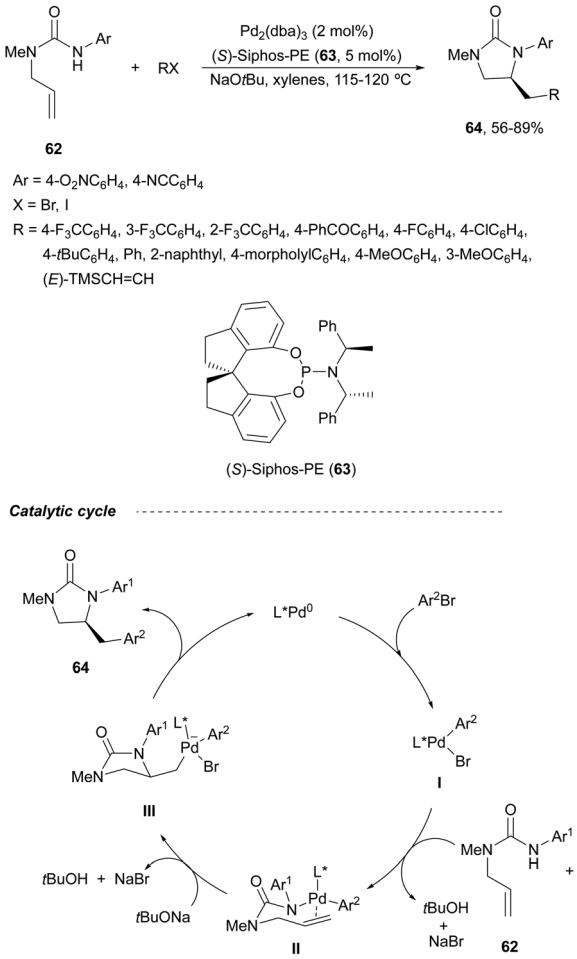
2.4. Amination of enamines

In this section, hydroamination of enamines by asymmetric hydrocupration, amination of enecarbamates or enamides under metal catalysis, and chiral phosphoric acid catalyzed amination of enecarbamates as well as photoredox processes will be discussed.

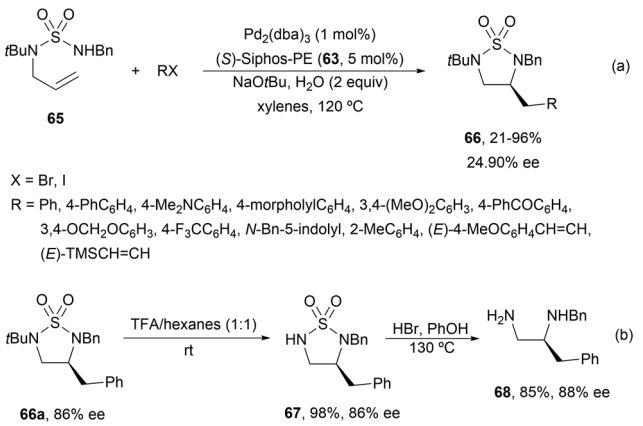
Based on the hydroamination reaction of allylic amines by asymmetric hydrocupration[55] (see, Scheme 23), Somfai and coworkers[65,66] reported the asymmetric formal HA of enamines **72** with *O*-acyl hydroxylamines **60** (Scheme 27). In the presence of $Cu(OAc)_2$/(*R*)-DTBM-Segphos (**23**) and with $(MeO)_2MeSiH$ as the stoichiometric hydride source, 1,2-diamines **73** were obtained with good yields and regio and enantioselectivities. A one-pot procedure involving the formation of enamine followed by the HA step has been also performed.[66] Starting form aldehydes and amines in the presence of anhydrous sodium sulfate (10 equivalents), the corresponding enamines are prepared quantitatively in dichloromethane at room temperature in only one hour. This HA method was applied to the synthesis of orthogonally protected dipiperazine **73a**, a precursor of the human melanocortin-4 (MC-4) receptor antagonist **74**.[67] The MC-4 receptor has been involved in the regulation of feeding, metabolism, sexual functions and emotional states such as anxiety and depression. Based on the previous proposed mechanism for the hydrocupration of alkenes, a catalytic cycle depicted in Scheme 27 was proposed. Hydrocupration of enamine **72** (R^1 = Ph; R^2 = R^3 = Bn) with the *in situ* generated CuH (**I**) forms alkylcopper intermediate **II** in an irreversible and enantiodetermining step. Oxidation of species **II** with hydroxylamine **60** generates the product **73** and releases the copper benzoate **III**. Final transmetallation of **III** with $(MeO)_2MeSiH$ regenerates the catalyst **I**. DFT calculations[66] supported that the insertion of the L*CuH catalyst into the enamine is the regio- and enantiodetermining step. In addition, TS(*R*) explains the stereocontrol of the process and the N–O bond in this TS also determines the enantioselectivity. The energy difference between TS(*R*) and TS(*S*) was calculated to be 3.0 kcal mol^{-1} in accordance with the experimental enantioselectivities.



Scheme 23 Asymmetric hydroamination of allylic pivalamides **59** with *O*-benzoylated hydroxylamines **60** by asymmetric hydrocupration.

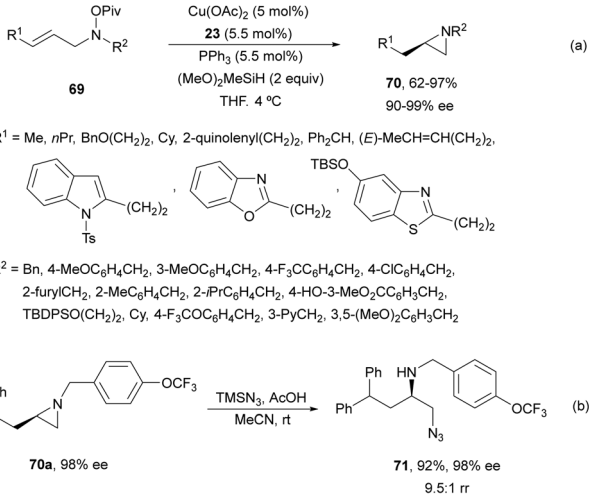


Scheme 24 Asymmetric carboamination of allylic ureas **62** with aryl/alkenyl halides under Pd/(*S*)-Siphos-PE (**63**) catalysis.



Scheme 25 Asymmetric carboamination of *N*-allylsulfamides **65** with alkyl/alkenyl halides under Pd/(*S*)-Siphos-PE (**63**) catalysis.

The first catalytic asymmetric amination of enecarbamates **72** with azodicarboxylate **75** using a diamine **76**-Cu complex was described by Matsubara and Kobayashi.[68] The resulting acylimines **77** were converted into diamine derivatives *syn*-**78** after stereoselective $NaBH_4$ reduction with >95 : 5 dr (Scheme 28a).

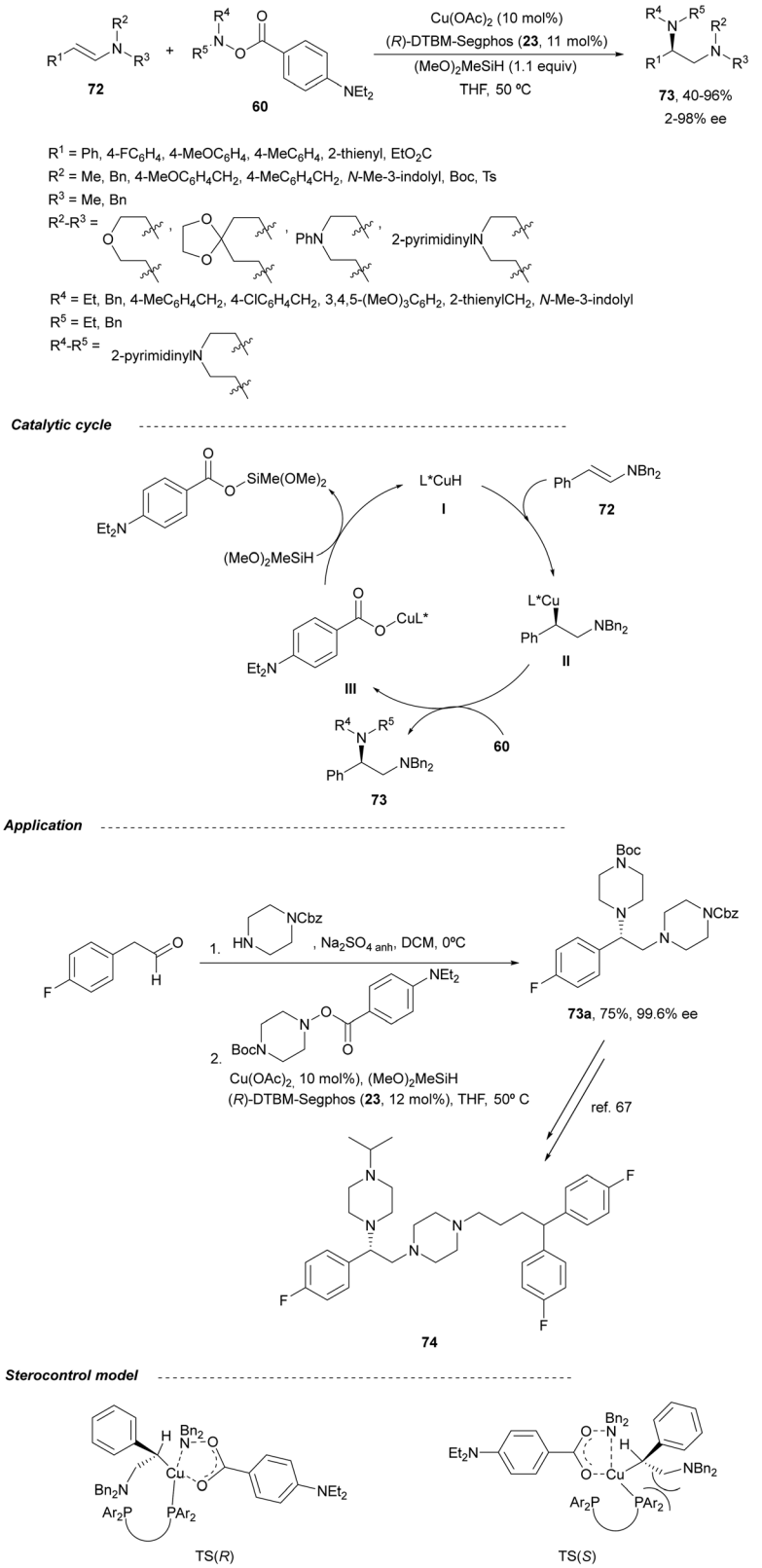


Scheme 26 Intramolecular hydroamination of allylic hydroxylamine esters **69** by asymmetric hydrocupration.

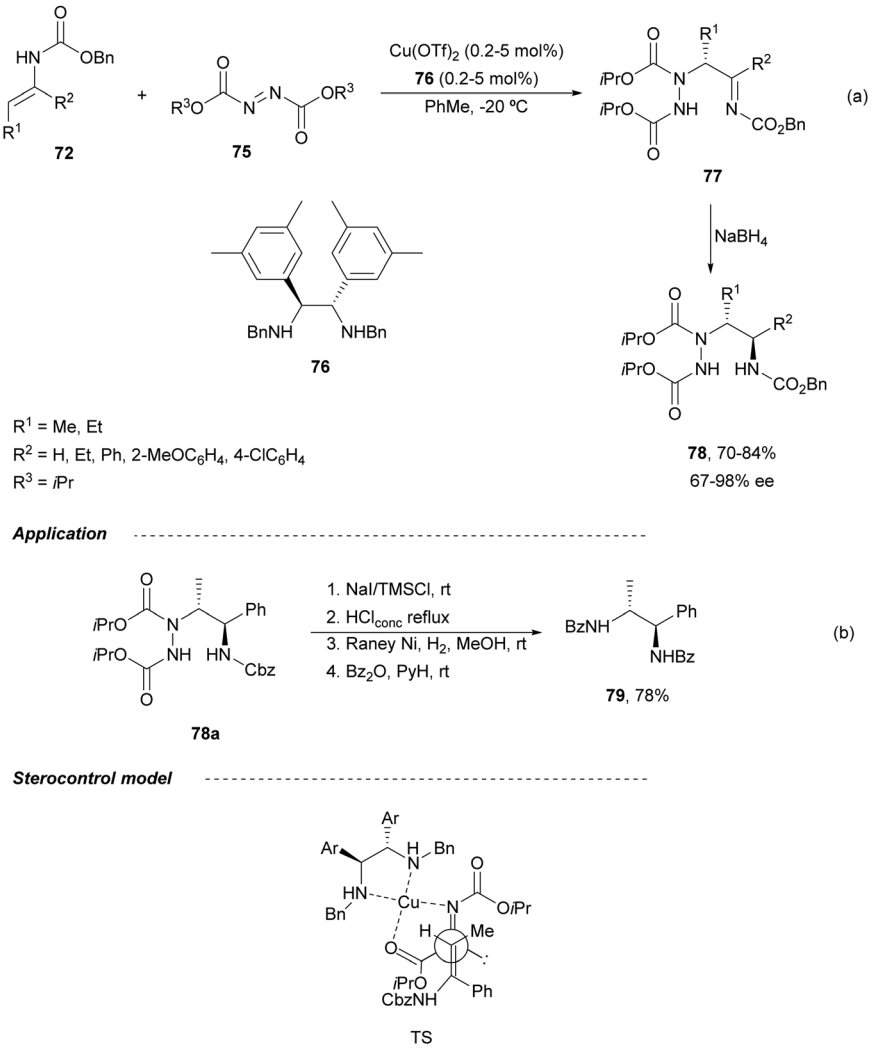
syn-1,2-Diamine **79** was obtained by Cbz-deprotection of **78a** followed by N–N cleavage with RANEY® Ni and benzoylation in 78% overall yield (Scheme 28b). Both *Z* and *E*-enecarbamates gave products with the same configuration. The authors proposed an acyclic concerted TS model in which the *Re*-face of the azodicarboxylate is shielded by the neighboring benzyl group of the diamine ligand and an enecarbamate attack from the *Si*-face predominantly. An antiperiplanar TS minimizes steric repulsion between the enecarbamate and the copper catalyst.

Feng and co-workers[69] developed later the same amination using (*Z*)-*N*-acetyl enamides **80** and dibenzyl azodicarboxylate **75** (R^3 = Bn) under $Cu(OTf)_2$ and *N*,*N*′-dioxide **19** (Fig. 2) catalysis (Scheme 29). Products **81** were reduced with $NaBH_4$ at −78 to −45 °C to the corresponding precursors of *syn*-1,2-diamines **82** in good yields and diastereoselectivities (>95 : 5) and without any loss of enantioselectivity. (*E*)-Enamides exhibited higher reactivity than the *Z* counterpart and were converted into the corresponding adducts with the opposite configuration although with lower enantioselectivities.

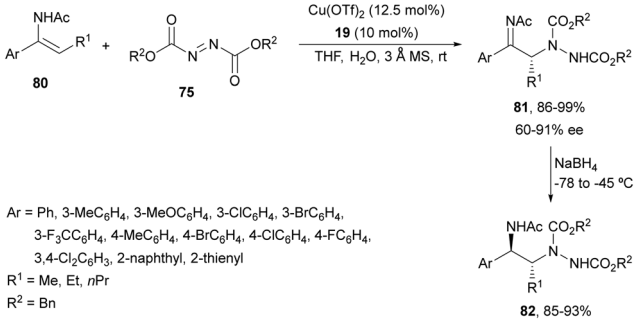
Calcium-bis(phosphate) complex **83** was employed as a catalyst by Masson, Zhu and co-workers[70,71] for the enantioselective electrophilic amination of (*E*)-enamides **80** with diisopropyl azodicarboxylate **75** (Scheme 30). This amination took place in dichloromethane at −35 °C followed by $NaBH_4$/MeOH reduction to provide *syn*-1,2-diamines **82** (R^2 = *i*Pr) in >95.5 dr and up to 95% ee. Experimental studies support a catalytic cycle according to nonlinear effects (NLEs) and kinetic measurements as well as DFT calculations.[71] After monocoordination of the monomeric complex with azodicarboxylate to form intermediate **I**, the enamide forms a hydrogen bond providing intermediate **II**, with the complex acting as a bifunctional catalyst. A *Si*-face attack of the enamide onto azodicarboxylate gives the zwitterionic species **III**, which undergoes a proton transfer to generate intermediate **IV**. Final dissociation and complexation with azodicarboxylate provide α-aminoimine **81** and regenerate intermediate **I**.



Scheme 27 Hydroamination of enamines **72** with *O*-acylhydroxylamines **60** by asymmetric hydrocupration.



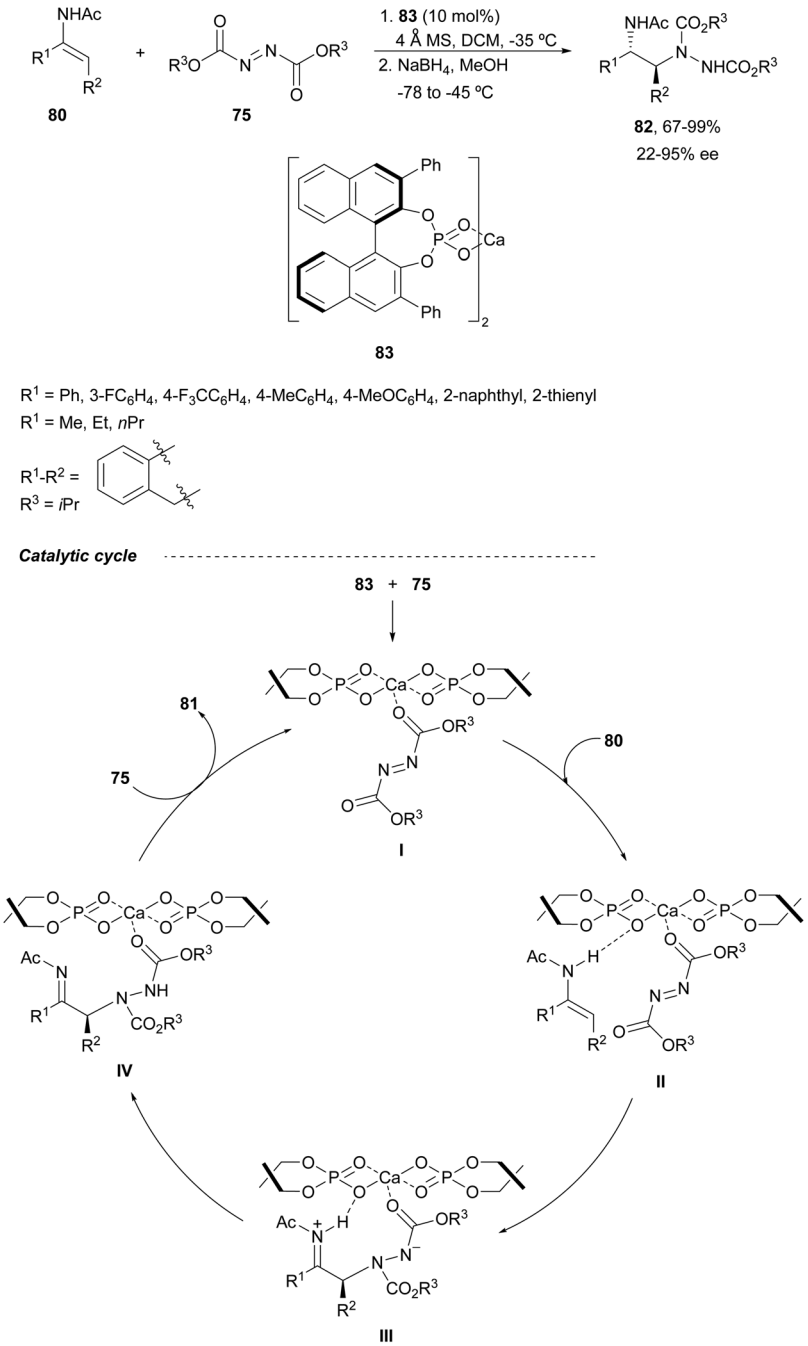
Scheme 28 Asymmetric amination of enecarbamates **72** with diisopropyl azodicarboxylate (**75**) under $Cu(OTf)_2$/diamine **76** catalysis.



Scheme 29 Asymmetric amination of enamides **80** with dibenzyl azodicarboxylate (**75**) under $Cu(OTf)_2$/*N*,*N*′-dioxide **19** catalysis.

Masson and co-workers have reported in a recent report[72] the difunctionalization of enamide derivatives for synthesizing α,β-substituted amines. Concerning the synthesis of enantioenriched 1,2-diamines, in 2015[73] they performed the amination of (*E*)-enecarbamates **72** with dibenzyl azodicarboxylate **75** in the presence of EtOH using a catalytic amount of the CPA **84** followed by reduction with triethylsilane (TESH) and trimethylsilyl triflate in a mixture of acetonitrile and methanol at 0 °C (Scheme 31). Under these reaction conditions, intermediates **85** were formed, precursors of α-hydrazinoimines **86**, which after reduction afforded diamine derivatives **87** in good yields and excellent enantioselectivities. In the proposed TS for the amination reaction, the CPA may act as a bifunctional catalyst to activate both the enecarbamate and the azodicarboxylate by hydrogen bonding. Accordingly, from this TS, the (*R*)-adduct **86** will be formed through an intramolecular *Si* face attack of **72** on **75.**

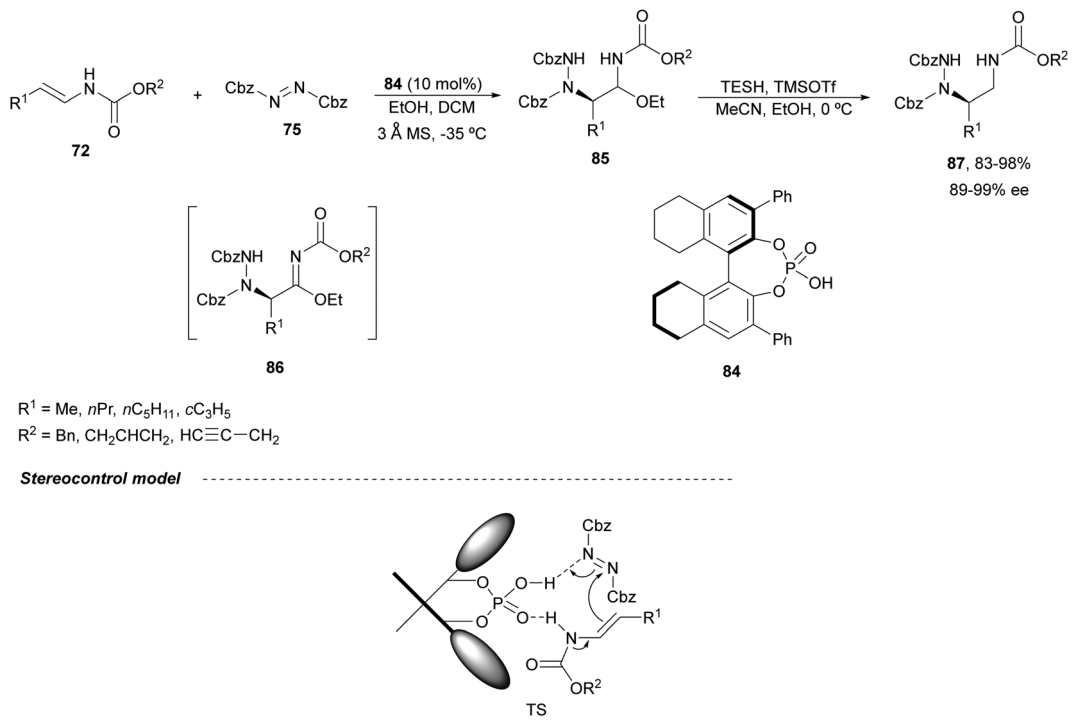
Electrophilic amination of enecarbamates using CPA **84** as a catalyst followed by nucleophilic addition to intermediates **86** allowed the synthesis of diamine derivatives.[74] When silylated nucleophiles were employed, products **88** were obtained with cyano, azido or allyl groups with 2 : 1 diastereoselectivity and good enantioselectivity by a two-step sequential procedure (Scheme 32). In this case, $BF_3{\cdot}Et_2O$ was used as Lewis acid to promote the formation of compounds **86.**



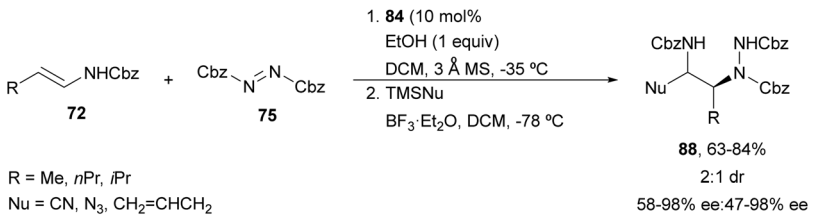
Scheme 30 Asymmetric amination of (*E*)-*N*-acetyl enamides **80** with diisopropyl azodicarboxylate (**75**) under calcium-bis(phosphate) complex **83** as a catalyst.

The former strategy was expanded to the synthesis of *N*-carbamoylthioethers **89**, which were subjected to a *N*-iodosuccinimide-assisted Friedel–Crafts reaction with 1,3,5-trimethoxybenzene resulting in compounds **90** with $>95:5$ diastereoselectivity and high enantioselectivity (Scheme 33).[74] However, furan gave product **91** in 72% yield and 2 : 1 dr with 98 and 93% ee. Hydrogenation of the hydrazine group provides diamines **92** in 95 : 5 dr for 1,3,5-trimethoxyphenyl derivatives and **93** in 2 : 1 dr for the furan derivative. When indoles were used in the Friedel–Crafts step double addition was observed leading to mainly bisindole **94** in 53–97% yields and 97–99% ee. On the other hand, other heterocyclic systems such as pyrazoles reacted through the nitrogen atom.

In order to avoid the double addition of indoles to intermediates **89** to form products **94**, the same group[75] used visible light photoredox catalysis. β-Amino substituted tryptamines **95** were obtained with up to $>99:1$% ee (Scheme 34). In the catalytic cycles, the Ru(II) photocatalyst reacts with oxygen to form a Ru(III) complex. This species abstracts an electron from the α-amidosulfide **89** (single electron transfer, SET) leading to



Scheme 31 Asymmetric amination of (*E*)-enecarbamates **72** with dibenzyl azodicarboxylate **75** under CPA **84** catalysis.



Scheme 32 Asymmetric amination of enecarbamates **72** with **75** under CPA **84** catalysis followed by functionalization with silylated nucleophiles.

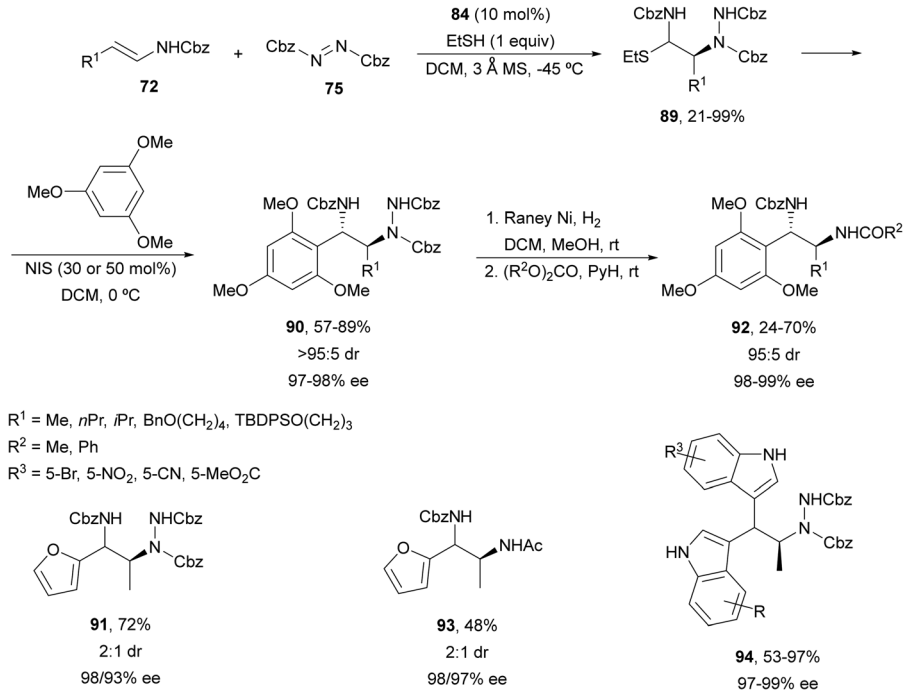
a radical cation **I**, which undergoes fragmentation regenerating iminium cation **II**. After the Friedel–Crafts reaction with indoles, the iminium cation **II** gives the corresponding tryptamines **95**.

Masson and co-workers[76] designed a chiral photosensitive organocatalyst **96**, which contains a CPA backbone and a visible-light-sensitive thioxanthone unit for the amination of enamides **72** with dibenzyl azodicarboxylate **75** (Scheme 35). This process was carried out in the presence of pyrazoles or 7-bromoindole as nucleophiles to give compounds **97** or **95**, respectively, in good yields, excellent enantioselectivity and moderate diastereoselectivity. In the proposed mechanism, intermediate α-carbamoylsulfide **89** would be oxidized by the excited chiral thioxanthone **96*** generating the ketal radical anion **I** and the sulfur radical cation **II**. A single electron transfer from **I** to O_2 would generate the thioxanthone catalyst **96** and produce the superoxide radical anion $O_2^{\bullet -}$ **III**. Intermediate **II** would undergo C–S cleavage to produce imine **86** and thiyl radical **IV**, which dimerizes to form diethyl disulfide. Finally, the imine **86** suffers addition of the azole and subsequent hydrogen atom abstraction from $O_2^{\bullet -}$ affording products **97** or **95**.

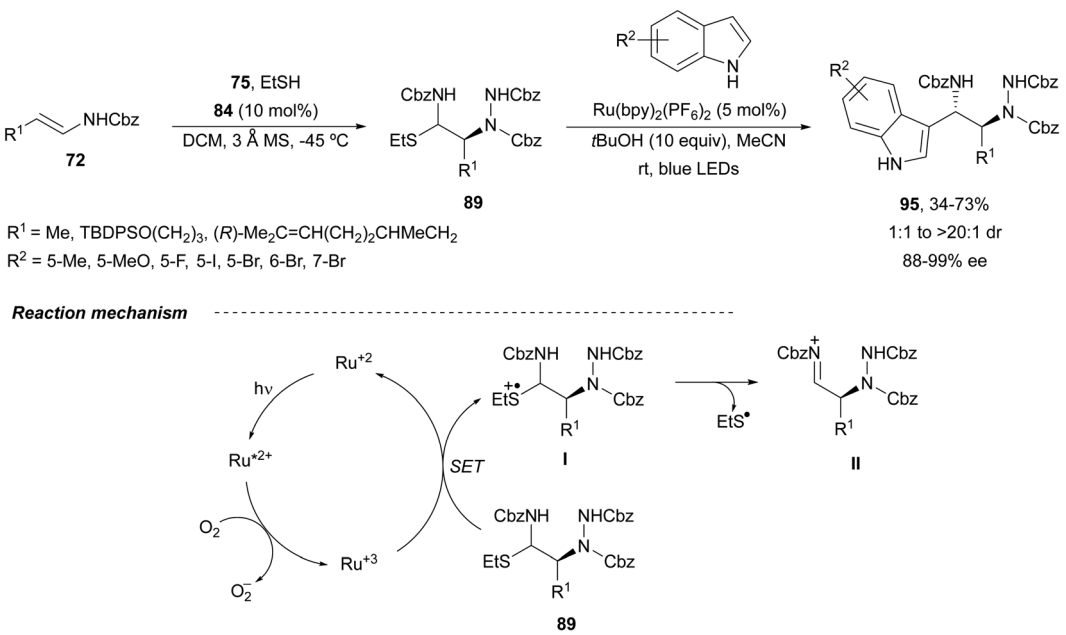
Direct hydroamination of enamines has been performed only under asymmetric hydrocupration conditions using acyl hydroxylamines as nucleophiles. This method has been successfully applied to the synthesis of melanocortin-4 receptor antagonists. For the amination of acetyl enamides dialkyl azodicarboxylates have been used as nucleophiles under copper asymmetric catalysis or with calcium-bis(phosphate) complex as a catalyst. In the case of enecarbamates, this asymmetric amination could be carried out using chiral phosphoric acids as catalysts in the presence of a nucleophile followed by functionalization with silylated nucleophiles or by a Friedel–Crafts reaction under conventional conditions or visible light photoredox catalysis. This amination requires further hydrogenation of the hydrazine group to provide 1,2-diamines, which were obtained mainly as *syn*-diastereomers.

2.5. Diamination of alkenes

Catalytic asymmetric diamination of C–C double bonds represents one of the most important C–N bond formation strategies to access enantioenriched 1,2-diamines. This subject has been recently reviewed by two groups.[13,14] In Scheme 36 are summarized the



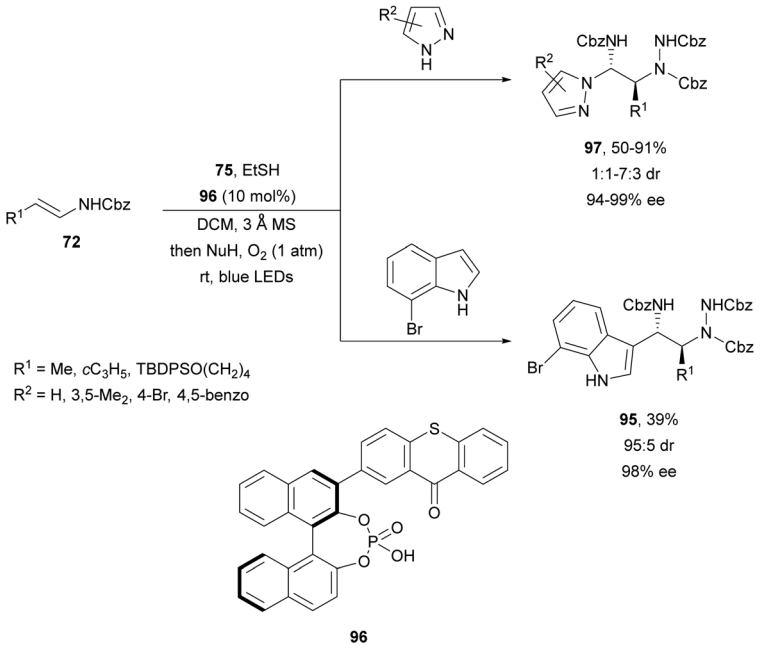
Scheme 33 Asymmetric amination of (*E*)-enecarbamates **72** with **75** under CPA **84** catalysis followed by functionalization by the Friedel–Crafts reaction.



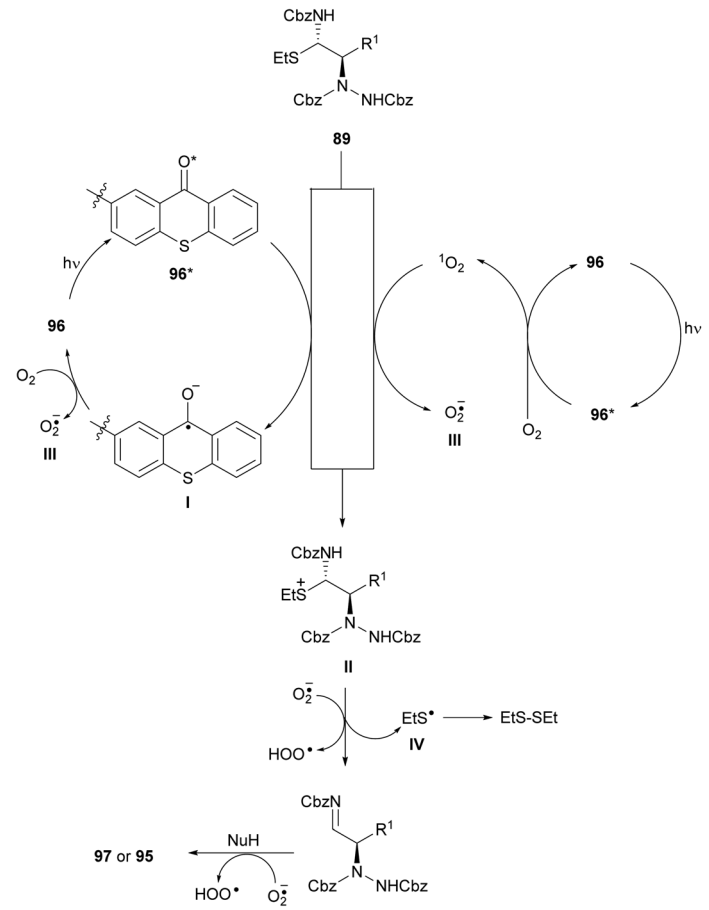
Scheme 34 Asymmetric amination of (*E*)-enecarbamates **72** with dibenzyl azodicarboxylate **75** and EtSH under CPA **84** catalysis followed by Friedel–Crafts reaction with indoles under photoredox catalysis.

most efficient synthetic strategies based on (a) the two-electron redox pathway using Pd(0)/Pd(II) or Pd(II)/Pd(IV), I(I)/I(III) and Se(II)/Se(IV) catalytic diaminations, and (b) the one-electron radical mechanism under Cu or Fe catalysis (Scheme 36).[14]

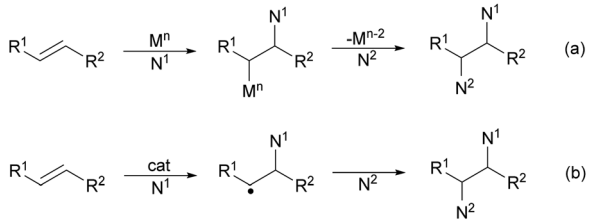
Pd(0)/Pd(II) intermolecular diamination was developed by Shi and co-workers[10] using di-*tert*-butyldiaziridinone or di-*tert*-butylthiadiaziridine-1,1-dioxide both as a nitrogen source and phosphoramidites **98** as chiral ligands or NHC-Pd(0) **99** as a chiral complex (Fig. 4) to provide *trans*-imidazolidinones **100** or **101**, respectively (Scheme 37a). In 2018, Gong and co-workers[77] employed simpler dialkylureas as diamination agents and a Pybox **102** (Fig. 4) as a chiral ligand to give imidazolidinones **103** (Scheme 37b). The regioselectivity occurs at the terminal C=C bond of conjugate 1,2-dienes, whereas Shi's method took



Reaction mechanism



Scheme 35 Asymmetric amination of (*E*)-enecarbamates **72** with dibenzyl azodicarboxylate **75** and EtSH under CPA-thioxanthone **96** photocatalysis and Friedel–Crafts reaction with pyrazoles and 7-bromoindole.



Scheme 36 Catalytic mechanisms for C=C diamination.

place at the internal C=C bond. Allylpalladium intermediates **I** and **II** provided by an intramolecular allylic amination products **100** and **103**, respectively.

Recently, Lin and co-workers[78] reported an asymmetric sequential diamination of 1,3-enynes using ureas as dinucleophiles (Scheme 38). This process was carried out using $Pd(OAc)_2$ and (*S*)-Segphos as chiral ligands, and 3,5-bis(*tert*-butyl)benzoic acid (30 mol%) and Et_3N to obtain imidazolidinones of type **104** in good yields and enantioselectivities. Mechanistic studies revealed the initial intermolecular hydroamination with a PdH complex to give an allene intermediate **I**, which by subsequent asymmetric intramolecular hydroamination furnished the imidazolidinone.

Pd(II)/Pd(IV) asymmetric intramolecular diamination was carried out by Michael and co-workers[79] on the basis of previous work of Muñiz and co-workers.[80] Intramolecular diamination of a tethered double bond in compounds **105** used Ph-quinox **106** (Fig. 4) as a chiral ligand and *N*-fluorobenzenesulfonimide (NFSI) as a second nitrogen nucleophile and for the oxidation of Pd(II) to Pd(IV) to provide aminomethyl-substituted pyrrolidines **107** (Scheme 39a). Intermediate **I** is the Pd(II) species which after reductive elimination or displacement furnished products **107**. When sulfonamide **108** was used as starting aminoalkene, it was possible to control the cyclization using ligand **106** or **109** (Fig. 4). Thus, Liu and co-workers[81] modulated the formation of 6-*endo*-cyclic piperidine **110** using ligand **106**, whereas ligand **109** favored the *exo*-cyclization to form pyrrolidine **111** (Scheme 39b).

Initial studies of intermolecular diamination of styrenes with bismesylimide by Muñiz and co-workers[82] employed a chiral λ^3-iodane reagent in stoichiometric amounts. In 2014, Wirth and co-workers[83] performed an intramolecular diamination using a sulfuryl diamide **112** as a difunctional nucleophile and a chiral λ^3-iodane generated from the aryl iodide **113** (20 mol%) as a catalyst with sodium perborate as the oxidant (Scheme 40). In this example, the resulting bicyclic product **114** was obtained in 72% yield and 86% ee.

The first intermolecular enantioselective diamination of alkenes using a chiral λ^3-iodane was reported by Muñiz and co-workers[84] using iodide **115** as a chiral catalyst with MCPBA as an oxidant for the *in situ* generation of the I(III) compound (Scheme 41). The combination of *tert*-butyl methyl ether (TBME) and hexafluoroisopropanol (HFIP) as a solvent was crucial to avoid competitive epoxidation. Terminal styrenes gave compounds **116** in good yields and high ee. Lower yields were obtained with internal alkenes providing *anti*-products **117**. Intermediate **I** would generate by reductive displacement of the intermediate **II** precursor of diamine derivative **117**.

The last methodology based on a two-electron redox pathway (Scheme 36a) is the Se(II)/Se(IV) intermolecular diamination of olefins described by Denmark and co-workers.[85] In this case, *syn*-diamination was achieved with *N*,*N*′-bistosylurea using the chiral organoselenium reagent **118** as a catalyst and *N*-fluorocollidinium tetrafluoroborate **119** as the stoichiometric oxidant (Scheme 42). Diaryl, aryl–alkyl and alkyl–alkyl olefins with a *trans*-configuration were diaminated to the corresponding *trans*-imidazolidinones **120** in moderate to good yields and enantioselectivities. This process takes place by formation of a seleniranium ion **II** by the reaction of the alkene with the species **I** generated by oxidation of the diaryl diselenide **118**. Ring opening of intermediate **II** by urea provides intermediate **III**, which after oxidation to Se(IV) forms intermediate **IV**. Subsequent cyclization gives the final product **120** and regenerates species **I**.

Enantioselective diaminations by the one-electron radical mechanism have been accomplished under copper or iron catalysis.[14] Initial studies of Shi and co-workers[10,86] on Cu-catalyzed diamination of dienes were performed with di-*tert*-butyldiaziridinone and (*R*)-DTBM-Segphos (**23**) as a chiral ligand to provide imidazolidinones **121** (Scheme 43a)

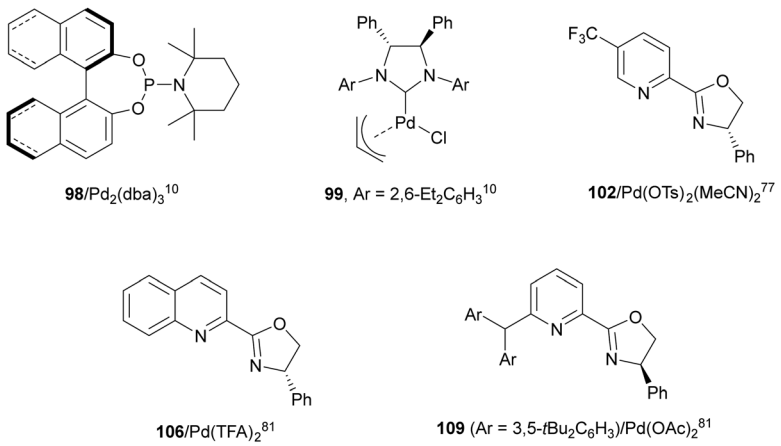
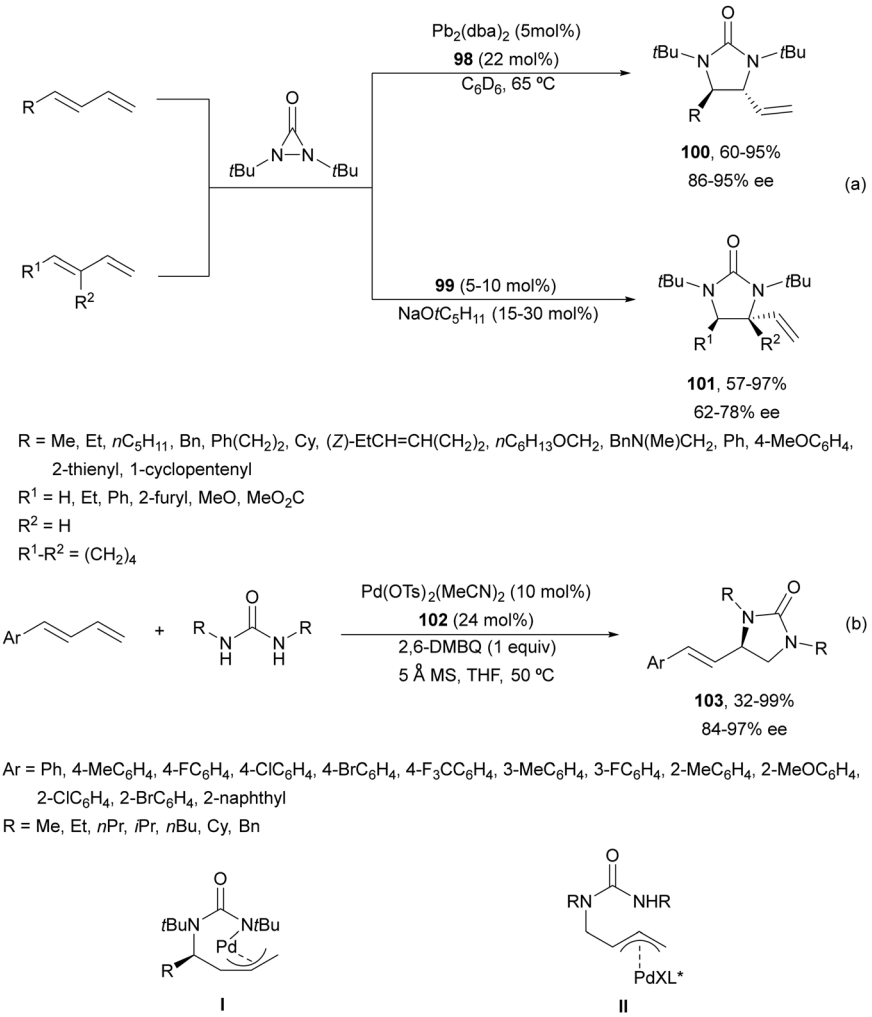
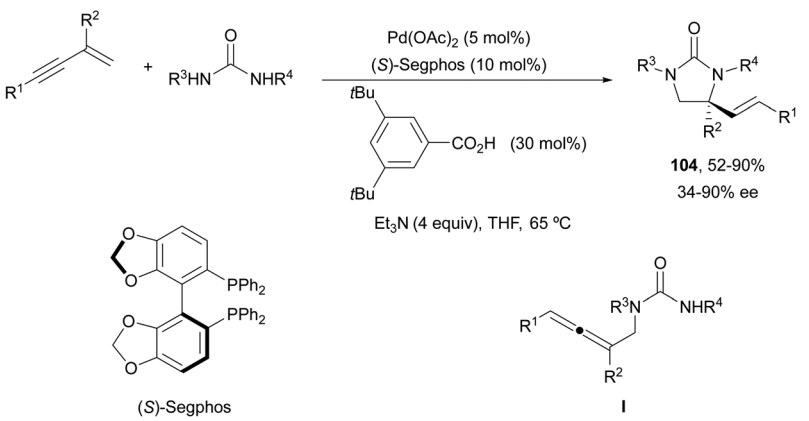


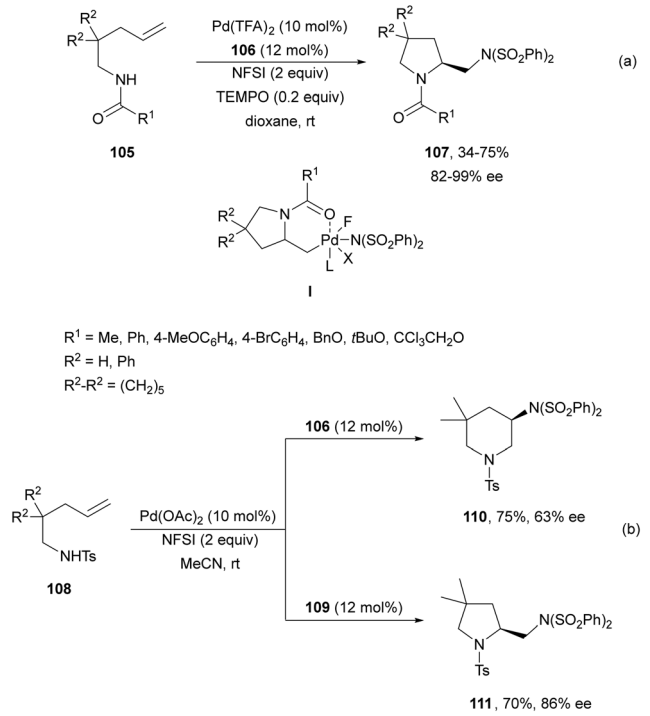
Fig. 4 Chiral Pd catalysts for intermolecular and intramolecular asymmetric diaminations.



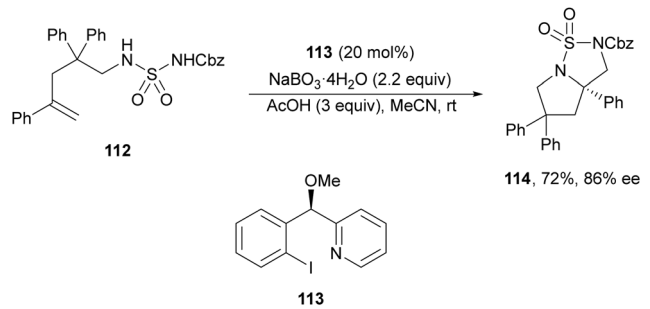
Scheme 37 Asymmetric intermolecular diamination of 1,3-dienes under Pd(0)/Pd(II) catalysis.



Scheme 38 Asymmetric diamination of 1,3-enynes under Pd(0)/Pd(II) catalysis.



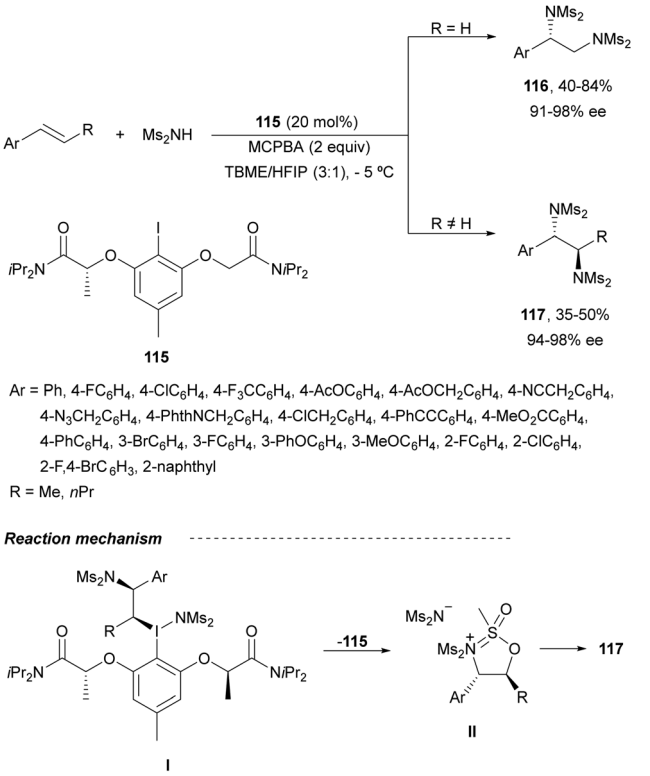
Scheme 39 Asymmetric intramolecular diamination under Pd(II)/Pd(IV) catalysis.



Scheme 40 Asymmetric intramolecular diamination under λ^3-iodane, from aryl iodide **113**, catalysis.

with different regioselectivity than in the Pd-catalyzed diamination[10,87] (Scheme 37). This diamination took place in good yields and moderate enantioselectivities at the terminal double bond (absolute configuration not assigned). In the radical mechanism, intermediate **I** is formed by N–N bond cleavage of the nucleophile by the Cu(I) catalyst through a SET process. This aminyl radical **I** adds to the less hindered side of the diene giving radical intermediate **II**, which reacts with Cu to provide intermediate **III**. Final reductive elimination of **III** gives the imidazolidinone **121**. Afterwards, the group described the same process using a Cu(I) phosphate **122** as a chiral catalyst (Scheme 43b).[88] A positive effect of a chiral phosphate as an anionic counterion was observed in the obtained enantioselectivity (absolute configuration not assigned).

Intramolecular enantioselective diamination of aminoalkenes has been performed under copper(I) catalysis similarly

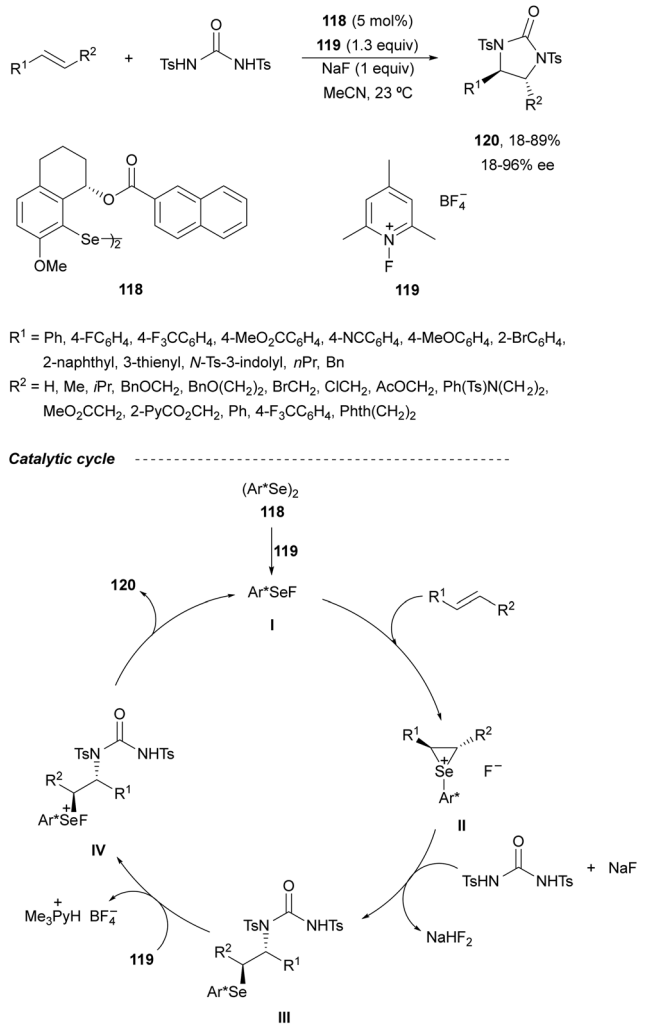


Scheme 41 Asymmetric intermolecular *anti*-diamination under λ^3-iodane, from aryl iodide **115**, catalysis.

to the Pd(II)/Pd(IV) redox diamination. Chemler and co-workers[89] reported in 2014 the cyclization-amination of γ-alkenyl sulfonamides **123** and **108** in the presence of sulfonamides as external amines using Cu(I)-Phbox **9** as a catalyst and MnO_2/$KMnO_4$ as an oxidant (Scheme 44). The corresponding 2-aminomethyl indolines **124** and pyrrolidines **125** were obtained, respectively, in good yields and enantioselectivities. In the proposed radical mechanism, after coordination of the substrate **123** with the catalyst to form intermediate **I**, *syn*-aminocupration takes place giving intermediate **II**. Subsequently, radical **III** is formed, which after recombination with Cu(II) species generates the Cu(III) intermediate **IV**. Final reductive elimination forms the second C–N bond to give products **124**.

In order to avoid the competitive formation of six-membered rings, Zheng and co-workers[90] described a double intramolecular diamination of *N*-alkenylureas **126** (Scheme 45). Under similar reaction conditions to those described by Chemler's group, bicyclic heterocycles **127** were obtained up to 86% yield and up to 98% ee. For one particular example **127** (R^1 = R^2 = Ph), the treatment with $Ba(OH)_2$ afforded (*S*)-pyrrolidine **128**.

Liu and co-workers[91] developed a general method for the asymmetric diamination of γ-alkenylureas **129** in the presence of *O*-arylhydroxylamines **130** as the external nitrogen source to form enantioenriched β-alkylamino substituted pyrrolidines **131** under mild reaction conditions (Scheme 46a). In this case, $Cu(MeCN)_4$ BF_4 and CPA **132** were used as catalysts to give products **131** in good yields and enantioselectivities. A similar chiral copper(I) phosphate derived from the CPA **133**



Scheme 42 Asymmetric intermolecular *syn*-diamination of alkenes under Se(II)Se(IV) catalysis.

(see Scheme 43) catalyzed the intramolecular amidation followed by intermolecular azidation using a λ^3-iodane reagent **134** to provide pyrrolidines **135** (Scheme 46b). In the proposed radical mechanism to explain the formation of products **131**, a SET process between the copper phosphate and the *O*-acylhydroxylamine **130** generates an aminyl radical **I**. After reaction of **I** with the starting urea **129**, a radical intermediate **II** is generated by intermolecular addition to the double bond. Subsequent second intramolecular amination followed by reductive elimination forms pyrrolidine **131** and regenerates the catalyst.

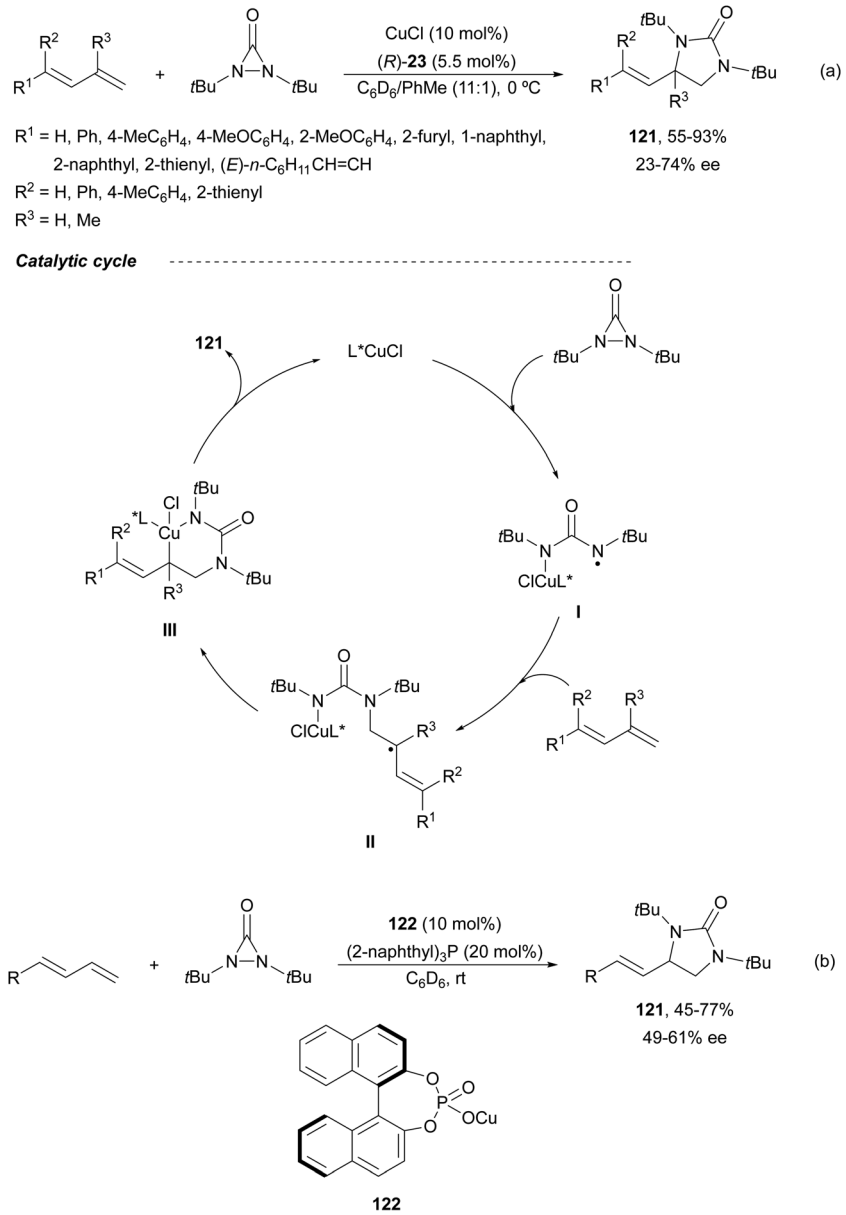
Recently, Bao and co-workers[92] reported the first example of asymmetric intermolecular diamination of styrenes using $Fe(OTf)_2$ and the chiral tridentate ligand **136** (Scheme 47). In the presence of $TMSN_3$ and NFSI, a three-component aminoazidation process took place to provide regioselectively products **137** with very good yields and enantioselectivities. According to experimental studies, a radical mechanism was proposed. The iron complex **I** reacts with $TMSN_3$ to form the iron(II) azide complex **II**. A subsequent SET process between NSFI and **II** forms a Fe(III) azide species **III** and a bis-sulfonylamidyl radical **IV**, which reacts with styrene to give a benzyl radical **V**. This radical **V** can react with the azide species **III** to provide the final product. Alternatively, intermediate **III** can be generated by a SET process between the catalyst **I** and NSFI to give intermediate **VI** followed by anion exchange with $TMSN_3$. Products **137** were transformed into different 1,2-diaminated products.

Asymmetric diamination processes can be performed intermolecularly with styrenes or dienes, whereas intramolecular diamination must be carried out with amine-tethered alkenes. They are based on a two-electron redox pathway under Pd(0)/Pd(II) or Pd(II)/Pd(IV) catalysis and also with λ^3-iodanes or diaryl selenides as chiral catalysts. In the case of the one-electron radical mechanism, Cu(I) and Fe(II) chiral complexes have been used. As nucleophiles, di-*tert*-butyldiaziridinone and ureas have been efficiently employed for intermolecular processes under Pd(0)/Pd(II) catalysis. However, intramolecular amination has been carried out with amides or sulfonamides and also with λ^3-iodanes and diselenides. Cu(I)-catalyzed reactions can be used in inter- and intramolecular processes with di-*tert*-butyldiaziridinone and with sulfonamides or ureas in the case of intramolecular diaminations. Intermolecular aminoazidation of styrenes can be carried out very efficiently under Fe(II)/bis(oxazoline) catalysis.

2.6. Other amination reactions

Trost and Fandrick[93] reported the dynamic kinetic asymmetric transformation (DYKAT) of vinylaziridines **138** to imidazolidinones **139** (Scheme 48a). This cycloaddition of isocyanates to vinylaziridines took place under Pd catalysis by use of the Trost ligand (*R*,*R*)-**140** in DCM at room temperature to give 4-vinylimidazolidinones **139** up to 95% yield and up to 99% ee. The presence of acetic acid was crucial to improve the enantioselectivity in order to equilibrate the diastereomeric π-allylpalladium intermediates **I** and **II** by protonation, which should be faster than cyclization in a DYKAT. Imidazolidinones **139** were converted into diamines firstly by reduction with $LiAlH_4$ affording imidazolidines, followed by hydrolysis with hydroxylamine in diluted HCl. This methodology was applied to the total synthesis of (+)-pseudodistomin D,[94] an alkaloid isolated from the Okinawa tunicate *Pseudodistamina megalarva*.[95] These types of alkaloids exhibit calmodulin-antagonist activity and potent cytotoxicity against murine leukemia and human epidermoid carcinoma KB cells.[96,97] Starting from vinylaziridine **138a** resulted imidazolidinone **139a** in 80% yield and 94% ee, which was further transformed into (+)-pseudodistomin D. An alternative method for the asymmetric cycloaddition was simultaneously described by Dong and Alper[98] using Binap (**46**) as a chiral ligand and $CeCl_3$ as Lewis acid (Scheme 48b). Imidazolidinones **139** (R^2 = H; absolute configuration not determined) were obtained in good yields and enantioselectivities. In this case, $CeCl_3$ increased the rate of equilibration of π-allylpalladium intermediates.

When vinylaziridines **138** were allowed to react with imido carboxylates **141**, a dynamic kinetic asymmetric allylic amination and subsequent aryl migration took place through intermediates **142** resulting orthogonally protected enantioenriched 1,2-diamines **143** (Scheme 49).[99] In this case, no additives were used and products **143** were obtained in very good yields and enantioselectivities. This dynamic kinetic asymmetric reaction

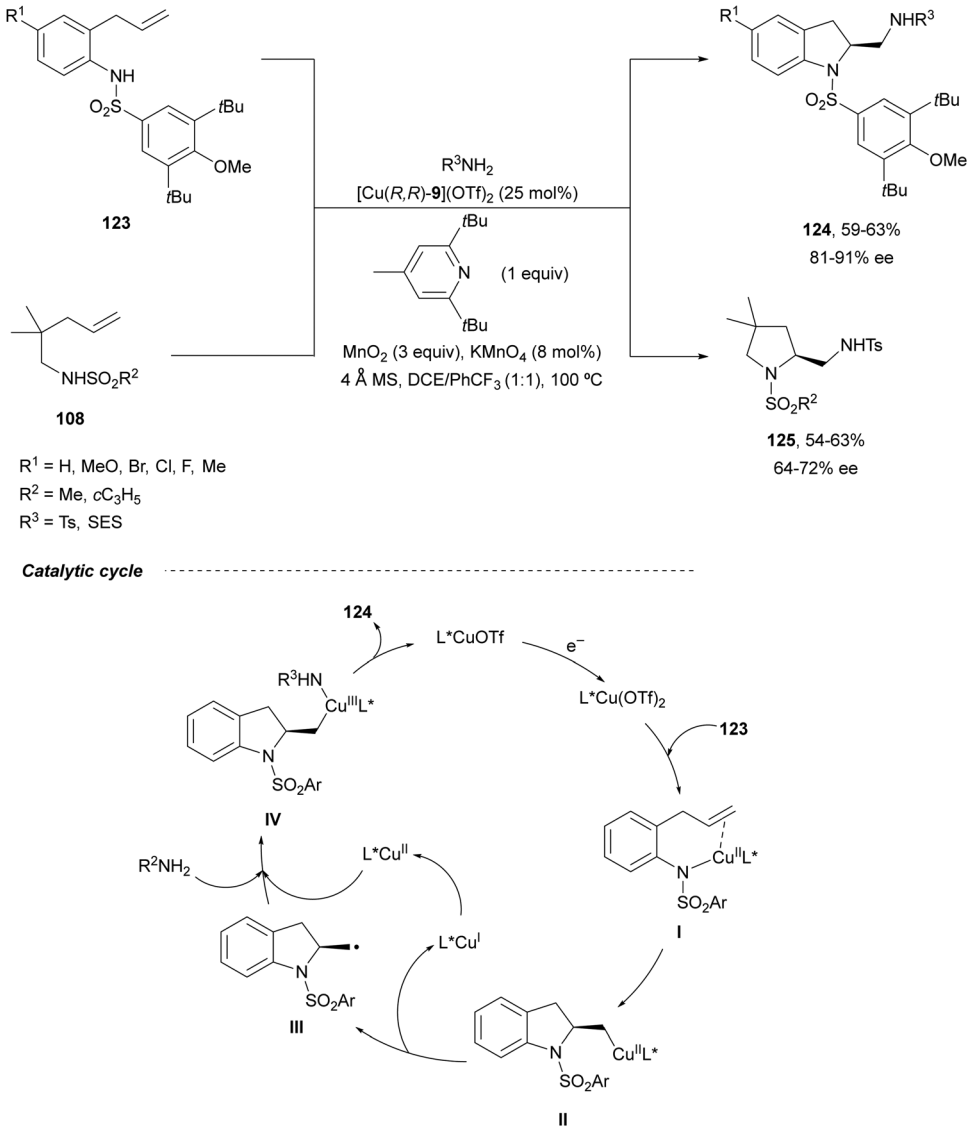


Scheme 43 Asymmetric radical intermolecular diamination of conjugated dienes under Cu(I) catalysis.

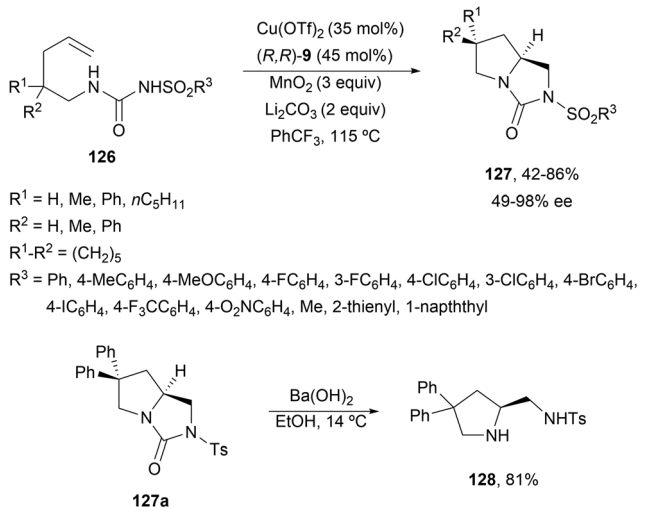
was also carried out with imido dicarboxylates **144** to provide diamines **145** with readily cleavable protecting groups, in lower yields than with benzoyl imido carboxylates **141**. This methodology has been applied to the synthesis of a potent protein kinase C (PKC) inhibitor balanol[100] starting from diamine **145a**.

Johnston and co-workers[101] have described an enantioselective synthesis of imidazolidinones from allylic amines and *N*-tosyl isocyanate using a C_2-symmetric bisamidine (BAM) **146** as organocatalyst. This amine-isocyanate capture-aminocyclization was carried out in the presence of *N*-iodopyrrolidone (NIP) to provide 5-*exo*-cyclization products **147** in very good yields and enantioselectivities (Scheme 50). However, for *E*-1,2-disubstituted allylic amines, the *endo* pathway was favored to produce six-membered urea precursors of 1,3-diamines. The obtained imidazolidinone **147a** was transformed into the corresponding diamine **148** by reduction with $LiAlH_4$. This method was also applied to the synthesis of the NK_1 antagonist **149** (Schering-Plough).

Heterocyclic diamine derivatives **153** have been prepared in an enantioselective manner by a three-component radical cascade reaction of quinolines with *N*-vinylacetamide and *O*-acyl hydroxylamines of type **150** (Scheme 51).[102] These reactions were performed under photoredox reaction conditions with $Ir(ppy)_3$ **151** as a catalyst and a (*R*)-TRIP **152** as chiral Brønsted acid under blue LED irradiation at 10–12 °C. Enantioenriched diamines **153** were obtained in 59–72% yields with high enantioselectivities. In this Minisci-type reaction, an amidyl radical **I**



Scheme 44 Asymmetric radical intra/intermolecular diamination of γ-alkenyl sulfonamides under Cu(I) catalysis.



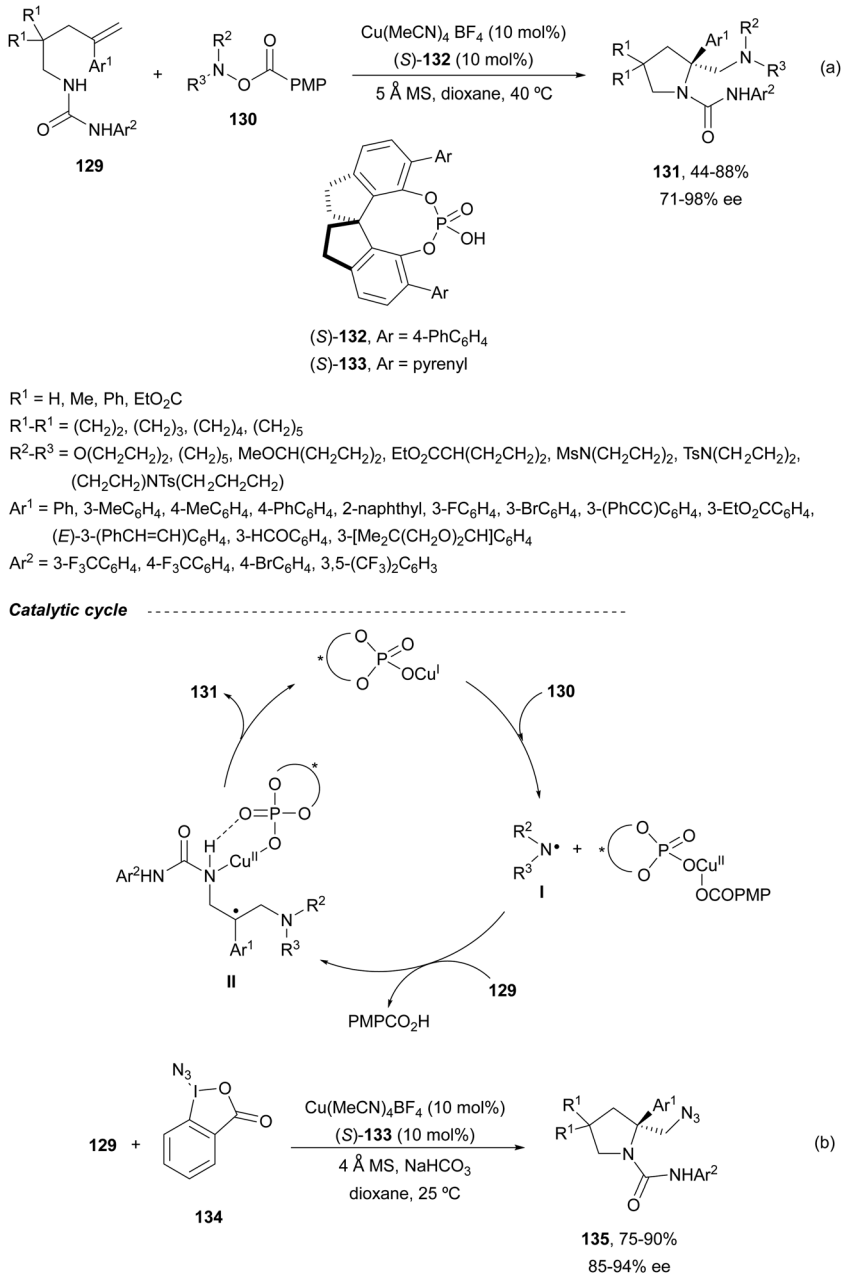
Scheme 45 Asymmetric radical intramolecular diamination of γ-alkenylureas **126** under Cu(I) catalysis.

is formed by a SET reduction of the *O*-acylhydroxylamine **150** under photoredox reaction conditions, which reacts with the enamine to form radical **II**. This radical **II** adds to protonated quinoline by hydrogen bonding formation in intermediate **III** to provide **IV**. Probably, **IV** is formed reversibly as a mixture of diastereomers and one of them is selectively deprotonated to give **V** and regenerates the CPA **152**. Finally, **V** is oxidized by excited Ir(III)* to provide the product after deprotonation.

3. C–C bond-forming reactions

3.1. Aza-Mannich ractions

In this section, the reaction of α-amino nucleophiles with aldimines or ketimines will be considered. As nucleophiles, imino esters, imino nitriles, azlactones, isocyano acetates and isothiocyanates have been used for the synthesis of α,β-diamino acid derivatives. Other nucleophiles such as α-azido

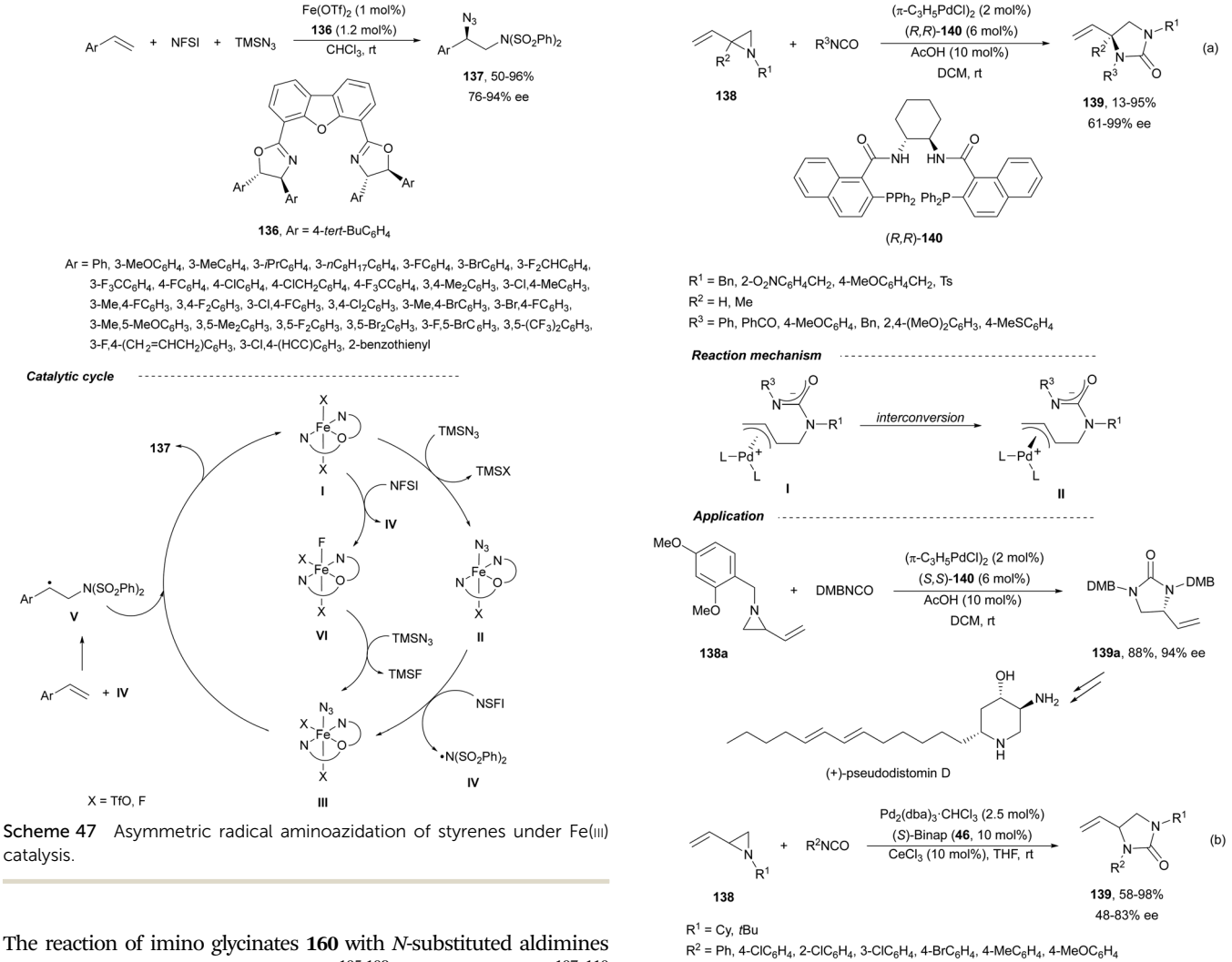


Scheme 46 Asymmetric radical inter/intramolecular diamination of γ-alkenylureas **129** under Cu(I) chiral phosphate catalysis.

ketones or amides gave α,β-diamino carbonyl compounds. In the case of α-amino acetaldehydes, β,γ-diamino alcohols were obtained. 3-Indoline-2-carboxylates provided β-amino ester derivatives. *N*-Aryl glycines reacted with hydrazones to provide 1,2-diamines under copper or photoredox catalysis.

3.1.1. Imino esters. The direct Mannich reaction between imino glycinates or related compounds and imines forms a C–C bond and two vicinal nitrogen-containing stereocenters at the same time to give α,β-diamino acids.[6] These compounds are key structural units in many bioactive natural products and pharmaceuticals as well as synthetic building blocks. Asymmetric aza-Mannich reaction has been performed under metal-catalyzed and organocatalyzed conditions and was recently reviewed in 2009[103] and 2013.[104] In this section, backgrounds and recent developments of this transformation under asymmetric metal and organocatalysis will be considered.

Coordination of the anion derived from alkyl imino glycinates with a Lewis acid should favor to act as a nucleophile in the aza-Mannich reaction rather than an azomethine ylide resulting in a 1,3-dipolar cycloaddition (see, Section 3.5). Since 2003,[105] copper(I) salt with chiral ligand catalysis (**154–156**) has been widely used for the aza-Mannich reaction of imino glycinates with aldimines (Fig. 5).[106,107] Imino glycinates and alaninates were also added to imines under copper(I) and Fesulphos ligand **157** catalysis.[108,109] Other ligands such as **158**[110] and **159**[111] have also been employed with $CuBF_4$ and $Cu(OAc)_2$ salts, respectively (Fig. 5).



Scheme 47 Asymmetric radical aminoazidation of styrenes under Fe(III) catalysis.

Scheme 48 Asymmetric cycloaddition of isocyanates with 2-vinylaziridines **138**.

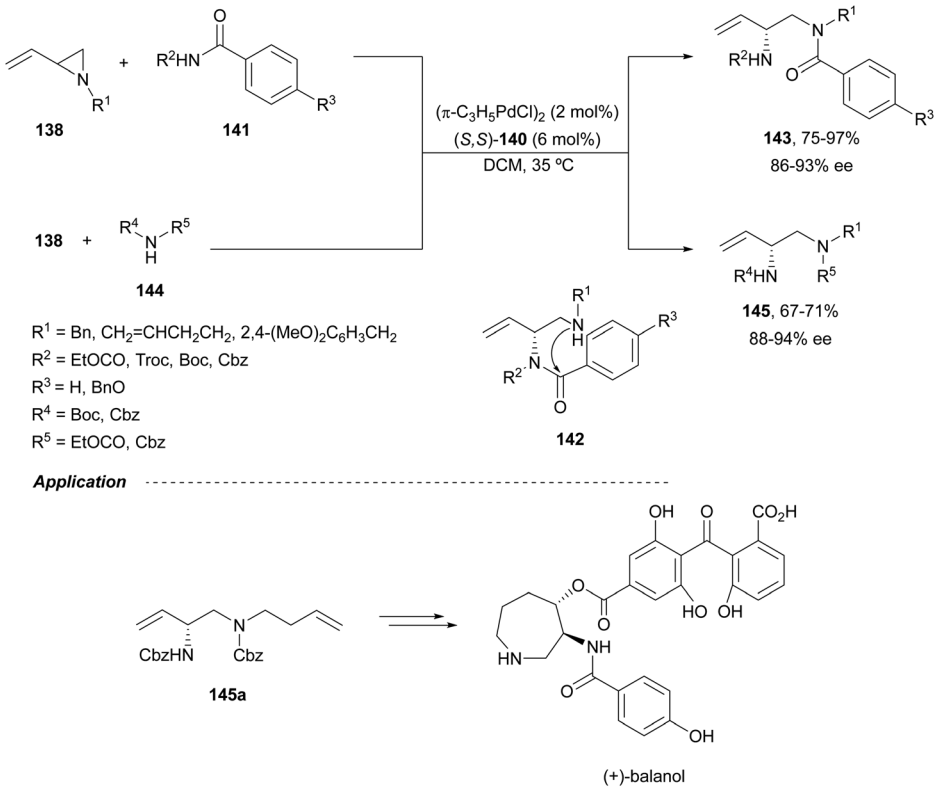
The reaction of imino glycinates **160** with *N*-substituted aldimines **161** gave mainly *syn*-products **162**[105,109] or *anti*-products[107–110] depending on electronic effects in the catalyst or in the imine protecting group (Scheme 52).

In 2012, Arai and co-workers[112] described a *syn*-diastereoselective asymmetric Mannich reaction of *N*-sulfonyl aldimines **161** with imino esters **160** catalyzed by a tridentate ligand PyBidine **163** and Cu(OTf)$_2$ (Scheme 53). α,β-Diamino acid precursors *syn*-**162** were obtained up to 96% yield and up to 99% ee with, in general, high diastereoselectivities. Starting from the *N*-nosyl product **162a**, *via* two deprotection steps, the α,β-diamino acid methyl ester **164** was obtained with the same diastereo- and enantioselectivities as the starting compound **162a**. In the proposed mechanism, the Cu enolate **II** was initially formed from intermediate **I**, which reacts with the imine by a *syn*-approach depicted in the TS to provide the *syn*-diastereomer **162**.

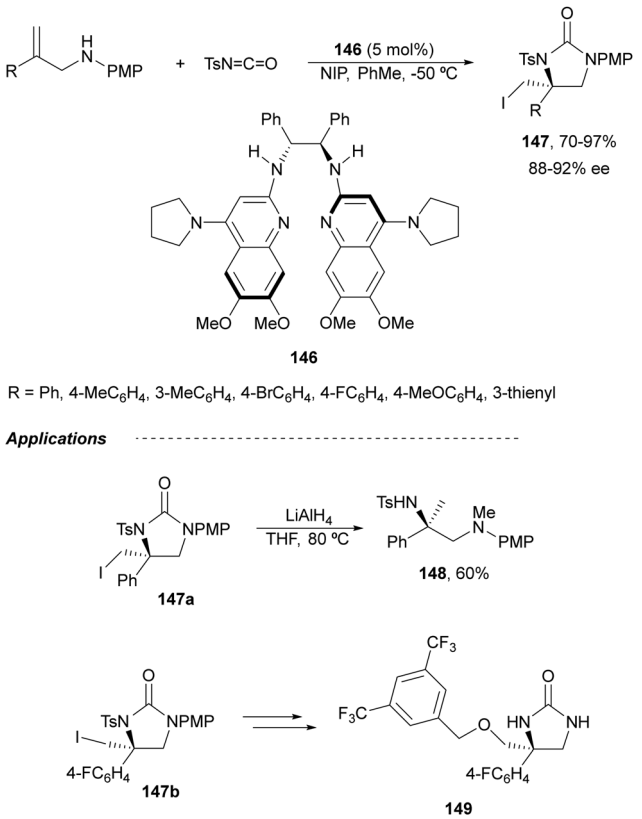
Kobayashi and co-workers[113] employed a copper amide CuHMDS, prepared from CuOTf and potassium hexamethyldisilazide (HMDS), and the chiral ligand (*R*)-DTBM-Segphos (**23**) for the asymmetric aza-Mannich reaction of glycine imino ester **160** with *N*-tosylaldimines **161** (R^3 = 4-MeC$_6$H$_4$) (Scheme 54). The chiral catalytic complex must be prepared *in situ* in order to avoid CuHMDS aggregation. Products **162** were obtained in good yields, moderate *syn*-diastereoselectivity and up to 98% ee.

In the case of the Cu(I)/Fesulphos (**157**)-catalyzed aza-Mannich reaction, a more practical method was described by Carretero's group.[114] Easy available and stable α-amido sulfones **165** were used as precursors of unstable aliphatic aldimines based on the previous described asymmetric aza-Mannich reaction of phosphonoglycine imino esters with α-amido sulfones.[115] In the presence of Cs_2CO_3 (1.5 equiv.) as a base, the corresponding *N*-tosylimines were generated *in situ* and reacted with glycine imino esters to provide *syn*-β-alkyl-α,β-diamino acid derivatives **162** with very good yields and high diastereoselectivities and enantioselectivities (Scheme 55). The *syn*-diastereocontrol was rationalized involving a severe steric repulsion of the bulky *N*-diarylmethylene group in the ketimine nucleophile with the tosyl group as it is shown in intermediate **I**. Thereby, the imine approaches from its *Si*-face *via* intermediate **II**, which affords the *syn*-product.

Recently, *N*-diphenylphosphinoyl (DPP) aldimines **167** have been used as electrophiles using a bifunctional Cu(I)/amido-phosphine-urea **168** catalyst.[116] The reaction of imino esters **166**,



Scheme 49 Asymmetric allylic amination and acyl migration of vinylaziridines **138** with imido carboxylates **141**.

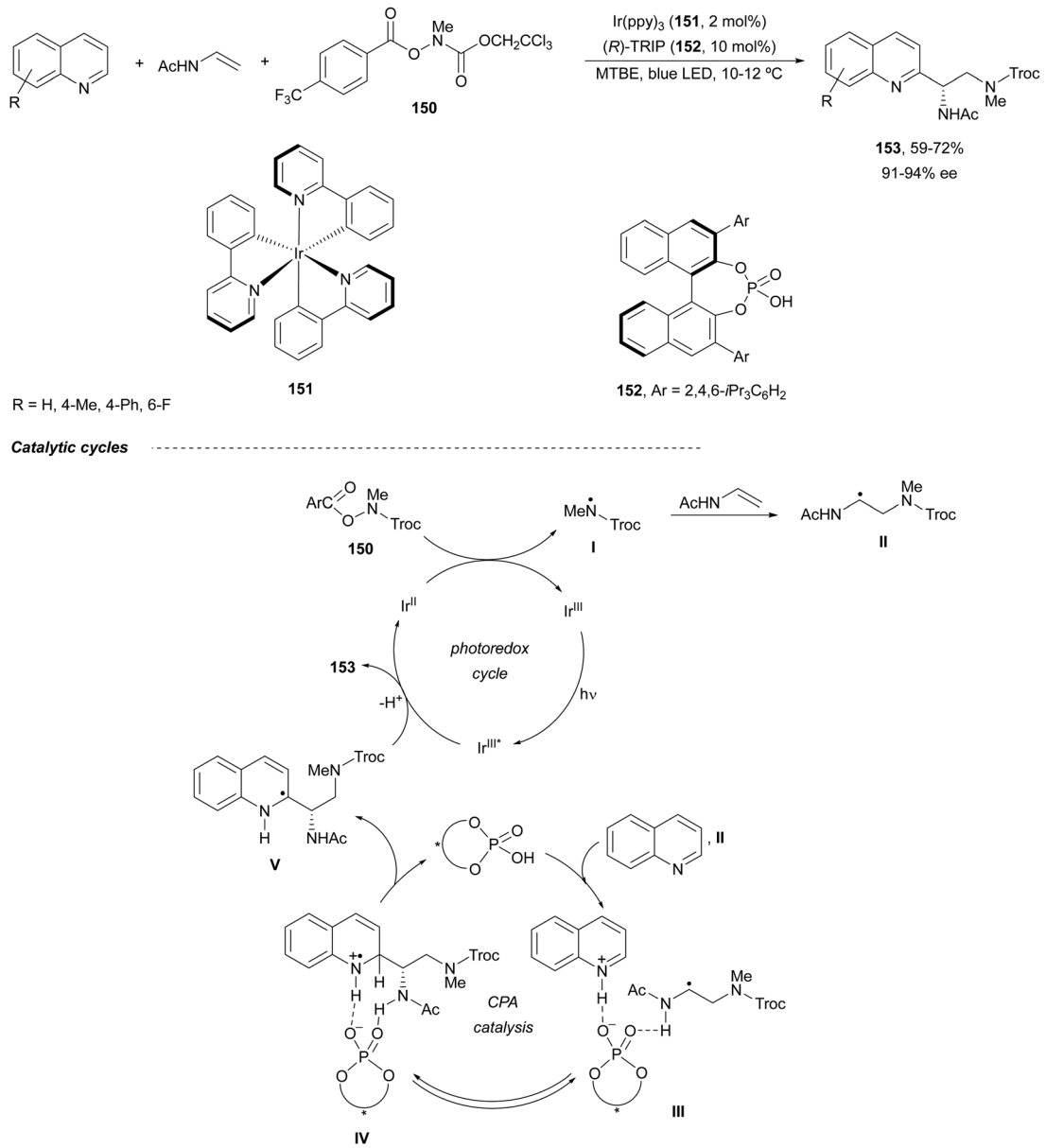


Scheme 50 Asymmetric alkene iodoamination by isocyanate capture by allylic amines.

derived from aldehydes, and imines **167**, followed by monodeprotection with aqueous $NH_2OH{\cdot}HCl$ of the crude reaction mixture, provided the aza-Mannich *syn*-adducts **169** in high yields and up to >99 : 1 dr and up to 99% ee (Scheme 56). On the basis of the experimental studies and theoretical calculations,[117] a plausible TS involving dual activation of the glycine imino ester and *N*-DPP imine has been proposed. The glycinate enolate is coordinated to the Cu(I) metal center and the *N*-phosphinoyl imine is activated and oriented by two hydrogen bondings between the urea moiety and the P=O unit. A preferential *Si*-face attack of the imino ester onto the *N*-phosphinoyl imine gives the (2*S*,3*R*)-adduct.

Ketimines **170** derived from isatins have been employed as electrophiles in the aza-Mannich reaction with glycine imino ester **160** under Cu(I)/Ph-Phosferrox **171** catalysis by Yang, Deng and co-workers.[118] This method allowed the asymmetric synthesis of 3-aminooxindoles **172** in high yields and enantioselectivities although with moderate to high diastereoselectivities (Scheme 57). The Mannich adduct **172a** was transformed into biologically important spirooxindoles[119,120] **173** and **174** in 99% ee.

Cyclic ketimines **175** derived from saccharine have been allowed to react with glycine imino esters **160** under Cu(II)/RuPhox **176** catalysis by Xie and co-workers.[121] Mannich-type adducts **177** were obtained up to 99% yield, up to >20 : 1 dr and 99% ee (Scheme 58). The sterically bulky *tert*-butyl imino glycinates gave generally better results and the absolute configuration for the (*S*,*S*)-diastereomer was determined by X-ray diffraction analysis.



Scheme 51 Asymmetric synthesis of diamines **153** by a three-component radical cascade reaction.

Silver acetate in combination with chiral ligands such as **178**[122] and **179**[123] have been used as catalysts for the aza-Mannich reaction of glycine methyl imino esters **160** and *N*-tosyl aldimines **161** (Fig. 6).[104] These procedures took place with high yields and enantioselectivities but with low diastereoselectivities.

Sansano and co-workers[124] reported this type of asymmetric aza-Mannich reaction using AgOTf and Feringa's phosphoramidite (S_a,*R*,*R*)-**180** as a catalyst (Scheme 59). Precursors of α,β-diamino acids **162** were obtained up to 70% yield, up to 90 : 10 dr and 99% ee for the *syn*-diastereomer. In the proposed TS, the silver enolate attacks the *N*-tosyl aldimine **161** whose tosyl group is placed far away from the benzylidene moiety of the enolate.

Hu and co-workers[125] have described that $Rh_2(OAc)_2$ and CPA (*R*)-**183** or (*R*)-**184** catalyzed the three-component aza-Mannich reaction of a diazo compound **181**, and a carbamate and a *N*-aryl aldimine **182** furnished both *anti*- and *syn*-α,β-diamino acid derivatives **185**, respectively (Scheme 60). This diastereodivergent[52] trapping of carbamate ammonium ylides with imines takes place by initial formation of the rhodium carbenoid **I**, which reacts with the carbamate to form the carbamate ammonium ylides **II**/**III**. These ylides are trapped by the imine to give products **185**, *via* zwitterion **IV**. The observed stereoselective control was explained by TS_{anti} and TS_{syn} formed with the different types of CPAs. In the case of the sterically demanding CPA (*R*)-**183**, an open-chain TS_{anti} was suggested. However, with CPA (*R*)-**184** a bifunctional role forms a N–H–OPO–H–N bridge in the TS_{syn}.

The former asymmetric three-component reaction was also carried out by the same group[126] with arylamines instead of carbamates. In this case, (*R*)-TRIP (**152**) was used as a CPA to

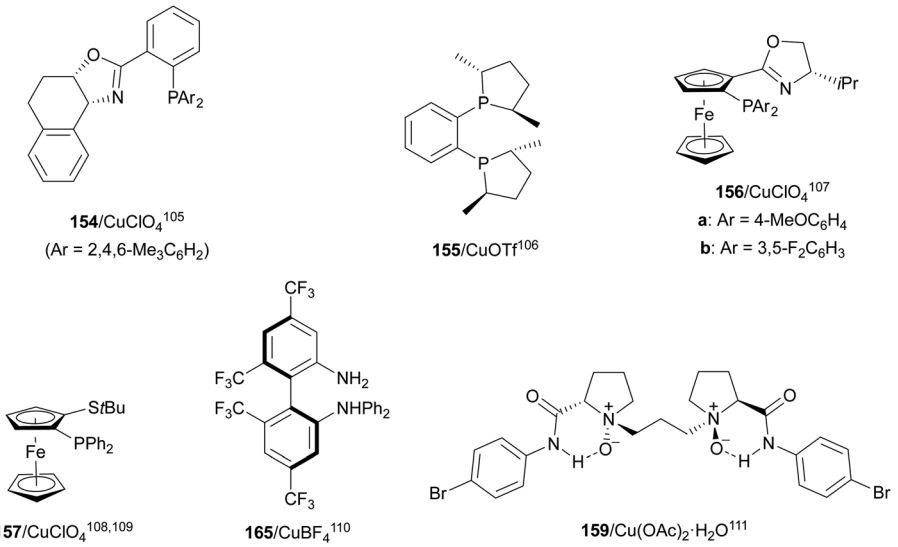
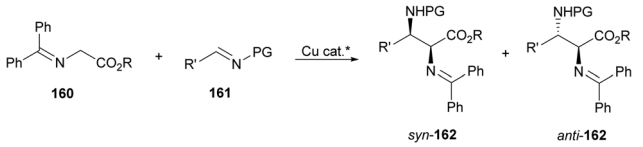


Fig. 5 Chiral copper catalysts for the aza-Mannich reaction of imino glycinates with imines.



Scheme 52 Asymmetric aza-Mannich reaction of benzophenoneimine glycinates with imines.

provide *anti*-α,β-diamino esters **186** up to 90% yield, up to >95 : 5 dr and 96% ee (Scheme 61).

When phosphoramides **187** and α-imino esters **188** were allowed to react with diazo compounds **181**, under Rh/CPA reaction conditions, 2,3-diaminosuccinic acid derivatives **190** were obtained (Scheme 62).[127] In this case, the 9-phenantryl (*S*)-**189** was used as Brønsted acid to give products **190** with good yields, moderate to high *syn*-diastereoselectivities and up to 98% ee. The trapping of protic phosphoramidate ammonium ylides with α-imino esters can be envisaged *via* intermediate **I**.

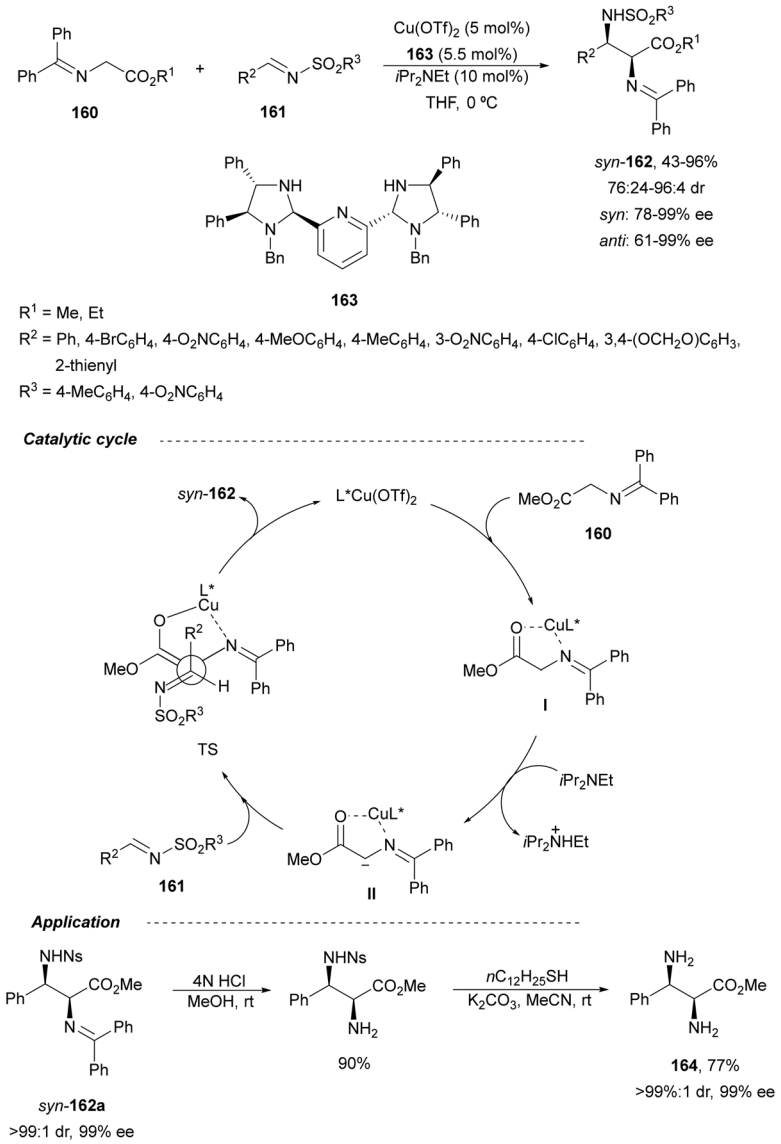
As a summary of the asymmetric metal-catalyzed aza-Mannich reaction, the most studied process between imino esters and imines was carried out under copper catalysis to give mainly *syn*-α,β-diamino acid derivatives. The three-component reaction of diazo compounds, amines or amides and imines under Rh/CPA catalysis is a versatile strategy which provided mainly the same *syn*- or *anti*-products depending on the CPA catalyst.

Organocatalytic asymmetric aza-Mannich reactions have been performed using chiral phase-transfer catalysts (PTC) but also chiral bases. Maruoka and co-workers[128] reported the phase-transfer-catalyzed aza-Mannich reaction of benzophenone imine of *tert*-butyl glycinate ester **160** with *N*-aryl-α-imino ester **188** using a *N*-spiro-C_2-symmetric chiral quaternary ammonium bromide **191** as a catalyst (Fig. 7). This method enabled the synthesis of a *syn*-3-aminoaspartate derivative, related to compound **190**, in 88% yield, 82 : 18 dr and 91% ee. This product was converted into a precursor of streptolidine lactam, a constituent of streptothricin antibiotics. A general method for the aza-Mannich reaction of **160** (R = *t*Bu) with *N*-Boc-aldimines was described by Ohshima, Shibasaki and co-workers[129,130] using tartrate-derived diammonium salts **192** as a chiral catalyst (Fig. 7). The corresponding *syn*-adducts **162** were obtained with high yields (88–96%), diastereoselectivities (97 : 3–99 : 1 dr) and good enantiocontrol (70–90% ee). This method was applied to the synthesis of the antipsychotic (+)-nemonapride.

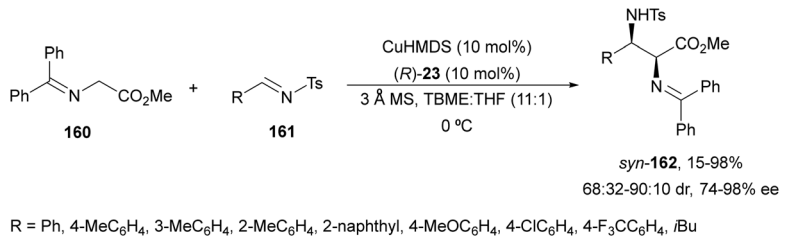
Cinchona-Alkaloid derived ammonium salts have been widely used as readily available catalysts in asymmetric PTC in organic synthesis.[131] Gong and co-workers[132] employed a quininium salt **193** bearing a (*R*)-binol unit for the asymmetric aza-Mannich reaction of imino ester **160** with *N*-Boc imines **161** in very high yields, high *syn*-diastereoselectivity and up to 96% ee (Scheme 63). This reaction was performed in toluene with Cs_2CO_3 as a base and in the presence of anhydrous Na_2SO_4 to remove residual water. The additional (*R*)-axial chirality exerted a great impact on the stereochemical control.

Maruoka and co-workers[133] employed *in situ* generated *N*-Boc imines from *N*-Boc aminals **194** under basic conditions. This procedure was very useful for *N*-Boc imines which cannot be prepared by traditional methods. Imino glycinates **160** reacted with *N*-Boc-aminals **194** under PTC in the presence of the binaphthyl-based catalyst **195** to furnish after acidic deprotection, products **196** in good yields and diastereo- and enantioselectivities (Scheme 64a). This aza-Mannich reaction was also carried out with the alanine Schiff base **197** and aminals **194** to provide *syn*-α,β-diamino acid derivatives **198** with a quaternary stereocenter in a diastereomeric ratio of >20 : 1 (Scheme 64b).

α,β-Diaminophosphonic acid derivatives **202** have been synthetized by an aza-Mannich reaction of a phosphoglycine Shiff base **199** with *in situ* generated *N*-Boc imines from α-amido sulfones **200** under asymmetric PTC by Bernardi, Ricci and co-workers.[134] The corresponding *syn*-products **202** were obtained in the presence of the quininium salt **201** as a chiral phase-transfer catalyst in good yields, total diastereoselectivity and up to 94% ee (Scheme 65).



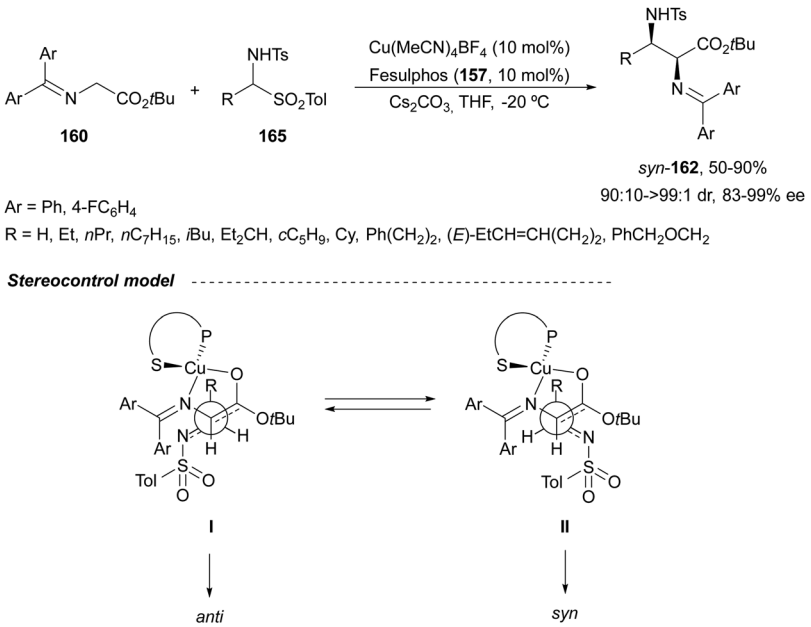
Scheme 53 Asymmetric aza-Mannich reaction of imino esters **160** with aldimines **161** under Cu/PyBidine **163** catalysis.



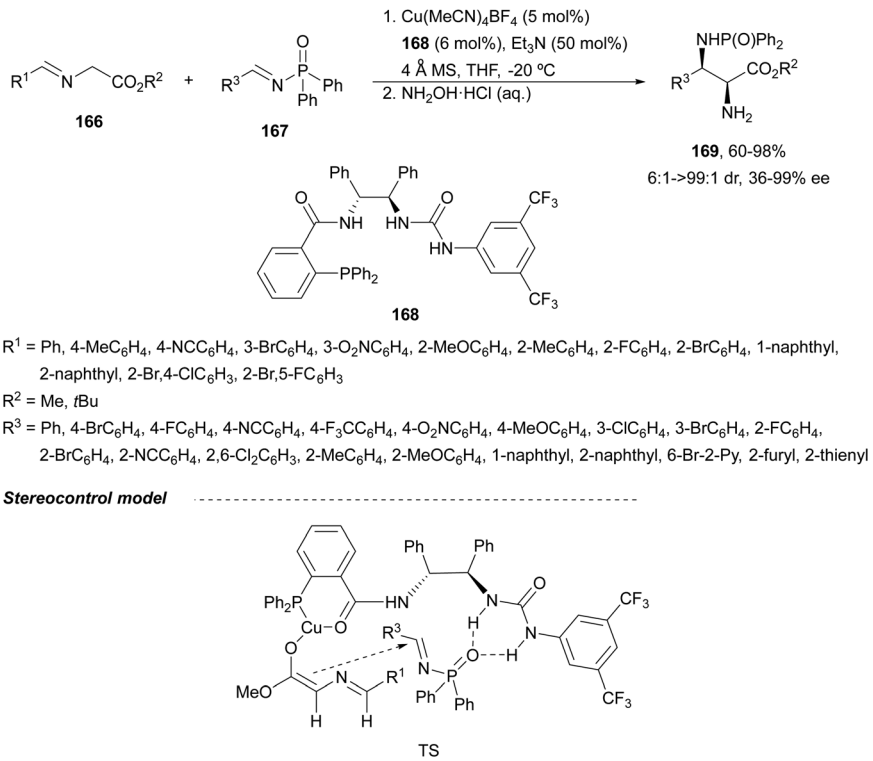
Scheme 54 Asymmetric aza-Mannich reaction of imino glycinate methyl ester **160** with *N*-tosylimines **161** under CuHMDS/(*R*)-DTBM-Segphos (**23**) catalysis.

The first example using a chiral base as a catalyst was described by Kobayashi and co-workers.[135] Fluorenone glycine imine **203** has been used for the aza-Mannich reaction with *N*-Boc imines **161** in the presence of chiral guanidine **204** as an organocatalyst (Scheme 66). α,β-Diamino acid derivatives *syn*-**205** were isolated diastereoselectively in good yields and ee's.

Glycine imino ester **160** (R = Me) has been allowed to react with *N*-Boc-aldimines generated *in situ* from amido sulfones **200** using a *Cinchona* alkaloid thiourea **206** as a chiral organocatalyst (Fig. 8). Barbas III and co-workers[136] performed this asymmetric direct aza-Mannich reaction in trifluoromethylbenzene in the presence of a saturated solution of Na_2CO_3 at 4 °C to



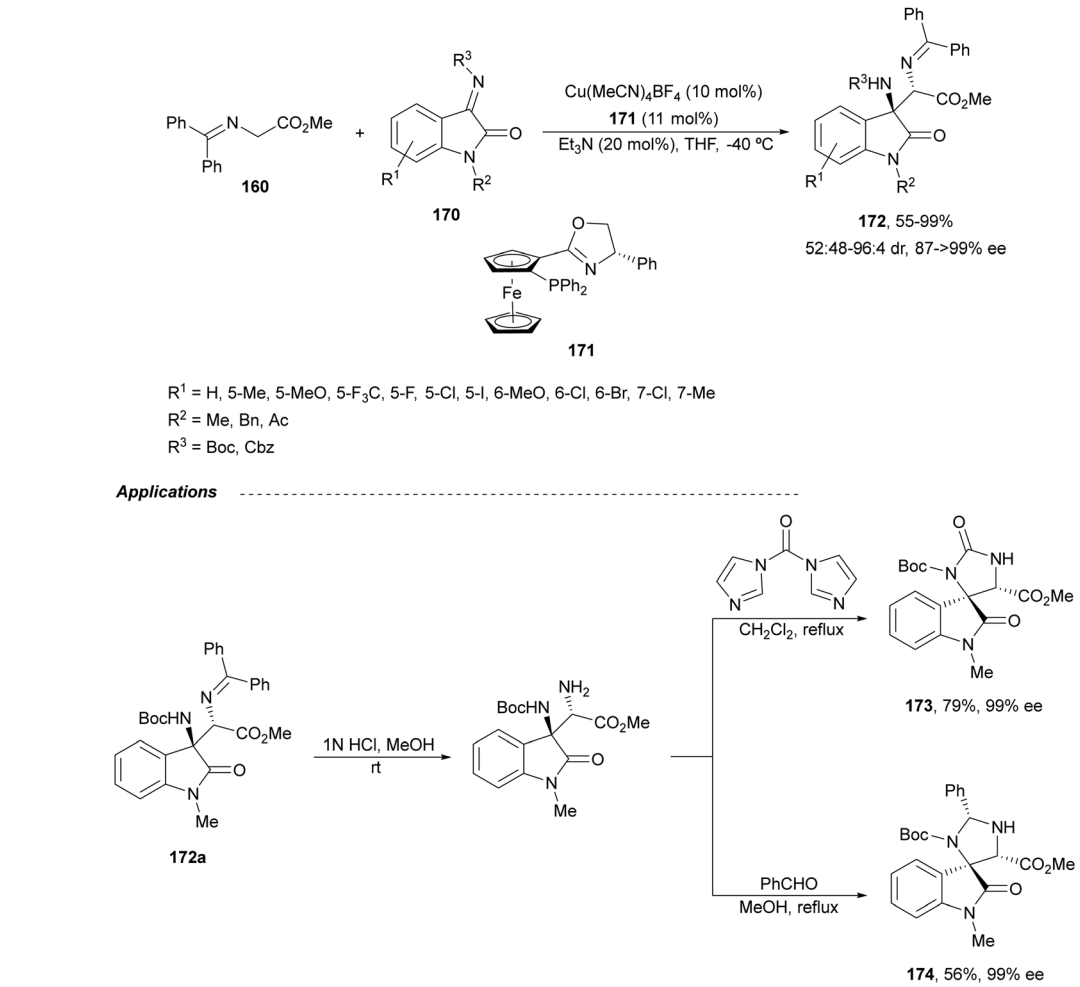
Scheme 55 Asymmetric aza-Mannich reaction of glycine imino esters **160** with α-amido sulfones **165** under Cu(I)/Fesulphos **157** catalysis.



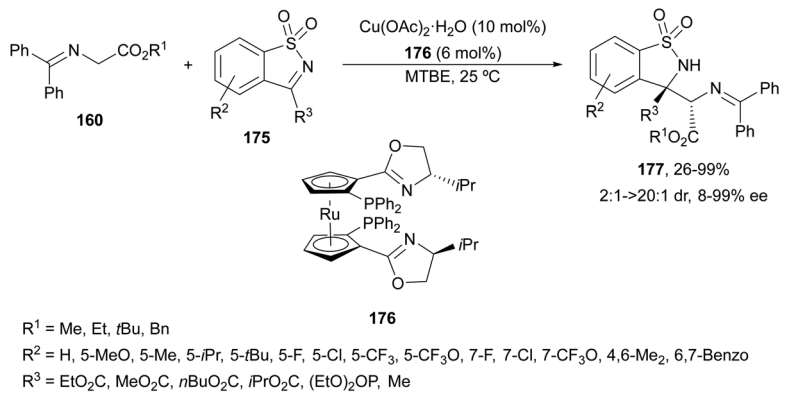
Scheme 56 Asymmetric aza-Mannich reaction of glycine imino esters **166** with *N*-diphenylphosphinoyl imines **167** under Cu(I)-amidophosphine-urea **168** catalysis.

provide products *syn*-**162** with high yields (62–98%) and excellent ee (>95–>97%) and dr (>99 : 1). Bandar and Lambert[137] employed a cyclopropenimine **207** as a chiral base for the reaction of glycine imino ester **162** (R = Me, *t*Bu, and Bn) with *N*-Boc imines from aromatic aldehydes, using NaO*t*Bu as a base in THF at 0 °C (Fig. 8). α,β-Amino acid derivatives *syn*-**162** were obtained in 63–99% yield, 96 : 4 dr and 38–97% ee.

The chiral guanidine **210** has been used as an organocatalyst for the aza-Mannich reaction of aldimino glycinate **208**, derived from 3,5-di-*tert*-butylsalicylic aldehyde with sterically hindered



Scheme 57 Asymmetric aza-Mannich reaction of glycine imino ester **160** with isatin derived ketimines **170** under Cu(I)/Ph-Phosferrox (**171**) catalysis.



Scheme 58 Asymmetric aza-Mannich reaction of glycine imino esters **160** with cyclic ketimines **175** under Cu(II)/Ruphox **176** catalysis.

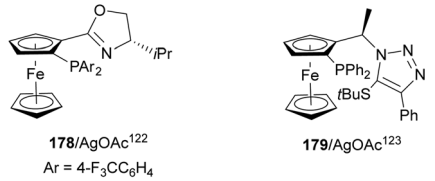
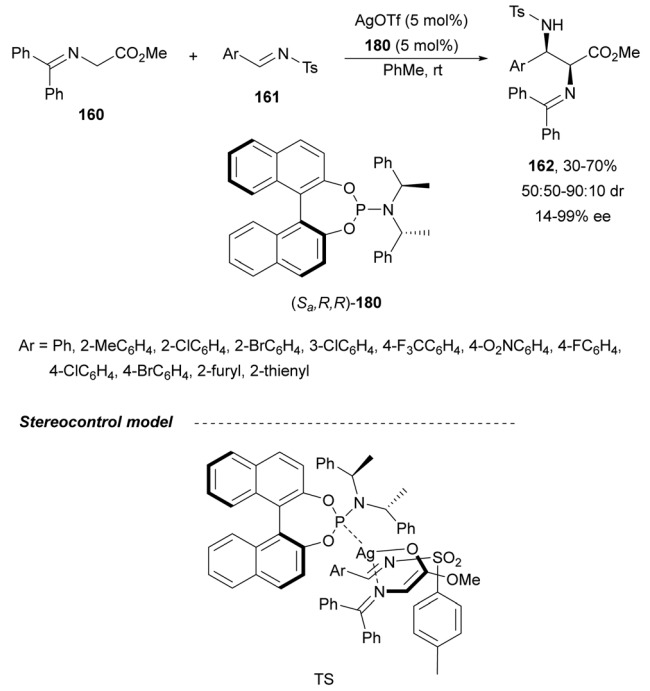


Fig. 6 Chiral silver catalysis for the aza-Mannich reaction of methyl iminoglycinate **160** with *N*-tosyl imines **161**.

N-(8-quinolyl)sulfonyl aldimines **209** (Scheme 67).[138] Products **211** resulted in very good yields but modest diastereo- and enantioselectivities.

Yuan, Zhao and co-workers[139,140] described a biomimetic asymmetric aza-Mannich reaction using carbonyl catalysis inspired by pyridoxal-depending enzymes. The reaction of unprotected *tert*-butyl glycinate hydrochloride with *N*-diphenylphosphinoyl imines



Scheme 59 Asymmetric aza-Mannich reaction of glycinate methyl imino ester **160** with *N*-tosyl aldimines **161** under AgOTf/phosphoramidite **180** catalysis.

167 was performed in the presence of the chiral pyridoxal (*R*,*S*)-**212** to furnish mainly *anti*-products **169** in good yields and excellent diastereo- and enantioselectivities (Scheme 68). In the plausible catalytic mechanism, initial condensation of the catalyst **212** with glycinate forms an imino ester **I**, which after deprotonation generates carbanion **II**. Subsequent addition of this enolate to imine **167** through a TS gives intermediate **III**, which after hydrolysis yields product **169** and regenerates the catalyst.

Organocatalytic methods for the asymmetric aza-Mannich reaction of imino glycinates with imines, which are based on chiral phase-transfer catalysis, are better and use more simple reaction conditions than with metal complexes. In the case of using chiral bases, mainly *syn*-diamino acid derivatives are obtained. However, the biomimetic carbonyl-based catalysis gave very efficient *anti*-products.

3.1.2. Imino nitriles. The first example on the asymmetric aza-Mannich reaction of *N*-fluorenylidene-protected α-amino nitrile **213** with *N*-diphenylphosphinoyl imines **167** was performed by Kobayashi and co-workers (Scheme 69).[141] This reaction was performed in the presence of a chiral base **214** as a catalyst, related to catalyst **204** for the Mannich reaction of *N*-fluorenylidene glycine *tert*-butyl ester **203** (Scheme 66).[135] Product *syn*-**213** was obtained in 62% yield, 87 : 13 dr and 73% ee.

The former *N*-fluorenylidene α-amino nitrile **213** was further employed as a nucleophile with ketimines **216** bearing a thiophosphinoyl group by Kumagai, Shibasaki and co-workers.[142] The Mannich reaction was carried out under Cu/(*R*)-DMM-Garphos **217** catalysis using LiO*t*Bu as a base at −78 °C to furnish mainly α,β-diamino alkanenitriles *anti*-**218** with a quaternary stereocenter up to 99% yield, up to 95 : 5 dr and 95% ee (Scheme 70). The thio-DPP protecting group was transformed into DPP by treatment with H_2O_2 and subsequently into a NH_2 group by hydrolysis with 12 M HCl at 40 °C.

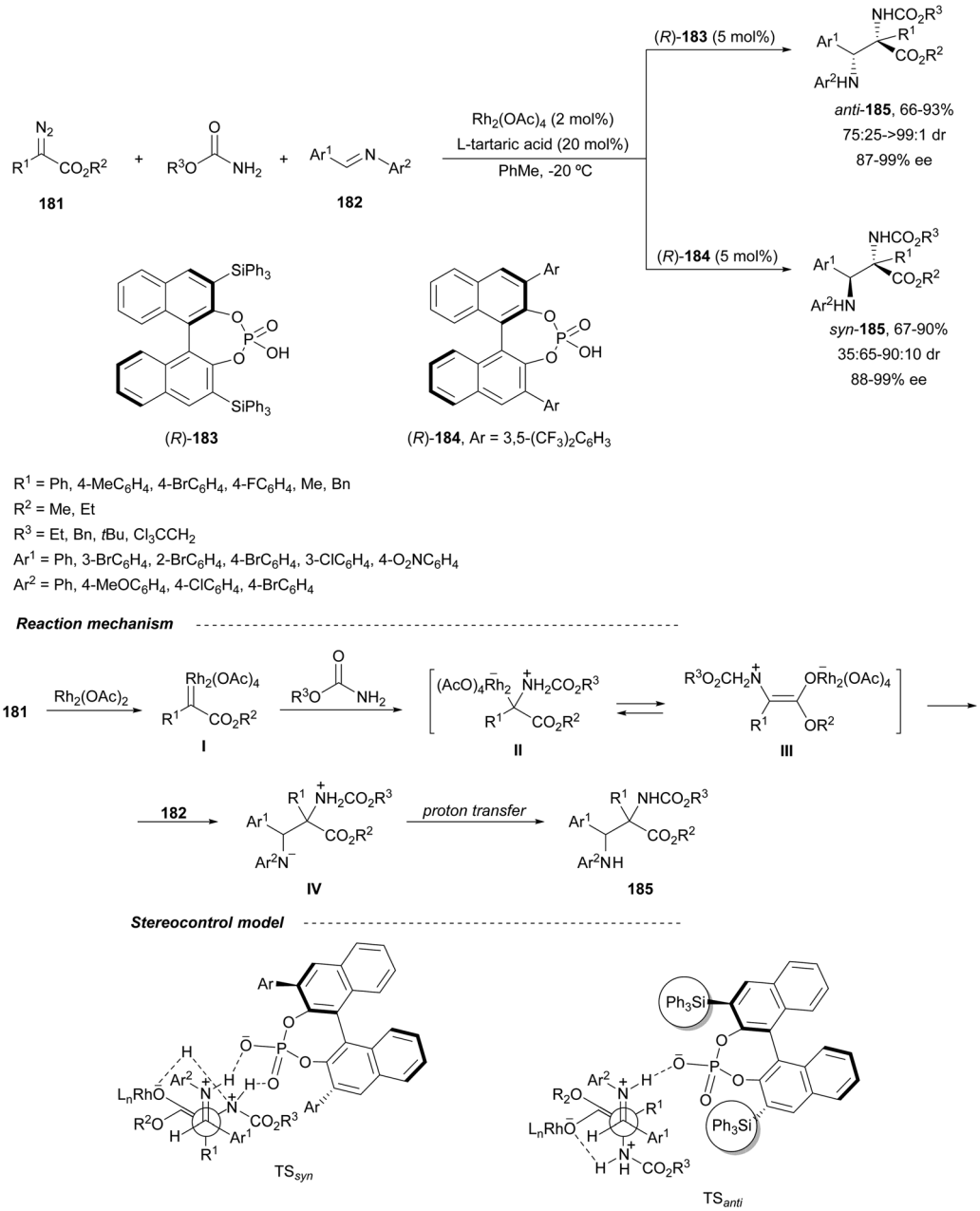
Nakamura and co-workers[143] reported the same year the benzylidene α-amino nitrile **219** reaction with *N*-(2-pyridinesulfonyl)imine **220** using a chiral bis(imidazoline)palladium complex **221** and Ag(acac) as a catalyst in THF at −60 °C (Scheme 71). The corresponding products **222** were obtained after deprotection of the benzylidene group with HCl in THF at room temperature. Total deprotection of compound **222a** was carried out with Mg in MeOH to provide product **223** in 60% yield. A plausible catalytic cycle was proposed starting from complex **I**, which reacts with the imino nitrile **219** to give intermediate **II** by coordination of the cyano group to the Pd atom. After deprotonation of **II**, the palladium complex **III** is formed. In the next step, the nucleophilic addition of **III** to the aldimine **220** gives intermediate **IV**, which undergoes protonation and decomplexation to provide the product and regenerates the catalyst. On the basis of theoretical calculations, a TS was proposed.

Imino nitriles underwent asymmetric aza-Mannich reaction with activated aldimines to give *syn*-adducts only under metal catalysis. Only ketimines provided *anti*-adducts under Cu-catalyzed conditions.

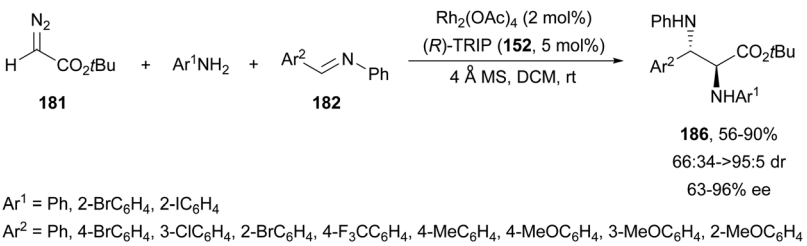
3.1.3. Azlactones. Azlactones (also known as oxazolones) are easily obtainable from α-amino acids and have been applied in a diversity of transformations.[144] Concerning asymmetric aza-Mannich reactions of azlactones **224** with *N*-protected imines **161**, several chiral organocatalysts have been successfully employed to provide *syn*/*anti* products **225** and also gold(I) or Ag(I) complexes (Scheme 72).[144]

Ooi and co-workers[145] described the reaction of azlactones **224** with *N*-sulfonyl imines **161** using a chiral tetraaminophosphonium carboxylate **226** as a phase-transfer catalyst to give mainly *syn*-products **225** up to 99% yield, 12 : 1 dr and 97% ee (Fig. 9). After two-step deprotection with aqueous H_2SO_4 in THF followed by hydrolysis with concentrated HCl, the corresponding α,β-diamino acid hydrochloride (R^1 = Bn, R^3 = Me) was obtained in 87% yield maintaining a 92% ee. The same group used a C_1 symmetric ammonium betaine **229** as a catalyst for the aza-Mannich reaction of thiazolones **227** with *N*-Boc imines **161** to give mainly products *anti*-**228** with high yields, up to 15 : 1 dr and 99% ee (Scheme 73). Compound **228a** was transformed in a two-step procedure into α,β-diamino acid ester derivative *anti*-**230** in 60% yield and 99% ee.[146]

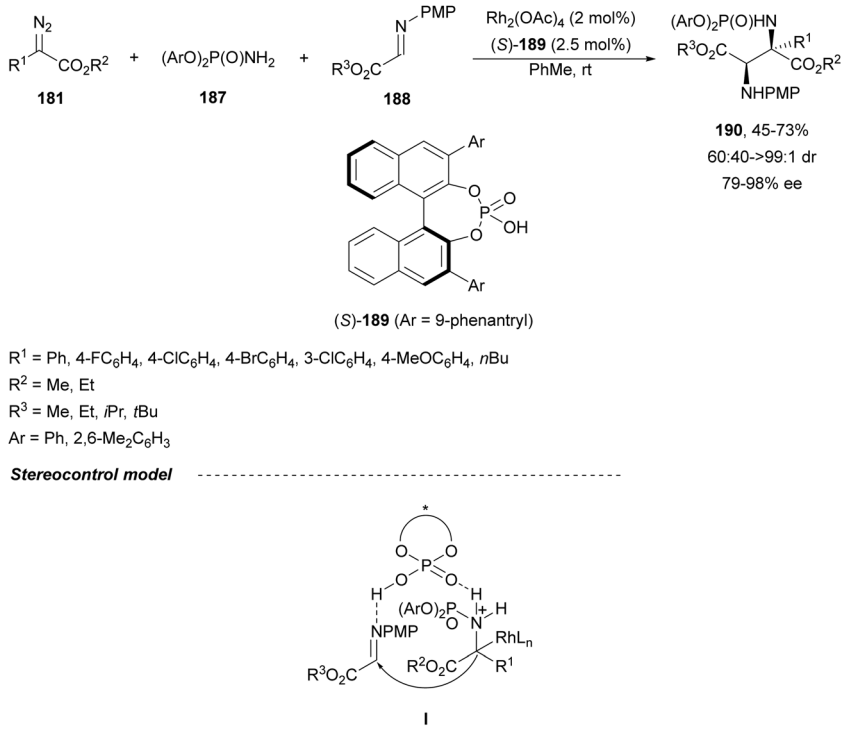
Wang and co-workers[147] employed a chiral *Cinchona*-derived base **231** for the aza-Mannich reaction of azlactones **224** with *N*-tosyl imines **161** to furnish *syn*-products **225** with 49–94% yields, 3 : 1–>30 : 1 dr and 80–97% ee (Fig. 9). A chiral bis(betaine) **232** catalyst was employed by Gong and co-workers[148] for the asymmetric aza-Mannich reaction of azlactones **224** with aliphatic *N*-tosyl imines **161** to obtain *anti*-products **225** with 76–99% yields, 2.1 : 7.1 dr and 96–99% ee (Fig. 9). The chiral CPA (*S*)-TRIP (**152**) was employed by Amarante and co-workers[149] for the addition of azlactones **224** to *N*-sulfonyl imines **161** to afford *anti*-products **225** up to 74% yield, >19 : 1 dr and 98% ee. Šebesta and co-workers[150] reported the use of a chiral thiourea **233** as a catalyst for



Scheme 60 Asymmetric three-component aza-Mannich reaction of diazo compounds **181** with carbamates and *N*-acyl aldimines **182** under $Rh_2(OAc)_4$/CPA (*R*)-**183** and (*R*)-**184** catalysis.



Scheme 61 Asymmetric three-component aza-Mannich reaction of *tert*-butyl diazoacetate **181** with arylamines and *N*-aryl aldimines **182** under $Rh_2(OAc)_4$/(*R*)-TRIP (**152**) catalysis.



Scheme 62 Asymmetric three-component aza-Mannich reaction of diazo compounds **181** with phosphoramides **187** and α-imino esters **188** under Rh/CPA (*S*)-**189** catalysis.

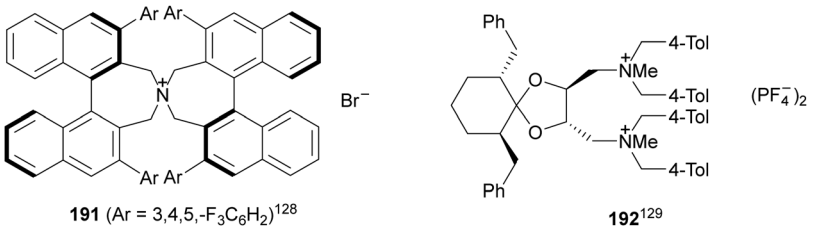
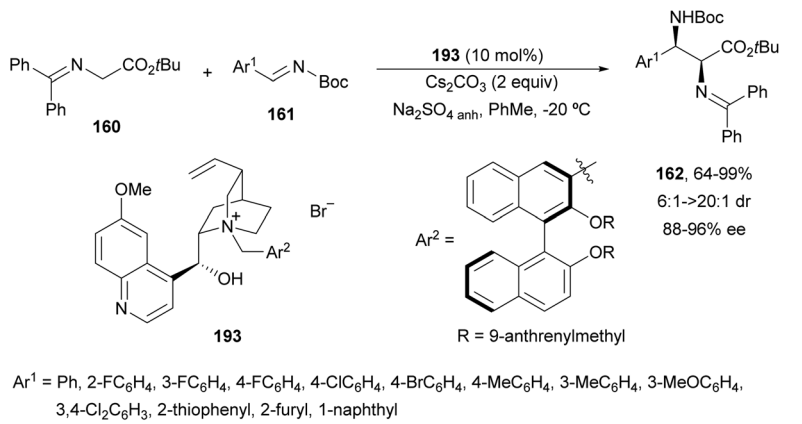
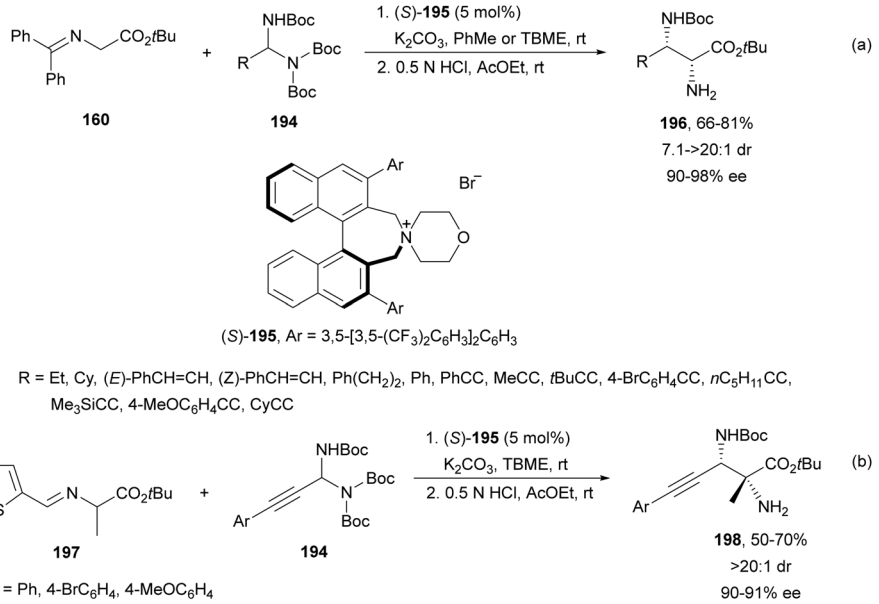


Fig. 7 Chiral phase-transfer catalysts for the aza-Mannich reaction of imino glycinates with imines.

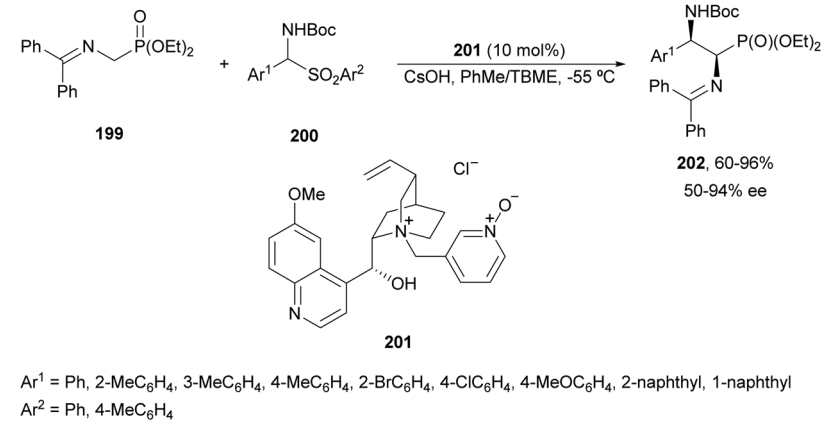


Scheme 63 Asymmetric aza-Mannich reaction of imino esters **160** with *N*-Boc imines **161** using a phase-transfer catalyst **193**.

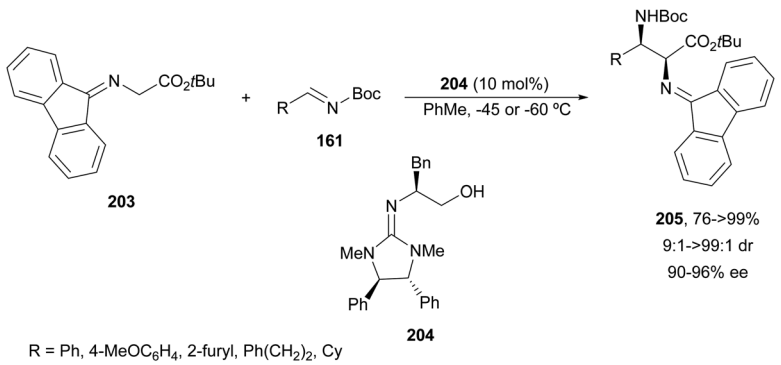
the addition of azlactones **224** to *N*-sulfonyl imines **161** to obtain *syn*-products **225** up to 82% yield, 12 : 1 dr and 95% ee (Fig. 9). In 2011, Toste and co-workers[151] reported the same aza-Mannich catalyzed by a chiral bisphosphine/$(AuOBz)_2$ complex **234**, which activates the azlactones **224** to give *anti*-products **225** with 50–98% yield, 6 : 1–> 20 : 1 dr and 83–94% ee (Fig. 9). The combination of a



Scheme 64 Asymmetric aza-Mannich reaction of imino esters **160** or **197** with *N*-Boc-aminals **194** using phase-transfer catalyst (*S*)-**195**.



Scheme 65 Asymmetric aza-Mannich reaction of phosphoglycine Shiff base **199** with *in situ* generated *N*-Boc imines using a phase-transfer catalyst **201**.



Scheme 66 Asymmetric aza-Mannich reaction of fluorenone glycine imino ester **203** with *N*-Boc imines **161** under base **204** catalysis.

chiral phosphate anion derived from the CPA (*S*)-**183** and silver ion **235** is an excellent ion pair catalyst for this type of aza-Mannich reaction to provide *syn*-products **225** up to 95% yield, 25 : 1 dr and 99% ee (Fig. 9).[152]

In the above mentioned examples, α,β-diamino acid precursors bear a quaternary stereocenter at the α-position. More recently, Ren and co-workers[153] reported the synthesis of α,β-diamino acid derivatives containing two consecutive quaternary

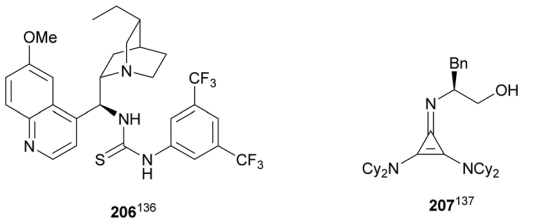


Fig. 8 Chiral bases used as organocatalysts for the aza-Mannich reaction of imino glycinates **160** with *N*-Boc imines.

stereocenters by the aza-Mannich reaction of azlactones **224** with isatin-derived ketimines **170** (Scheme 74). In this case, a chiral bifunctional squaramide **236** was used as an organocatalyst affording Mannich adducts **237** in 40–95% yields, up to >20 : 1 dr and up to 97% ee. Compound **237a** was transformed into the α,β-diamino acid derivative **238** by treatment with K_2CO_3 in MeOH.

In the case of asymmetric organocatalytic aza-Mannich reactions, azlactones are the appropriate nucleophiles for the synthesis of α,β-diamino acids with a quaternary stereocenter at the α-position in the case of aldimines and two quaternary stereocenters in the case of ketimines.

3.1.4. Isocyano acetates. Isocyano acetates **239** have been used as nucleophiles with *N*-protected imines to obtain 2-imidazolines, by an aza-Mannich/cyclization process, which can be hydrolyzed to α,β-diamino acids. The asymmetric version of this reaction has been performed under metal or organocatalytic conditions.[103,104]

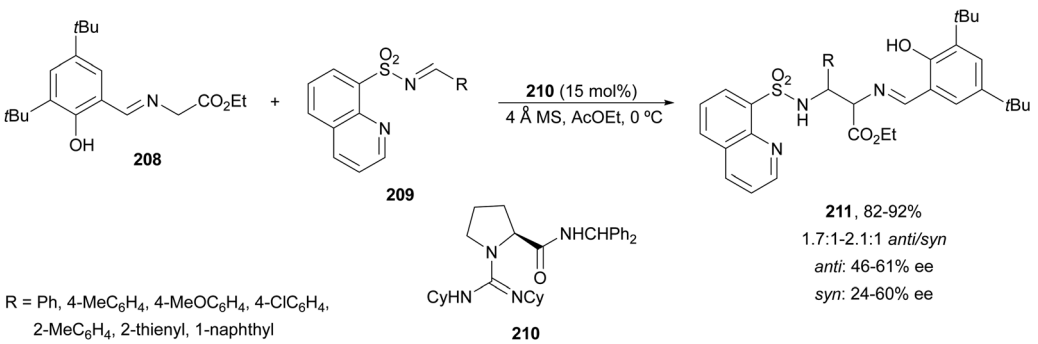
Lin and co-workers[154–156] reported for the first time the aza-Mannich type reaction of ethyl isocyano acetate **239** with *N*-tosyl imines **161** in the presence of Au(I)/diphosphine **240** to provide diastereoselectively *cis*-2-imidazolines **241** in moderated yields and up to 99% ee (Scheme 75). These imidazolines were transformed into *anti*-α,β-diamino esters **242** by treatment with concentrated HCl in EtOH with 22–56% yields after the two step process.

The same transformation was carried out by Szabó and co-workers[157] using chiral palladium-pincer complexes based on binol or biphenantrol to obtain 2-imidazolines **241** (R = Ph) as a mixture of *cis* and *trans* diastereomers (up to 1 : 4) with high yields (98%) and modest enantioselectivities.

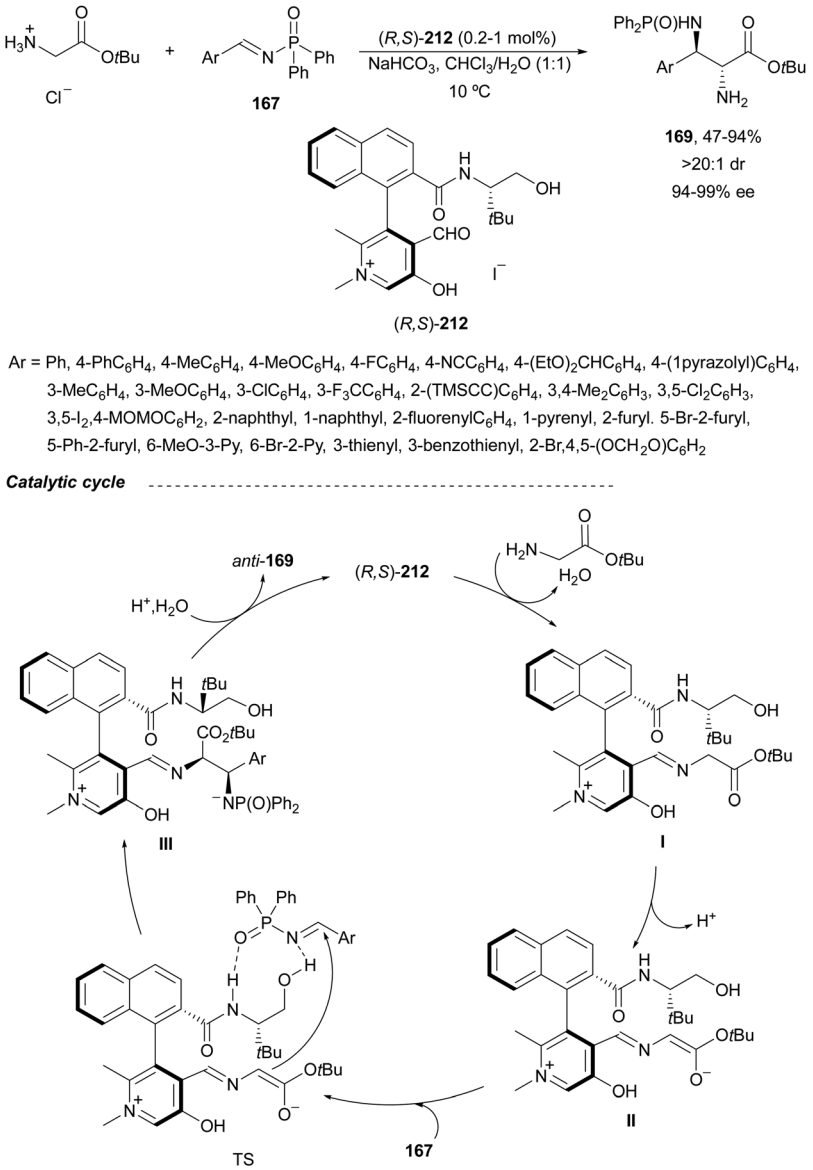
Shi and co-workers[158] employed a *Cinchona* alkaloid squaramide **244** in combination with AgOAc for the reaction of α-substituted isocyano acetates **239** with cyclic trifluoromethyl ketimines **243** to obtain tetrahydroimidazo[1,5-*c*]quinazoline derivatives **245** in excellent yields and good to excellent diastereo- and enantioselectivities (Scheme 76). In the proposed TS model, the α-proton of isocyano acetate **239a** (R^1 = Ph, R^2 = Me) is deprotonated by the quinuclidine unit of catalyst **244** due to the activation of silver by chelation of the terminal carbon atom of isocyano acetate. This organocatalyst **244** forms a hydrogen bonding of the MeO group of the enolate of **239** and then NH of the squaramide forcing the isocyanate to be delivered through the *Re* face to its *Si* face of C=N. Subsequent 5-*endo*–*dig* cyclization of intermediate **I** affords the cyclic product **245a**.

Oxazole-imidazolines **248** have been prepared by Zhao and co-workers[159] using cyclic α-imino esters **246** and 2 equivalents of isocyano acetates **239** (Scheme 77). In this case, Ag_2O and the quinine derived phosphine **247** were used as catalysts to furnish products **248** in high yields, total diastereoselectivity and up to 99% ee. Hydrolysis of product **248a** with TsOH in $CHCl_3/H_2O$ (2 : 1) at room temperature formed the α,β-diamino ester **249** in 90% yield and the same ee.

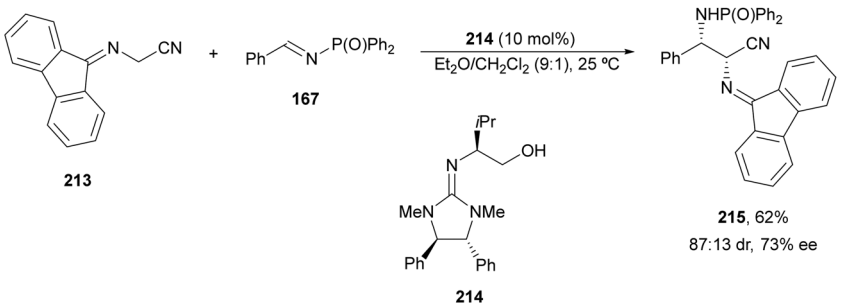
Dixon and co-workers[160] reported the aza-Mannich/cyclization of isocyano acetates **239** and *N*-diphenylphosphinoyl (DPP) ketimines **250** using Ag_2O and the chinchonine-derived aminophosphine **251** as a catalyst (Scheme 78). *trans*-2-Imidazolines **252** (R^1 = H) were obtained with high yields, up to 99 : 1 dr and up to 99% ee. The removal of the DPP group was performed with 1 M HCl in DCM at room temperature to provide 2-imidazolines **253** in 59–95% yields. In one example, **253a** was chosen to hydrolyze under aqueous KOH to α,β-diamino acid **254** in 45% yield without deterioration of enantiopurity. Later, the same group studied the same process with α-substituted isocyano acetates **239**.[161] Tetrasubstituted 2-imidazolines **252** ($R^1 \neq$ H) were prepared using AgOAc and the quinine-derived aminophosphine **255** as a catalyst (Scheme 78), which were isolated as unprotected derivatives *trans*-**253** in 28–90% yields and 87–95% ee by treatment of compounds **253** with 1 M HCl in DCM at room temperature. In the proposed TS based on experimental studies, the N atom of the ketimine forms a hydrogen bonding with the N–H of the amide, both of which



Scheme 67 Asymmetric aza-Mannich reaction of glycine imino ester **208** with aldimines **209** under guanidine **210** catalysis.



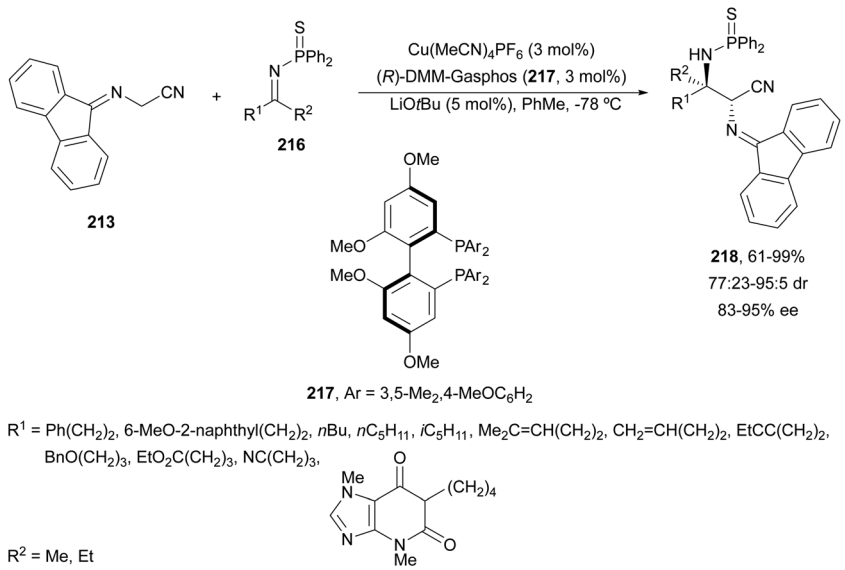
Scheme 68 Asymmetric aza-Mannich reaction of *tert*-butyl glycinate hydrochloride with imines **167** under carbonyl catalysis.



Scheme 69 Asymmetric aza-Mannich reaction of imino nitrile **213** with imines **167** under base **214** catalysis.

orientate the electrophile **250** towards the nucleophilic addition of the enolate of the isocyano acetate bonded to the Ag atom. The ester group of **239** is oriented away from the aromatic ring of the ketimine **250.**

Nakamura's group reported independently similar aza-Mannich/cyclization processes of unsubstituted[162] and α-substituted[163] isocyano acetates **239** with *N*-DPP ketimines **250.** In the first case,[162] they employed $Cu(OTf)_2$ and picolinamide ligand



Scheme 70 Asymmetric aza-Mannich reaction of imino nitrile **213** with ketimines **216** under Cu/**217** catalysis.

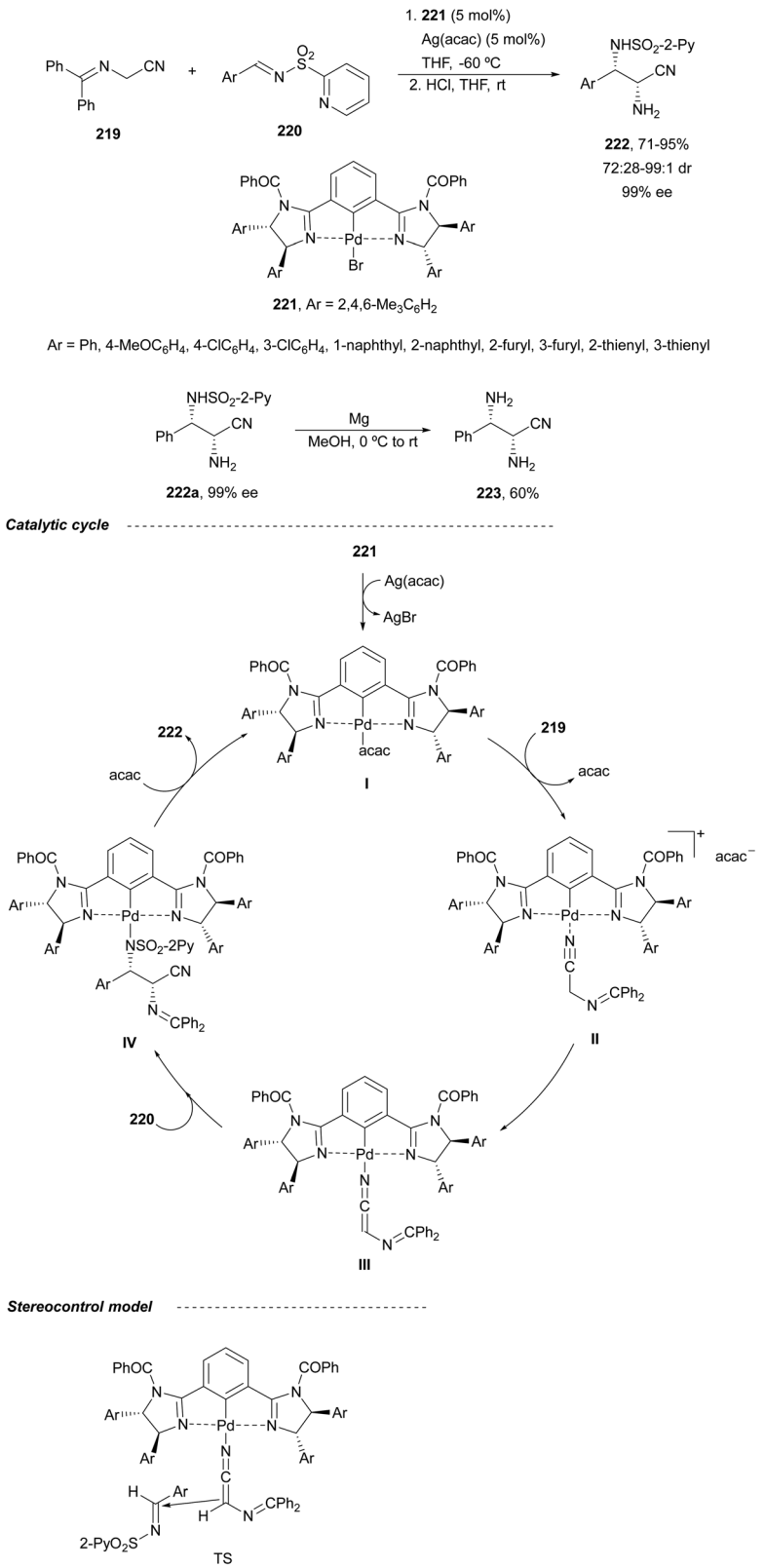
256, derived from cinchonine, as a catalyst in the presence of Cs_2CO_3 as a base (Scheme 79). Products *cis*-**252** were not isolated due to thermal instability, instead, the corresponding tosyl imidazolines **257** resulted by a two-step process based on hydrolysis with 4 M HCl in dioxane followed by tosylation with TsCl/Et_3N, up to 92 : 8 dr and 99% ee. Compound **257a** was further transformed into the α,β-diamino acid methyl ester derivative **258** quantitatively and in 99% ee. Starting from α-substituted isocyano acetates,[163] the same process was carried out with $NiCl_2$ as Lewis acid and 9-amino-9-*epi*-cinchonidine **259** as catalysts (Scheme 79). In this case, *N*-DPP imidazolines *trans*-**252** were isolated in high yields and diastereo- and enantioselectivities. Removal of the DPP group was also carried out with 4 M HCl in dioxane for compound **252b** (R^1 = R^2 =Me, R^3 = *p*-tol) to obtain product **253b** in 79% yield. Both catalytic cycles with $Cu(OTf)_2$[162] and $NiCl_2$[163] were proposed. In Scheme 79 is depicted the last case for the synthesis of tetrasubstituted imidazolines *trans*-**252**.[163] The reaction of isocyano acetate **239** with catalyst **259** and $NiCl_2$ in the presence of Cs_2CO_3 as a base forms intermediate **I**. Subsequent coordination of **I** with ketimine **250** (R^4 = Me) forms intermediate **II**, which undergoes aza-Mannich reaction to give intermediate **III**. Cyclization of **III** promotes imidazolidine formation giving intermediate **IV**, which regenerates **I** and affords product **252**. In the TS for the Mannich reaction, the oxygen of ketimine **250**, two nitrogen atoms from the picolinoyl moiety in **259** and the isocyano group coordinate to the nickel atom in a distorted tetrahedral form. In addition, the quinuclidine moiety makes hydrogen bonding with the ketene hemiacetal of α-isocyano acetate, which attacks the ketimine approaching by the *Si* face in both cases avoiding steric repulsion between the two methyl groups.

The former aza-Mannich/cyclization process has been applied by Zhao, Shi and co-workers[164] to cyclic sulfamide ketimines **260** to obtain imidazoline-fused sulfahydantoin derivatives **262** (Scheme 80). Isocyano acetates **239** reacted with 4-aryl-3-carbonyl-1,2,5-thiadiazole-1,1-dioxide type ketimines **260** under cooperatively catalysis by squaramide **261** and AgOAc as Lewis acid to provide compounds **262** in excellent yields and good to excellent stereoselectivities. A plausible TS was proposed to explain the observed stereochemical results. Enolization of isocyano acetate by the quinuclidine nitrogen of catalyst **261** due to activation of Ag chelating to the isocyano group resulted in a hydrogen bonding between the OH group and the tertiary amine. In addition, the squaramide unit directed the ketimine **260** and isocyano acetate **239** through a hydrogen bonding interaction between the NH and the sulfonyl groups, ketimine nitrogen atoms or methoxy groups. These orientation forces the approach of **239** by the *Si* face to the *Re* face of the C=N giving for **262** the two stereocenters with a (*R*,*S*)-configuration.

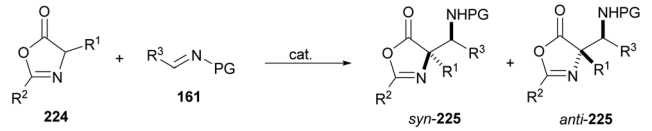
Organocatalyzed aza-Mannich/cyclization processes have been carried out with *Cinchona*-based tertiary amines as catalysts. Chan and co-workers[165] employed *O*-acetyl quinidine **263** (10 mol%) (Fig. 10) for the reaction of methyl isocyano acetate **239** with *N*-tosyl imines **161** to furnish mainly *trans*-2-imidazolines **241** in 35–79% yields, 91 : 9–>99 : 1 *trans*/*cis* dr and 5–70% ee. Nakamura, Shibata and co-workers[166] employed chiral thiourea **264** (10 mol%) as an organocatalyst for the aza-Mannich/cyclization of α-substituted isocyano acetates **239** with 2-pyridylsulfonyl imines **220** (Fig. 10). The resulting trisubstituted (4*R*,5*S*)-*trans*-2-imidazolines were obtained in 71–99% yields, 73 : 27–99 : 1 dr and 74–96% ee.

Chiral thiourea **265** derived from quinidine has been used as an organocatalyst for the aza-Mannich reaction of α-substituted isocyano acetates **239** with isatin-derived ketimines **170** to obtain products **266** up to 93% yield, >20 : 1 dr and up to 98% ee (Scheme 81). These products **266** were transformed into spirooxindole imidazolines **268** in the presence of thiourea **267** as an organocatalyst.[167]

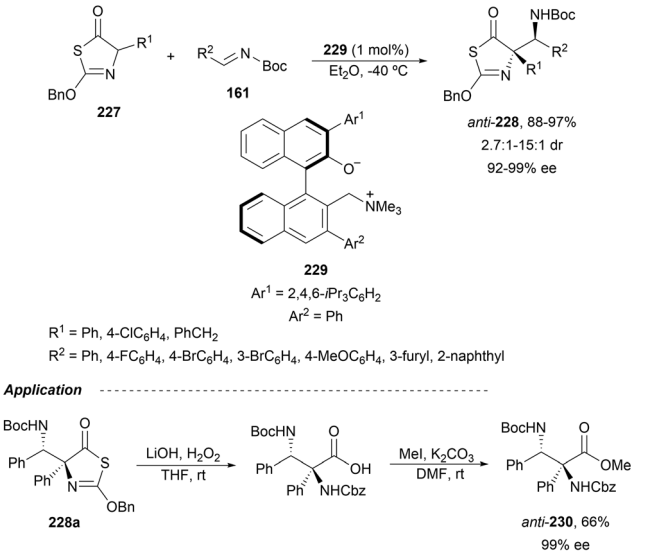
Recently, Zhao and co-workers[168] reported the aza-Mannich/cyclization of α-substituted isocyano acetates **239** with *N*-(2-benzothiazolyl)



Scheme 71 Asymmetric aza-Mannich reaction of imino nitrile **219** with aldimines **220** under Pd complex **221**/Ag(acac) catalysis.



Scheme 72 Aza-Mannich reaction of azlactones **224** with *N*-protected imines **161**.



Scheme 73 Asymmetric aza-Mannich reaction of thiazolones **227** with *N*-Boc imines **161** under betaine **229** catalysis.

imines **269** to obtain benzothiazole-dihydroimidazoles **270** with good to excellent yields, modest dr and excellent ee's (Scheme 82). In this case, the squaramide organocatalyst **261** was used as in the case of cyclic sulfamide ketimines **260**.[164] Product **270a** was treated with $NaBH_3CN$ and AcOH in methanol to obtain benzothiazole-imidazolidine **271** as the only diastereomer which has been hydrolyzed using concentrated sulfuric acid to the corresponding *N*-(2-benzothiazolyl)-α,β-diamino acid **272** in 75% yield and >99% ee.

Isocyano acetates react with aldimines and ketimines under metal (Ag, Cu, and Ni) salts and a *Cinchona*-derived base or under phosphine catalysis to give 2-imidazolines through a aza-Mannich/cyclization process. Organocatalysts derived from *Cinchona* alkaloids have also been employed for these types of aza-Mannich reactions. These imidazolines are transformed by hydrolysis mainly into *anti*-α,β-diamino acid derivatives.

3.1.5. Isothiocyanates. Carboxylic acid derivatives bearing an isocyanato group at the α-position have been used as glycine equivalent in the aza-Mannich reaction with imines.[103,104] The enantioselective addition has been performed under metal catalysis and also with organocatalysts.

In 2007, Willis and co-workers[169] reported the enantioselective addition of the isothiocyanate-substituted oxazolidinone **273** to *N*-tosyl aldimines **161** in the presence of $Mg(ClO_4)_2$ and ligand Ph-Dbfox **274** using the Hünig base DIPEA (Scheme 83). *cis*-Cyclic thioureas **275**, precursors of *anti*-α,β-diamino acid derivatives, resulted from *in situ* cyclization of the acyclic *anti*-adducts in high yields, moderate to high diastereoselectivity and high enantioselectivity. Compound **275a** was transformed into its *i*Pr ester **276** by reaction with MeMgBr in THF/*i*PrOH, which by treatment with DBU could be epimerized to the *syn*-Mannich adduct **277**.

Based on the aldol reaction of α-methyl-α-isothiocyanato ester **278**,[170] Matsunaga, Shibasaki and co-workers[171] described the Mannich reaction of this isothiocyanate **278** with *N*-DPP ketimines **250** under nBu_2Mg/Schiff base **279** catalysis

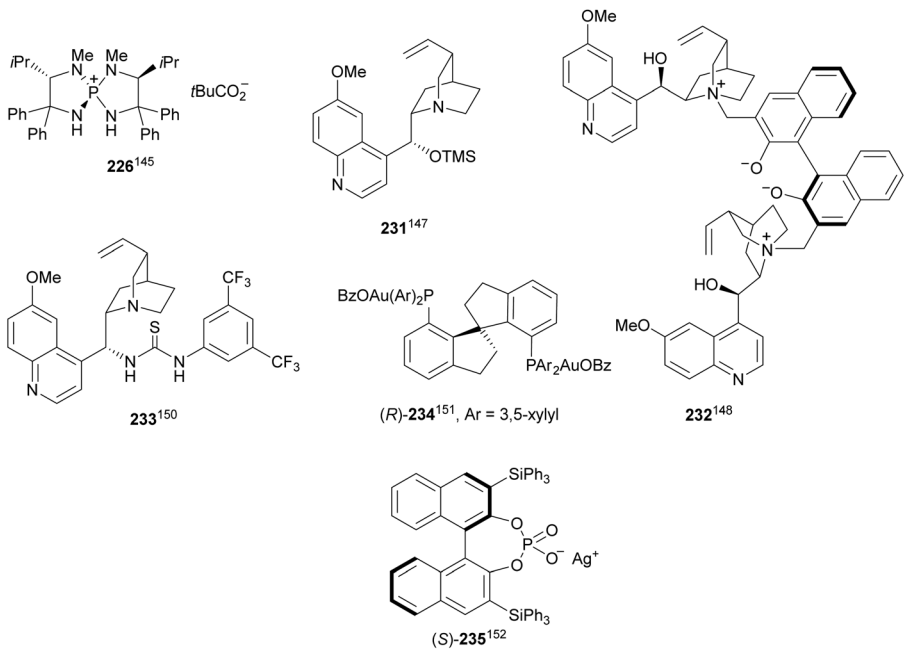
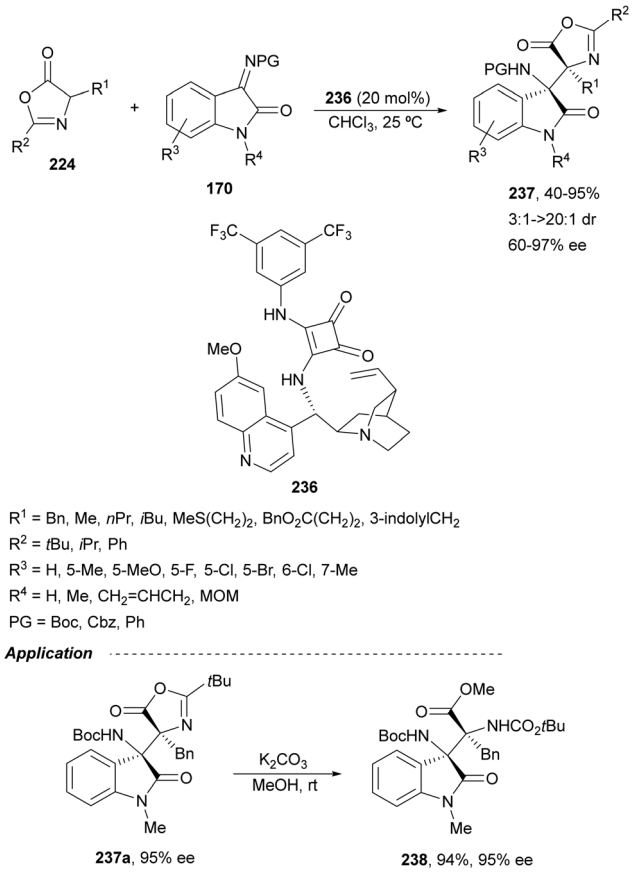


Fig. 9 Chiral catallysts used for the asymmetric aza-Mannich reaction of azlactones **224** with *N*-arylsulfonyl imines **161**.



Scheme 74 Asymmetric aza-Mannich reaction of azlactones **224** with isatin-derived ketimines **170** under squaramide **236** catalysis.

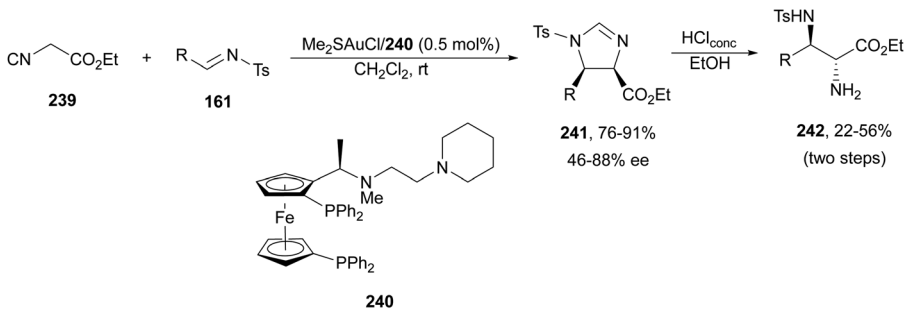
(Scheme 84). Cyclic thioureas *cis*-**280** were mainly obtained in good to high yields, dr and good enantioselectivities. However, *trans*-**280** were mainly obtained when Sr(O*i*Pr)$_2$ was used as the metal source. Circular dichroism (CD) spectra of *n*Bu$_2$Mg/**279** and Sr(O*i*Pr)$_2$/**279** complexes were different suggesting that chiroptically different aggregates were formed. Moreover, the different dihedral angle of the binaphthyl unit in both complexes can play a key role in the sterodiscriminating step and would cause these diastereodivergent[52] results.

The same group[172] performed the asymmetric synthesis of spirooxindoles **283** by an aza-Mannich reaction of isothiocyanato-oxindoles **281** with *N*-DPP aldimines **167** under Sr(O*i*Pr)$_2$/ligand **282** catalysis (Scheme 85). In this case, the use of *n*Bu$_2$Mg, Ca(O*i*Pr)$_2$, Ba(O*i*Pr)$_2$, Al(O*i*Pr)$_3$ or Ni(OAc)$_2$ gave very poor enantioselectivities. Products **283** were isolated in excellent yields and stereoselectivities and compound **283a** was transformed into a spiro[imidazoline-4,3′-oxindole] core. Benzoylation of **283a** to give **284** followed by Pd-catalyzed desulfurative cross-coupling with phenylboronic acid, developed by Liebeskind and co-workers,[173] afforded product **285**, which is related to nutlin,[174] an imidazoline-based inhibitor of p53/E3-ubiquitin ligase Mdm2 interaction, and to MI-219,[175] a spiro[pyrrolidine-3,3′-oxindole]-based p53/Mdm2 inhibitor.

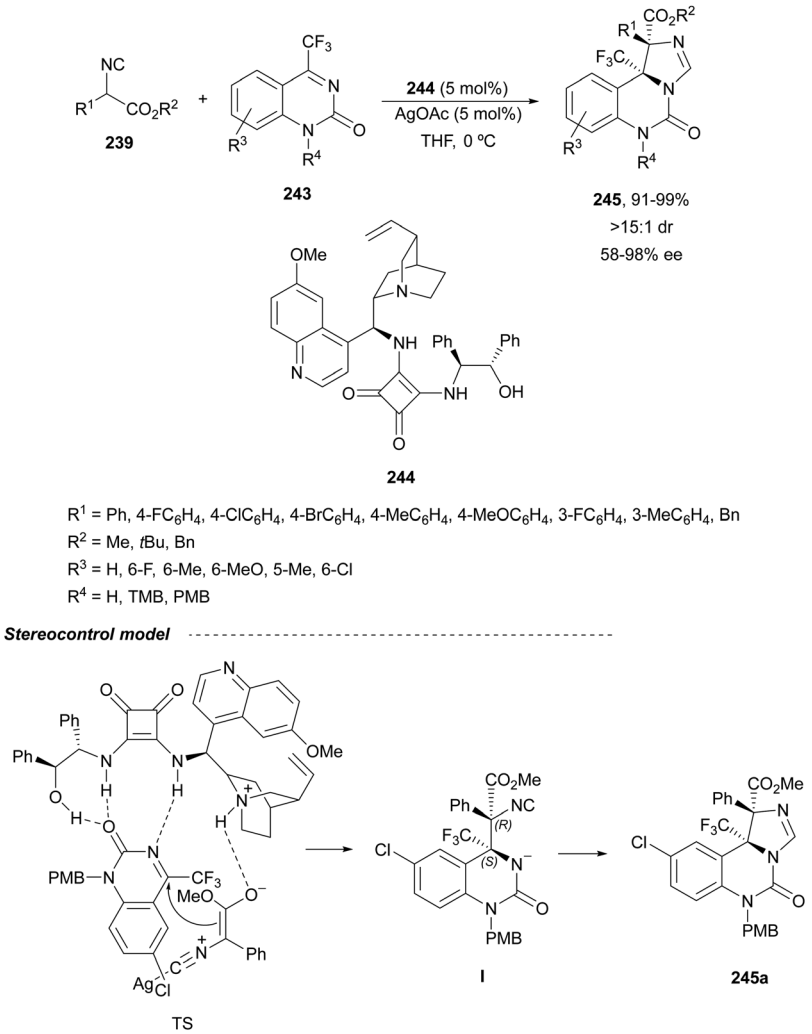
Seidel and co-workers[176] described for the first time the addition of isothiocyanate **273** to *N*-sulfonyl imines **161** using the quinidine derivative **263** (1 mol%) as a chiral organocatalyst in toluene at room temperature to furnish products *trans*-**275** in 53–99% yields, 72 : 28–>95 : 5 dr and 89–99% ee (Scheme 86a). The same process was simultaneously described by Zhong and co-workers[177] using a quinine-derived organocatalyst **286**. In this case, after the reaction was completed the solvent (*m*-xylene) was removed and MeMgBr in THF was added as well as EtOH at 0 °C to obtain *trans*-thiooxazolidines **287** in high yields, up to 97 : 3 dr and >99% ee (Scheme 86b).

Chiral bisguanidine **288** (5–10 mol%) has been employed by Liu, Feng and co-workers[178] for the aza-Mannich reaction of isothiocyanato-oxazolidinone **273** and *N*-tosyl imines **161** to obtain *trans*-**275** working in the presence of 4-MeC$_6$H$_4$CO$_2$H (7.5 mol%) as an additive in THF/DCM at −12 °C (Fig. 11). Products *trans*-**275** were isolated in 82–99% yields, 80 : 20–>95 : 5 dr and 90–>99% ee. The authors proposed a TS in which the catalyst is protonated by the acid to obtain a guanidinium salt. This salt activates the *N*-Ts imine *via* hydrogen bonding. The other guanidine unit deprotonates the isothiocyanato-imidazolidine **273**, which attacks the *Si*-face of **161** to form the major (4*S*,5*R*)-**275** product (Fig. 11).

Independently, Liu[179] and Yuan[180] groups have described the reaction of isocyanato-oxindoles **281** with *N*-tosyl imines **161** to obtain the corresponding spirooxindoles **290**. In the first case, thiourea **289** (Takemoto organocatalyst[181]) was used as a chiral organocatalyst and with or without 4-NCC$_6$H$_4$CO$_2$H as an additive



Scheme 75 Asymmetric aza-Mannich-cyclization reaction of methyl isocyano acetate **239** with *N*-tosyl imines **161** under Au(I)/diphosphine **240** catalysis.



Scheme 76 Asymmetric aza-Mannich/cyclization of α-substituted isocyano acetates **239** with cyclic trifluoromethyl ketimines **243** under AgOAc/squaramide **244** catalysis.

in acetone at −20 °C to room temperature (Scheme 87a). Products **290** were obtained in good yields and excellent enantioselectivities. In the second case, just quinine was used as an organocatalyst (1 mol%) in toluene at 0 °C to provide products *ent*-**290** in moderate to high yields and stereoselectivities (Scheme 87b).

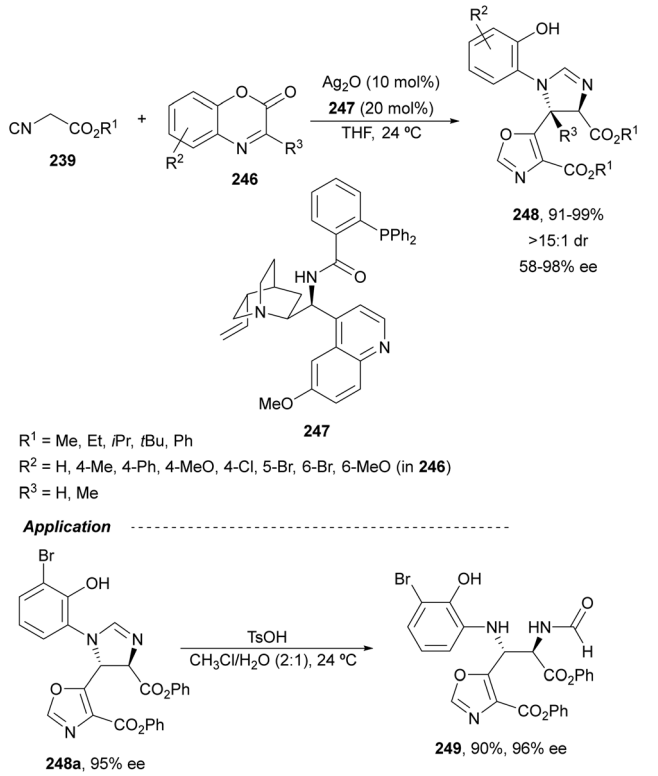
Isothiocyanate derivatives have been mainly used as glycine or other amino acid equivalents for the synthesis of enantioenriched *cis*- or *trans*-imidazolidinthiones, precursors of α,β-diamino acids, under Mg or Sr catalysis or under organocatalysis with chiral bases, guanidines and thioureas.

3.1.6. Other nucleophiles. α-Azido ketones and amides have been used in aza-Mannich reactions under organocatalysis or copper catalysis. Barbas III and co-workers[182] reported a three-component aza-Mannich reaction of α-azido ketones **291** with aldehydes and 4-methoxyaniline in the presence of L-proline-derived tetrazole **292** as an organocatalyst (Scheme 88). 1,2-Azidoamines **293** were obtained with good yields, *syn*-diastereoselectivity and up to 99% ee. Product **293a** was transformed into the α,β-diamino acid derivative **294** using Pd/C in the presence of Boc_2O under a H_2 atmosphere.[183] A plausible TS was proposed in which the (*E*)-enamine gives the *syn*-product.

Cyclic α-azido ketones **295** was reacted with *N*-Boc imines **161** to obtain aza-Mannich adducts **297** possessing a α-quaternary stereocenter with modest to high yields, diastereoselectivities and enantioselectivities (Scheme 89).[184] In this case, the H8-CPA (*S*)-**296** was used as an organocatalyst in DCM at 40 °C. Hydrogenation of **297a** gave 1,2-diamine **298** in 63% yield without reduction of ee.

α-Azido amides **299** of 7-azaindoline have been used as nucleophiles by Kumagai, Shibasaki and co-workers[185] in the asymmetric aza-Mannich reaction with *N*-thiophosphinoyl imines **300** catalyzed by Cu(I)/(*R*)-xyl-Segphos **301** and Barton's base **302** (Scheme 90). *anti*-Products **303** were isolated and β-azido-α-amino acid hydrochlorides **304** were obtained by treatment with 6 M HCl at 80 °C with good yields, high diastereoselectivities and enantioselectivities.

Maruoka and co-workers[186] employed *N*-protected α-amino acetaldehydes **305** in the aza-Mannich reaction with *N*-Boc



Scheme 77 Asymmetric aza-Mannich/cyclization of isocyano acetates **239** with cyclic imino esters **246** under Ag/phosphine **247** catalysis.

imines **161** (Scheme 91). A diastereodivergent[52] process was achieved using either L-proline or the axially chiral amino sulfonamide (*S*)-**306** to obtain, after $NaBH_4$ reduction, products **307**. In the first case, *syn*-adducts were mainly obtained according to a (*E*)-*s*-*trans*-enamine TS1, whereas (*E*)-*s*-*cis*-enamine TS2 is mainly involved in the formation of *anti*-adducts. The former process was applied to the formal synthesis of the marine alkaloid (−)-agelastatin A, which possesses a potent antitumor activity. Mannich product **308a** was transformed into the key intermediate **309**.[187]

Subba Reddy and co-workers[188] have employed 3-indolinone-2-carboxylates **310** as nucleophiles in the asymmetric aza-Mannich reaction using thiourea **311** as an organocatalyst (Scheme 92). Chiral β-amino esters **312** were obtained in good yields with ee up to 99% by reaction of compounds **310** with *in situ* generated *N*-Boc imines from α-amido sulfones **200**. A plausible TS was proposed to explain the mechanism of this organocatalytic process, which involves the formation of hydrogen bonding between the enol of **310** and the tertiary amine. Subsequently, the *N*-Boc imine is activated by hydrogen bonding with the thiourea unit to form a ternary complex. A preferential *Re*-face attack of the enolate from **310** onto *N*-Boc imine would give product **312**.

Recently, an aza-Mannich reaction between *N*-aryl glycines **313** and hydrazones **314** has been carried out by Cu/bisoxazoline **315** and visible light-induced photoredox catalysis.[189] The decarboxylative radical coupling/cyclization reaction of glycine derivatives **313**, hydrazones **314** and aldehydes gave chiral imidazolidines **318** with high yields and enantioselectivities (Scheme 93). In the absence of paraformaldehyde, diamines **317** could be isolated in good yields and enantioselectivities. Based on electron paramagnetic resonance investigations, a possible reaction mechanism was proposed. The SET between the excited photocatalyst 4CzIPN* (**316***) and *N*-phenylglycine **313** leads to the formation of the radical cation **III**, which after decarboxylation resulted the radical cation **IV**. Intermediate **I** was reduced to intermediate **II** through a SET pathway and the photocatalyst **316** is generated. Radicals **II** and **IV** undergo a radical coupling reaction to provide complex **V**, which after protonation and ligand exchange generates product **317**. Final cyclization of **317** with paraformaldehyde furnishes imidazolidines **318**.

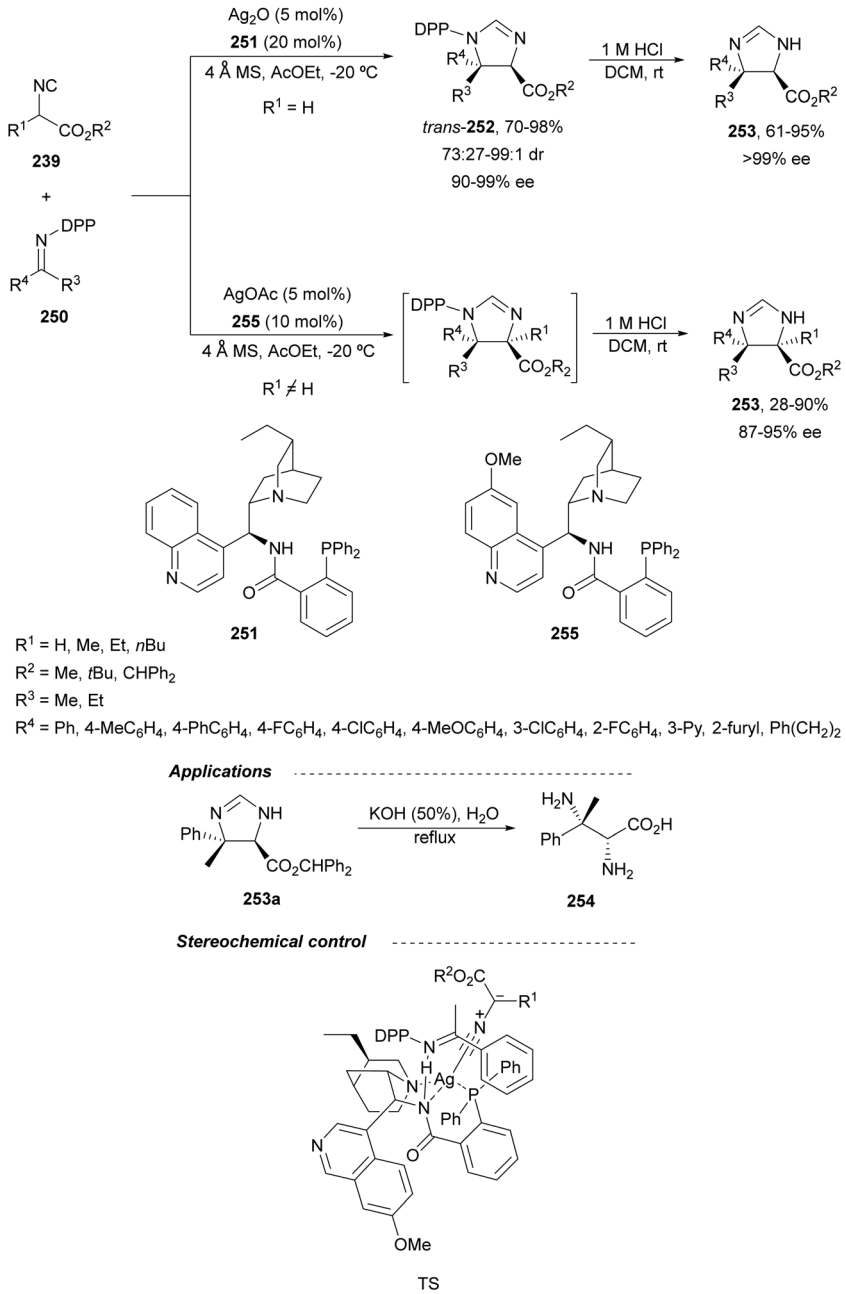
Different nucleophiles such as α-azido ketones and amides, α-amino acetaldehydes, and 3-indoline-2-carboxylates have been used in the asymmetric aza-Mannich reaction mainly under organocatalysis. Recently, a Cu/Box complex and a photocatalyst have been used to co-catalyze the aza-Mannich reaction of *N*-aryl glycines and hydrazones to obtain 1,2-diamine derivatives.

3.2. Aza-Henry reaction

The aza-Henry reaction, alternatively the nitro-Mannich reaction, involves the nucleophilic addition of nitroalkanes to imines to provide β-nitroamines, which can be easily reduced to 1,2-diamines. Several revisions have been published based on stereoselective transformations for the synthesis of natural products and biologically active compounds.[190,191] Asymmetric reactions are based on the use of chiral metal complexes and mainly with organocatalysts.[103,104,192,193] In this section, the most significant recent catalytic methods will be considered.

3.2.1. Metal catalysis. Since the initial report of Shibasaki and co-workers[194] using heterobimetallic metal–binolate complexes and Jørgensen and co-workers[195] with $Cu(OTf)_2$/bisoxazoline complexes, several Cu, Zn, La and Ni complexes have been employed as catalysts.[193] More recent examples have been described by Meggers and co-workers[196] based on the use of chiral-at-metal Ir(III) complexes. Octahedral Ir complex **319a** based on a 3-aminopyrazolate, which served as a chiral Brønsted base, catalyzed the asymmetric aza-Henry reaction of nitroalkanes with *N*-Boc imines **161** to give *anti*-β-nitroamines **320** in high yields and diastereo- and enantioselectivities (Scheme 94a). This process was applied by the same group[197] to the aza-Henry reaction of nitroalkanes with isatin-derived ketimines **170** using **319b** as a catalyst (Scheme 94b). Kinetically favored diastereomers (3*S*,8*S*)-**321** were epimerized using Et_3N as a base to the thermodynamically favored diastereomers (3*S*,8*R*)-**321**, which were isolated in high yields and diastereo- and enantioselectivities. In the proposed TS, a proton is transferred from the nitroalkane to the Brønsted base which allows the formation of two hydrogen bonds between the aminopyrazole unit and the nitronate. In addition, a three center hydrogen bond is established between the two carbonyl groups of the ketimine and the hydroxy group of the catalyst promoting the *Re*-face/*Si*-face attack of the nucleophile on the imine group.

Arai and co-workers[198] reported bis(imidazolidine)pyridine (PyBidine) **163** and $NiCl_2$ (5 mol%) catalyzed aza-Henry reaction of isatin *N*-Boc ketimines **170** with nitromethanes in the presence of

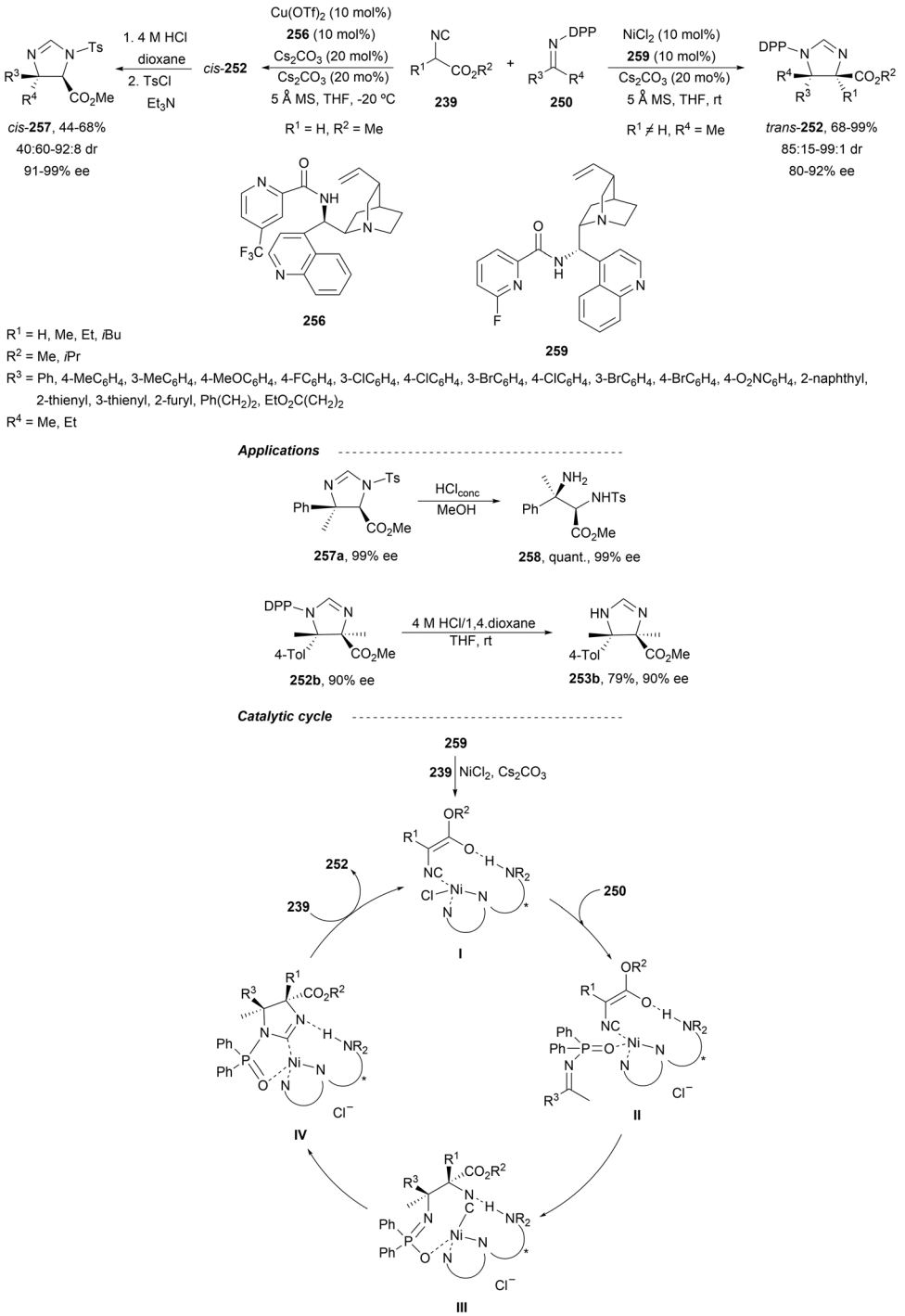


Scheme 78 Asymmetric aza-Mannich/cyclization of isocyano acetates **239** with *N*-diphenylphosphinoyl ketimines **250** under Ag/phosphines **251** and **255** catalysis.

10 mol% of DIPEA. The resulting 3-amino-2-oxindoles (3*R*)-**321** (R^1 = H) were obtained in toluene at 30 °C with 19–99% yields and 78–95% ee. For the reduction of the nitro group (3*R*)-**321,** (R^1 = R^2 = H, R^3 = Me) was treated with $NiCl_2{\cdot}6H_2O/NaBH_4$ in MeOH at 0 °C to give the corresponding diamine in 99% yield and 97% ee. Blay, Pedro and Holmquist[199] carried out the same aza-Henry reaction using 10 mol% of $Cu(BF_4)_2$ and the bisoxazoline (*S*,*S*)-**9**. Products (3*S*)-**321** (R^1 = H) from nitromethane were prepared in the presence of iPr_2NH (13 mol%) at room temperature in 82–99% yields and 6.6–99.9% ee.

Chiral dimeric ligand **322** derived from (*R*)-binol, salen and (1*R*,2*S*)-2-aminodiphenylethanol has been used by Kureshy and co-workers[200] in the Cu-catalyzed aza-Henry reaction of *N*-tosyl imines **161** with nitroalkanes (Scheme 95a). This process was performed in toluene at room temperature to give products **323** up to 82% yield and up to >99% ee, mainly as *anti*-diastereomers in the case of nitroethane up to 98 : 2 dr. The catalyst $Cu(OAc)_2$/**322** was recyclable 5 times in the reaction of **161** (R^2 = 2-$MeOC_6H_4$) with nitromethane without apparent loss in activity and enantioselectivity. This process was employed to the synthesis of (*S*)-levamisole, an anthelmintic agent at 1 g scale starting from **323a** (Scheme 95b).

The same group[201] reported a chiral binol linked monomeric macrocycle Cu(II)-salen complex as a catalyst (5 mol%) for

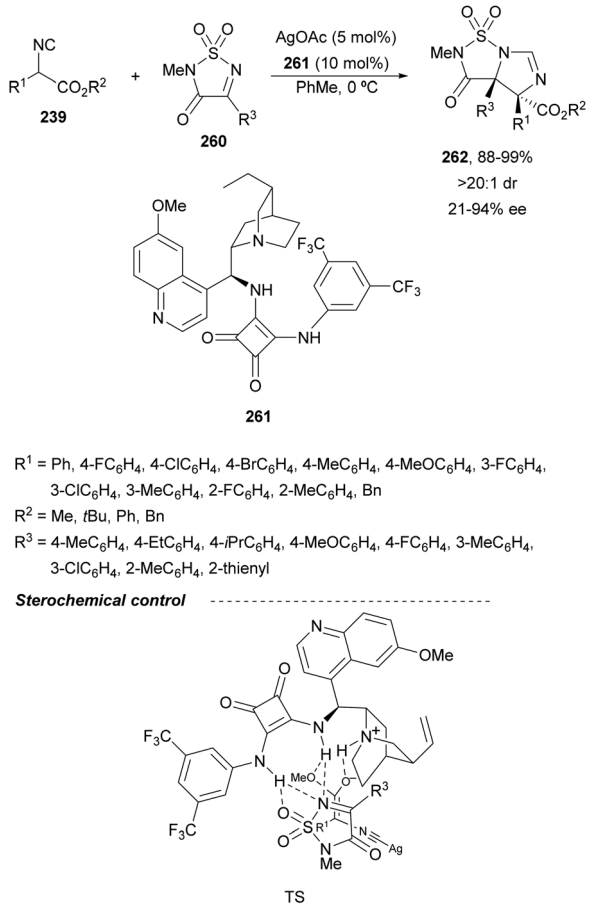


Scheme 79 Asymmetric aza-Mannich/cyclization of isocyano acetates **239** with *N*-DPP ketimines **250** under $Cu(OTf)_2$/cinchonine derivative **256** and $NiCl_2$/cinchonidine derivative **259** catalysis.

the asymmetric aza-Henry reaction of *N*-Boc ketimines derived from isatins **170** with nitromethane at room temperature. The corresponding adducts (3*S*)-**321** (R^1 = H) were obtained in 77–80% yields and 46–99% ee.

The first asymmetric aza-Henry reaction mediated by $Fe(OTf)_2$ and (*R*,*R*)-TPS-he-Pybox **324** has been reported by Dudek and Mlynarski[202] in 2017. Nitromethane reacted with *N*-diphenylphosphinoyl imines **167** using TEA (0.5 equivalents) as a base in THF at room temperature to give β-nitroamines **325** with good yields and high ee (Scheme 96). However, other secondary nitroalkanes afforded compounds **325** as 1 : 1 mixture of diastereomers.

Recently, Yasukawa, Nakamura and co-workers[203] reported the enantioselective reaction of cyclic imino esters **326** with nitroalkanes using *Cinchona* alkaloid derived sulfonamide **327**/zinc complex as a catalyst (Scheme 97). The reaction with



Scheme 80 Asymmetric aza-Mannich/cyclization of isocyano acetates **239** with cyclic sulfamide ketimines **260** under AgOAc/squaramide **261** catalysis.

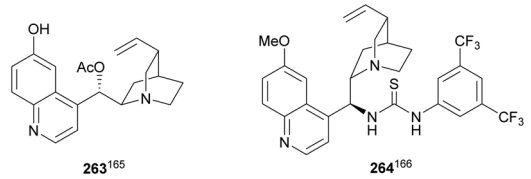


Fig. 10 Organocatalysts used for the asymmetric aza-Mannich/cyclization of isocyano acetates **241** with *N*-sulfonyl imines.

nitromethane was also carried out with 6-membered cyclic ketimine **326a** and with the benzene fused 5-membered ketimine ester **326b** to obtain the corresponding adducts **328a** and **328b** in 56% yield and 92% ee and in 42% yield and 83% ee, respectively. Products **328** derived from the five-membered ketimines **326** were obtained in 52–86% yields and 70–92% ee with moderate diastereoselectivity.

3.2.2. Organocatalysis. Different types of organocatalytic methods have been described for the asymmetric aza-Henry reaction, such as using chiral thioureas, phase transfer catalysts, Brønsted bases and Brønsted acids.[103,190–193] This methodology has been proven to be superior to metal catalysis.

In 2004, Takemoto and co-workers[204] reported for the first time a thiourea **289** as a bifunctional organocatalyst for the asymmetric aza-Henry reaction of *N*-DPP imines **169** with nitromethane to provide compounds **325** (R^1 = H) up to 91% yield and 78% ee. Chiral thioureas **289**[205] and **329**[206] have been developed for the addition of nitroalkanes to *N*-Boc imines **161** to obtain *anti*-**320** (Fig. 12). Thiourea **331** bearing 1,2-diamine (DPEN) as a chiral unit showed excellent results for the addition of activated α-nitro esters **330** to *N*-Boc imines **161** to furnish mainly (2*S*,3*S*)-α-nitro-β-amino esters **332** (Scheme 98).[207]

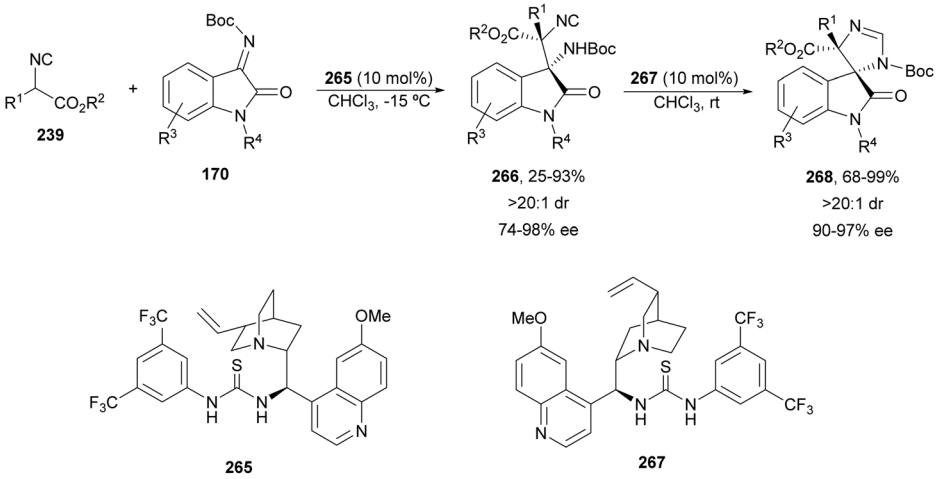
For the asymmetric aza-Henry reaction of *N*-Boc imines **161** with nitroalkanes, Zhao and co-workers[208] employed a combination of a new bifunctional phosphine-thiourea **333** and an acrylate able to generate *in situ* a zwitterion which acted as a catalyst. This reaction gave the corresponding adducts *anti*-**320** with high yields and diastereo- and enantioselectivities (Scheme 99). According to ^{31}P NMR and mass analysis of **333** and methyl acrylate, the zwitterion intermediate **A** was detected, which forms an ion-pair with the nitronate. A possible TS has been proposed to explain the observed stereoselectivity.

Quinine-derived thiourea **335**[209] has been employed by Wang and co-workers[210] as an organocatalyst for the enantioselective addition of nitroalkanes to cyclic trifluoromethyl ketimines **243** up to 97% yield and up to 98% ee. This method was applied to the synthesis of anti-HIV drug DCP 083 employing 2(1*H*)-quinazolinone **243a** and 1-nitro-2-cyclopropylethane **334** to obtain adduct **336** in 91% yield as a mixture of 1.5 : 1 of diastereomers in 90% and 70% ee, respectively (Scheme 100).

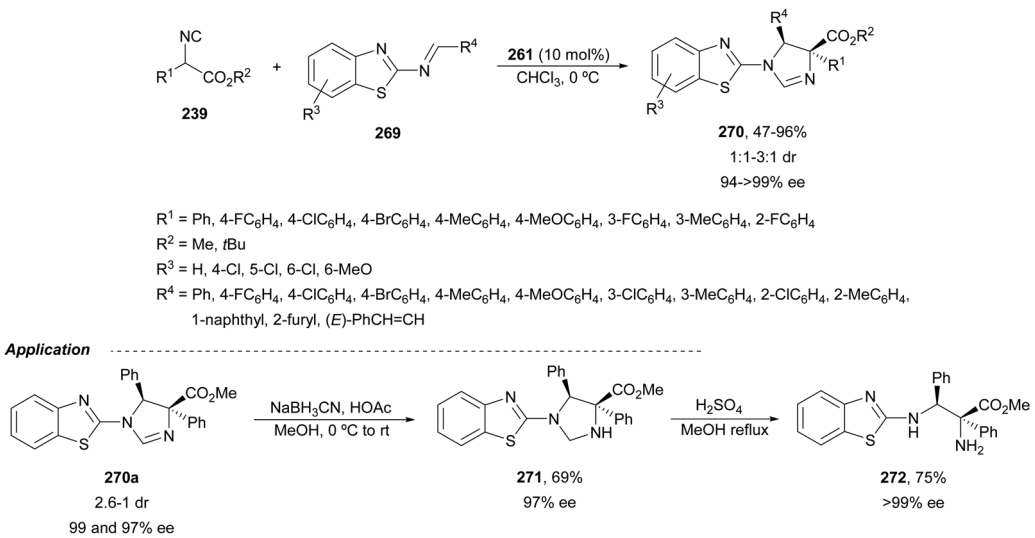
Alemán and co-workers[211] described the asymmetric aza-Henry reaction of cyclic α-carbonyl ketimines **337** with nitromethane catalyzed by the hydroquinine thiourea **338** (Scheme 101). 2-Aryl-3*H*-indol-3-ones **337** were allowed to react with nitromethane in *p*-xylene at room temperature to furnish products **339** up to >98% yield and 96% ee. It was proposed that the thiourea unit forms hydrogen bonding with ketimine **337** and the nitronate is coordinated with the catalyst according to the depicted TS. Nitroethane gave product **339** (R = Ph) with low 3 : 1 dr in 97% yield.

Miao and co-workers[212] performed the aza-Henry reaction of α-substituted nitroacetates **330** with *N*-phosphoryl imines **340** under *Cinchona*-derived thiourea **341** catalysis (Scheme 102). Products **342** were obtained working in toluene at −20 °C in good yields, modest to high *anti*-diastereoselectivity and up to >99% ee. In the proposed catalytic cycle, the organocatalyst forms a double hydrogen bonding between the two NH groups and the P=O group of the imine to give intermediate **I**. Hydrogen bonding of methyl nitropropanoate with the protonated quinuclidine unit resulted intermediate **II**. Subsequently, the *Si*-face attack of the imine through the *Si*-face of the enolate furnishes intermediate **III** with (*S*,*S*)-configuration. This mechanism was corroborated by ^{31}P NMR spectroscopy.

Chiral squaramides behave as thioureas like hydrogen donors in organocatalysis.[213,214] Du and co-workers[215] reported the asymmetric aza-Henry reaction of *N*-benzothiazolyl imines **269** with nitromethane in the presence of squaramide **236** as a better organocatalyst than the related thiourea. Compounds **343** were obtained in high yields and enantioselectivities (Scheme 103a). Alternatively, a three-component process was



Scheme 81 Asymmetric aza-Mannich reaction of isocyano acetates **239** with *N*-Boc-isatin-derived ketimines **170** under thiourea **265** catalysis.



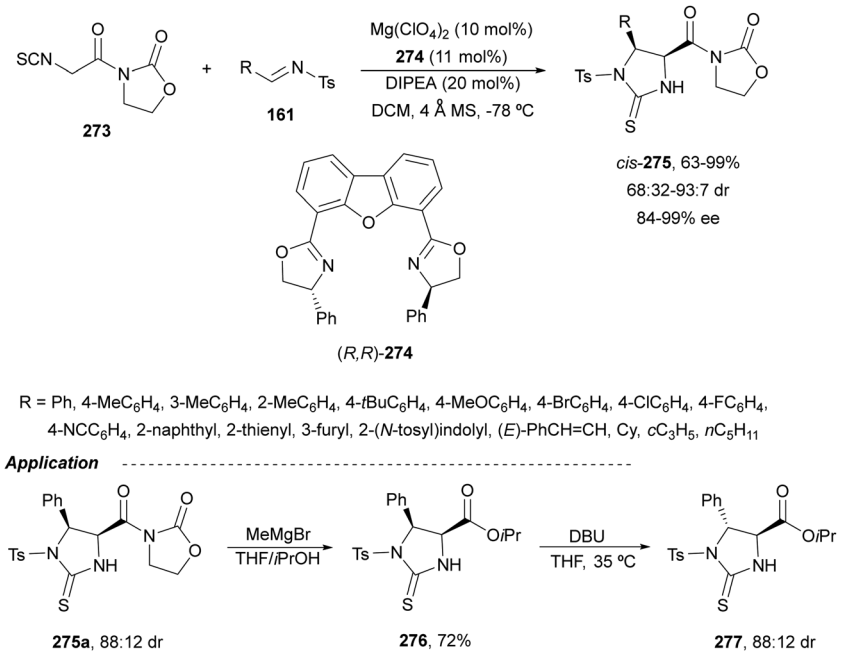
Scheme 82 Asymmetric aza-Mannich/cyclization of isocyano acetates **239** and *N*-(2-benzothiazolyl)imines **269** under squaramide **261** catalysis.

carried out using 2-aminobenzothiazoles **344**, aldehydes and nitromethane (Scheme 103b). The corresponding aza-Henry adducts **343** were isolated in modest to good yields and enantioselectivities lower than those of imines **269**.

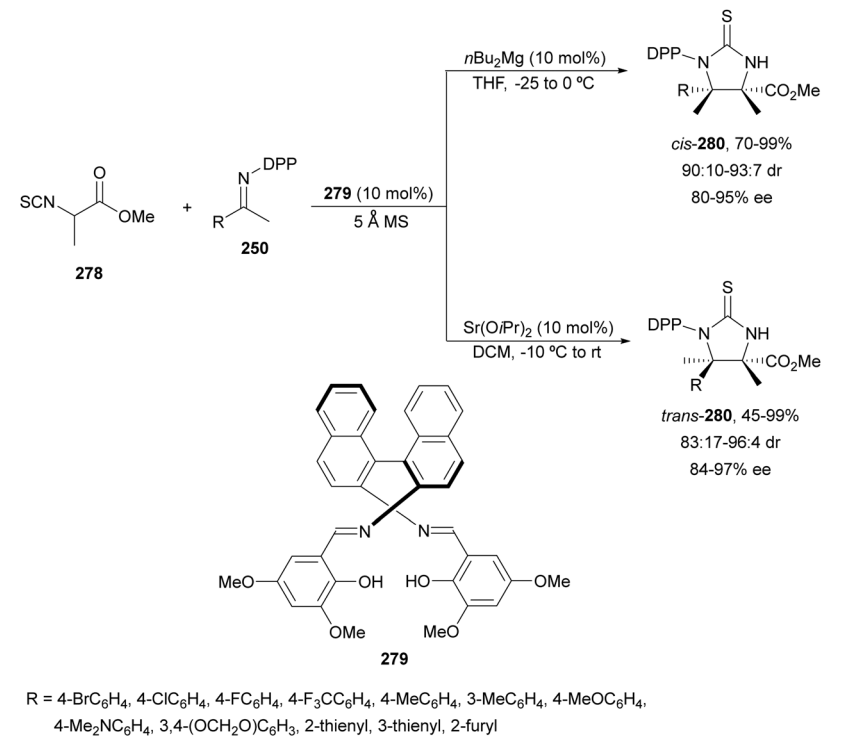
Chiral thiourea **345** bearing a basic iminophosphorane moiety as a Brønsted superbase has been designed by Dixon and co-workers.[216] This bifunctional organocatalyst was able to promote the aza-Henry reaction of nitromethane with *N*-diphenylphosphinoyl ketimines **250** to provide β-nitroamines **346** with high yields and enantioselectivities (Scheme 104). However, when a cinchonine-derived thiourea, such as **341**, was used as an organocatalyst no product was detected. This aza-Henry reaction was performed on a multigram scale and product **346a** was transformed into 1,2-diamine derivative **347** *via* a nickel boride reduction of the nitro group followed by Cbz protection and final DPP removal.

Phosphorylated ketimines **348** have been transformed into tetrasubstituted α-amino-β-nitrophosphonates **349** by Palacios and co-workers.[217] The corresponding asymmetric aza-Henry reaction with nitromethane was carried out under thiourea **341** catalysis (Scheme 105). Products **349** were isolated in good yields and enantioselectivities, and enantiopure compound **349a** was transformed into (*S*)-α,β-diaminophosphonate **350** under hydrogenation conditions in 95% yield.

Aryl α-keto ester-derived *N*-tosyl ketimines **351** have been subjected to the aza-Henry reaction with nitromethane by Lin, Duan and co-workers[218] under thiourea **352** organocatalysis (Scheme 106). This reaction was carried out in fluorobenzene at



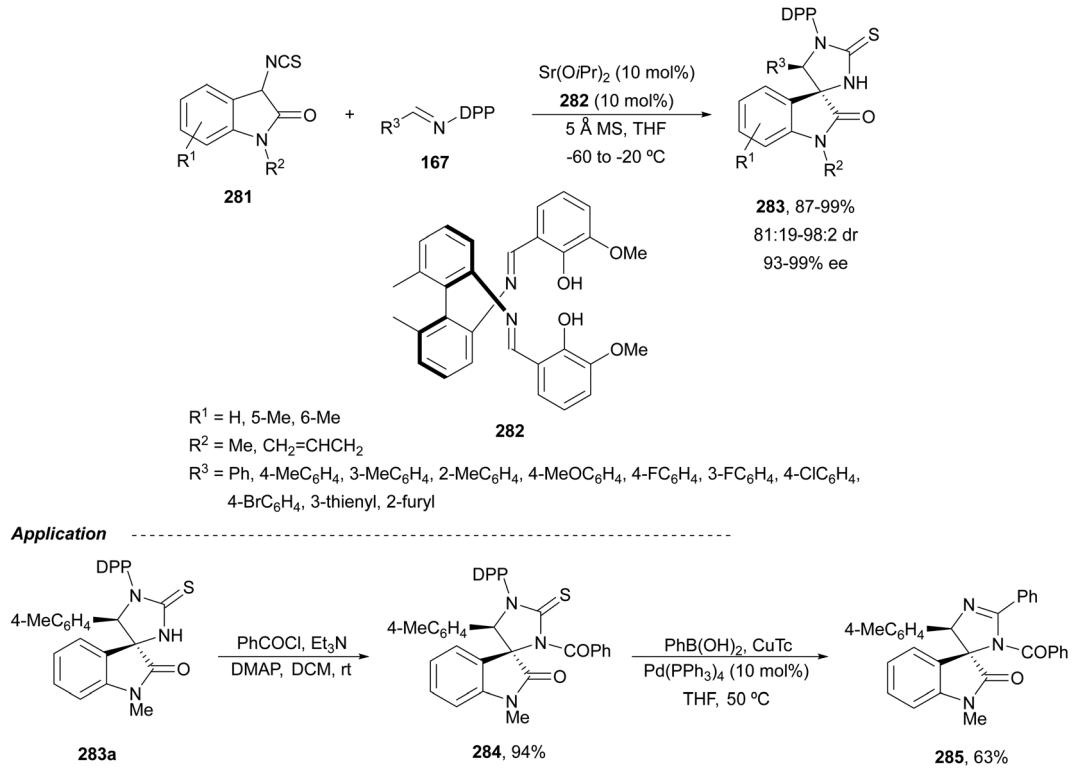
Scheme 83 Asymmetric aza-Mannich reaction of α-isothiocyanate *N*-acyl oxazolidinone **273** with *N*-tosyl imines **161** under $Mg(ClO_4)_2$/Ph-Dbfox **274** catalysis.



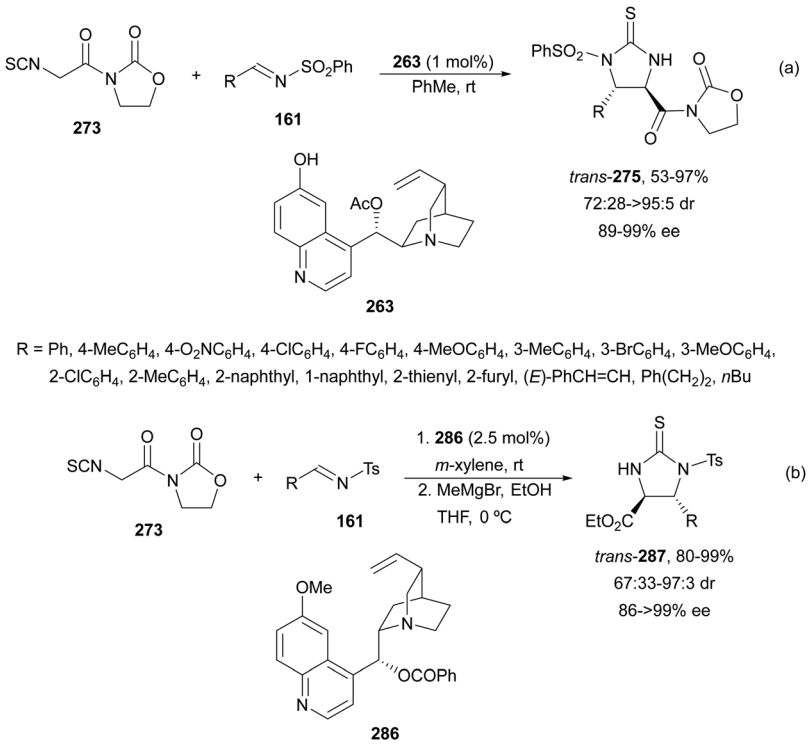
Scheme 84 Asymmetric diastereodivergent aza-Mannich reaction of α-mehtyl-α-isothiocyanato ester **278** with ketimines **250** under nBu_2Mg or $Sr(OiPr)_2$ and ligand **279** catalysis.

room temperature to obtain the corresponding products **353** up to 99% yield and 99% ee. A plausible TS was proposed involving the formation of hydrogen bonding between the thiourea and the α-keto ester imine **351** as well as with one of the oxygen atoms of the nitronate. The nitronate also interacts by hydrogen bonding with the nitrogen atom of the quinuclidine unit.

The same group[219] recently reported that *N*-Boc ketimines **170** derived from isatins were reacted with nitroalkanes using thiourea **354** derived from hydroquinine and (*S*)-phenylglycinol



Scheme 85 Asymmetric aza-Mannich reaction of isothiocyanato-oxindoles **281** with *N*-DPP aldimines **167** under Sr(O*i*Pr)$_2$/ligand **282** catalysis.



Scheme 86 Asymmetric aza-Mannich reaction of isothiocyanato-oxazolidinone **273** with *N*-sulfonyl imines **161** under quinidine or quinine-derived organocatalysis.

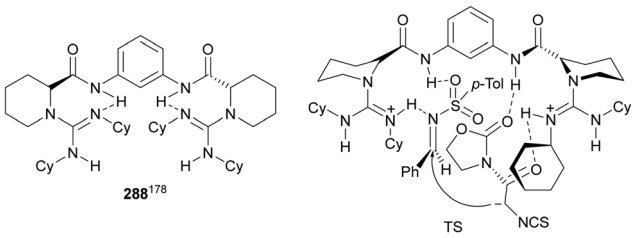
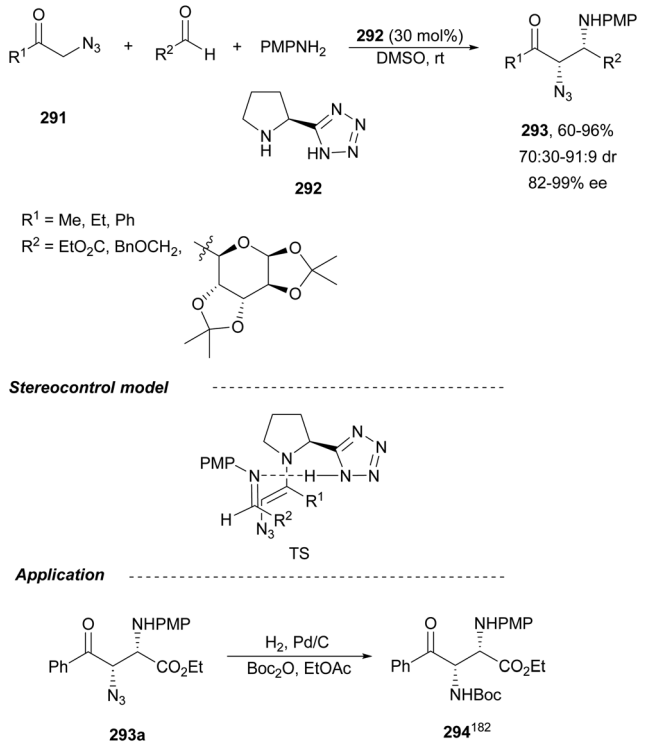


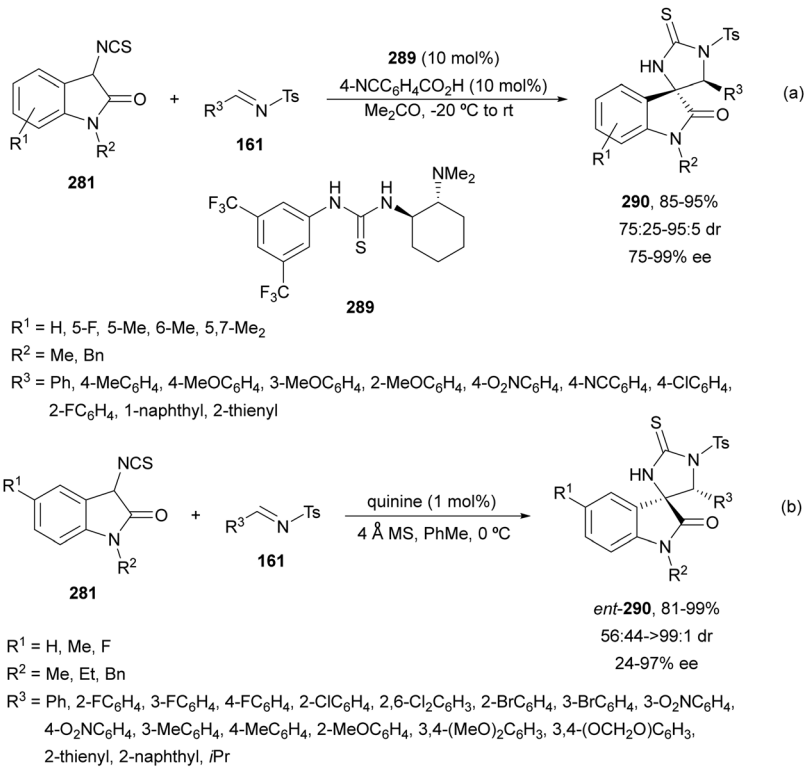
Fig. 11 Bisguanidine organocatalyst **288** for the asymmetric aza-Mannich reaction of isothiocyanato-oxazolidinone **273** with *N*-tosyl imines **161** and proposed TS.

as an organocatalyst (Scheme 107). After screening of different hydroquinine-derived thioureas, **354** gave the best results affording products **355** up to 99% yield, 99 : 1 dr and 99% ee. This process was performed on a gram-scale with isatin-derived imine **170** (R^1 = H) and nitroethane obtaining product **355** in 98% yield, 90 : 10 dr and 98% ee. In the proposed TS, the ketimine is coordinated with the thiourea and the hydroxy units and the nitronate with the protonated nitrogen from the quinuclidine moiety.

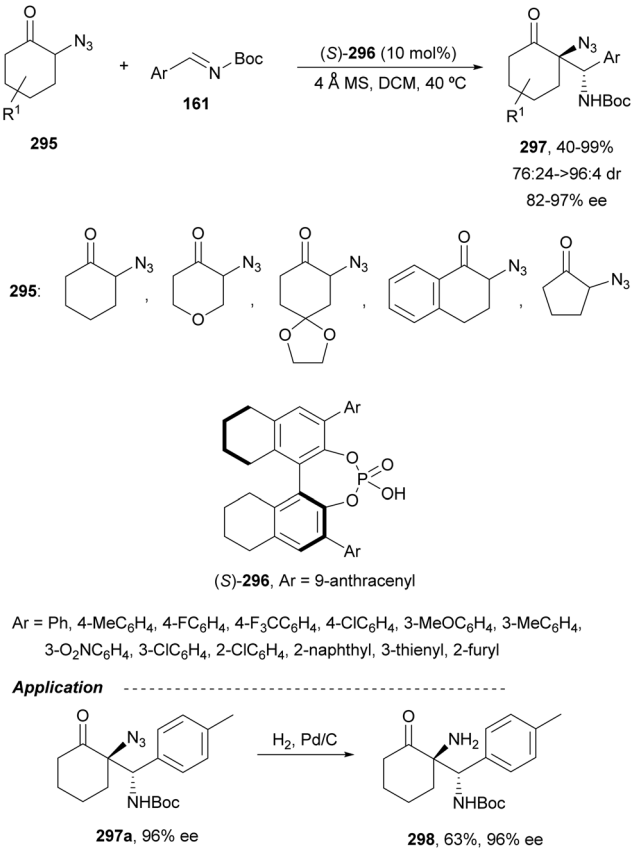
Fluoromethyl imines **356** were reacted with nitromethane under mild reaction conditions using the hydroquinine-derived thiourea **352** to furnish fluoromethylated β-nitroamines **357** in good yields and enantioselectivities (Scheme 108).[220] However, other α-alkylated nitroalkanes gave poor results. The trifluoromethyl product **357** (R_F = CF_3) was reduced to the corresponding diamine *via* a nickel boride reduction with 68% yield and subsequently transformed into a 4-trifluoromethyl-2-imidazolidone.



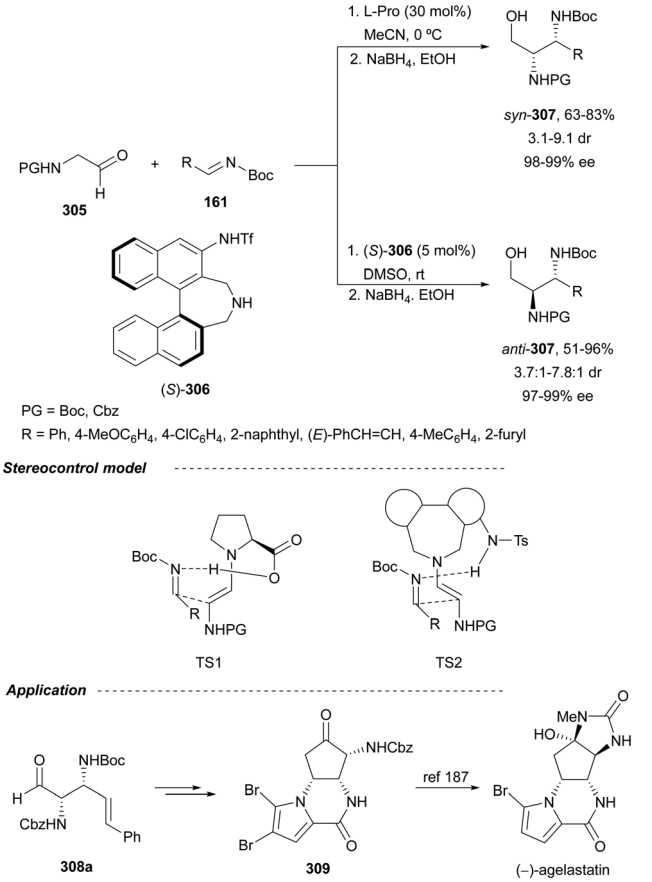
Scheme 88 Asymmetric three-component aza-Mannich reaction of α-azido ketones **291** with aldehydes and *p*-anisidine under **292** catalysis.



Scheme 87 Asymmetric aza-Mannich reaction of isothiocyanato-oxindoles **281** with *N*-tosyl imines **161** under thiourea **289** or quinine catalysis.



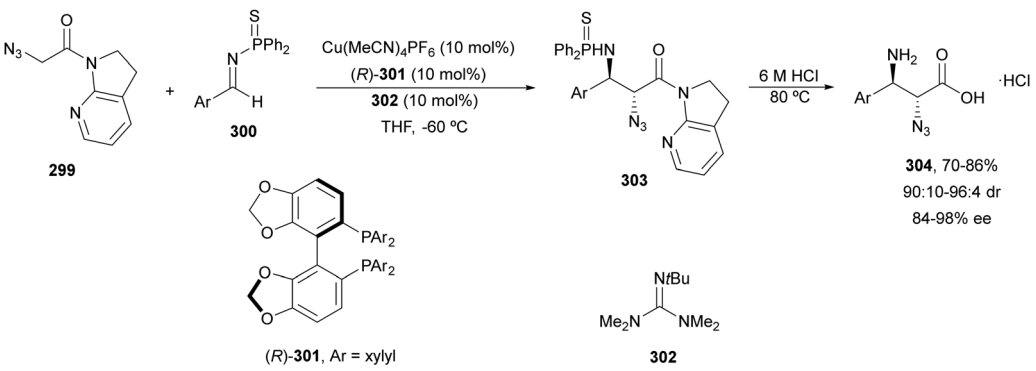
Scheme 89 Asymmetric aza-Mannich reaction of α-azido cyclic ketones **295** with *N*-Boc imines **161** under CPA (*S*)-**296** catalysis.



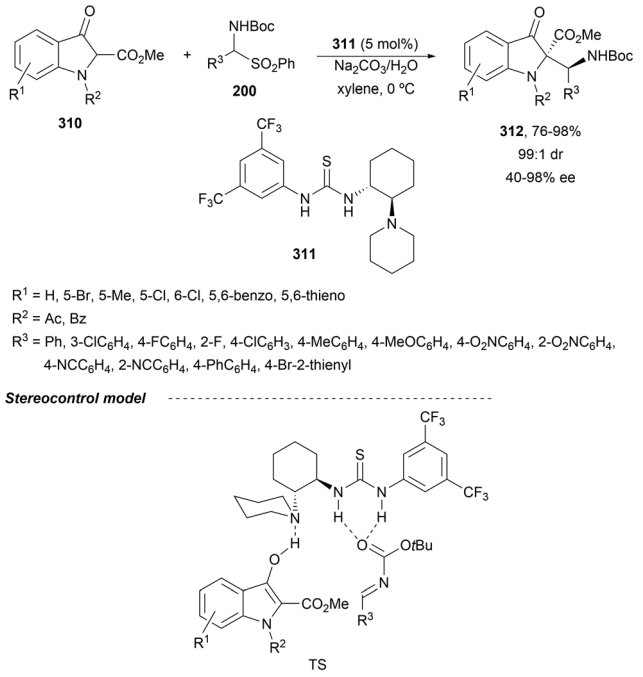
Scheme 91 Asymmetric aza-Mannich reaction of α-amino acetaldehydes **305** with *N*-Boc imines **161** under L-Pro or (*S*)-**306** diastereodivergent catalysis.

Seven-membered cyclic imines **358** reacted with nitromethane in the presence of quinine-derived thiourea **264** to provide the corresponding adducts **359** in good to excellent yields and enantioselectivities (Scheme 109).[221] The inactivated dibenzo[*b*,*f*]-[1,4]oxazepine **358a** gave product **359a,** which was reduced into a 1,2-diamine derivative by hydrogenation and further tosylated to **360** or underwent reductive amination to product **361** with potential application for the synthesis of bioactive molecules. In the proposed TS, hydrogen bonding interactions between the nitronate group of the thiourea moiety, the protonated quinuclidine and the imine promote the nucleophilic attack on the *Si*-face of the cyclic imine leading to (*R*)-enantiomer **359.**

The same group[222] performed the aza-Henry reaction catalyzed by thiourea **264** of nitromethane with indolenines **362** to



Scheme 90 Asymmetric aza-Mannich reaction of α-azido amides **299** with *N*-thiophosphinoyl imines **300** under Cu(I)/(*R*)-xyl-Segphos **301** catalysis.



Scheme 92 Asymmetric aza-Mannich reaction of methyl 3-indolinone-2-carboxylates **310** with *N*-Boc imines under thiourea **311** catalysis.

obtain 2-nitromethyl indolines **363** in good yields and high enantioselectivities (Scheme 110). This protocol was scaled-up to 3 mmol of 3*H*-indole [R^1 = 4,6-Me_2, R^2–R^2 = $(CH_2)_5$] **362a** giving the corresponding product **363a** in 90% yield and 94% ee. The same product **363a** was transformed into diamine **364** in 84% yield and *ca.* 94% ee.

Recently, Di Mola, Massa and co-workers[223] reported an asymmetric cascade aza-Henry/lactamization reaction of α-amido sulfones **365** with nitromethane under Takemoto's thiourea **289** catalysis. α-Amido sulfones **365**, prepared from 2-formyl benzoates, generated *in situ* the corresponding *N*-protected imines which reacted with nitromethane to form intermediates **366**. These compounds underwent *in situ* cyclization at room temperature to give 3-(nitromethyl)isoindolin-1-ones **367** in good yields and enantioselectivities (Scheme 111). Reduction of the nitro group of product **367a** was efficiently carried out with Zn and a small amount of HCl in MeOH at 0 °C to furnish product **368** with 61% yield and the same ee.

McHardy and co-workers[224] recently performed the synthesis of two protein kinase C (PKC)-epsilon inhibitors to treat alcohol use disorder.[225] Starting from α-amido sulfone **369**, the aza-Henry reaction with nitromethane using Zhao thiourea **333** as an organocatalyst,[208] product **370** was obtained with the highest enantioselectivity (95% ee) and with 98% yield (Scheme 112a). Adduct **370** was further transformed in four steps into CIDD-0072424 **371**. In the case of compound **373**, they started from *N*-acylimine **372** and used a Takemoto catalyst (*S*,*S*)-**289** for the aza-Henry reaction with nitromethane (Scheme 112b). Product **373** was isolated in 95% yield and 93% ee, and was further converted into compound (*S*)-**374** in 27% overall yield over eight-step sequence.

It can be generalized that chiral thioureas, especially *Cinchona* alkaloids derived thioureas, are excellent and versatile organocatalysts for the asymmetric aza-Henry reaction of acyclic and cyclic aldimines as well as ketimines.

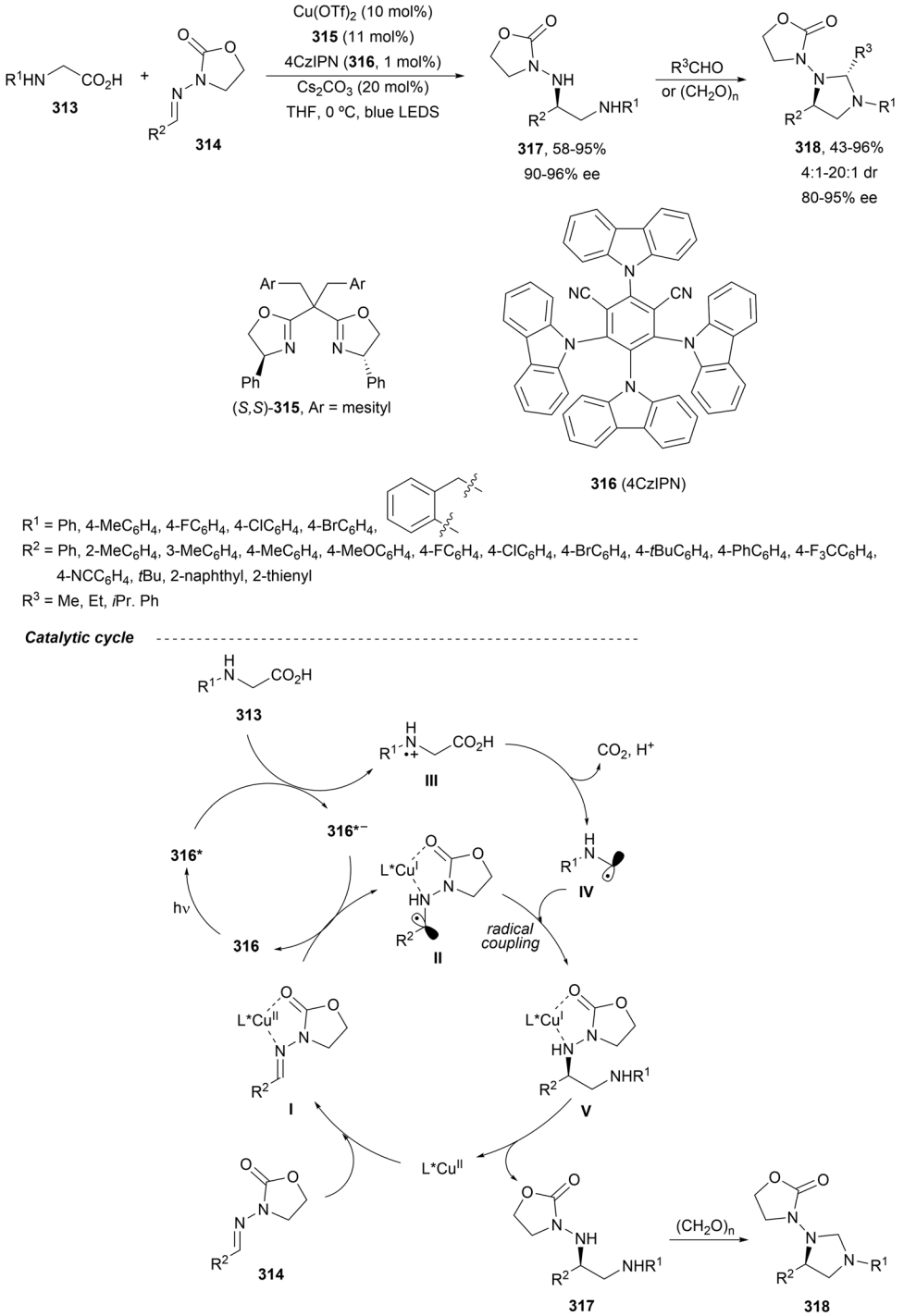
In 2005, phase transfer-catalyzed asymmetric aza-Henry reactions were simultaneously reported by Herrera, Bernardi and co-workers[226] and by Palomo and co-workers[227] using α-amido sulfones of type **165** as precursors of *N*-carbamoyl imines. *N*-Benzyl quininium chloride **375** (Fig. 13) was used in both cases as a catalyst in the presence of KOH[226] and $CsOH{\cdot}H_2O$[227] as bases in toluene at −45[226] and −50 °C,[227] respectively. The corresponding (*R*)-β-nitroamines **320** were obtained in 53–98% yields and 73–98% ee,[226] whereas Palomo reported 72–83% yields and 82–98% ee.[227] In the last case, the reaction with nitroethane afforded *anti*-products **320** with 85–88% yields, 75 : 25–95 : 5 dr and 91–98% ee. They also studied the reaction mechanism using experimental work and theoretical calculations.[228] In the proposed catalytic cycle, the nitronate anion is the base to generate the *N*-Boc imine from the α-amido sulfone (slow step). The nitronate is also responsible for the addition of the *in situ* generated imine (fast step) and TS with several hydrogen bonds explains the observed enantioselectivity.

In Fig. 13, several PTCs such as the *N*-benzotriazole-quininium salt **376** were used by He and co-workers,[229] for the aza-Henry reaction of *N*-tosyl α-amido sulfones **165** with nitromethane and nitroethane to obtain β-nitro amines **323** with reversal of enantioselectivity than the *N*-benzyl quininium salt **375**. Takada and Nagasawa[230] used the guanidinium-*cis*-thiourea **377** (Fig. 13) for the reaction of *N*-Boc imines with nitroalkanes obtaining β-nitroamines **320** up to 96% yield, 99 : 1 dr and 99% ee. Peng, Han and co-workers[231] used the same catalyst **377** (Fig. 13) starting from *N*-Boc α-amido sulfones but with lower diastereoselectivities than *N*-Boc imines. Dixon and co-workers[232] used a quininidium-urea catalyst **378** (Fig. 13) for the aza-Henry reaction of α-amido sulfones and nitroalkanes to obtain products **320** with 83–100% yields, 6 : 1–24 : 1 dr and 84–95% ee.

Kumaraswamy and Pitchaiah[233] applied Palomo's reaction conditions[227] to the synthesis of furyl derived β-nitroamines **323**, which were transformed into orthogonally protected (2*S*)-2,3-diaminopropanoates **380** (Scheme 113). The furan moiety was oxidatively cleaved to obtain the carboxylic acids, which were esterified with diazomethane to provide methyl esters **379**. Subsequent reduction of the nitro group provided 2,3-diaminopropanoates **380**, which were further protected as Fmoc derivatives.

The same Indian's group[234] applied this aza-Henry reaction to the enantioselective synthesis of (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **383**. In this case, the nitro compound **381** was allowed to react with α-amido sulfone **200** (R = Boc) under asymmetric Palomo's PTC conditions[227] to afford mainly the corresponding nitro adduct **382**, which was further transformed into the pipecolic acid derivative **383** (Scheme 114).

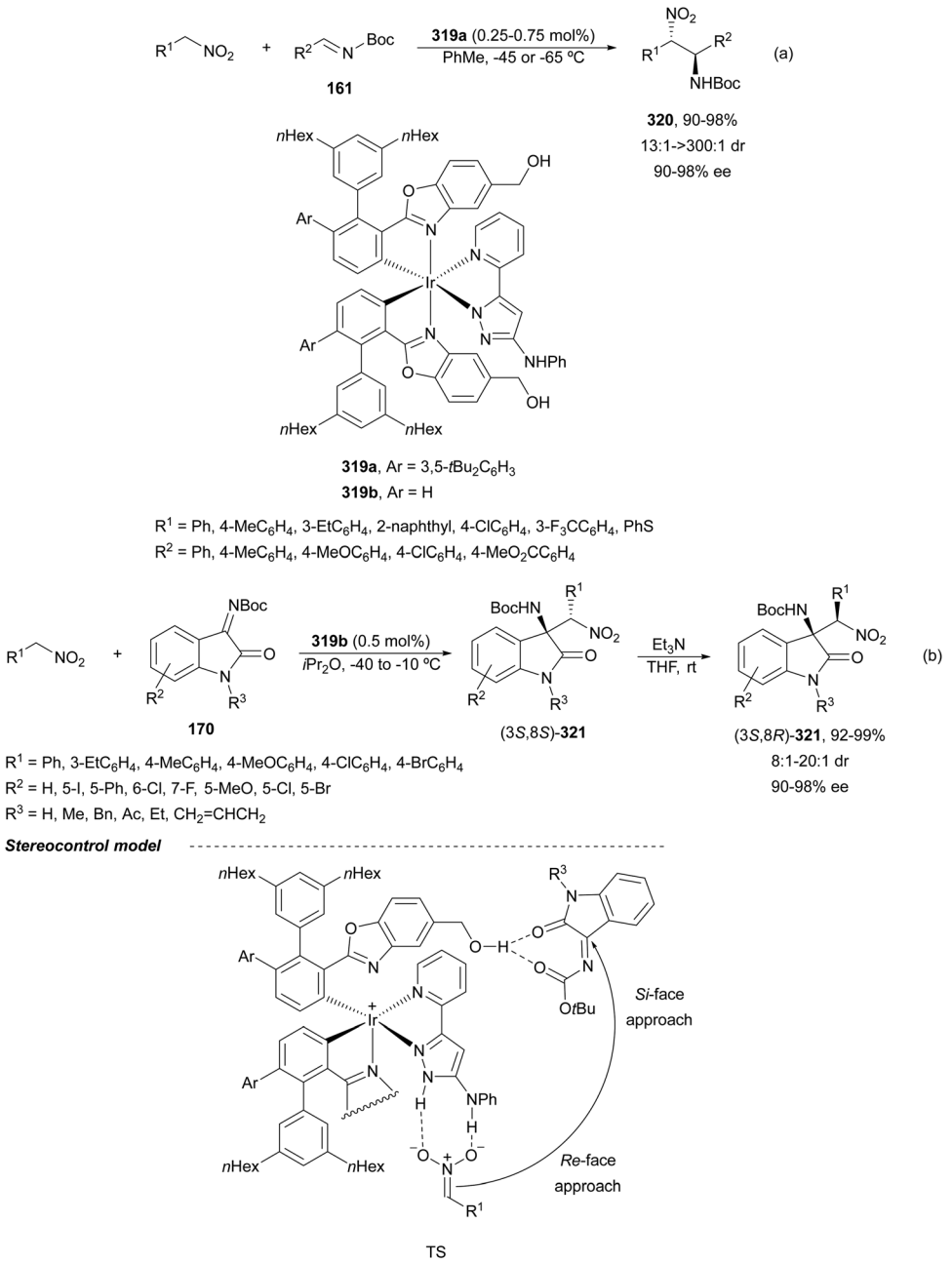
Cinchona alkaloid-derived bifunctional ammonium salts **384** derived from quinine and **385** derived from quinidine bearing a urea unit with a β-amino alcohol have been used by Lin, Duan and



Scheme 93 Asymmetric aza-Mannich reaction of *N*-aryl glycines **313** and hydrazones **314** under Cu/**315** and photoredox catalysis.

co-workers[235] for the enantiodivergent[52] aza-Henry reaction of α-amido sulfones **165** with nitroalkanes (Scheme 115). Enantiomeric β-nitroamine derivatives **320** were obtained with good yields and diastereo- and enantioselectivities. Walvoord and Kozlowski[236] employed cinchonidinium acetate as a phase-transfer catalyst for the asymmetric synthesis of *cis*-stilbene diamines. The reaction of α-aryl nitromethanes with *N*-Boc benzylidene imines **161** using cinchonidine (10 mol%) and HOAc (10 mol%) in dichloromethane at −30 °C provided products *anti*-**320** (R^1 = Ar) with 29–99% yields, 97 : 3–99 : 1 dr and 26–79% ee. Lin, Duan and co-workers[237] performed the same reaction using α-amido sulfones **165** and catalyst **386**. Products *anti*-**320** (R^1 = Ar) were obtained with excellent yields (93–99%) and diastereo- (96 : 4–>99 : 1 dr) and enantioselectivities (91–99% ee).

For the synthesis of the quinolone-fused lactam LP99, the groups of Brennan and Dixon[238] developed an aza-Henry

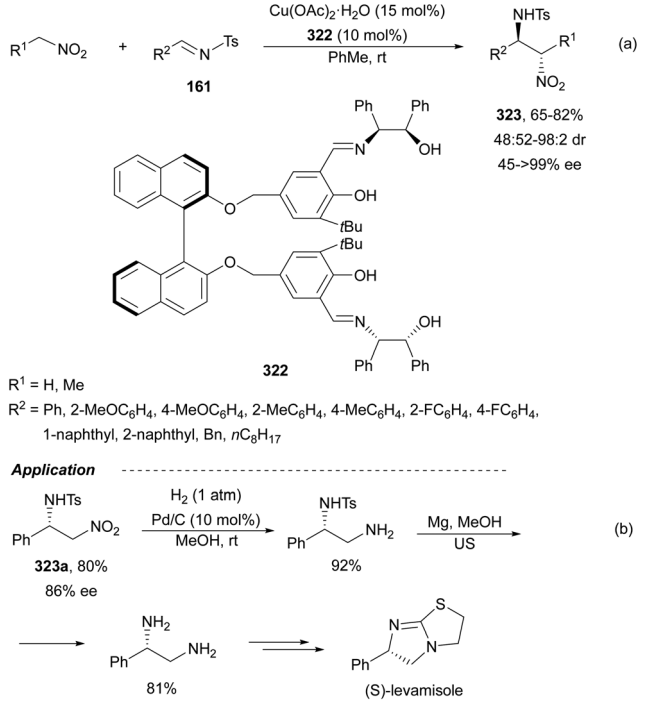


Scheme 94 Asymmetric aza-Henry reactions of nitroalkanes with *N*-Boc imines **161** and isatin ketimines **170** under Ir(III) complex **319** catalysis.

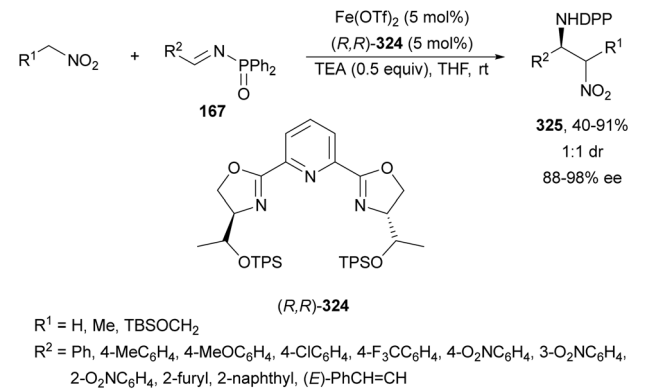
reaction/lactamization cascade process. Reaction of the 4-nitrobutanoate **387** with *N*-Boc imine **388**, using the bifunctional quinidinium-urea catalysis **378**[232] under solid–liquid PTC conditions, provided adducts **389** on a gram scale with 70% yield, 7 : 1 dr and 90% ee (Scheme 116). Deprotection of *N*-Boc followed by cyclization and reduction of the NO_2 group and subsequent steps gave the corresponding LP99 with a K_D value of 99 nM against BRD9. Treatment with LP99 led to displacement of BRD7 and BRD9 from chromatin and down-regulation of the pro-inflammatory cytokine IL-6.

Nitroalkenes **390** were reacted with α-amido sulfones **200** under PTC using the quininium salt **386**, and LiOH as a base in DCM at −40 °C (Scheme 117).[239] This bifunctional catalyst with multiple hydrogen bonding donors provided compounds **391** in excellent yields and diastereo- and enantioselectivities. Based on DFT calculations, a TS has been proposed in which the *in situ* generated *N*-Boc imine forms hydrogen bonding with the urea and the hydroxy group of the amino alcohol unit. In addition, the nitronate forms hydrogen bonding with two hydrogen atoms of the quinuclidine moiety.

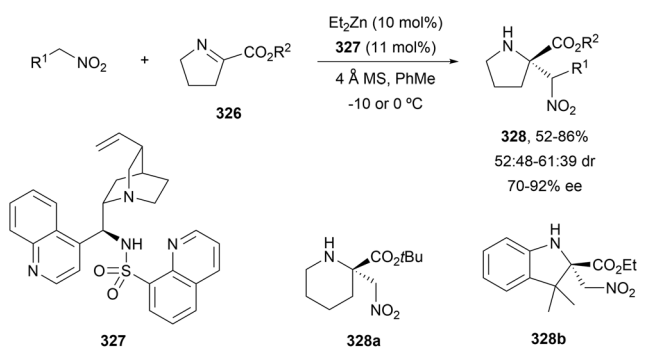
Bifunctional thiourea-ammonium salts derived from α-amino acids have been developed by Zhao and co-workers.[240] The best phase-transfer catalyst **392** for the aza-Henry reaction of α-amido sulfones **200** with nitroalkanes gave products (*S*)-**320** and (*S*,*S*)-**320** with 80–99% yields, 6 : 1–> 25 : 1 dr and 68–99.5% ee. In the proposed TS, the thiourea unit has



Scheme 95 Asymmetric aza-Henry reaction of nitroalkanes with *N*-tosyl imines **161** under $Cu(OAc)_2$/**322** catalysis.



Scheme 96 Asymmetric aza-Henry reaction of nitroalkanes with *N*-diphenylphosphinoyl imines **167** under $Fe(OTf)_2$/(*R*,*R*)-**324** catalysis.



Scheme 97 Asymmetric aza-Henry reaction of nitroalkanes with cyclic imino esters **326** under Et_2Zn/sulfonamide **327** catalysis.

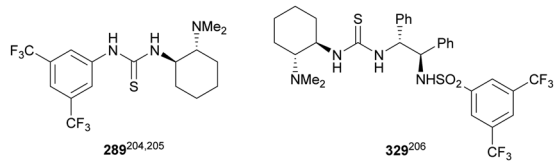
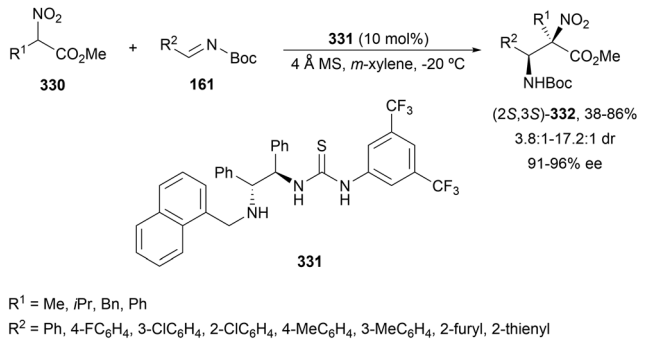
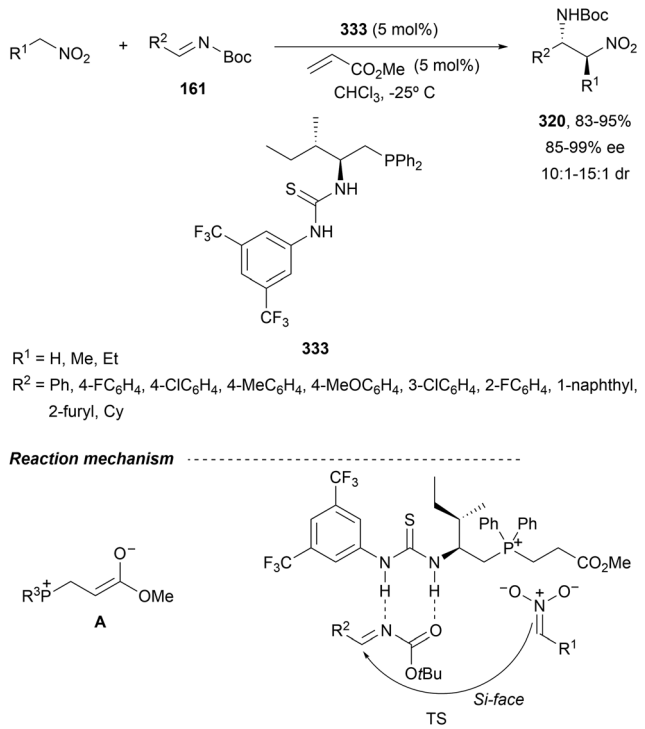


Fig. 12 Chiral thioureas as catalysts for the aza-Henry reaction of nitroalkanes with *N*-protected imines.

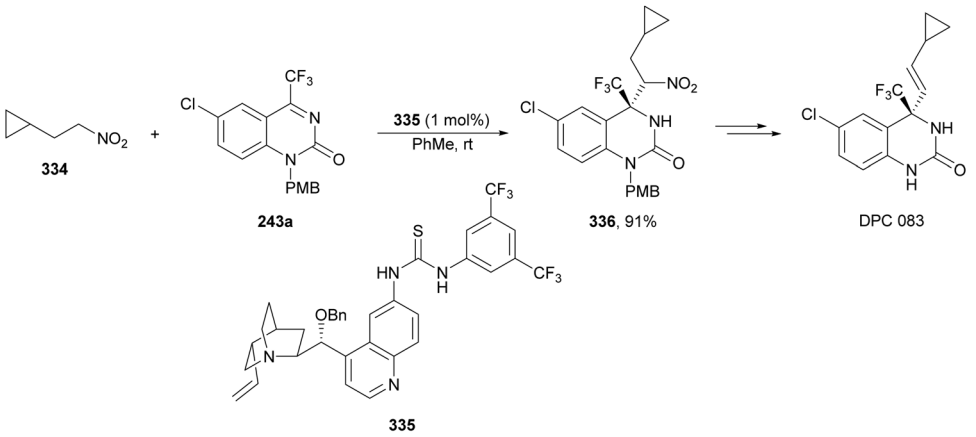


Scheme 98 Asymmetric aza-Henry reaction of α-nitro esters **330** with *N*-Boc imines **161** under thiourea **331** catalysis.

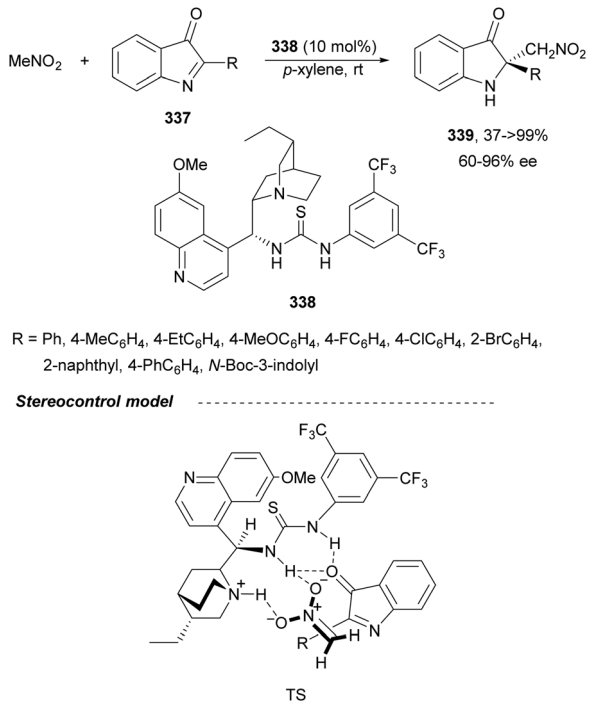


Scheme 99 Asymmetric aza-Henry reaction of nitroalkanes with *N*-Boc imines **161** under ion-pair catalysis formed by phosphine-thiourea **333** and methyl acrylate.

hydrogen-bonding interactions with the *in situ* generated *N*-Boc imine and the nitronate interacts with the ammonium center by Coulomb force (Fig. 14). The same group[241] employed for the same aza-Henry reaction thiourea-phosphonium salts also derived from α-amino acids. Catalyst **393** (Fig. 14) and also



Scheme 100 Asymmetric aza-Henry reaction of 1-nitro-2-cyclopropylethane **334** with cyclic trifluoromethyl ketimine **243a** towards the synthesis of anti-HIV drug DPC 083.



Scheme 101 Asymmetric aza-Henry reaction of nitromethane with 2-aryl-3*H*-indol-3-ones **337** under thiourea **338** catalysis.

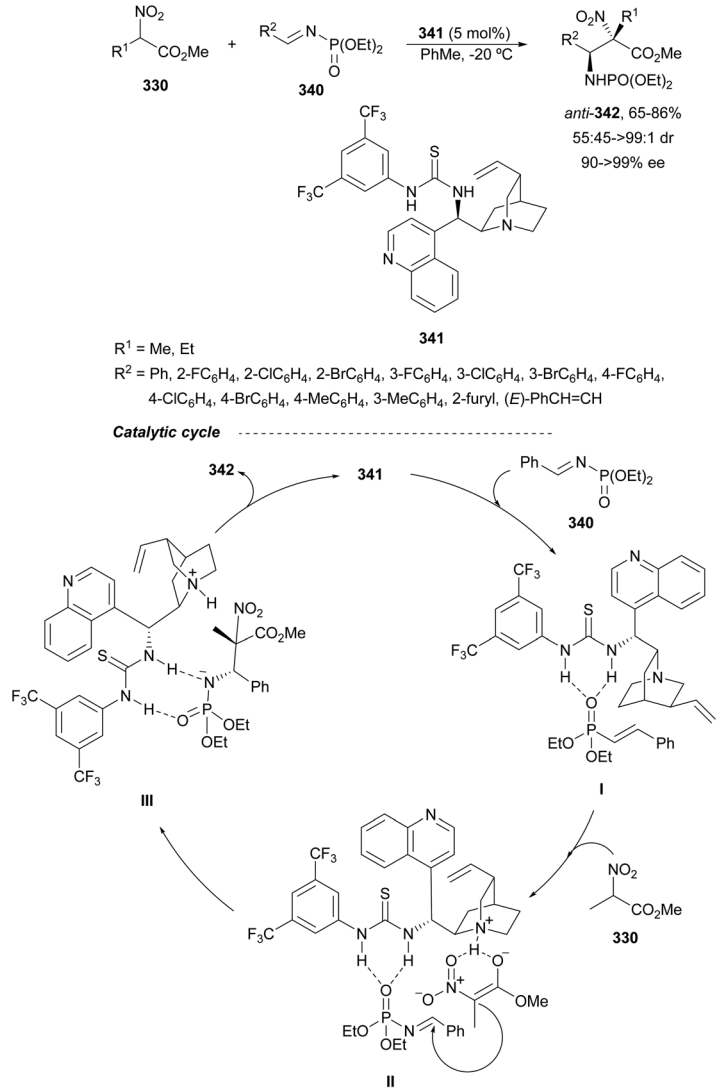
KOH as a base in toluene at −20 °C provided products (*S*)-**320** and (*S*,*S*)-**320** in 68–99% yields, moderate diastereoselectivities (*syn* : *anti* = 22 : 78–47 : 53) and excellent enantioselectivities (86–98% ee). Lin, Duan and co-workers[242] performed this type of asymmetric aza-Henry reaction using bifunctional phase-transfer catalysts **394a** and **394b** derived from α-amino acids (Fig. 14). The corresponding products (*S*)-**330** and (*S*,*S*)-**320** were prepared with KOH as a base in $CHCl_3$ at −20 °C with excellent yields (93–99%), 90 : 10–92 : 8 dr and 90–>99.9% ee. More recently, this group[243] performed the reaction of α-aryl nitromethanes with α-amido sulfones in the presence of catalyst **395** in good yields and stereoselectivities (Scheme 118).

Ketimines **396** bearing a 6-methyl-2-pyridylsulfonyl protecting group were active electrophilic substrates for the asymmetric aza-Henry reaction under PTC conditions. Lin, Duan and co-workers[244] used a modified Dixon's catalyst **378** with a 2-methoxyphenyl group instead of a phenyl group at the quinuclidine nitrogen and a thiourea instead of the urea moiety **397**. The addition of nitromethane to ketimines **396** took place with good yields and enantioselectivities giving products **398** (Scheme 119). Based on DFT calculations, a TS with a Wynberg ion-pair hydrogen bond type mechanism as well as the formation of hydrogen bonds with the thiourea unit leading to the *Si*-face addition of ketimine was proposed.

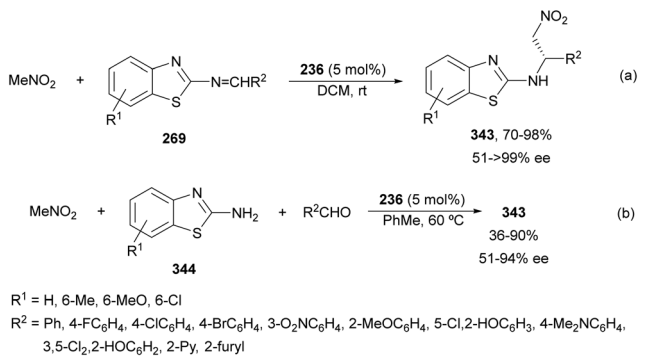
Lin, Duan and co-workers[245] modified catalyst **397** for the asymmetric aza-Henry reaction of α-keto esters-derived *N*-tosyl ketimines **351** with nitromethane. In this case, a 3,5-di-*tert*-butyl benzyl moiety at the quinuclidine nitrogen was proved to be the best phase-transfer catalyst **399** to give products **353** with very good yields and moderate to high enantioselectivities (Scheme 120). Product **353a** was reduced with Zn in HOAc and after acetylation the α,β-diamino ester derivative **400** was obtained in 81% yield and 97% ee.

Acyclic trifluoromethyl ketimines **401** have been used for the first time as electrophiles in the asymmetric aza-Henry reaction with nitromethane by Lin, Duan and co-workers.[246] After screening of several quininium salts, including Dixon's catalyst **378**,[232] the catalyst containing (*S*)-phenylglycinol moiety **386** (Scheme 115) gave the best results (Scheme 121). The resulting fluorinated β-nitroamines **402** were obtained with excellent yields with high enantioselectivities. Product **402a** was reduced to *N*-Boc diamine **403** in 90% yield, using $NiCl_2/NaBH_4$, and by further treatment with DBU it was transformed into the imidazolidinone **404** in 90% yield.

The group of Lin and Duan has applied the phase-transfer catalyst **386** to the asymmetric aza-Henry reaction of nitromethane[247] and aryl nitromethanes[248] to *N*-Boc ketimines derived from isatins **170**. The 3-substituted 3-aminooxindoles **355** were obtained with excellent yields and good enantioselectivities (Scheme 122). In the case of α-aryl nitromethanes,



Scheme 102 Asymmetric aza-Henry reaction of methyl α-nitro esters **330** with *N*-phosphoryl imines **340** under thiourea **341** catalysis.

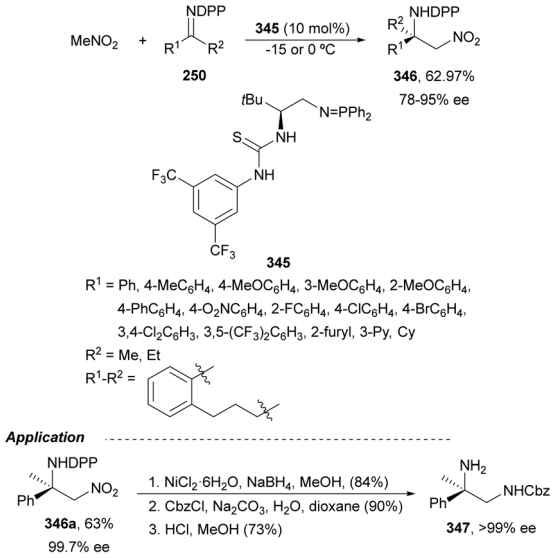


Scheme 103 Asymmetric aza-Henry reaction of nitromethane with *N*-benzothiazolyl imines **269** under squaramide **236** catalysis.

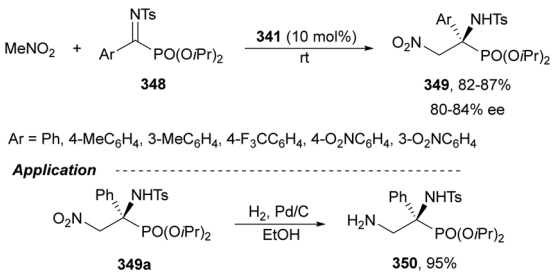
they also employed[249] the (*S*)-*tert*-leucine-derived urea-ammonium salt **405** as a phase-transfer catalyst to obtain products **355** with similar results (Scheme 122). In the proposed TS for catalyst **405**, the urea forms hydrogen-bond interactions with the *N*-Boc group of the ketimine and the ammonium unit would form an ion pair with the nitronate.

Phase-transfer catalysis for the asymmetric aza-Henry reaction is based on *Cinchona*-alkaloids ammonium salts not only for aldimines but also for ketimines. For less reactive ketimines, an extra thiourea unit enhances its reactivity with nitromethane. Under these PTC reaction conditions, α-amido sulfones can be used as precursors of the corresponding aldimines.

Chiral bases are able to deprotonate the nitro compound to form the corresponding nitronate. Ooi and co-workers[250] reported in 2008[251] a chiral ammonium betaine **406** as a bifunctional base, which catalyzed the aza-Henry reaction of α-nitro esters **330** with *N*-Boc imines **161**, with only 1 mol% catalyst loading, to provide mainly compounds *syn*-**332** (Scheme 123). This process was carried out with only 1 mol% of organocatalyst in toluene at 0 °C giving products **332** in excellent yields, modest diastereoselectivities and excellent enantioselectivities for both diastereomers. The catalytic performance of C_1-symmetric chiral ammonium betaine **407** was studied for the same aza-Henry reaction.[252]



Scheme 104 Asymmetric aza-Henry reaction of nitromethane with *N*-diphenylphosphinoyl ketimines **250** under thiourea-iminophosphorane **345** catalysis.

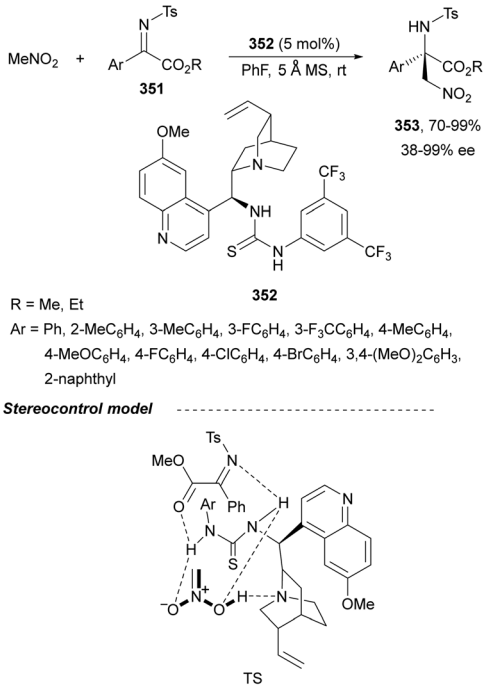


Scheme 105 Asymmetric aza-Henry reaction of nitromethane with phosphorylated ketimines **348** under thiourea **341** catalysis.

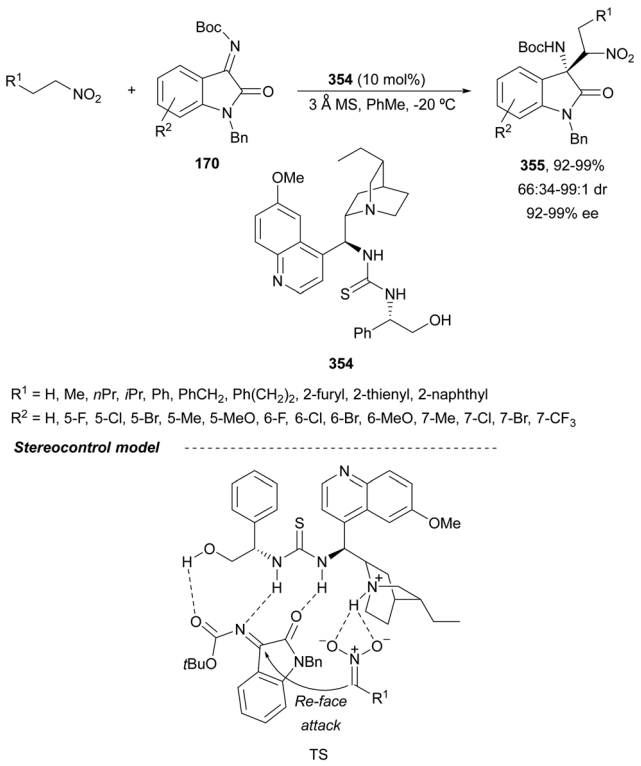
Products *syn*-**332** were obtained with similar yields and diastereo- and enantioselectivities.

In the case of β,β-disubstituted nitroolefins **408,** the addition of *N*-Boc aldimines **161** was catalyzed by the axially chiral ammonium betaine **409a** (Scheme 124).[253] Intermediate vinylogous nitronate **I** underwent α-addition to the imine to provide mainly β-nitroamines *anti*-**410** in high yields and diastereo- and enantioselectivities. Intermediate **II** was postulated to be formed by interaction of nitronate **I** with the catalyst **409a**. The reduction of *anti*-**410a** ($R^1 = R^3 = Ph$, $R^2 = H$) with Zn/HCl in EtOH followed by Boc-protection gave diamine **411,** which under hydrogenation conditions gave diastereomers **412,** and was also transformed into α,β-diamino ketone **413** by ozonolysis.

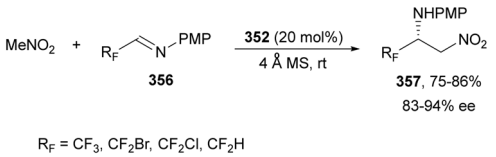
The same group reported[254] the aza-Henry reaction of α-aryl-β-monosubstituted nitroolefins **414** with *N*-Boc imines **161** using the betaine **409b** as a chiral base and catalyst. This base formed by γ-deprotonation of **414** the vinylogous nitronate **I** to provide *anti*-adducts **415** with >55% α-selectivity in good to excellent yields and diastereoselectivities, and high enantioselectivities (Scheme 125). Compound **415a** ($R^1 = H$, $R^2 = Ar = Ph$) was reduced with Zn/HCl and protected with CbzCl to the corresponding diamine **416,** which was further transformed by ozonolysis into aldehyde **417** and oxidized to the orthogonally protected α,β-diamino acid **418.**



Scheme 106 Asymmetric aza-Henry reaction of nitromethane with α-keto ester-derived imines **351** under thiourea **352** catalysis.



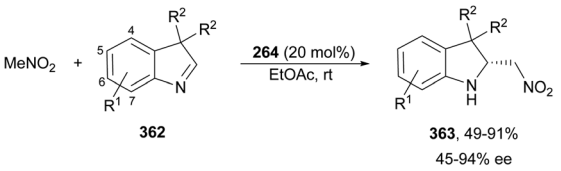
Scheme 107 Asymmetric aza-Henry reaction of nitroalkanes with ketimines **170** under thiourea **354** catalysis.



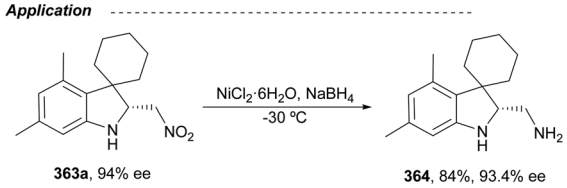
Scheme 108 Asymmetric aza-Henry reaction of nitromethane with fluoromethyl imines **356** under thiourea **352** catalysis.

When α-aryl nitromethanes were allowed to react with *N*-Boc imines **161** in the presence of the base **409a,** mainly *anti*-products **320** were obtained with high yields and enantioselectivities (Scheme 126).[255] The β-nitroamines **320a** (R = Ar = Ph) and **320b** (R = Ph, Ar = 2-FC_6H_4) were transformed into the corresponding *anti*-1,2-diamines **419** by reduction with $CoCl_2$/$NaBH_4$. Compound **419b** was deprotected by treatment with TFA to obtain diamine **420b**, and **419a** was tosylated to the orthogonally protected diamine **421a.**

The addition of nitromethane to ketimines derived from α-keto ester **351a** or isatin **170a** has been performed with quinine-derived bifunctional catalyst **422** (Scheme 127). Zhou and co-workers[256] found out that DBU was an appropriate base and catalyst for this addition and as a proof of concept employed **422** for the enantioselective version. Products **353a** or **423a** were obtained in 68 or 71% ee, respectively.

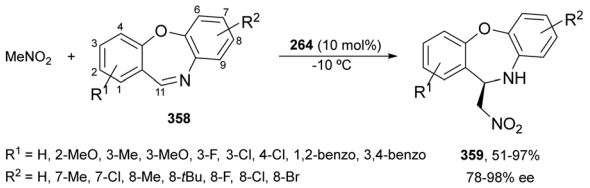


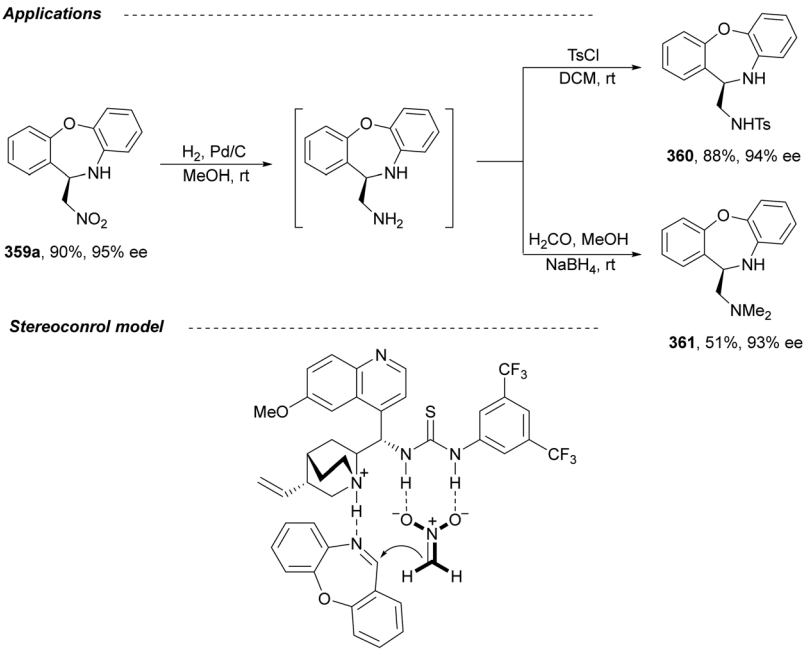
R^1 = H, 5-Me, 5-MeO, 5-Cl, 5-Br, 5-CF_3, 7-Me, 4,6-Me_2, 4,6-Cl_2
R^2 = *n*Bu
R^2-R^2 = $(CH_2)_5$, $O(CH_2CH_2)_2$, $(CH_2)_6$



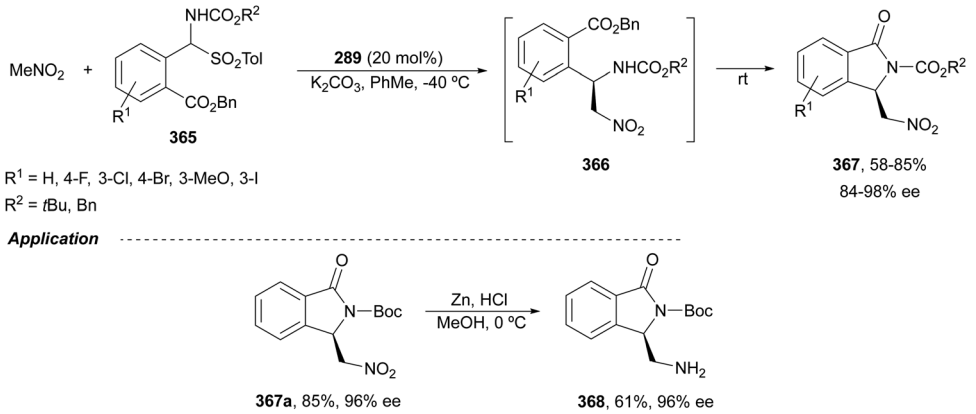
Scheme 110 Asymmetric aza-Henry reaction of nitromethane with 3*H*-indoles **362** under thiourea **264** catalysis.

Chimni and co-workers[257] employed the same quinine-derived 6′-OH organocatalyst **422** for the addition of nitroalkanes to isatin-derived *N*-Boc ketimines **170** to obtain products **423** in 60–80% yields, 54 : 46–72 : 28 dr and 56–89% ee (Fig. 15). In the proposed model for the TSI, the quinuclidine tertiary amine can deprotonate the nitroalkane which attacks on the *Re*-face of the

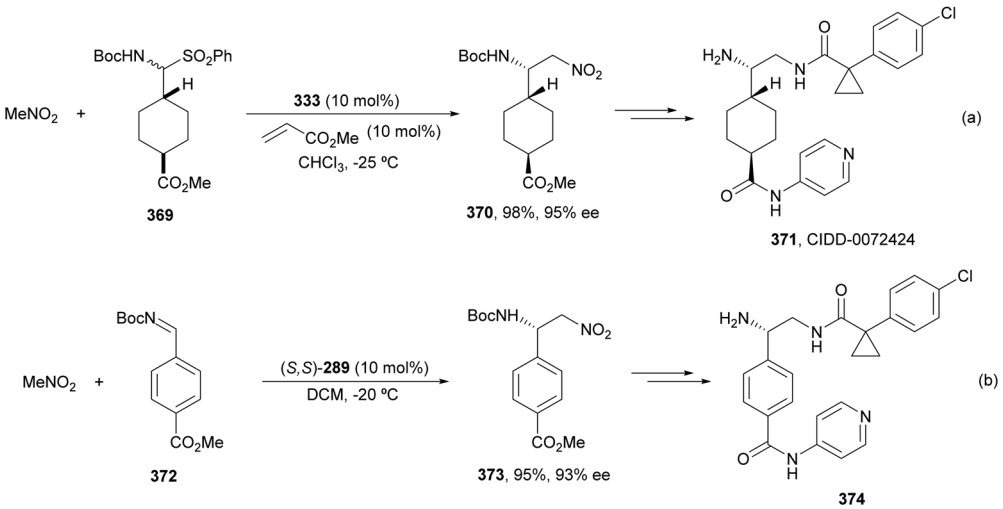




Scheme 109 Asymmetric aza-Henry reaction of nitromethane with dibenzo[*b*,*f*][1,4]oxazepines **358** under thiourea **264** catalysis.



Scheme 111 Asymmetric aza-Henry reaction of nitromethane with α-amido sulfones **365** under thiourea **289** catalysis followed by *in situ* lactamization.



Scheme 112 Asymmetric aza-Henry reaction of nitromethane with α-amido sulfone **369** and *N*-Boc-imine **372** catalyzed by thioureas **333** and **289** towards PKC-epsilon inhibitors **371** and **374**, respectively.

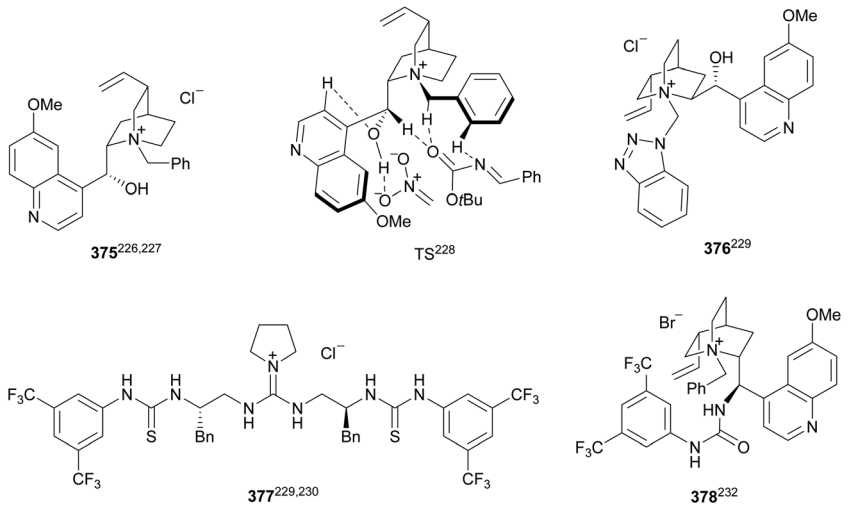
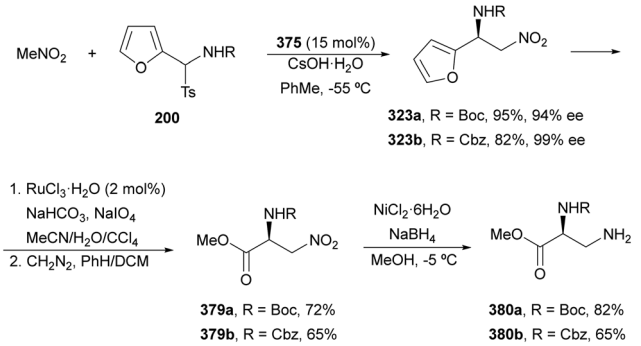


Fig. 13 Phase-transfer catalysis for the asymmetric aza-Henry reaction of *N*-acyl imines with nitroalkanes.

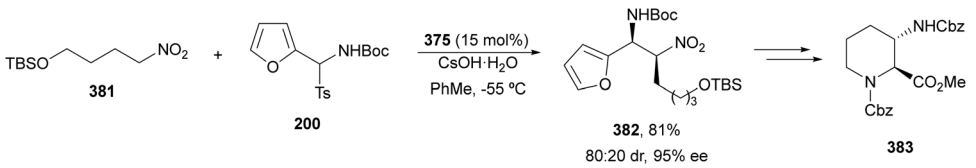


Scheme 113 Asymmetric aza-Henry reaction of nitromethane with furfural derived α-amido sulfones **200** using **375** as a phase-transfer catalyst.

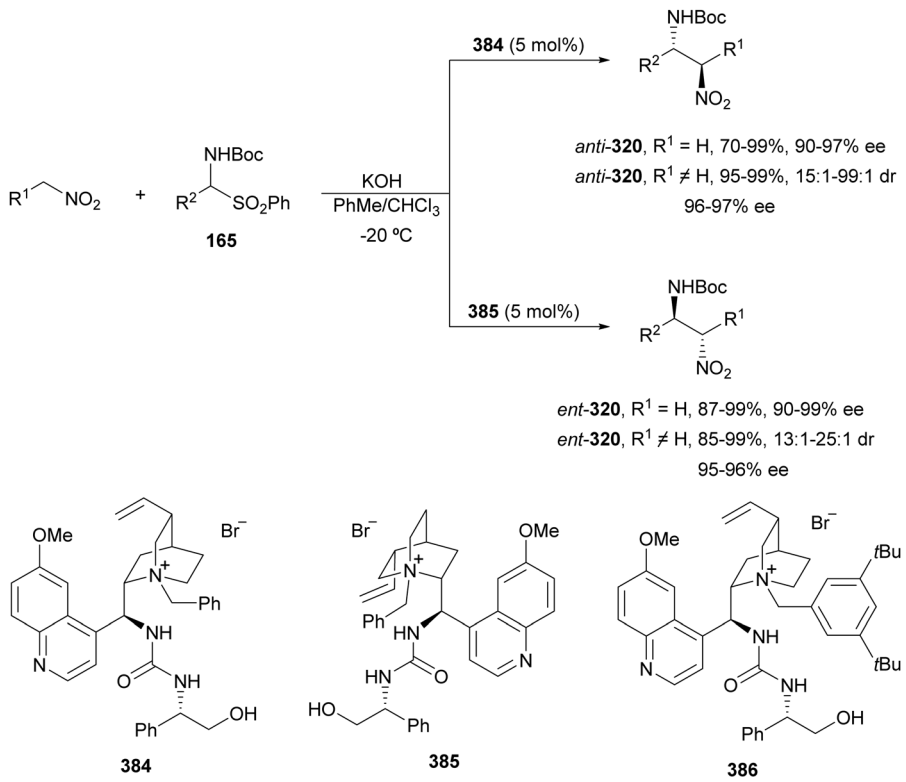
ketimine activated through hydrogen bonding with the C6′–OH of the catalyst. Feng and co-workers[258] employed a chiral bifunctional guanidine **424** (Fig. 15) for the aza-Henry reaction of nitromethane with isatin-derived *N*-Boc ketimines **170**. The resulting 3-aminooxindoles **423** were obtained in 81–99% yields and 85–94% ee. In the proposed TSII, the guanidine deprotonates the nitroalkane and forms a dual hydrogen bonding and the amide acts as a Brønsted acid to activate the ketimine by hydrogen bonding.

The addition of nitromethane to trifluoromethyl aryl ketimines **401** has been recently carried out by Krstić and co-workers[259] using a bifunctional iminophosphorane **425** (Scheme 128). β-Nitroamines **402** were isolated in moderate to good yields and enantioselectivities. A possible TS was proposed in which the thiourea unit interacts by hydrogen bonding with the ketimine and the nitromethane with the iminophosphorane and the thiourea.

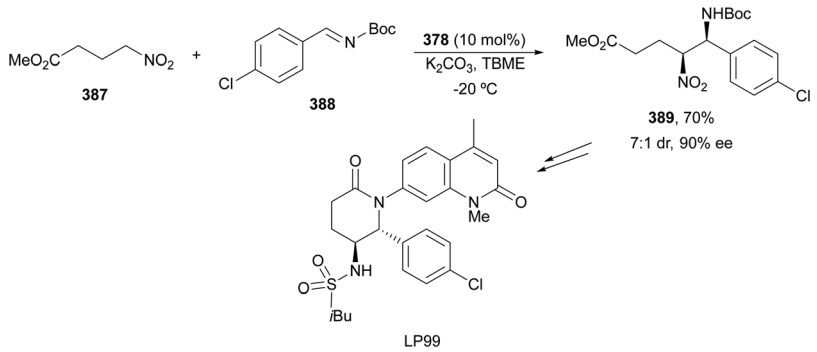
N-Acyl hydrazones **426** have been used as electrophiles in the asymmetric aza-Henry reaction using *Cinchona*-derived bases as catalysts.[260] Under quinine catalysis, β-nitrohydrazides **427** derived from nitromethane were obtained in moderate to good



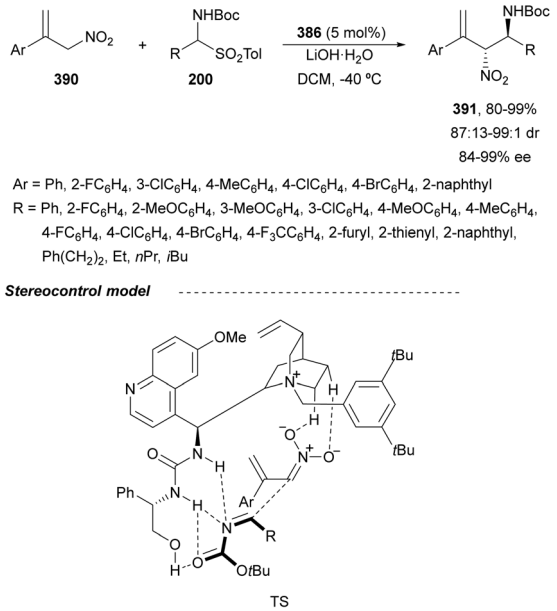
Scheme 114 Asymmetric aza-Henry reaction of nitroalkane **381** with α-amido sulfone **200** using **375** as a phase-transfer catalyst.



Scheme 115 Asymmetric enantiodivergent aza-Henry reaction of nitroalkanes with α-amido sulfones **165** using **384–386** as phase-transfer catalysts.



Scheme 116 Asymmetric aza-Henry reaction of methyl 4-nitrobutanoate (**387**) with *N*-Boc imine **388** using **378** as a phase-transfer catalyst.



Scheme 117 Asymmetric aza-Henry reaction of nitroalkenes **390** with α-amido sulfones **200** using phase-transfer catalyst **386**.

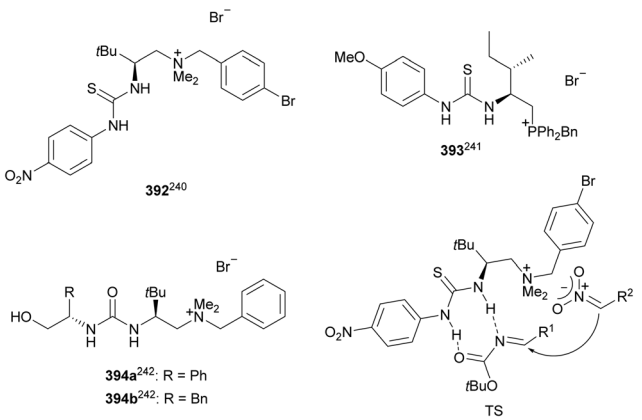
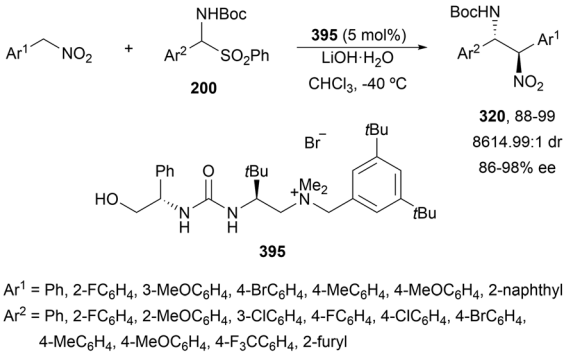


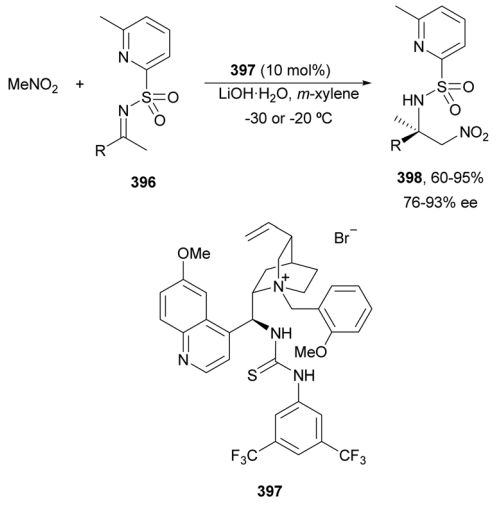
Fig. 14 Catalysts used for the asymmetric aza-Henry reaction of nitroalkanes with *N*-Boc α-amido sulfones **200**.



Scheme 118 Asymmetric aza-Henry reaction of α-aryl nitromethanes with α-amido sulfones **200** using phase-transfer catalyst **395**.

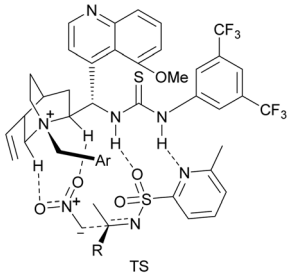
yields and modest enantioselectivities (Scheme 129). In the case of nitroethane, low diastereoselectivity was observed (up to 2.4 : 1). According to experimental studies, including kinetics, the catalyst activates both reagents and in the TS the hydrazone protonation and the C–C bond forming reaction occurs through a concerted process.

In 2004, Johnston and co-workers[261] reported an enantioselective aza-Henry reaction of nitromethane and nitroethane with *N*-Boc imines **161** catalyzed by the Brønsted acid salt **428** (Fig. 16). This process was carried out at −20 °C to obtain *anti*-β-nitroamines **320** with 50–69% yields, 7 : 1–19 : 1 dr and 59–90% ee. A modified chiral bis(amidine) (BAM) Brønsted acid **429** (Fig. 16) was employed as a catalyst for the addition of nitroacetates **330** (R^1 = H) to *N*-Boc imines **161** in toluene at −78 °C to provide mainly *anti*-products **332**, which were further reduced with $NaBH_4/CoCl_2$ to the corresponding *anti*-α,β-diamino acid derivatives **196** in 67–95% overall yield, 1 : 2–11 : 1 dr and 69–88 ee.[262] In the case of α-substituted nitroacetates **330** ($R^1 \neq$ H) a methoxy substitution in the catalyst **430**[263] (Fig. 16) improved the results to afford *syn*-α-nitro-β-amino acid derivatives **332** with 59–88% yield, 5 : 1–>20 : 1 dr and 94–99% ee. Pyrrolidine BAM $\mathbf{431}_2\cdot(HOTf)_3$[264] (Fig. 16) was the most efficient catalyst to improve the enantioselectivity in the reaction of substituted nitroalkanes with *N*-Boc imines **161** providing nitroamines **320** with 61–100% yield, 7 : 1–35 : 1 dr and 71–95% ee working in toluene at −20 °C.

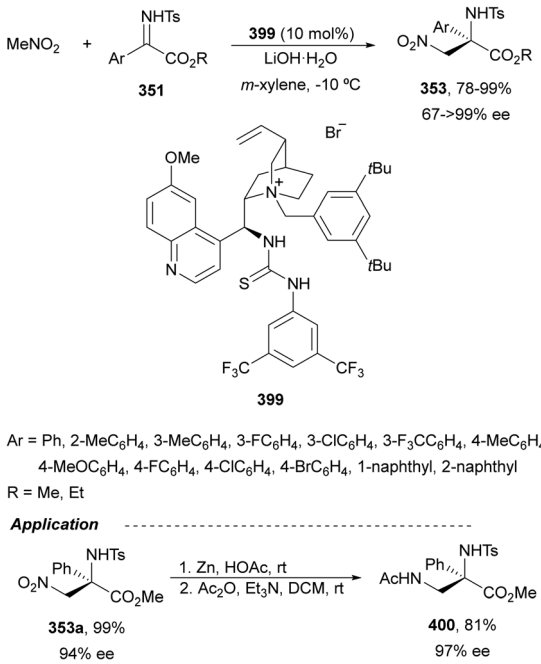


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-FC_6H_4, 3-BrC_6H_4, 3-$MeOC_6H_4$, 2-naphthyl, 2-furyl

Stereocontrol model



Scheme 119 Asymmetric aza-Henry reaction of nitromethane with ketimines **396** using a phase-transfer catalyst **397**.



Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 3-FC_6H_4, 3-ClC_6H_4, 3-$F_3CC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 1-naphthyl, 2-naphthyl

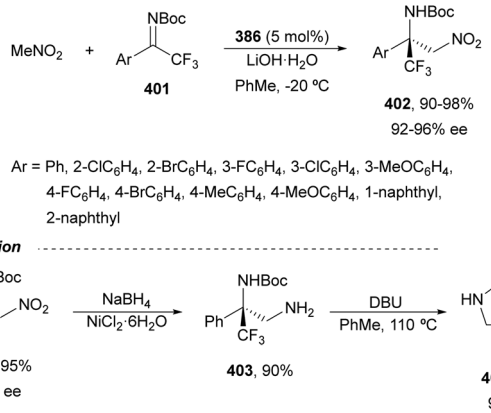
R = Me, Et

Application

353a, 99%
94% ee

400, 81%
97% ee

Scheme 120 Asymmetric aza-Henry reaction of nitromethane with ketimines **351** using the phase-transfer catalyst **399**.



Ar = Ph, 2-ClC_6H_4, 2-BrC_6H_4, 3-FC_6H_4, 3-ClC_6H_4, 3-$MeOC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, 2-naphthyl

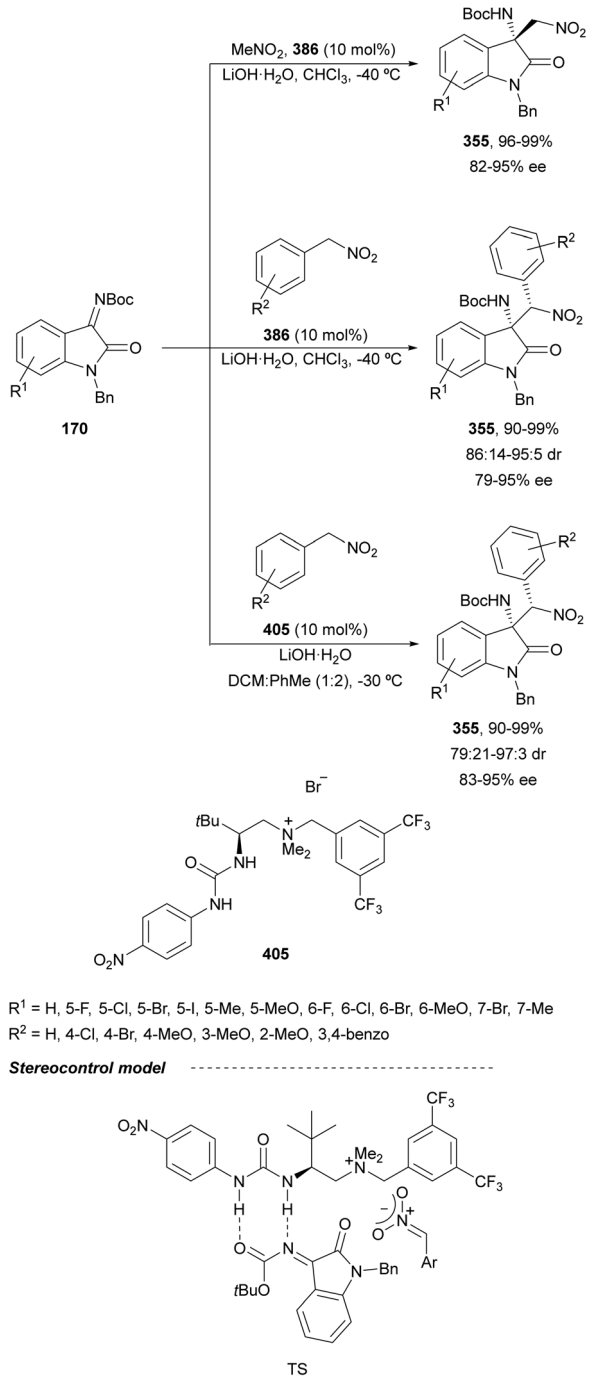
Application

Scheme 121 Asymmetric aza-Henry reaction of nitromethane with trifluoromethyl ketimines **401** using a phase-transfer catalyst **386**.

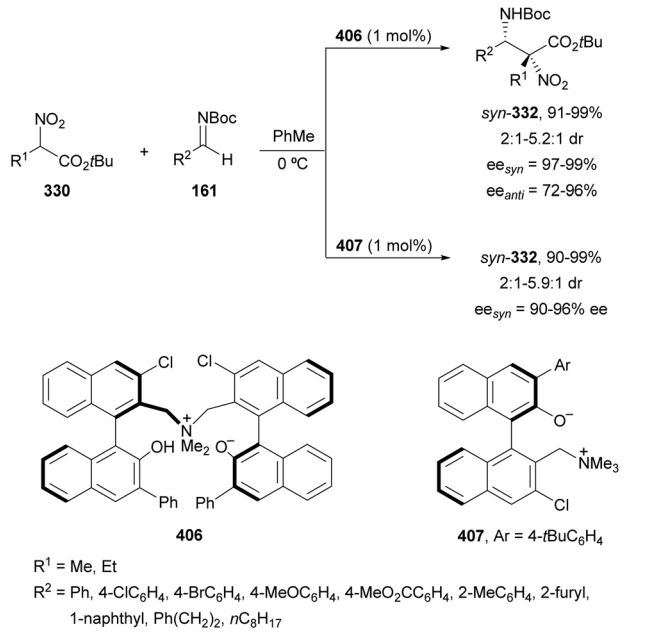
Subsequent studies of Johnston and co-workers were focused on the synthesis of therapeutics. Based on the asymmetric aza-Henry reaction of α-aryl nitromethanes to *N*-Boc aldimines **161**, *anti*-products **320** were obtained up to 99% yield, 131 : 1 dr and 93% ee under modified pyrrolidine BAM **432** catalysis (Fig. 16).[265] They found out that the free base was equally effective than the Brønsted acid salt of the BAM compounds. The *cis*-stilbene **320a** was prepared on a large scale using β-MeO PBAM **433** as a catalyst (5 mol%) in toluene at −20 °C (Scheme 130).[266] After recrystallization, 15.98 g of product **320a** was obtained in 62% yield of diastereo- and enantiomerically pure compound. This compound is the key product for the synthesis of (−)-nutlin-3, a potent *cis*-imidazoline p53/MDM2 inhibitor discovered by Hoffmann-La Roche.[174] *cis*-Imidazolines could disrupt the protein–protein interaction between p53 and MDM2, thereby including apoptosis in cancer cells. Non-symmetric *cis*-stilbene diamines and *cis*-imidazolines were accessible by asymmetric aza-Henry reactions of different aryl aldimines with differently substituted α-aryl nitromethanes using different mono(amidine) MAM **434** and **435** (Fig. 16) as an organocatalyst.[267] Further development of an intermittent-flow enantioselective aza-Henry reaction for the synthesis of **320a** on a multigram scale has been reported by Johnston and co-workers.[268]

The first enantioselective synthesis of a potent GlyT1 inhibitor, which can increase glycine levels and NMDA signaling thereby providing a promising therapeutic target for the treatment of schizophrenia,[269] was described by Johnston and co-workers.[270] Nitroazetidine **436** reacted with *N*-Boc benzylidene imine under PBAM (**437**)·HOTf catalysis in toluene at −20 °C to obtain product **438** in 93% yield and 92% ee, whereas the free amine afforded product **438** with 87% yield and 86% ee (Scheme 131). This intermediate **438** was transformed into the target azetidine (−)-**439** through a short reaction sequence.

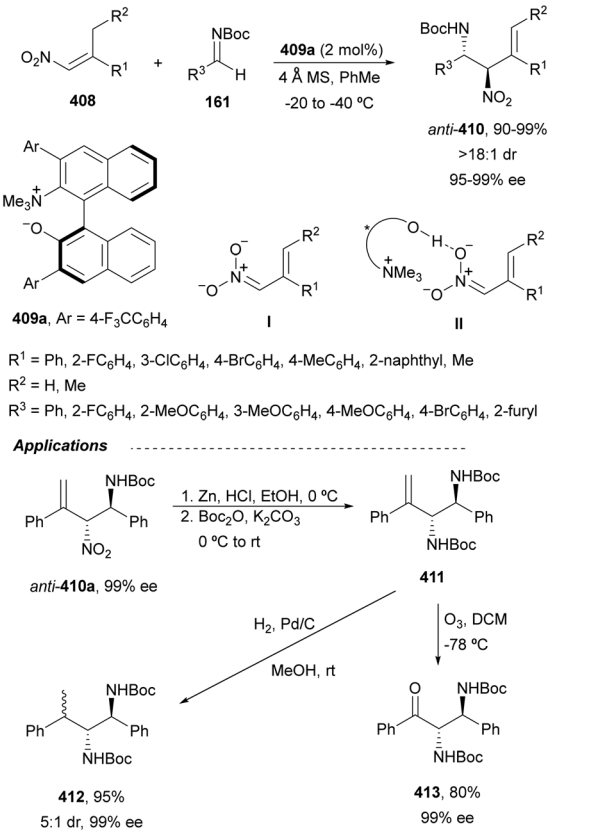
Enantioselective synthesis of VNI, a potent inhibitor of CYP51, which showed a parasitological cure of mice infected with *T. cruci* (Chagas disease), has been performed by Johnston and co-workers.[271] The reaction of α-bromo nitromethane **440** with 2,4-dichlorobenzylidene imine **161** in toluene at −20 °C



Scheme 122 Asymmetric aza-Henry reaction of nitroalkanes with isatin-derived *N*-Boc ketimines **170** using phase-transfer catalysts **386** and **405**.

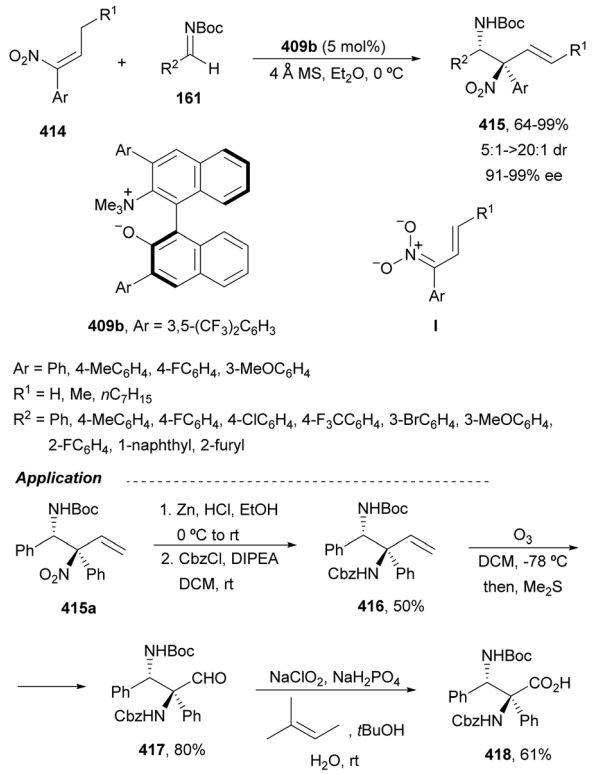


Scheme 123 Asymmetric aza-Henry reaction of α-nitro esters **330** with *N*-Boc imines **161** using betaines **406** and **407** as catalysts.

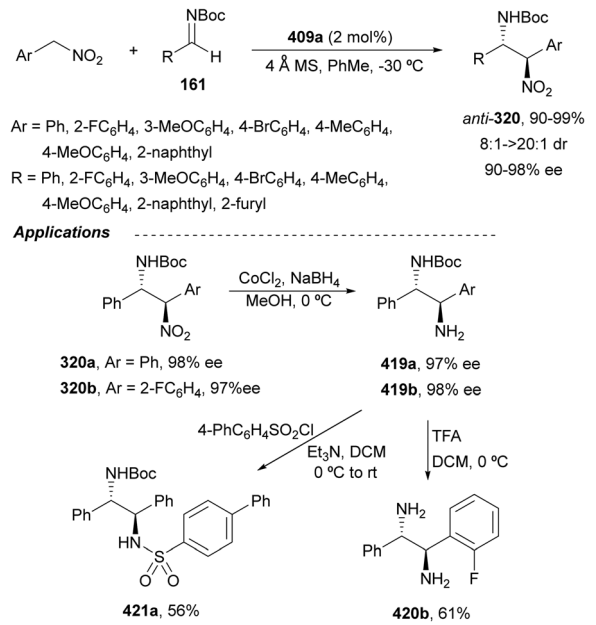


Scheme 124 Asymmetric aza-Henry reaction of β,β-disubstituted nitroalkenes **408** with *N*-Boc imines **161** under betaine **409a** catalysis.

using **431** as an organocatalyst gave product **441** in >98% yield and 98% ee as a 1:1 mixture of diastereomers on 47 mmol scale (Scheme 132). Treatment of the mixture with cobalt boride provided diamine derivative **442** in 52% yield. However, the aza-Henry reaction with nitromethane as a solvent gave a mixture of mono and diaddition products. Compound **442** was further transformed into (+)-VNI after three more steps. This aza-Henry reaction was performed with *N*-Boc aliphatic aldimines using the BAM *ent*-**431**·HOTf as a catalyst to obtain products of the type *ent*-**441** with 39–94% yield and 76–93% ee, which were transformed into α-amino amides.[272]

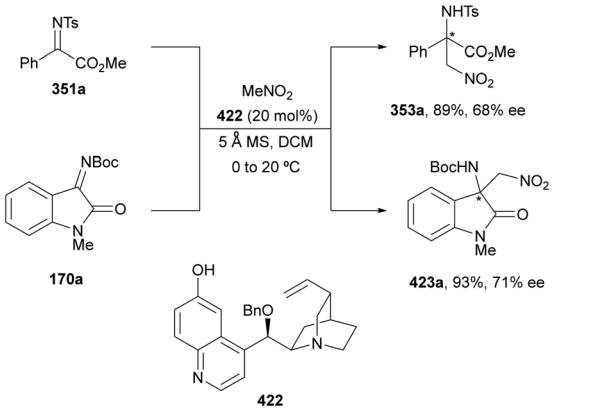


Scheme 125 Asymmetric aza-Henry reaction of α-aryl-β-monosubstituted nitroolefins **414** with *N*-Boc imines **161** under betaine **409b** catalysis.



Scheme 126 Asymmetric aza-Henry reaction of α-aryl nitromethanes with *N*-Boc imines **161** under betaine **409a** catalysis.

DFT calculations by Dudding and co-workers,[273,274] *e.g.* for the reaction of nitromethane with *N*-Boc benzylidene imine using the BAM **428** as a catalyst, supported the cooperative role of this catalyst. In the TS, the imine formed a dual hydrogen bonding as



Scheme 127 Asymmetric aza-Henry reaction of nitromethane with α-keto ester **351a** or isatin-derived ketimine **170a** under quinine-derived **422** catalysis.

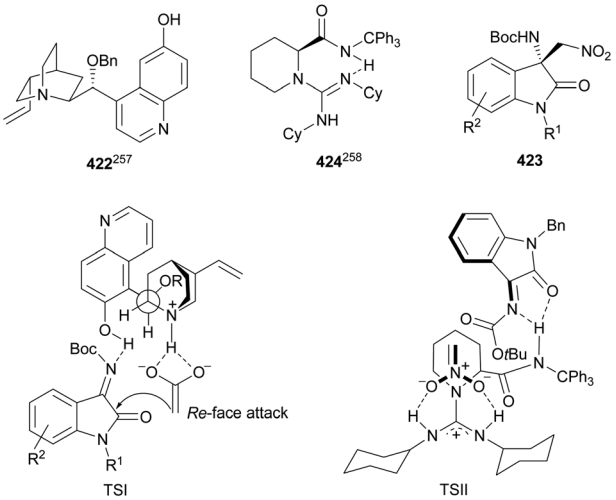
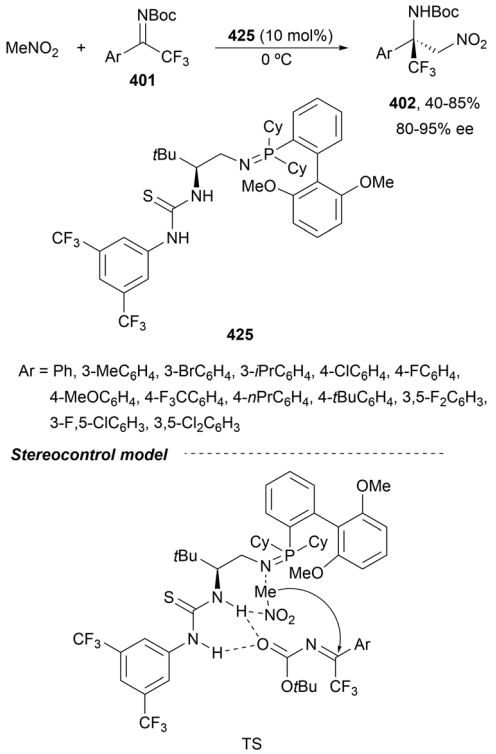


Fig. 15 Chiral bases used as catalysts for the addition of nitromethane to isatin-derived *N*-Boc ketimines **170**.

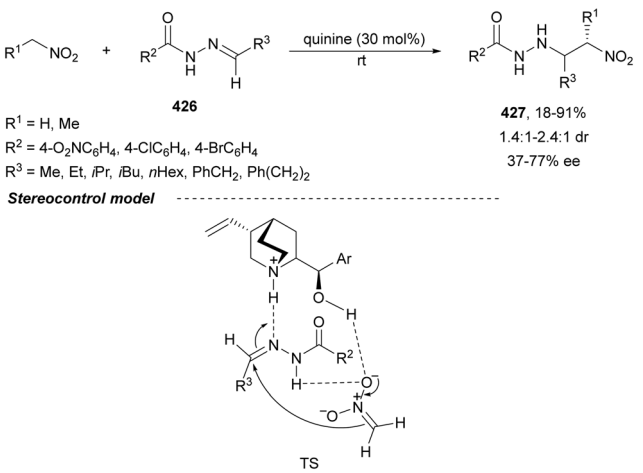
well as the nitronate (Fig. 17). A synclinal alignment of both reagents maximized orbital and electrostatic interactions.

Hindered α-substituted α-nitro esters **330** were used as nucleophiles for the addition of *N*-Boc imines **161** using **431**·$HNTf_2$ as a catalyst.[275] In this case, *anti*-**332** were obtained, whereas using catalyst **430**[263] resulted *syn*-products. These results are another example of diastereodivergence[52] based on the BAM derived Brønsted acid–base organocatalyst (Scheme 133). Compounds *anti*-**332** were obtained with 46–76% yields, 4 : 1–> 20 : 1 dr and 78–99% ee. Reduction of the nitro group provided α-substituted *anti*-α,β-diamino esters. Stereochemical-determining arrangements to obtain *anti* and *syn* diastereomers are depicted in Scheme 133.

In a recent work of Johnston and co-workers,[276] α-fluoro nitroalkanes **443** were allowed to react with *N*-Boc imines **161** using **432** or **432**·$HNTf_2$, or *N*-benzylquininium chloride (**375**).[227] This study was also carried out with non-fluorinated nitroalkanes in order to compare the resulted diastereoselectivity. In the case



Scheme 128 Asymmetric aza-Henry reaction of nitromethane with trifluoromethyl ketimines **401** under phosphorane **425** catalysis.



Scheme 129 Asymmetric aza-Henry reaction of nitroalkanes with *N*-acyl hydrazones **426** under quinine catalysis.

of α-fluoro nitroalkanes **443,** four possible diastereomers **444** can form type **I–IV** depending on the substituents (Scheme 134). *anti*-Diastereoselectivity was mainly observed with nitroalkanes (1 : 1–20 : 1) and α-aryl-α-fluoro nitromethanes (2.7 : 1–5.2 : 1) using the three catalysts, whereas reversal *syn*-diastereoselectivity was mainly obtained only with type **III** and type **IV** α-alkyl-α-fluoro nitromethanes (2.4 : 1–7.2 : 1). The stereochemistry-determining arrangements are depicted in Scheme 134. Regardless of the employed catalyst, the imine *Si*-face is favored and the bifunctional activation of the imine and nitronate favored a synclinal arrangement of the amine nitrogen and NO_2 according to Dudding's analysis.[273,274]

Chiral bases such as alkoxides in ammonium betaines can be used for the asymmetric aza-Henry reaction of activated nitro compounds with aldimines. In the case of ketimines, the reaction with nitromethane was efficiently performed with *Cinchona*-derived alkaloids, guanidines and phosphoranes. Chiral Brønsted acids derived from bis(amidine) and mono bis(amidine) have been employed in the reaction of activated nitro compounds with aldimines. This strategy has been applied to the synthesis of 1,2-diamines, precursors of therapeutics such as (−)-nutlin-3, azetidine (−)-**439** and (+)-VNI.

3.3. Imine–imine coupling reactions

Asymmetric imine–imine coupling reactions to provide diastereoselectively and enantiomerically enriched 1,2-diamines under catalytic conditions are some of the most direct and challenging strategies. This type of process has been performed (a) by a homocoupling process of unprotected imines such as an aza-pinacol coupling and (b) by a reaction of *N*-alkyl imines with aldimines *via* formation of an azaallyl anion.

In 2017, Tang and co-workers[277] reported the asymmetric reductive coupling of isoquinolines mediated by chiral diborons (D–B) under mild reaction conditions. Diboron **445** derived from (1*S*,2*S*)-1,2-diphenylethane-1,2-diol (0.75 equivalents) reacted with isoquinolines to form intermediates **I,** which underwent a concerted [3,3]-sigmatropic rearrangement to give products **446.** These compounds were treated with acetyl chloride to obtain bisisoquinoline diacetamides **447** in good yields and high enantioselectivities (Scheme 135). Mechanistic investigations[278] suggested the activation of the B–B bond *via* double N–B coordination followed by [3,3]-sigmatropic migration from intermediate **I**.

The former methodology was applied by the same group[279] to unsubstituted aldimines prepared *in situ* by conventional methods using a non-C_2-symmetric chiral diboron **448**. A broad scope of aromatic, heteroaromatic and aliphatic imines as well as cyclic imines and *N*-methyl aldimines gave the corresponding *syn*-1,2-diamines **420**, **449** and **450** in high yields and enantioselectivities (Scheme 136a–d). This process was scaled-up to 50 g starting from benzaldehyde and ammonia in MeOH, followed by a reaction with **448** in THF at room temperature with recovery of the diol. Stable aromatic imines such as benzaldimine and *N*-methylbenzaldimine were transformed into the corresponding 1,2-diamines using a stoichiometric amount of $(BNeop)_2$ and a catalytic amount of chiral diol **451** (30 mol%). In the case of *N*-methylbenzaldimine, the diamine **450a** was obtained in 88% yield and 96% ee, after treatment of N–BNeop diamine with MeOH (Scheme 136e).

The homocoupling of alkyl aryl ketimines **452** provided tetrasubstituted *syn*-1,2-diamines **453**. Tang's group[280] performed the reductive coupling of aryl methyl ketimines **452** (R = Me) with diboron **448** to obtain diamines **453** up to 96% yield and 99% ee (Scheme 137). However, for other ketimines **452** with R ≠ Me, the diboron **454** gave better results than **448** affording products **453** (R ≠ Me) up to 92% yield and 99% ee. DFT calculations revealed that the two chiral diborons utilize

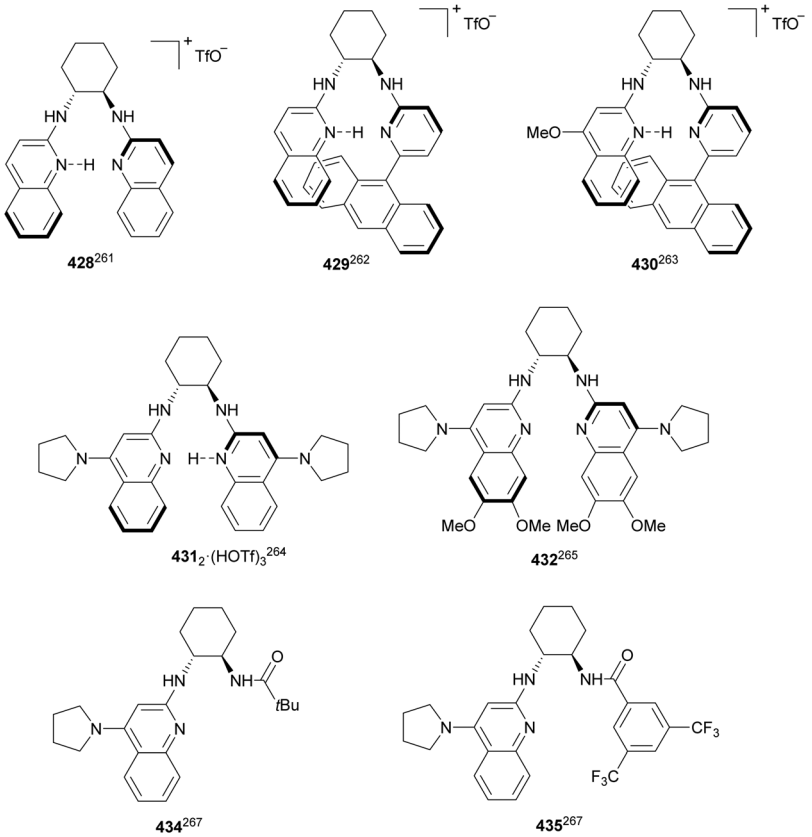
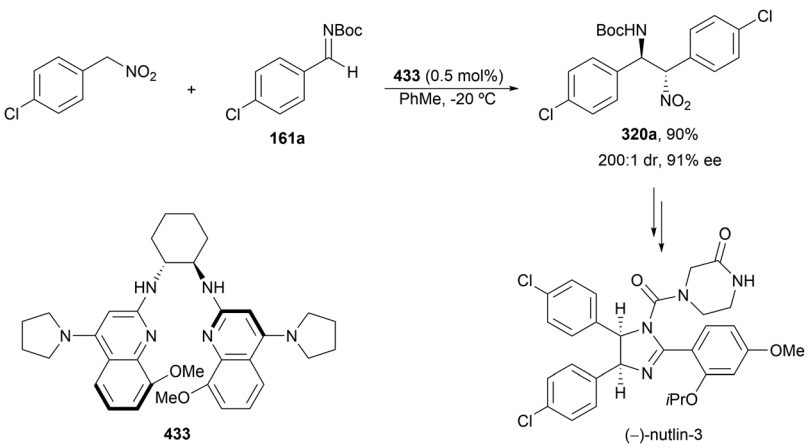


Fig. 16 Mono and bis(AMidine)-derived catalysts for the asymmetric aza-Henry reaction.

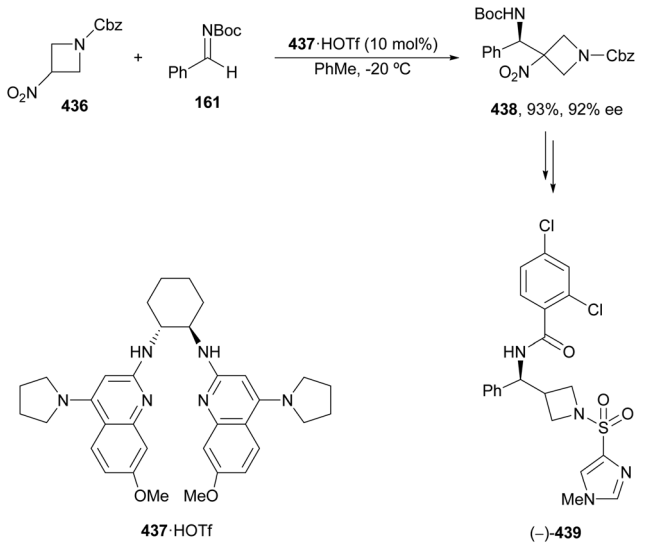


Scheme 130 Asymmetric aza-Henry reaction of α-(4-chlorophenyl)nitromethane with *N*-Boc-4-chlorobenzylidene imine under β-MeO PBAM (**433**) catalysis and application to (–)-nutlin-3.

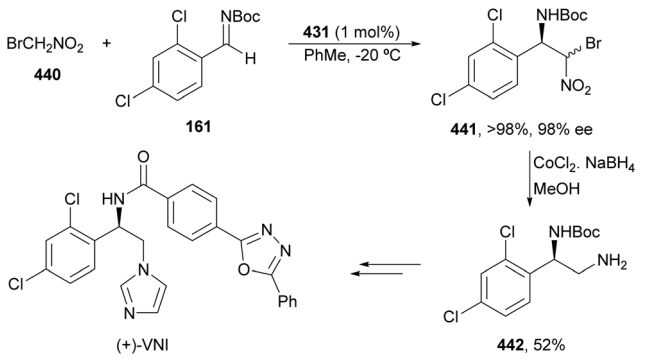
two different conformational assembling to direct the reductive homocoupling.

Zhu and co-workers[281] have reported the nucleophilic addition of hydrazones **455** to *N*-Boc aldimines **161** under CPA catalysis. In the presence of (*S*)-**456** working in toluene at −20 °C, *N*-alkyl hydrazones behaved as α-azo carbanion equivalents to provide 1,2-diamine derivatives *anti*-**457** in excellent yields with high chemo-, diastereo, and enantioselectivity (Scheme 138). Product **457a** was transformed into monoprotected diamine **458** in two steps and into unprotected diamine **459** in 43 and 96% yield, respectively. The stereochemical outcome was explained by formation of two hydrogen bonding with bifunctional CPA through the TS depicted in Scheme 138.

With respect to the second strategy based on the reaction of imines with *N*-alkyl imines by formation of azaallyl anions,[282] Kobayashi and co-workers[283] described an imine–imine cross-coupling using imines bearing a 9-fluorenyl moiety at the nitrogen atom and in the presence of a catalytic amount of potassium



Scheme 131 Asymmetric aza-Henry reaction of nitroazetidine **436** with *N*-Boc benzylidene imine **161** under ^{7}(MeO) PBAM (**437**)·HOTf catalysis and application to (–)-**439**.



Scheme 132 Asymmetric aza-Henry reaction of bromomethane **440** with 2,4-dichlorobenzylidene imine under BAM **431** catalysis.

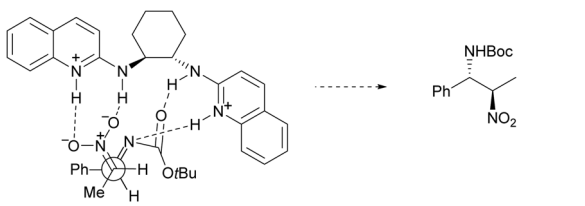
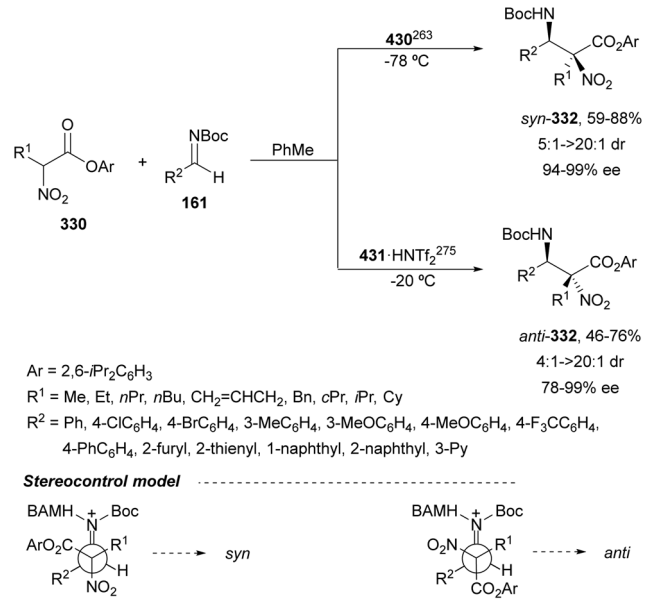
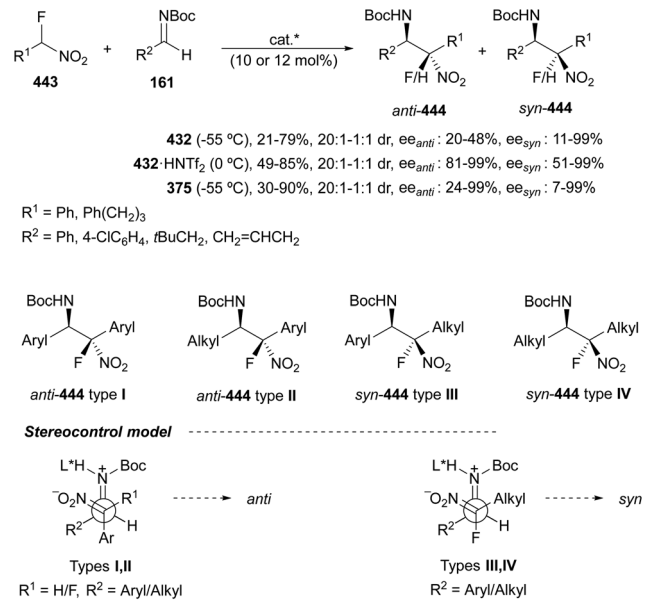


Fig. 17 Proposed TS for the asymmetric aza-Henry reaction catalyzed by BAM **428**.



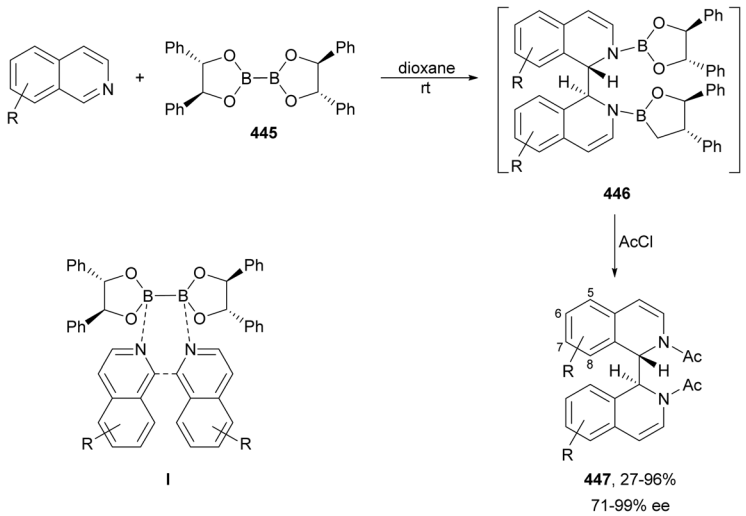
Scheme 133 Asymmetric aza-Henry reaction of α-substituted α-nitro esters **330** with *N*-Boc imines **161** under **430** or **431**·HNTf$_2$ catalysis.



Scheme 134 Asymmetric aza-Henry reaction of α-fluoro nitroalkanes **443** with *N*-Boc imines under BAM **432** or **432**·HNTf$_2$ or **375** catalysis.

2,2,2-trifluoroethoxide as a base. The asymmetric version was performed with a chiral guanidine **204** as a base for the cross-coupling of *N*-Boc benzaldimine **161** with *N*-fluorenyl glyoxylateimine **203** to furnish adduct *syn*-**205** in 90% yield, 98 : 2 dr and 98% ee (Scheme 139). Compound **205** was transformed into a 3-amino-β-lactam by cyclization of the α,β-diamino acid *tert*-butyl ester. It is assumed that the carbanion **I** is formed and reacts through the α-position of the ester group.

The former imine umpolung was recently applied by Luo, Deng and co-workers[284] to the imine cross-coupling of ketimines **460** with *N*-methoxycarbonyl imines **161** under asymmetric PTC conditions (Scheme 140). Newly designed *Cinchona*-alkaloid ammonium salt **461** or its pseudoenantiomer **462** gave products **463** or *ent*-**463**, respectively, and the regioisomer **464** with good yields and diastereo- and enantioselectivities, although with moderate to good regioselectivity. In this procedure, intermediate **I** is formed by the azaallyl anion and the tetraalkyl ammonium cation. On the basis of ^{1}H NMR titration studies, interaction modes **A** or **B** between the BArF^{-} ammonium salts **461′** or **462′**



Scheme 135 Asymmetric aza-pinacol coupling of isoquinolines mediated by diboron **445**.

with the electrophilic imine were postulated. Computational studies performed by Smith and co-workers[285] proposed hydrogen bonding interactions between ammonium α-CH_8 with the nitrogen of the imine and H_{12} and $H_{12'}$ with the carbonyl group was proposed in activation mode **A**. Hydrogen bonding interactions between H_2, H_6 and $H_{12'}$ of ammonium salts shifted downfield **462′** in the titration studies (mode **B**).

Ketimine–ketimine cross-coupling was described by Lin, Lu and co-workers[286] using chiral squaramide **236** and thiourea **465** as bifunctional organocatalysts. Isatin-derived *N*-2,2,2-trifluoromethyl ketimines **466** were used as pronucleophile and *N*-Boc ketimines **170** as electrophiles to provide, in the presence of squaramide **236**, products **467** in high yields and diastereo- and enantioselectivities (Scheme 141). This type of cross-coupling was carried out with ketimines **468** and isatin-derived *N*-Boc ketimines **170**. In this case, the best organocatalyst was thiourea **465** to provide compounds **469** in high yields and enantioselectivities. Both processes were scaled-up to grams maintaining yields and stereoselectivities.

The copper(I)-catalyzed asymmetric ketimine–imine cross-coupling allows the synthesis of *syn*-1,2-diamines. Tian, Yin and co-workers[287] have performed the addition of ketimines derived from trifluoroacetophenone **470** to *N*-Boc aldimines **161** using mesitylcopper and (R,R_P)-Taniaphos **471** as a chiral catalyst (Scheme 142). A broad scope of products **472** were obtained regioselectively in moderate to good yields and diastereoselectivities, with very good enantioselectivities. A gram-scale reaction was carried out with 4-nitrobenzylamine-derived trifluoroacetophenone imine and *N*-Boc benzaldimine to obtain *syn*-**472a** in 75% yield, >20 : 1 dr and 96% ee. This product was transformed into *N*-tosyl diamine **473** by reduction with Zn/HOAc, removal of the ketimine moiety with concentrated HCl and tosylation. Intermediate **I** has been proposed to explain the formation of the azaallyl anion.

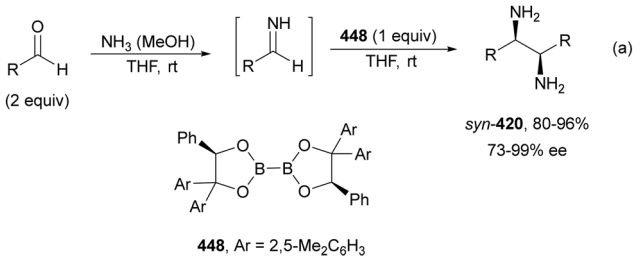
Asymmetric homocoupling of imines has been promoted by chiral diborons in stoichiometric amounts to provide *syn*-1,2-diamines. However, cross-coupling of hydrazones and imines using a CPA formed *anti*-1,2-diamine derivatives. In the case of a second strategy *via* formation of an azaallyl anion, *N*-alkyl imines were added to imines using a chiral organocatalyst (PTC or squaramides and thioureas) to furnish *anti*-1,2-diamine derivatives. When a Cu/phosphine chiral complex was used as a catalyst, *syn*-diamines were formed.

3.4. Other addition to imines

Reductive coupling of enamines with imines under asymmetric copper catalysis as well as photocatalytic enantioselective α-amino alkylation of imines will be considered in this section as also other strategies for the synthesis of 1,2-diamines.

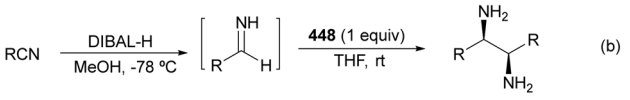
Asymmetric copper-catalyzed reductive coupling of azadienes **474** with *N*-diphenylphosphinoyl (DPP) imines **167** or ketimines **250** allowed the synthesis of *anti*-1,2-diamines. Malcolmson and co-workers[288] described this chemoselective transformation by using $Cu(OAc)_2$ and (*S*,*S*)-Ph-Bpe (**475**) as a chiral ligand in the presence of dimethoxymethylsilane (DMMS) as a reducing agent and *t*BuOH as an additive in THF at 5 °C (Scheme 143). The resulting diamines **476** and **477** were obtained in >20 : 1 diastereomeric ratio and excellent enantioselectivities. Under these reaction conditions, a Cu-catalyzed imine hydroxylation was carried out to form a azaallyl copper intermediate **I** which added to the electrophilic imines. Product **476a** was transformed into orthogonally protected diamine **478** in two steps in 85% yield and into **479** in 80% yield.

The same group[289] recently reported an asymmetric diastereodivergent[52] synthesis of *syn*- and *anti*-1,2-diamines by a Cu-catalyzed reductive coupling of 2-azatrienes **480** with imines **167**. With (*S*,*S*)-Ph-Bpe (**475**) as a chiral ligand, *anti*-diamines **481** were obtained (up to 97% yield, >20 : 1 dr, >20 : 1 rr and 76% ee), whereas with

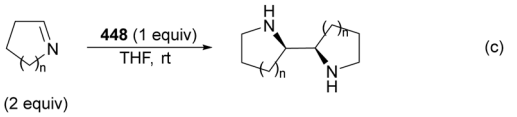


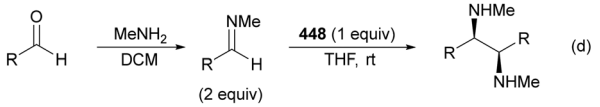
448, Ar = 2,5-$Me_2C_6H_3$

R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$F_3COC_6H_4$, 4-$MeO_2CC_6H_4$, 4-$HCCC_6H_4$, 2-ClC_6H_4, 2-BrC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2-PhC_6H_4, 3-ClC_6H_4, 3-$F_3CC_6H_4$, 3-$EtOC_6H_4$, 3,5-$F_2C_6H_3$, 3,5-$Me_2C_6H_3$, 2,4,6-$F_3C_6H_2$, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-naphthyl, 1-naphthyl, 4-(BzMeN)C_6H_4

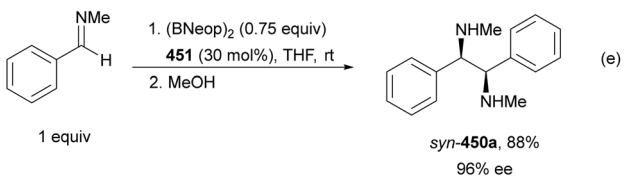


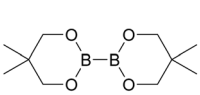
R = *n*Pr, *n*Bu, *i*Pr, *i*Bu, Cy, Bn, 2-$BrC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 3-$ClC_6H_4CH_2$, 2-thienylCH_2, $HCC(CH_2)_3$, CH_2=$CH(CH_2)_3$, CH_2=$CH(CH_2)_2$, $Me(CH_2)_{10}$



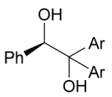


R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3OC_6H_4$, 4-$MeO_2CC_6H_4$, 4-$HCCC_6H_4$, 2-ClC_6H_4, 2-BrC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 3-ClC_6H_4, 3-FC_6H_4, 3-$EtOC_6H_4$, 3,5-$F_2C_6H_3$, 2-naphthyl, 1-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl





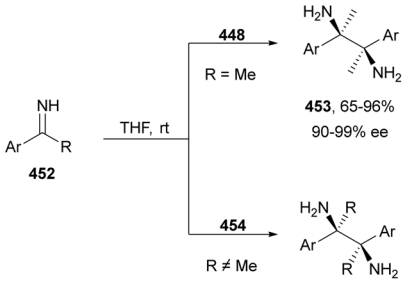
(BNeop)$_2$

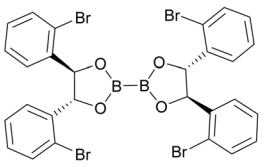


451, Ar = 2,5-$Me_2C_6H_3$

Scheme 136 Asymmetric aza-pinacol coupling of aldimines mediated by diboron **448**.

*t*Bu-BDPP (**482**) resulted *syn*-diamines **481** (up to 76% yield, >20 : 1 dr, >20 : 1 rr and 94% ee) (Scheme 144). Diastereodivergent models **I** and **II** were proposed, for Ph-Bpe model **I** is formed through *O*-coordination of the imine and for *t*Bu-BDPP in model **II** the nitrogen atom of the imine was coordinated.

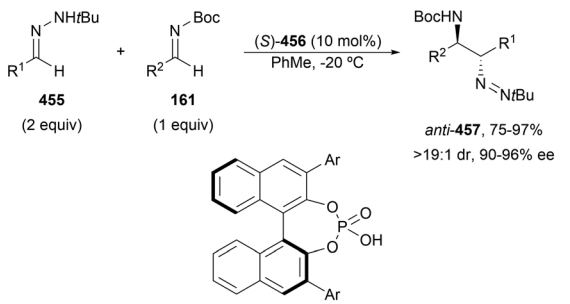




454

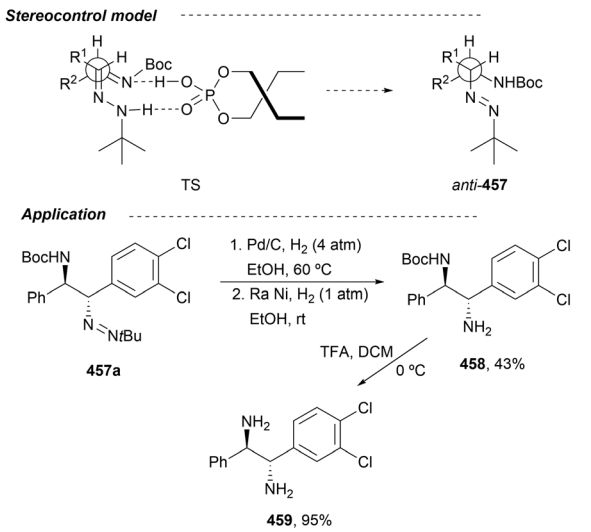
R = Me, Et, *n*Pr, *n*Bu, *i*Bu, *n*Hex
Ar = Ph, 2-MeC_6H_4, 2-$MeOC_6H_4$, 3-ClC_6H_4, 3-$MeOC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 4-*t*BuC_6H_4, 4-PhC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 4-AcC_6H_4, 4-morpholinylC_6H_4, 2-naphthyl

Scheme 137 Asymmetric aza-pinacol coupling of ketimines mediated by diborons **448** and **454**.

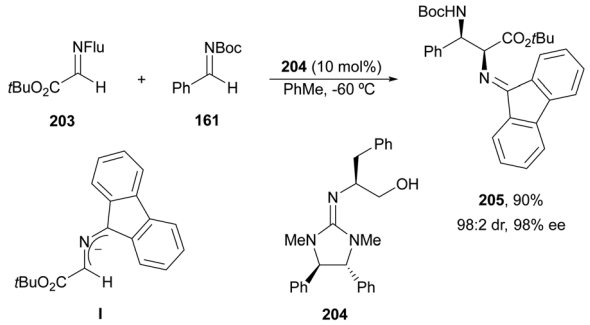


(*S*)-**456**, Ar = 2,4,6-$Cy_3C_6H_2$

R^1 = 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 4-$MeO_2CC_6H_4$, 4-NCC_6H_4, 3,4-$Cl_2C_6H_3$, 3,5-$Br_2C_6H_3$
R^2 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-PhC_6H_4, 4-$AcOC_6H_4$, 2.naphthyl, 3-thienyl



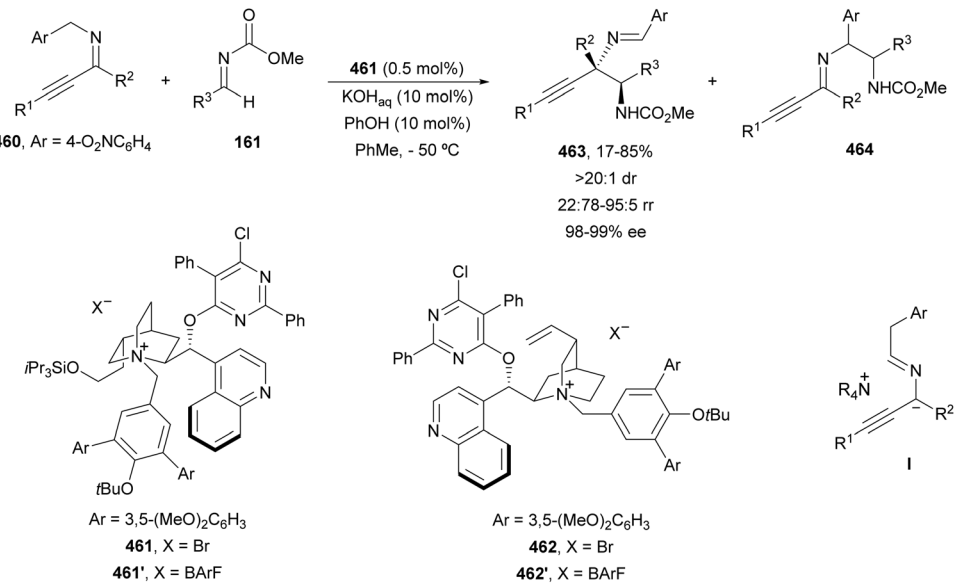
Scheme 138 Asymmetric coupling of hydrazones **455** with *N*-Boc imines **161** under CPA (*S*)-**456** catalysis.



Scheme 139 Asymmetric imine–imine cross-coupling of *N*-fluorenyl glyioxylateimine **203** with *N*-Boc benzaldimine **161** under guanidine **204** catalysis.

For the enantioselective α-amino alkylation of imines, Ooi and co-workers[290] developed a synergistic catalysis based on an ionic Brønsted acid and a photocatalyst. The α-coupling of *N*,*N*-disubstituted α-aminomethanes **483** with *N*-mesyl imines **161** (PG = Ms) gave 1,2-diamine derivatives **486** under visible light irradiation in the presence of the *P*-spiro chiral arylaminophosphonium barfate **484** as a Brønsted acid and [Ir(ppy)$_2$(Me$_2$phen)]BArF **485** as a photosensitizer (Scheme 145). Diamines **486** were obtained in toluene at room temperature in good yields and enantioselectivities for aromatic aldimines. In contrast, aliphatic imines with a lower reduction potential remained intact. The authors proposed that the imine quenches the photoexcited Ir(III) species with proton loss delivering the α-amino radical **I**. At the same time, the imine is reduced by the Ir(II) species to give the *N*-mesyl radical anion which forms an ion-pair with the positive Ir(III) ground state complex. Subsequent ion exchange with the aminophosphonium cation forms the chiral radical ion pair **II**. After radical–radical coupling with the amino radical, the product is formed enantioselectively. In 2016,[291] the authors utilized α-silyl amines as precursors of α-amino radicals which participate in the same catalytic cycle giving diamines **486** in 28–86% yields and 78–97% ee.

Gong and co-workers[292] have described this type of amino alkylation of imines under copper-based asymmetric photocatalysis. α-Silylamines **487** reacted with *N*-acyl hydrazones **488** with a bis-oxazoline (*S*,*S*)-**489** copper complex as a catalyst under irradiation with a 24 W blue LED at −40 °C in THF to provide 1,2-diamine derivatives **490** in good yields and

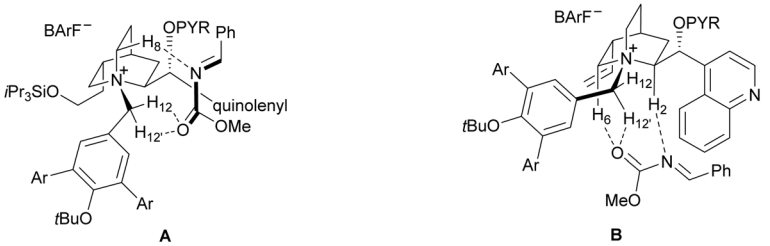


R^1 = H, Et, TIPS, TMS, Et$_3$Si, Ph

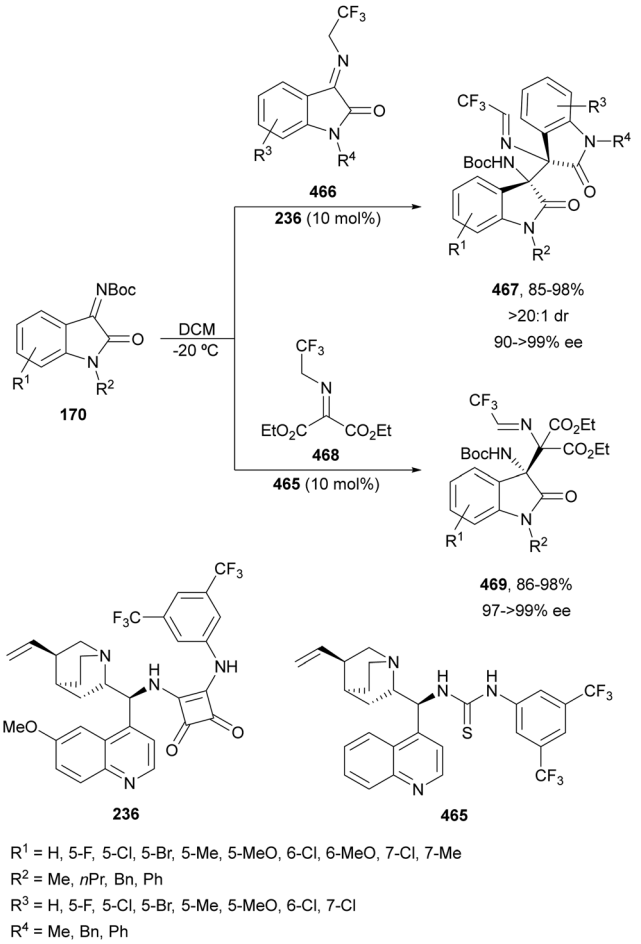
R^2 = Me, CH$_2$CH(CH$_2$)$_2$, BnOCH$_2$, Phth(CH$_2$)$_2$, 3-Py(CH$_2$)$_2$, Ph(CH$_2$)$_2$, HCC(CH$_2$)$_2$, 5-Me-2-furyl(CH$_2$)$_2$, 3-thienyl(CH$_2$)$_3$, 4,5-Ph$_2$-2-oxazolyl(CH$_2$)$_2$, Cl(CH$_2$)$_4$. *t*BuO$_2$C(CH$_2$)$_2$

R^3 = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeSC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-Br,3-MeC$_6$H$_3$, 2-naphthyl

Stereocontrol model



Scheme 140 Asymmetric imine–imine cross-coupling of ketimines **460** and **161** (PG = CO$_2$Me) under chiral PTC conditions.



Scheme 141 Asymmetric imine–imine cross-coupling of ketimines **466** and **468** with isatin-derived *N*-Boc ketimines **170** under squaramide **236** and thiourea **465** catalysis.

enantioselectivities (Scheme 146). In the proposed catalytic cycle, the hydrazone **488** forms complex **I** with the [L*Cu(II)] catalyst. Meanwhile, a single-electron transfer (SET) between the silylamine **487** and [L*Cu(II)] leads to the formation of the radical cation **II** and [L*Cu(I)]. Dissociation of the TMS cation from **II** affords the α-amino alkyl radical **III**. This nucleophilic radical **III** adds to the C=N of intermediate **I** to give N-radical species **IV**. Reduction of **IV** by the excited [L*Cu(I)] provides cationic complex **V**, which after protonation and ligand exchange releases the diamine **490** and regenerates intermediate **I**. Diamine **490a** gave protected diamine **491** after reaction with RANEY® nickel in EtOH at 80 °C for one hour in 71% yield and 94% ee.

Reductive coupling of azadienes with imines has been carried out with a Cu/diphosphine chiral catalyst to obtain *anti*-1,2-diamine derivatives by hydrocupration and to obtain an azaallylcopper intermediate. In the case of 2-azatrienes, diastereodivergent[52] formation of *syn*- and *anti*-1,2-diamines was controlled by the chiral diphosphine ligands. Asymmetric α-aminoalkylation of imines can be performed under photocatalytic conditions using a phosphonium salt or Cu/bisoxazoline as a chiral catalyst.

3.5. Cycloaddition reactions

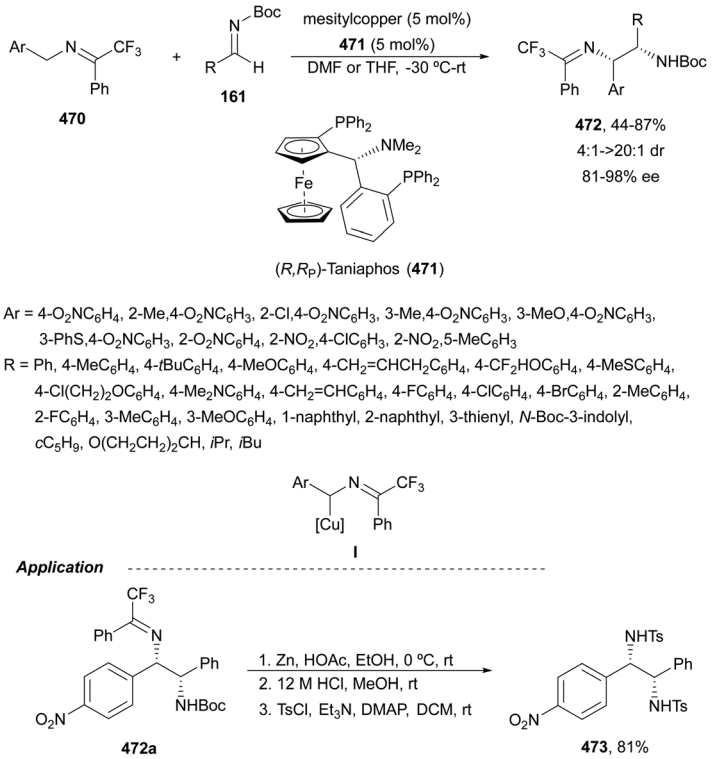
In this section, asymmetric 1,3-dipolar cycloadditions (1,3-DC) of azomethine ylides and 5-vinyloxazolidinones with imines to obtain imidazolidine precursors of 1,2-diamines will be mainly considered. In addition, [2+2] cycloaddition of allenamides was also included.

In 2008, Gong and co-workers[293] reported a three-component 1,3-DC of aldehydes, diethyl aminomalonate and anilines catalyzed by CPA (*R*)-TRIP (**152**). This process took place in toluene at −10 °C to give chiral imidazolidines **492** up to 99% yield, 91 : 9 dr and 98% ee (Scheme 147). In the proposed mechanism, the condensation of the aldehyde with aminomalonate is controlled by the CPA to obtain an azomethine ylide coordinate with the CPA **I**. Meanwhile, condensation of the aldehyde with aniline can be activated by formation of a species **II** by the CPA. Both intermediates undergo an enantioselective [3+2] cycloaddition to provide imidazolidines **492**. Reduction of **492a** with $NaBH_4$/LiCl followed by hydrolysis with aqueous phosphoric acid generated a diamine **493** in 50% overall yield.

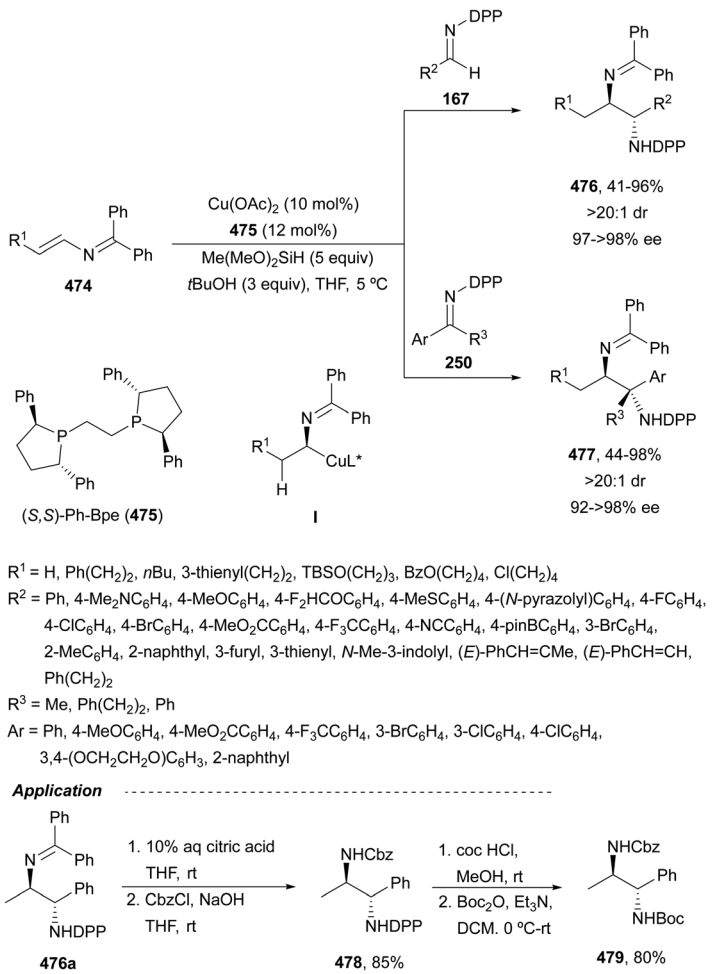
Fluorinated imidazolidines have been prepared by asymmetric $CuBF_4$/(*S*,R_P)-PPFOMe (**494**) catalysis of azomethine ylides with fluorinated imines. Wang and co-workers[294,295] performed the 1,3-DC of *N*-PMP-trifluoromethyl imines with metallo-dipoles A derived from imino esters **166** (Scheme 148). In the case of aldimines **356**, the reaction was carried out with Et_3N as a base in ether at −20 °C to obtain 2,5-*trans*-imidazolidines **495** in good yields and diastereo- and enantioselectivities through TS **I**, resulting from *exo*-selective cycloaddition. On the other hand, trifluoromethylated ketimine **496** was reacted with imino esters **166** in the presence of Cs_2CO_3 through an *endo*-approach to obtain 2,5-*cis*-imidazolidines **497** *via* TS **II**. This mechanistic proposal is based on labelling experiments to discard epimerization processes, and linear effect studies which explain the formation of a monomeric Cu(I) complex. Imidazolidine **495a** was transformed into α,β-diamino acid derivative **498** by treatment with *p*-toluenesulfonic acid in MeOH at room temperature in 80% yield and the same 97% ee.

The first asymmetric homo-1,3-DC of azomethine ylides was described by Shi and co-workers[296] using a (*R*)-SPINOL-derived CPA **499**. This cycloaddition was carried out starting from an aldehyde and aminomalonate in order to generate *in situ* the corresponding imino ester working in $CHCl_3$ at −40 °C in the presence of 4 Å MS resulting 2,4-*cis*-imidazolidines **500** with modest to good yields, high diastereoselectivity and moderate to good enantioselectivities (Scheme 149). In the proposed TS, the catalyst activates both the azomethine ylide and the imine moiety *via* hydrogen bonding interactions with subsequent *endo*-[3+2] cycloaddition.

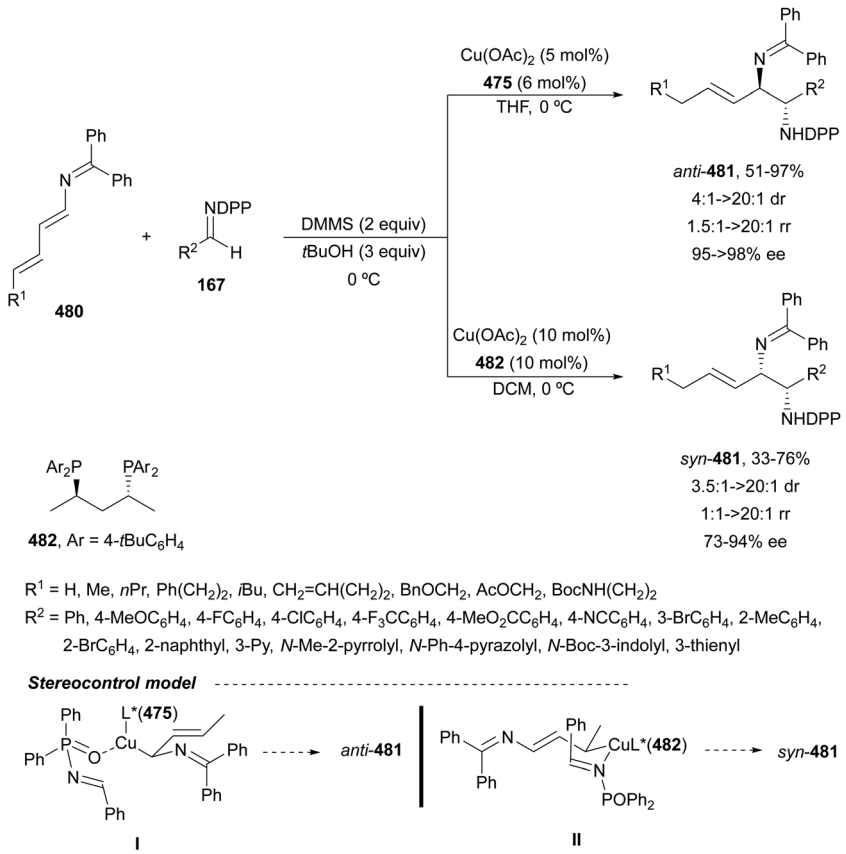
Xu and co-workers[297] performed the homo-1,3-DC of imino esters **166** by employing AgOAc/Xing-Phos **501** as catalyst to furnish all-*cis*-imidazolidines **502** with good to excellent diastereo- and enantioselectivities as well as good yields (Scheme 150). The diastereoselectivity of this 1,3-DC was explained by an *endo*-approach in the TS, which after Mannich addition gave intermediate **I**. Subsequent intramolecular *N*-cyclization of **I** provided the



Scheme 142 Asymmetric imine–imine cross-coupling of ketimine **470** with *N*-Boc aldimines **161** under mesitylCu/(*R*,*R*$_P$)-Taniaphos (**471**) catalysis.



Scheme 143 Asymmetric reductive coupling of enamines **474** with aldimines **167** and ketimines **250** under Cu(OAc)$_2$/(*S*,*S*)-Ph-Bpe (**475**) catalysis.



Scheme 144 Asymmetric diastereodivergent reductive coupling of 2-azatrienes **480** with imines **167** under $Cu(OAc)_2$/**475** and $Cu(OAc)_2$/**482** catalysis.

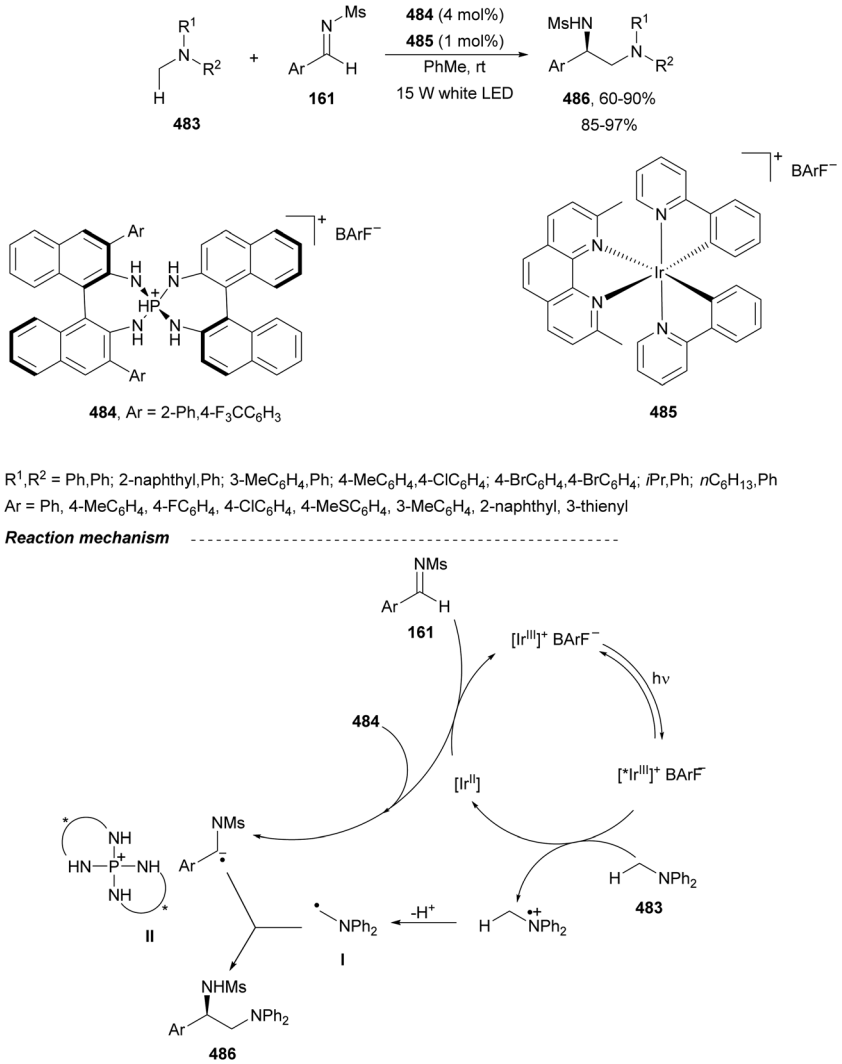
corresponding *cis*,*cis*-**502**. Products *cis*,*trans*-**502** were obtained as secondary products.

The same group[298] reported a diastereodivergent[52] 1,3-DC of azomethine ylides with imines. Glycine-derived imino esters **166** reacted with *N*-alkyl aromatic imines **503** to give under AgOAc/Xing-Phos (**501**) catalysis all-*cis*-**504** up to 75% yield, 98 : 2 dr and 99% ee (Scheme 151). On the other hand, 2,3-*cis*-2,5-*trans*-imidazolidines **504** were mainly obtained using AgOAc/DTBM-Segphos (**23**) with 57–74% yields, up to 99 : 1 dr and 99% ee. The chiral ligand control of the diastereo- and enantioselectivity was explained by steric repulsion in the case of DTBM-Segphos *via* pathway B and by hydrogen bonding interactions with Xing-Phos (pathway A).

Shi and co-workers[299] described a chemoselective 1,3-DC of azomethine ylides with isatin-derived imines **170** using (*R*)-TRIP (**152**) as a CPA. This asymmetric [3+2] cycloaddition was performed *via* a three-component reaction of imines, aldehydes and diethyl aminomalonate in toluene at 0 °C to obtain spiro[imidazolidine-2,3′-oxindole] derivatives **505** up to 76% yield, >95 : 5 dr and 94% ee (Scheme 152). Based on control experiments, initial homo-1,3-DC of *in situ* generated imino ester gives product **500**, which undergoes a cascade reaction with ketimine **170** promoted by CPA **152** by a dual hydrogen bonding interaction. When racemic **500** was used, product **505** was obtained in 84% ee, whereas **500** was recovered in the racemic form, therefore kinetic resolution during the cascade reaction was discarded.

Guo and co-workers[300] performed a tandem [3+2] cycloaddition/1,4-addition reaction of azomethine ylides and aza-*o*-quinone methides to obtain imidazolidines **507**. Starting from *N*-tosyl-*o*-(chloromethyl)anilines **506** and imino esters **166** in the presence of AgOTs/ferrocenylphosphine **48** as catalyst, with KOH as a base and 18-crown-6 as an additive in dichloromethane at −30 °C, resulted imidazolidines all-*cis*-**507** in good yields and diastereo- and enantioselectivities (Scheme 153). Based on control experiments, a plausible mechanism was proposed involving the homo-1,3-DC of the silver dipole with the imino ester to obtain imidazolidine all-*cis*-**502a**, which reacts with the aza-*o*-quinone methide **I** to provide product **507a**.

A tandem nucleophilic addition of imino esters **166** to arynes to give an azomethine ylide followed by a 1,3-DC with a metalated α-imino esters afforded the corresponding imidazolidines all-*cis*-**509**. This process was described by Shi, Guo and co-workers[301] using $AgNTf_2$/ferrocenylphosphine ligand **48** as a catalyst, CsF as a base and 18-crown-6 as an additive in acetonitrile at −10 °C (Scheme 154). *O*-Silyl aryl triflates **508** were employed as precursors of arynes which by reaction with imino esters **166** derived from aromatic aldehydes provided imidazolidines **509** with a 2*S*,4*S*,5*S* configuration in good yields and enantioselectivities. Two concurrent pathways have been proposed, the [3+2] cycloaddition of aryne-induced ylides with metalated α-imino esters and the metal-catalyzed [3+2] cycloaddition of azomethine ylide with α-imino esters. Imino ester



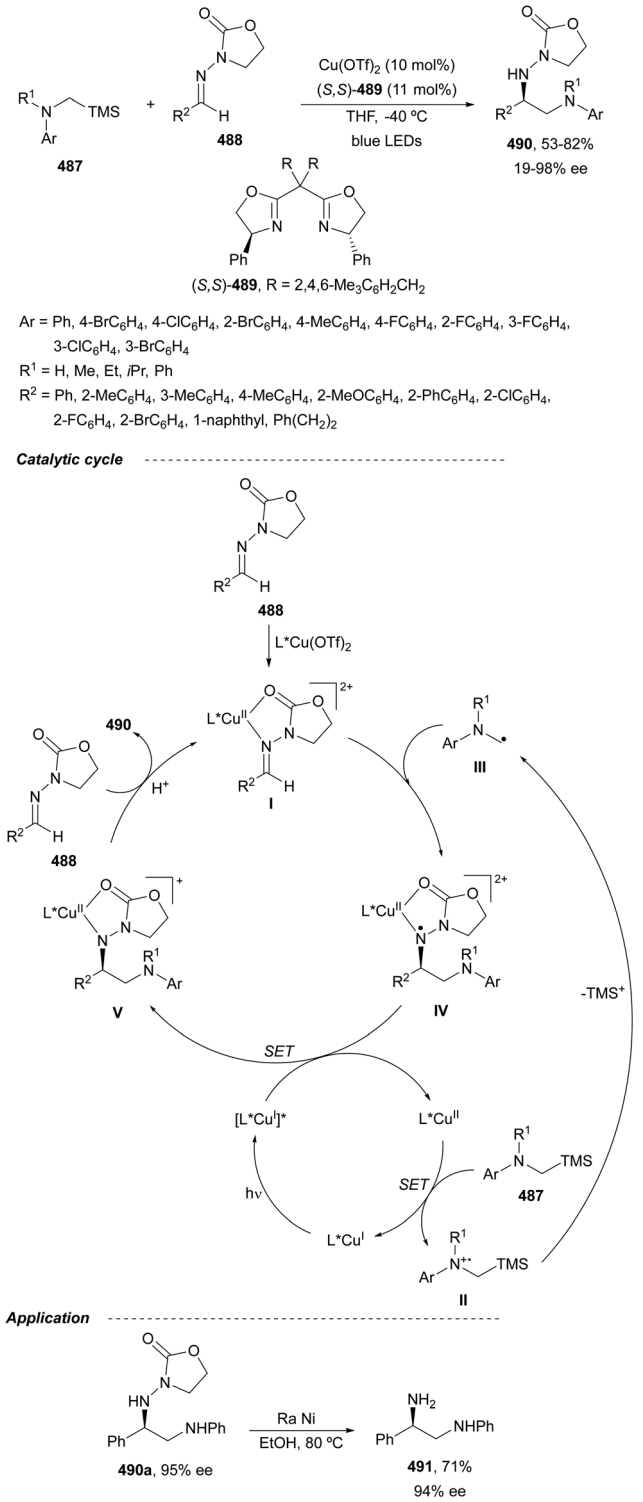
Scheme 145 Asymmetric α-amino alkylation of imines **161** with α-aminomethanes **483** under aminophosphonium barfate **484** and Ir complex **485** photocatalysis.

166a reacts with benzyne, generated from **508** (R^1 = H) to form zwitterion **I**, which after 1,4-hydrogen transfer gives the azomethine ylide **II**′ and the *trans*-isomer **II**. Meanwhile, **166a** reacts with the silver catalyst to provide the metalo-dipole **III**, which undergoes a regioselective *endo*-[3+2] cycloaddition to give **509a**. In the other pathway, azomethine ylide **IV** reacts with **166a** to provide **502a**. Subsequent capture of **502a** by benzyne generates the product **509a**.

Ooi and co-workers[302] have reported a Pd-catalyzed [3+2] cycloaddition of 5-vinyloxazolidinones **510** with imines **161** to yield imidazolidines **512** (Scheme 155). In the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol%) and a chiral ammonium-phosphine **511** hybrid ligand, the corresponding imidazolidines *cis*-**512** were obtained in high yields and diastereo- and enantioselectivities. Oxazolidinones **510** undergo ring opening by Pd to provide the π-allylPd intermediate **I**, which after decarboxylation generates the dipole **II**. Imidazolidine **512a** bearing a quaternary stereocenter was transformed into the 1,2-diamine **513** by deprotection of the mesyl group with dodecanethiol.

Rhodium-catalyzed [2+2] cycloaddition of allenamides **514** has been reported by Kang and co-workers.[303] This intermolecular head-to-head enantioselective [2+2] cycloaddition was carried out in the presence of 5 mol% of $[Rh(cod)Cl]_2$ and (*S*)-Binap (**46**) in 1,2-dichlorobenzene at 40–60 °C to furnish *trans*-3,4-bis(methylene)cyclobutene-1,2-diamines **515** in good yields and enantioselectivities (Scheme 156). In the proposed mechanism, two allenamide molecules coordinate to the Rh catalyst to produce the rhodiacyclopentane intermediate **I**. Subsequent enantioselective controlled reductive elimination affords the cyclobutene-1,2-diamine **515**.

The asymmetric [3+2] cycloaddition of azomethine ylides with imines gave diastereo- and enantioenriched imidazolidines which are easily transformed into 1,2-diamines. These 1,3-DC are catalyzed by CPA, chiral silver or copper complexes, generally with *endo*-selectivity to provide *cis*-imidazolidines in good yields and diastereo- and enantioselectivities. A Rh-catalyzed [2+2] cycloaddition of allenamides provided bis(methylene)-1,2-diamines up to 99% ee.



Scheme 146 Asymmetric α-amino alkylation of hydrazones **488** with α-silylamines **487** under $Cu(OTf)_2$/bisoxazoline (*S*,*S*)-**489** photocatalysis.

4. C–H bond-forming reactions

In this section, hydrogenation reactions of C=N bonds with molecular hydrogen under metal-catalyzed processes, transfer hydrogenation conditions or hydrogen autotransfer are considered.

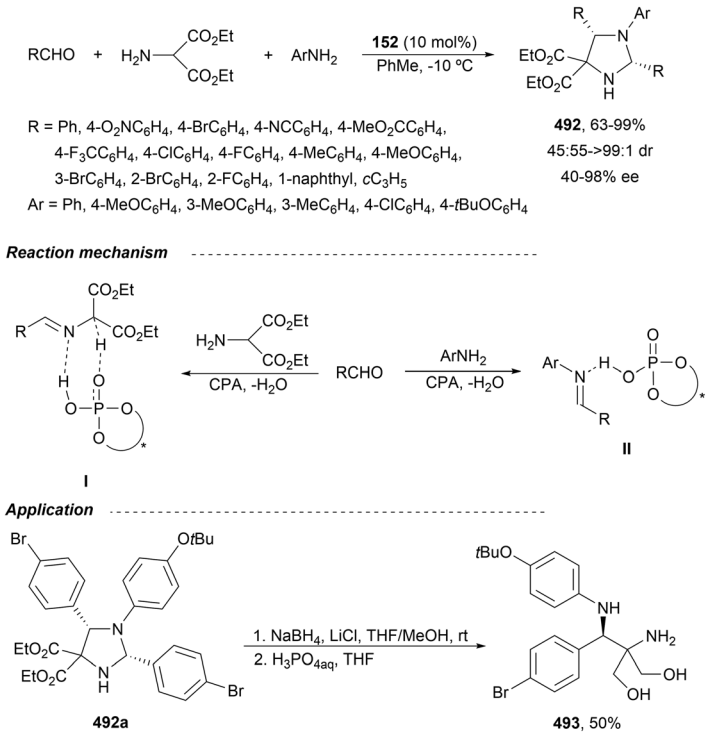
The synthesis of chiral piperazines **519–521** has been performed by asymmetric hydrogenation (AH) of *N*-alkylpyrazinium salts **516–518** under Ir-catalysis, respectively. Zhou and co-workers[304] employed (R,S_P)-Josiphos (**44**) as a chiral ligand in the case of 3-substituted pyrazinium salts **516** to obtain chiral piperazines **519** up to 95% yield and 92% ee, whereas (*R*)-Segphos (**23**) and (*S*,*S*)-**522** were the ligands for AH of 3,5- and 2,3-disubstituted pyrazinium salts, **517** and **518**, respectively, to provide piperazines **520** and **521** with high yields and enantioselectivities (Scheme 157). This methodology made the pyrazine ring more electron deficient, weakening its coordination ability and facilitating its reduction. In the proposed mechanism, the salt **516a** undergoes 1,4-hydride addition to furnish the 1,4-dihydropyrazine **I** and HBr. In the presence of HBr, intermediate **I** tautomerizes to **II**. Subsequent hydrogenation of iminium salt **II** gives **III** and then the finally piperazine **519a**. This procedure was applied to the synthesis of vestipitant, a potent and selective NK1 receptor antagonist, an antiemetic and anxiolytic drug, in only three steps from piperazine **519b**. In the case of mirtazapine, for the treatment of insommia and climacteric symptoms, the precursor piperazine *N*-Boc-**519a** was prepared from pyrazinium salt **516a** by AH with (R,S_P)-**44** as a catalyst in 87% yield and 90% ee.

AH of 2,2′-bisquinoline and quinoxaline derivatives **523** has been described by Fan and co-workers[305] using chiral cationic Ru(diamine) complexes **524** or **525** under 50 atmospheres. Endocyclic vicinal diamines **526** were obtained in high yields with excellent diastereo- and enantioselectivities (Scheme 158a). This methodology has been previously applied by the same group[306] to 2-substituted and 2,9-disubstituted 1,10-phenanthrolines **527** by means of (*R*,*R*)-**525** to obtain OPhen derivatives **528**. In the case of 2,9-disubstituted **527**, *trans*-OPhen **528** were diastereoselectively obtained in high yields and excellent enantioselectivities (Scheme 158b). Products **526** and **528** can be transformed into chiral N-heterocyclic carbene ligands by reaction with neat triethyl orthoformate.

The same group[307] reported a highly enantioselective Ir- or Ru-catalyzed intermolecular reductive amination/asymmetric hydrogenation of 2-quinolinecarbaldehydes **529** and aromatic amines. Chiral vicinal diamines **531** were obtained in good yields and enantioselectivities using the Ir complex (*R*,*R*)-**530** as a chiral catalyst (Scheme 159). When sterically hindered aromatic amines were used, the Ru(diamine) complex (*R*,*R*)-**524** in the presence of TfOH was the best catalyst for this transformation. These chiral diamines **531** and their corresponding bulky chiral NHC were used as ligands for the Suzuki–Miyaura cross-coupling reaction and for ring-opening cross-metathesis, respectively.

Stoltz and co-workers[308] described the AH of 1,3-disubstituted isoquinolines to provide chiral 1,2,3,4-tetrahydroisoquinolines (Scheme 160). In the case of the 1-(*N*-Boc-aminomethyl)-3-phenylisoquinoline **532**, the AH was carried out with $[Ir(cod)Cl]_2$ ligand **533**, TBAI as an additive, 60 bar H_2, 9 : 1 THF/AcOH as solvents at 60 °C to obtain *cis*-diamine derivative **534** in 71% yield, 9 : 1 dr and 90% ee.

2,3-Disubstituted quinoxalines **535** were transformed by Zhang and Du[309] into the corresponding *cis*-1,2,3,4-tetrahydroquinoxalines **537** by AH using bis(pentafluorophenyl)borane



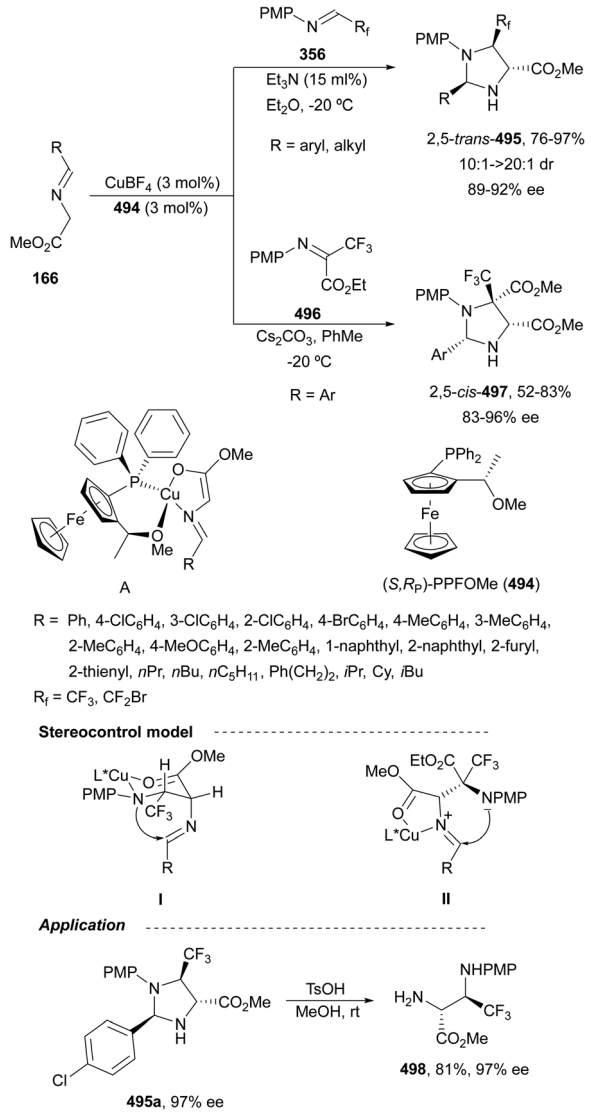
Scheme 147 Asymmetric three-component 1,3-DC of aldehydes, diethyl aminomalonate and anilines under (*R*)-TRIP (**152**) catalysis.

(Piers's borane[310]) and a chiral diene **536** as a ligand (Scheme 161). This metal-free hydrogenation took place under 20 bar in hexane at room temperature to provide *cis*-2,3-disubstituted tetrahydroquinoxalines **537** with good yields and enantioselectivities and high diastereoselectivities.

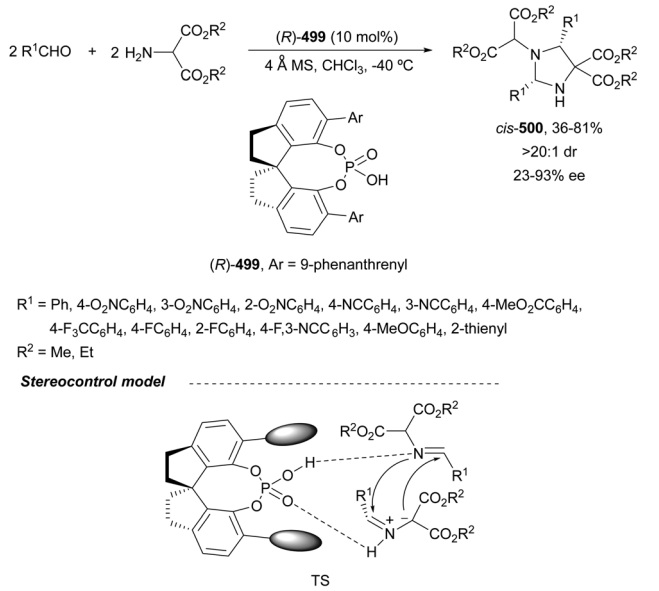
Asymmetric transfer hydrogenation (ATH) has been employed for the enantioselective synthesis of 4-alkylidenethiadiazolines **540** from thiadiazole-1,1-dioxides **538** prepared from 1,2-diketones, by Zezschwitz and co-workers.[311] This ATH was carried out with the Noyori catalyst RuCl(TsDpen) **539** working with a 5/2 mixture of formic acid and triethylamine in acetonitrile at −15 °C to provide products **540** up to 97% yield and 98% ee (Scheme 162). Subsequent diastereoselective reduction of compounds **540** with $LiBH_4$ in THF at room temperature afforded *cis*-1,2,5-thiadiazolidine-1,1-dioxides **541** in high yields and enantioselectivities. These *cis*-thiadiazolidine derivatives **541** were transformed into the *trans*-diastereomers by treatment with trifluoroacetic acid or sulfuric acid under preservation of the enantioselectivity. Both *cis*- and *trans*-**541a** were transformed into the *anti*- and *syn*-diamines **542**, respectively, by refluxing in hydrazine monohydrate. These diamines have been further converted into α,β-diamino acids by oxidation of the PMP group.

Yang, Zhao and co-workers[312] have recently reported an enantioconvergent[313] synthesis of diamines from diols through a catalytic borrowing hydrogen autotransfer process. Readily available secondary-primary diols **543** bearing an aryl substituent were diaminated with amines using $[Ir(cod)Cl]_2$ (2.5 mol%), a chiral bisphosphine **544** (5 mol%) and a CPA (*R*)-TRIP (**152**, 10 mol%) as cooperative catalysts to furnish diamines **545** in toluene at 90 °C up to 89% yield and 94% ee (Scheme 163). According to control experiments, a catalytic pathway was proposed. Mono-oxidation of diol by Ir gives the α-hydroxy aldehyde **I**, which after CPA catalyzed condensation with the amine provides the α-hydroxy imine **II**. Heyns rearrangement of **II** forms the α-amino ketone **III**, which reacts with the amine to give the α-amino imine **IV** and after reduction of the ketimine with [Ir]H resulted the diamine **545**. Alternatively to the enantioconvergent process, a dynamic kinetic asymmetric transformation (DYKAT) can take place by tautomerization of **IV** to enamine **V**, and then in the presence of the CPA **VI** and **VI′** are formed. A faster reduction by [Ir]H of **VI** in preference over **VI′** leads to diamine **545**.

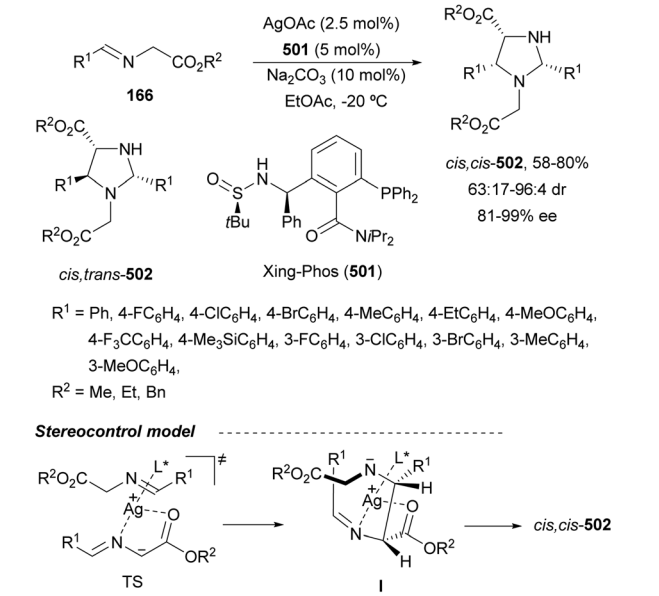
Asymmetric hydrogenation of *N*-containing heterocyclic compounds such as *N*-alkylpyrazinium salts, 2.2′-bisquinoline and quinoxaline derivatives, and isoquinolines can be carried out under Ir/bisphosphine or Ru(diamine) chiral complexes to provide chiral 1,2-diamines. In the case of 2,3-disubstituted quinoxalines, Pier's borane and a chiral diene gave the corresponding chiral *cis*-2,3-disubstituted tetrahydroquinoxalines. Asymmetric transfer hydrogenation is an efficient reduction for thiadiazoles using RuCl(TsDpen) as a catalyst and formic acid allowed the synthesis of *anti*- and *syn*-diamines. Diols have been transformed into chiral diamines under hydrogen autotransfer conditions by means of Ir/bisphosphine and a CPA cooperative catalysis.



Scheme 148 Asymmetric 1,3-DC of imino esters **166** with fluoromethylated imines **356** and **496** under $CuBF_4$/(S,R_P)-PPFOMe (**494**) catalysis.



Scheme 149 Asymmetric homo-1,3-DC of azomethine ylides with imino esters under CPA (*R*)-**499** catalysis.



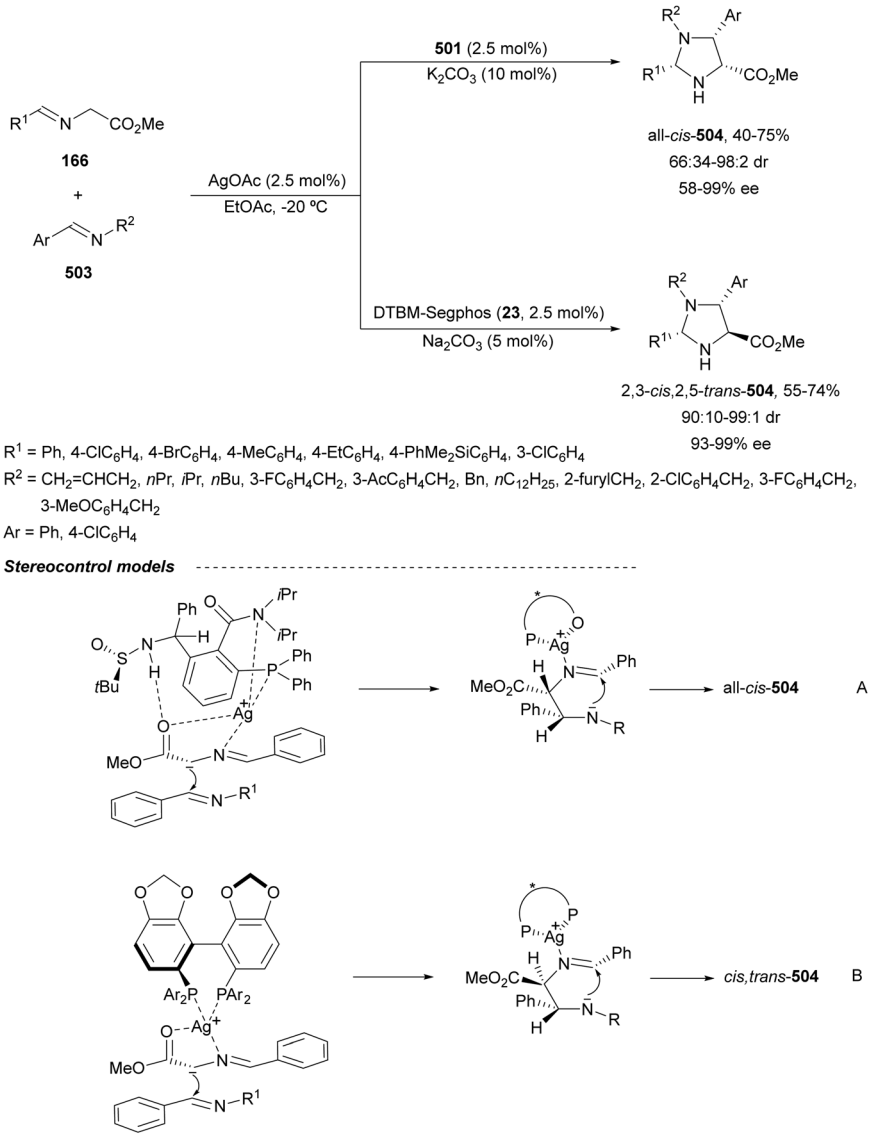
Scheme 150 Asymmetric homo-1,3-DC of imino esters **166** under AgOAc/Xing-Phos (**501**) catalysis.

5. C–H amination reactions

Intramolecular radical C–H amination by metal nitrenoid species and atroposelective C–H amination will be considered in this section.

Zhang and co-workers[314] described in 2018 the enantioselective intramolecular C–H amination of sulfamoyl azide compounds under cobalt-amideporphyrin complexes as catalysts to obtain 1,6-aminated products. One year later, the same group[315] reported the enantiodivergent[52] 1,5-C–H amination of sulfamoyl azides **546** using Co-porphyrin complexes **547a** (n = 2, Ar = 2,6-$(MeO)_2C_6H_3$) and **547b** (n = 3, Ar = 2,6-$t Bu_2C_6H_3$) as catalysts (Scheme 164). This catalytic radical amination *via* enantiodifferentiative H-atom abstraction (HAA) and stereoselective radical substitution (RS) afforded cyclic sulfamides **548** in a highly enantioenriched form precursors of chiral 1,2-diamines. Deuterium labelling studies and DFT calculations demonstrated that the cavity size of the cobalt-amideporphyrin affects the enantiodivergence of this process. In the proposed catalytic pathway, a Co(III)-amidyl radical **I** is formed, which after H-atom abstraction results an alkyl radical **II** able to undergo RS to give the sulfamide **548** and regenerating the catalyst.

Liu, Arnold and co-workers[316] used a mutated variant of cytochromes P441, designed as $P441_{Dianel3}$, for the intramolecular amination of sulfamoyl azides **546** to cyclic sulfamides (*S*)-**548** in 91–99% ee. Meggers and co-workers[317,318] reported the same

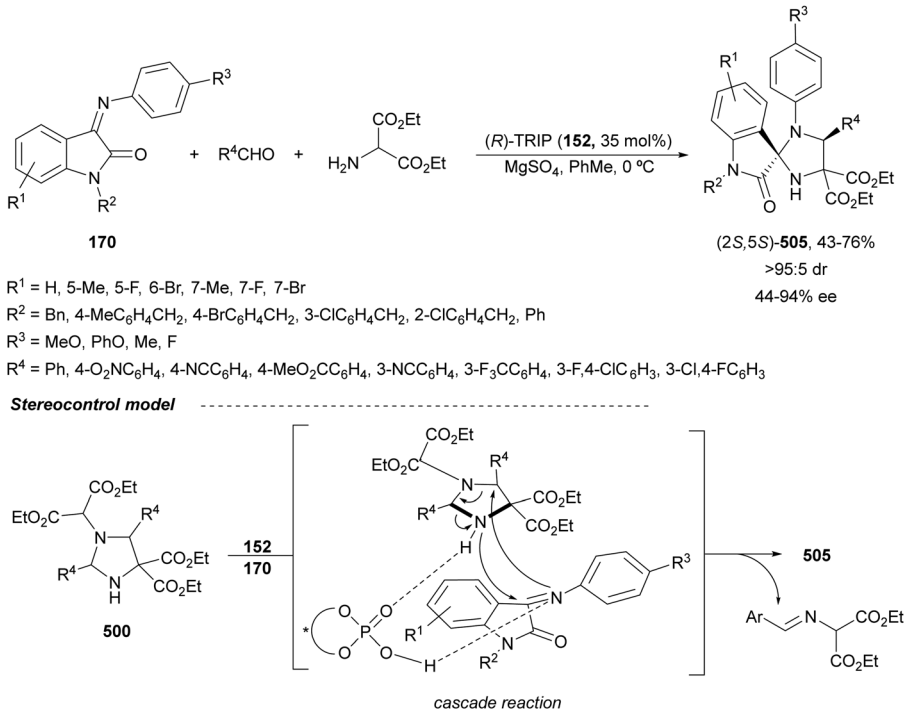


Scheme 151 Asymmetric diastereodivergent 1,3-DC of imino ester **166** with *N*-alkyl aldimines **503** under AgOAc/Xing-Phos (**501**) or DTBM-Segphos (**23**) catalysis.

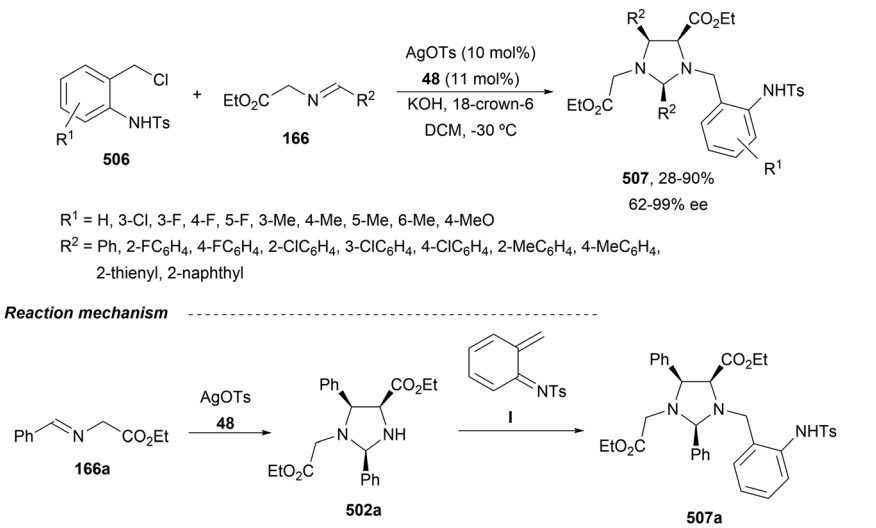
cyclization using a chiral Ru(II)/pybox complex **549** as a catalyst to obtain cyclic sulfamides (*S*)-**548** up to 98% yield and up to 88% ee (Scheme 165). The reaction of azide **546** (R = Ph) was carried out on a gram-scale to provide (*S*)-**548** (R = Ph) in 95% yield and 95% ee, which was further transformed into the corresponding chiral 1,2-diamine by treatment with hydrazine at 110 °C[311] in 95% yield and 95% ee. Mechanistic experiments support a stepwise mechanism in which a Ru-nitrenoid intermediate $\mathbf{I}^{\mathbf{S}}$ is formed under release of molecular nitrogen. This initially formed nitrenoid in a singlet state is converted to a triplet state $\mathbf{I}^{\mathbf{T}}$ to form a nitrenoid radical complex, which initiates a 1,5-hydrogen atom transfer (HAT) at the benzylic position to provide diradical **II**. Subsequent radical–radical rebound forms intermediate **III**, which releases the product and regenerates the catalyst.

The same group[319] described the C(sp^3)–H amination of urea derivatives **550** by using a chiral-at-metal Ru catalyst **551**, providing cyclic ureas **552** up to 99% yield and 99% ee (Scheme 166). This process was carried out with very low catalyst loading down to 0.05 mol% under mild reaction conditions. These products were transformed into chiral 1,2-diamines by treatment with concentrated HCl in AcOH at 85 °C under microwave conditions. In the proposed mechanism, upon release of benzoic acid from *N*-benzoyloxy urea **550**, the Ru catalyst forms a Ru nitrenoid which evolves triplet state **I**. Subsequent 1,5-HAT provides intermediate **II** followed by C–N bond formation though radical recombination to give intermediate **III**. Finally, the release of chiral 2-imidazolidinone **552** and regeneration of the catalyst take place.

Zhang and co-workers[320] reported an unusual enantioselective C–H amination of *N*-aryl-2-naphthylamines **553** with azodicarboxylates under CPA (*R*)-**189** catalysis to provide naphthalene-1,2-diamine derivatives **554** (Scheme 167). This



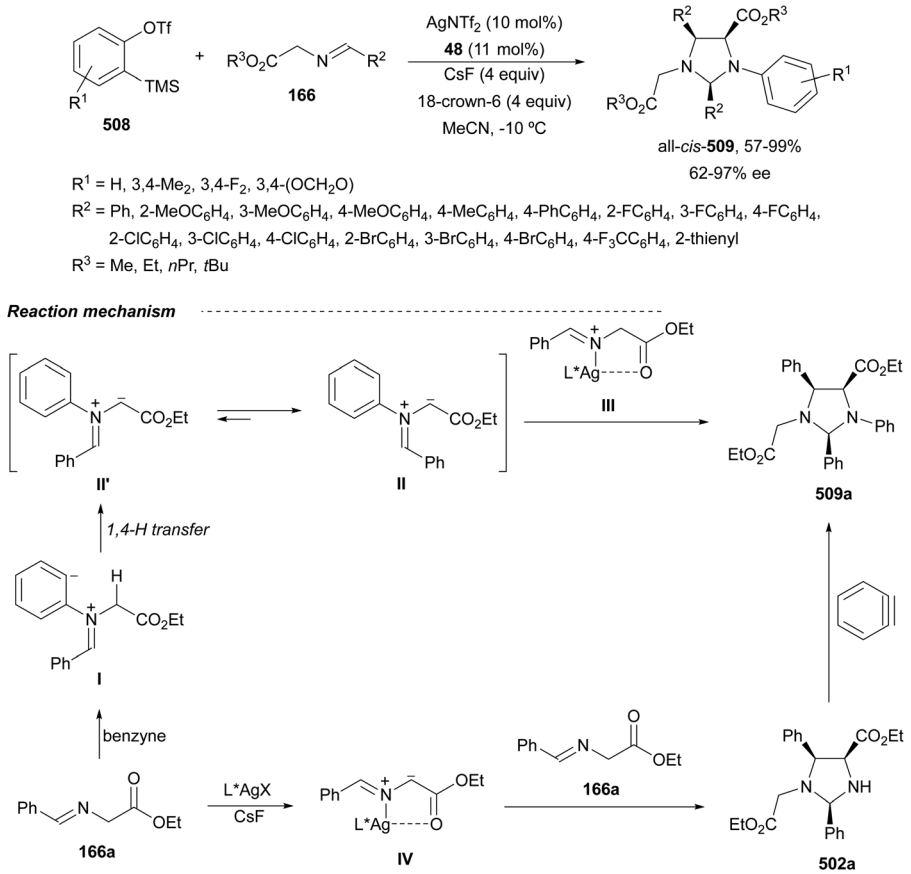
Scheme 152 Asymmetric three-component 1,3-DC of aldehydes, diethyl aminomalonate and isatin-derived imines **170** under (*R*)-TRIP (**152**) catalysis.



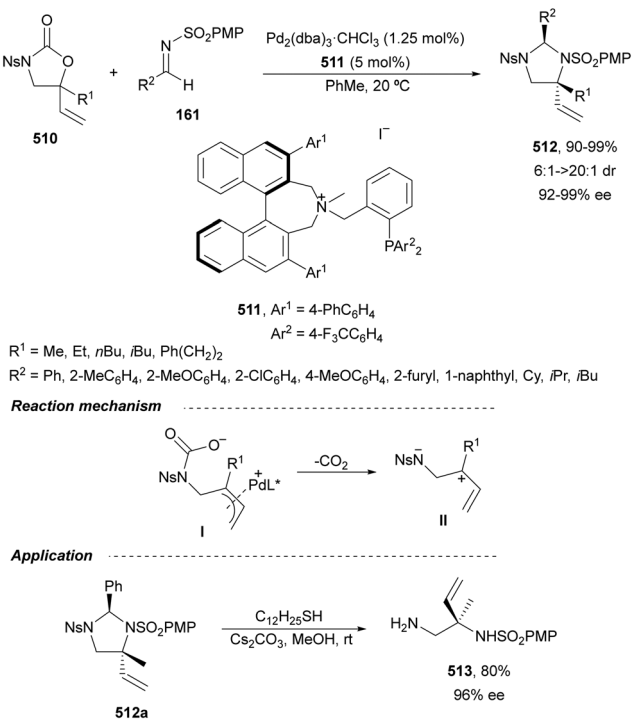
Scheme 153 Asymmetric tandem 1,3-DC/1,4-addition of imino esters **166** with *N*-tosyl-*o*-(chloromethyl)anilines **506** under AgOTs/ferrocenylphosphine **55** catalysis.

atroposelective direct C–H amination occurred *via* a concerted control of π–π interactions and dual hydrogen-bonding illustrated in the proposed reaction mechanism. First, the CPA activates the *N*-phenyl-2-naphthylamine **553a** and also the azodicarboxylate to form intermediate **I** by dual hydrogen-bonding. Then, the π–π interaction assisted by the nucleophilic addition of **553a** to *N*-Boc azodiacarboxylate to form intermediate **II** followed by rearomatization and stabilization of product **554a** by intramolecular hydrogen-bonding.

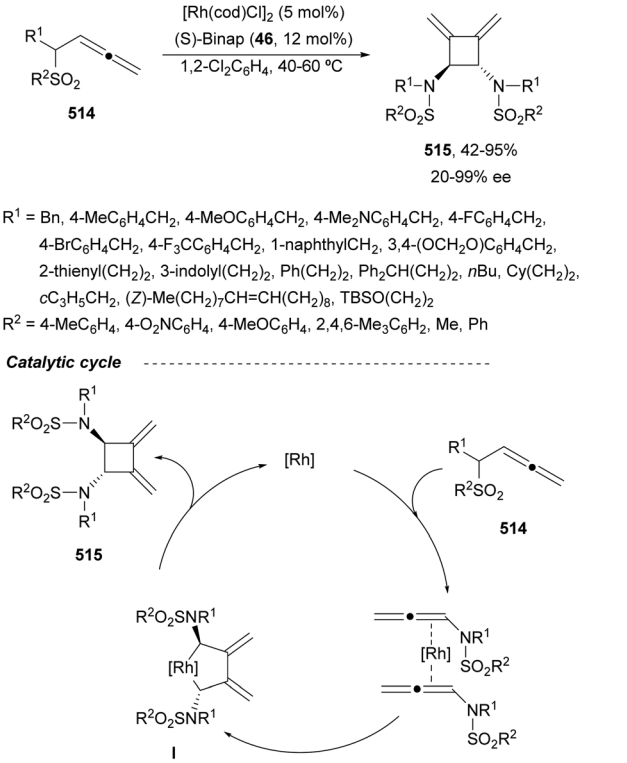
Asymmetric intramolecular radical C–H amination of sulfamoyl azides or *N*-benzoyloxyureas has been carried out efficiently with Ru(II) cationic complexes as catalysts to give enantioenriched cyclic sulfamides or imidazolidinones, respectively, precursors of 1,2-diamines. In the case of *N*-aryl-2-naphthylamines, an asymmetric atroposelective C–H amination has been performed using CPA as catalyst and azodicarboxylates as electrophiles to obtain naphthalene-1,2-diamine derivatives.



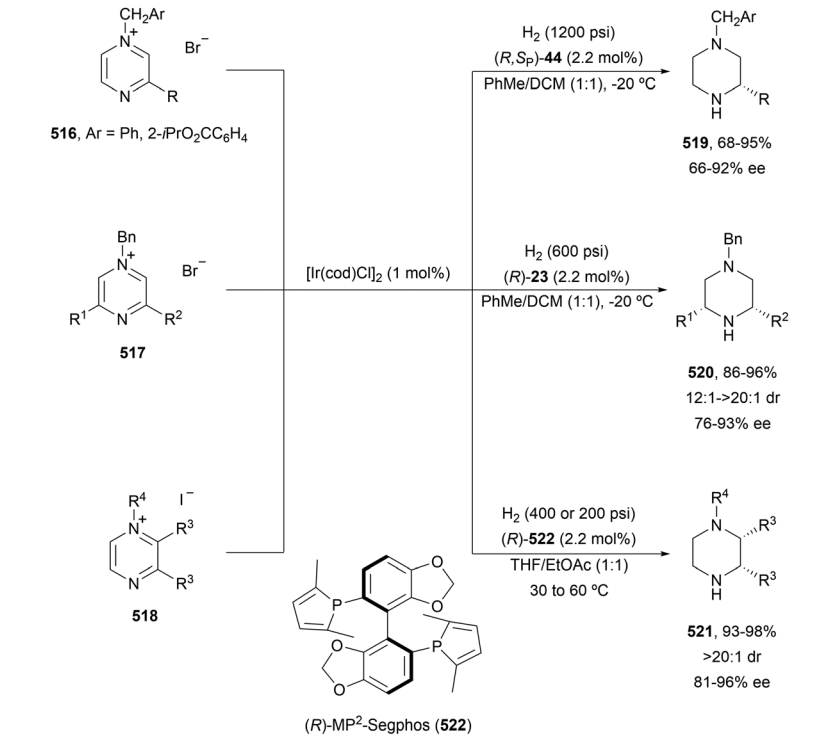
Scheme 154 Asymmetric 1,3-DC of imino esters **166** with arynes under $AgNTf_2$/ferrocenylphosphine **48** catalysis.



Scheme 155 Asymmetric 1,3-DC of 5-vinyloxazolidinone **510** with imines **161** under Pd(0)/**511** catalysis.



Scheme 156 Asymmetric [2+2] cycloaddition of allenamides **514** under Rh(I)/(*S*)-Binap (**46**) catalysis.



R = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 3,5-Me$_2$C$_6$H$_3$, 3-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-PhC$_6$H$_4$, 2-naphthyl, 2-Me,4-FC$_6$H$_3$, *c*C$_3$H$_5$

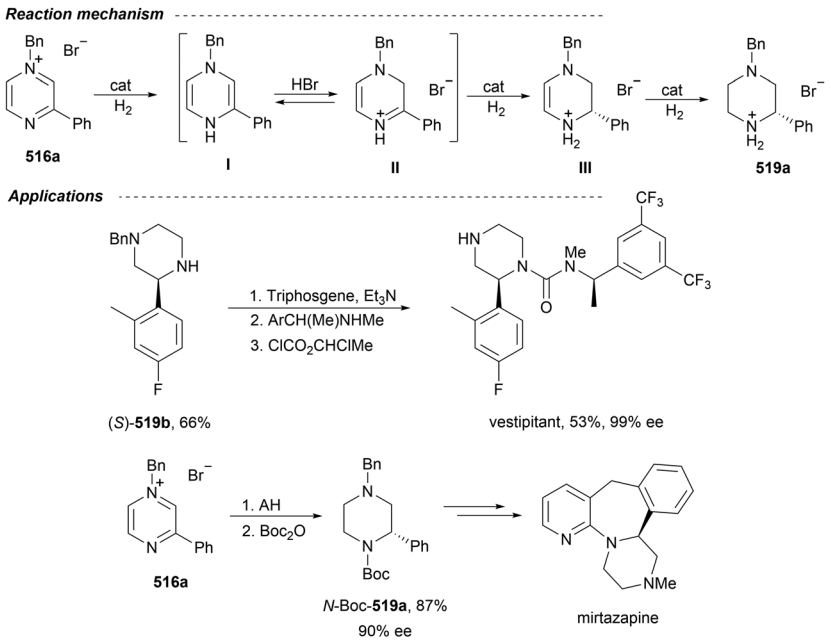
R^1 = Me, Et, *n*Pr, *n*Bu, *i*Bu, *c*C$_3$H$_5$

R^2 = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 3,5-Me$_2$C$_6$H$_3$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BnOC$_6$H$_4$, 4-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-PhC$_6$H$_4$, 2-naphthyl, 1-naphthyl

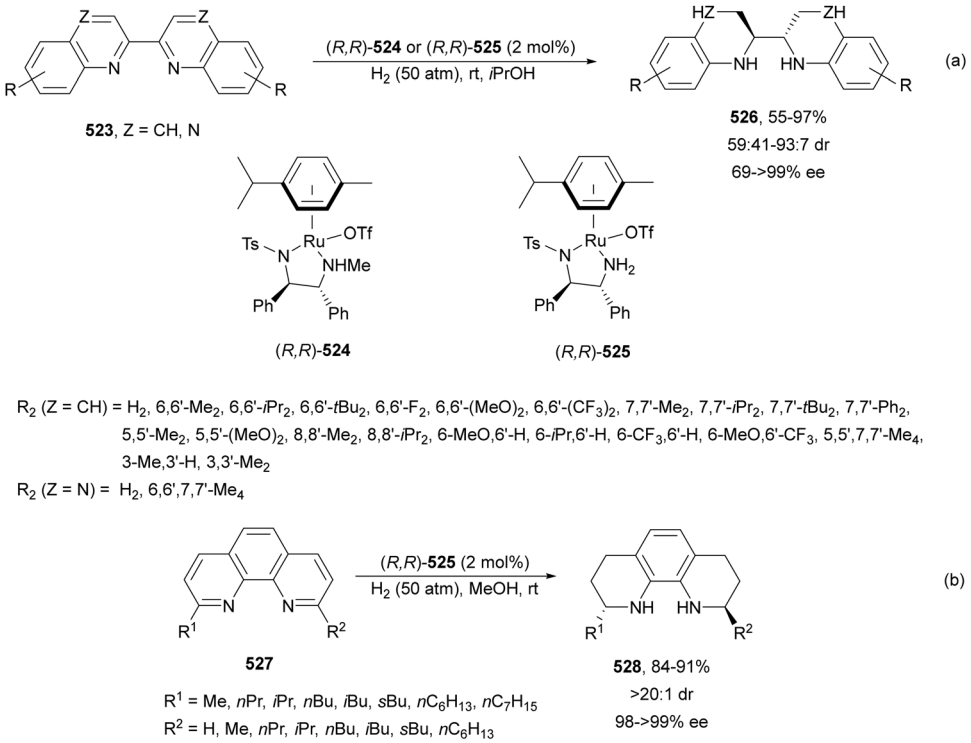
R^3 = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 2-naphthyl, Me

R^2-R^3 = (CH$_2$)$_4$

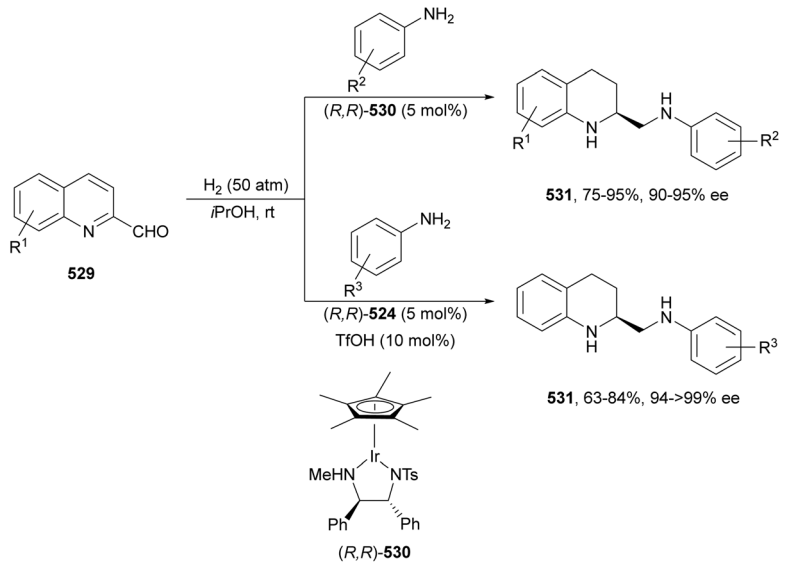
R^4 = Me, Bn



Scheme 157 Asymmetric hydrogenation of *N*-alkyl pyrazinium salts **516–518** to piperazines **519–521** under Ir/ligand **44**, **23** and **522** catalysis.



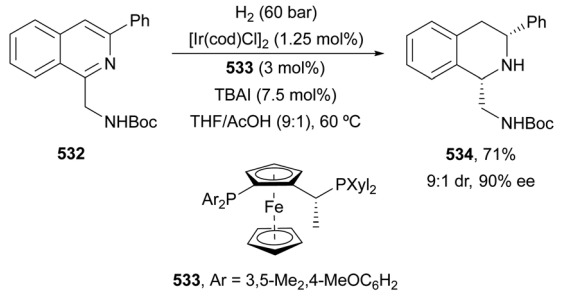
Scheme 158 Asymmetric hydrogenation of 2,2′-bisquinolines or quinoxalines **523** and 1,10-phenanthrolines **527** under Ru(diamine) (*R,R*)-**524** or **525** catalysis.



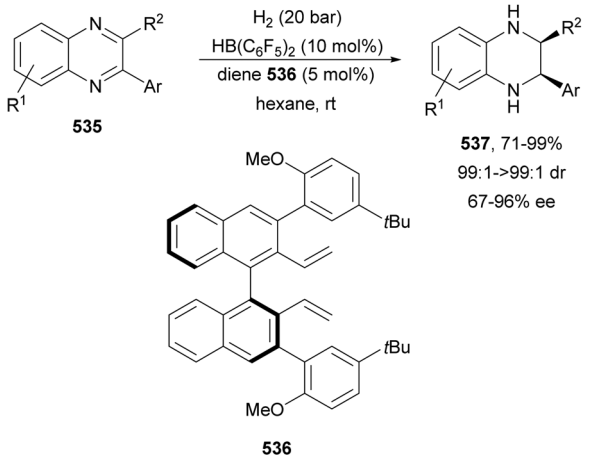
Scheme 159 Reductive amination/asymmetric hydrogenation of quinoline-2-carbaldehydes **529** with aromatic amines under Ir or Ru complex (*R,R*)-**530** or (*R,R*)-**524** catalysis.

6. Other catalytic methods

Enantioselective desymmetrization[15] of *meso*-diamines **555** has been accomplished by monobenzylation under organocatalysis by De and Seidel.[321] The cooperative action of two catalysts, DMAP as an achiral nucleophile and diamide-thiourea **556** as a chiral anion receptor catalyst gave the monoacylated products *anti*-**557** in good yields and good enantioselectivities (Scheme 168). In the

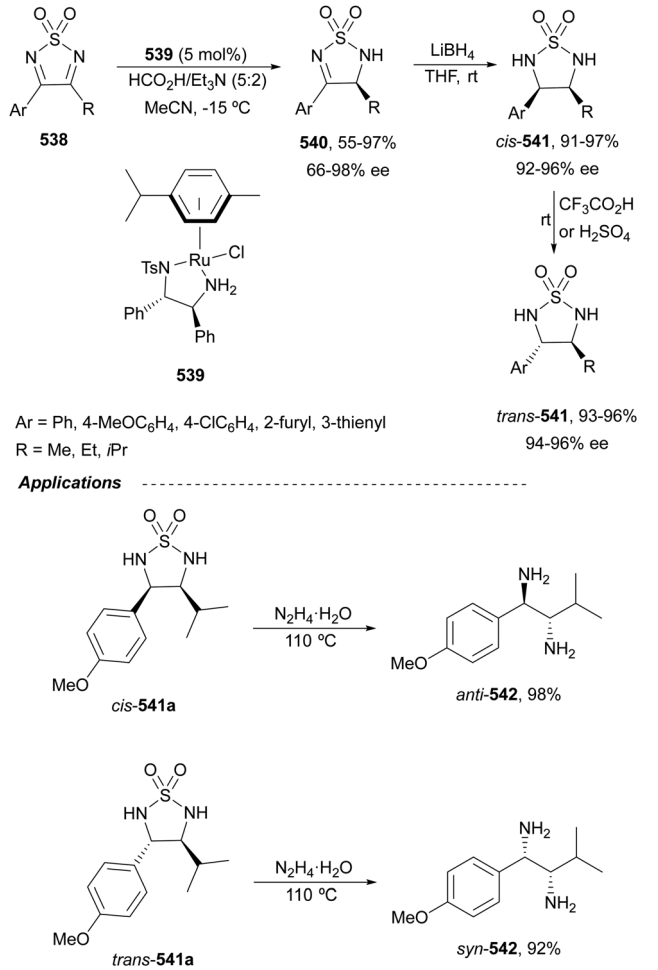


Scheme 160 Asymmetric hydrogenation of 1-(*N*-Boc-aminomethyl)-3-phenylisoquinoline (**532**) under Ir/bisphosphine **533** catalysis.



R^1 = H, 5-Me, 6-MeO, 6-Cl, 6-Br, 7-Cl, 7-Br, 8-Me, 6,7-Cl_2, 6,7-Me_2, 6,7-benzo
R^2 = Me, Et
Ar = Ph, 4-MeC_6H_4, 3-BrC_6H_4

Scheme 161 Asymmetric hydrogenation of 2,3-disubstituted quinoxalines **535** under bis(pentafluorophenyl)borane and chiral diene **536** catalysis.



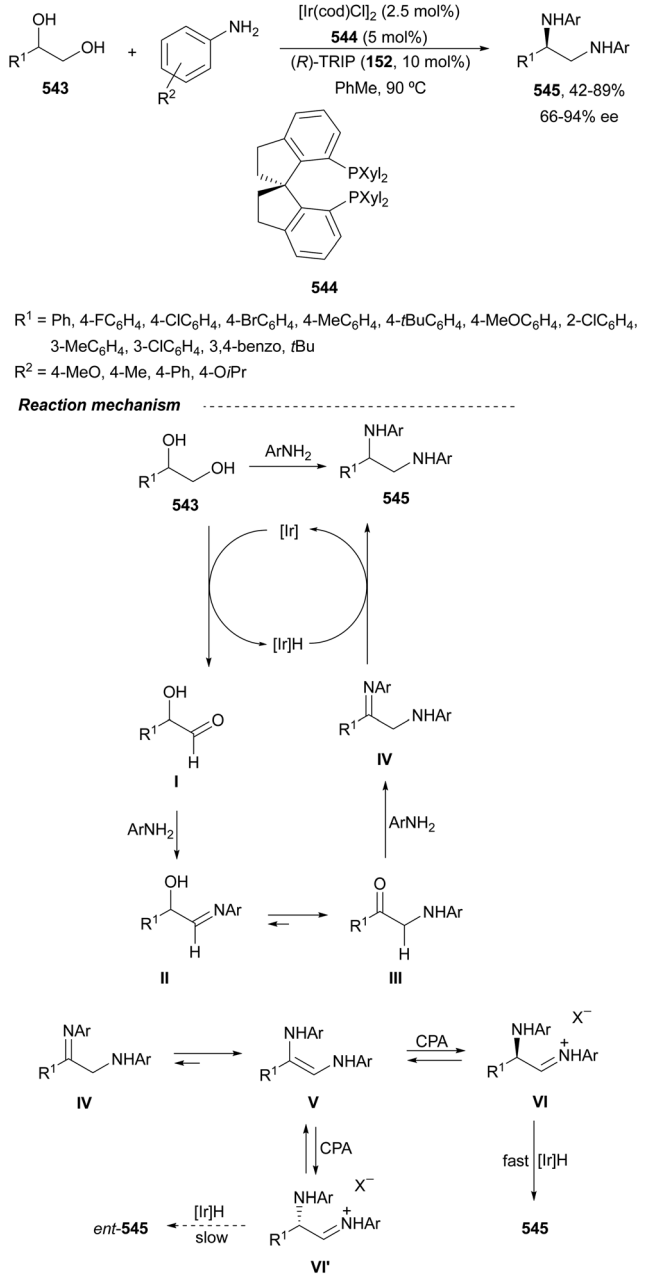
Scheme 162 Asymmetric hydrogen transfer of thiadiazoles **538** under RuCl(TsDpen) **539** catalysis.

proposed mechanism, DMAP reacts with benzoic anhydride to give intermediate **I**, an achiral ion pair, which interacts with thiourea to form the chiral ion pair **II** able to carry out the monobenzylation.

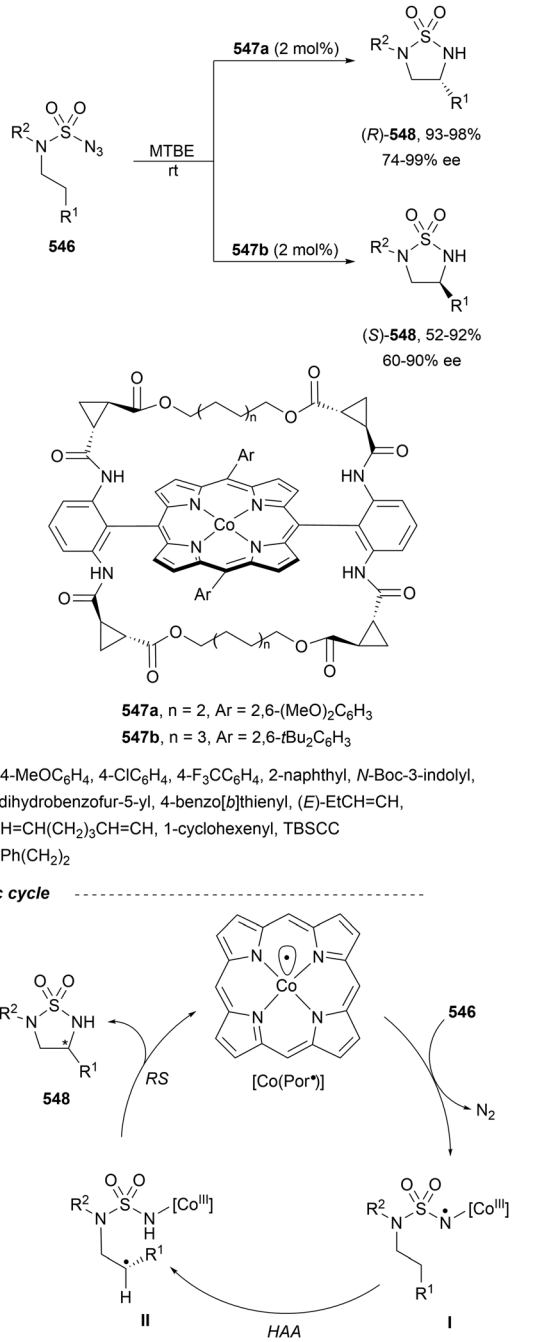
The same group performed[322] the kinetic resolution of 1,2-diaryl-1,2-diaminoethanes **555** by monobenzylation using the dual catalysis approach described in Scheme 168. In this case, amide-urea **558** was used as a chiral anion receptor and 4-(di-*n*-propylamino)pyridine (**559**) as an achiral nucleophile to form the ion pair **II** (Scheme 168). The crude reaction mixture was treated with TrocCl to provide a mixture of products **560** and **561** up to 53% conversion and a *s*-factor up to 30 (Scheme 169).

Kinetic resolution (KR) of 1,2-diamines **562** and **563** has also been performed *via* organocatalyzed electrophilic amination with dibenzyl azodicarboxylate (**75**) by He, Yang and co-workers.[323] In the case of 1,2-diamines **562** with a α-secondary amine, (*R*)-**456** was used as CPA to obtain (*S*)-**562** (up to >99% ee) and products (*R*)-**564** (up to 94% ee), which were separated by column chromatography (Scheme 170a). For the KR of α-tertiary amines **563**, (*S*)-**565** was employed as CPA to provide (*R*)-**563** (up to 97% ee) and compounds (*S*)-**566** (up to 96% ee) (Scheme 170b). Based on control experiments with **562a** (R = Ph, R = H) a plausible mechanism was proposed. Under catalyst (*S*)-**456**, the dual hydrogen bonding activation of matched (*S*)-1,2-diamine substrate **563a** by the CPA catalyst facilitates the electrophilic addition of the aniline moiety with the diazo group in **I** to provide dearomatized intermediate **II**. Subsequent aromatization of **II** forms (*S*)-**566a**. Product (*S*)-**566a** (Ar = Ph, R^1 = Me, R^2 = H) was transformed into (*S*)-**563a** by treatment with KOH at 70 °C by removing of the hydrazine moiety. Moreover, oxidative cleavage of the *N*-aryl group of (*S*)-**566a** by using trichloroisocyanuric acid (TCCA) at 80 °C produced the primary amine **567a** in 58% yield.

More recently, Waser and co-workers[324] reported the enantioselective desymmetrization of *meso*-diaminocyclopropane **568** under Cu(II)/bis(oxazoline) **569** catalysis. This Friedel–Crafts alkylation of indoles and a pyrrole delivered enantioenriched diastereomerically pure imidazolidinones **570** and **571**, respectively (Scheme 171). The *trans*-relative configuration of products **570** and **571** supports a S_N2-like mechanism for the ring-opening of the cyclopropane unit.



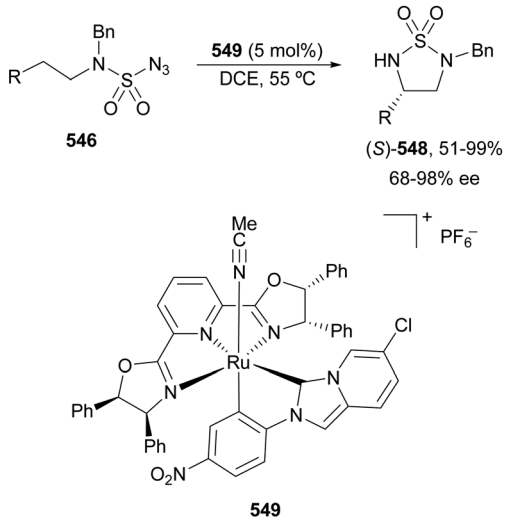
Scheme 163 Asymmetric hydrogen autotransfer of diols **543** with amines under $[Ir(cod)Cl]_2$/bisphosphine **544** and (*R*)-TRIP (**152**) catalysis.



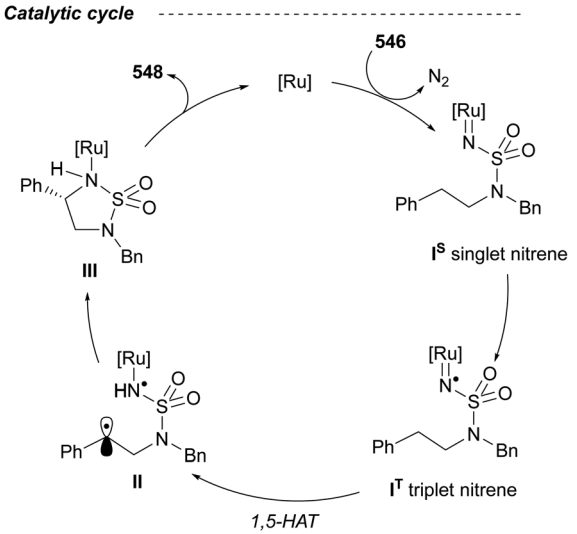
Scheme 164 Asymmetric enantiodivergent radical C–H amination of sulfamoyl azides **546** under Co-porphyrin **547** catalysis.

Rhodium-catalyzed dynamic kinetic asymmetric transformations (DYKAT) of racemic allylic trichloroacetimidates **572** and **573** were employed by Mwenda and Nguyen[325] for the enantioselective synthesis of 1,2-diamines **575** and **576**, respectively. Chiral diene **574**-ligated Rh-catalyst promoted the amination of allylic tetrachloroacetamidates **572** with aromatic amines to provide 1,2-diamines **575** and **576** with tertiary and quaternary stereocenters with good diastereo- and enantioselectivities (Scheme 172). This process occurs by intermediacy of a π-allylrhodium intermediate **I**, which undergoes fast nucleophilic attack of aniline suppressing vinyl aziridine formation.

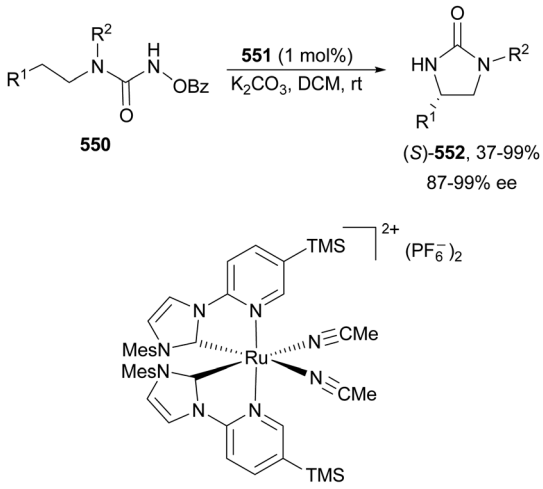
Pyrrolidine-3,4-diamine skeleton is present in some biologically active compounds.[326] Enantioselective 1,3-DC of azomethine ylides and (*E*)-β-naphthalimidonitroethene **577** has been described by Yu, Deng and co-workers[327] for the preparation of *trans*-3,4-diamino derivatives **579** using CuI/*N*,*O*-ligands **578** (Scheme 173). Imino esters **166** reacted with dipolarophile **577** to give *endo*-adducts **579** in high yields and diastereo- and enantioselectivities. The authors propose a TS with the two phenyl groups adjacent to the oxygen atom in the 1,2-dihydroimidazo[1,2-*a*]quinolone ligand **578** blocking the dipolarophile **577** approaching



R = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-PhC_6H_4, 4-$MeOC_6H_4$, 3,4-$(OCH_2O)C_6H_3$, 4-$F_3CC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2-naphthyl, 2-thienyl, *N*-Boc-3-indolyl, 1-cyclohexenyl, PhCC

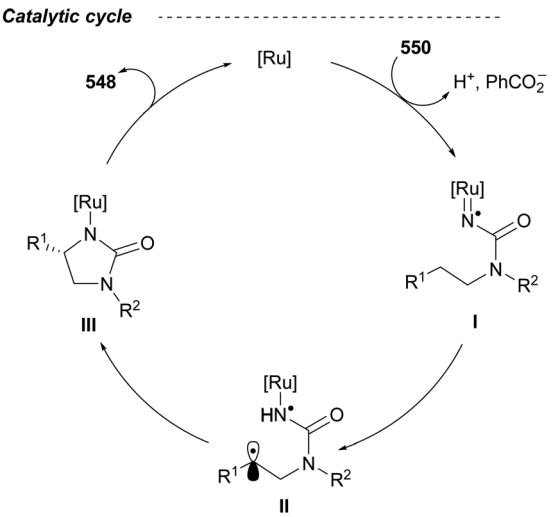


Scheme 165 Asymmetric radical C–H amination of sulfamoyl azides **546** under Ru(II) complex **549** catalysis.



R^1 = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2-naphthyl, 1-naphthyl, 2-thienyl, PhCC

R^2 = H, Me, Et, *n*Bu, *i*Bu, Bn, $Ph(CH_2)_2$

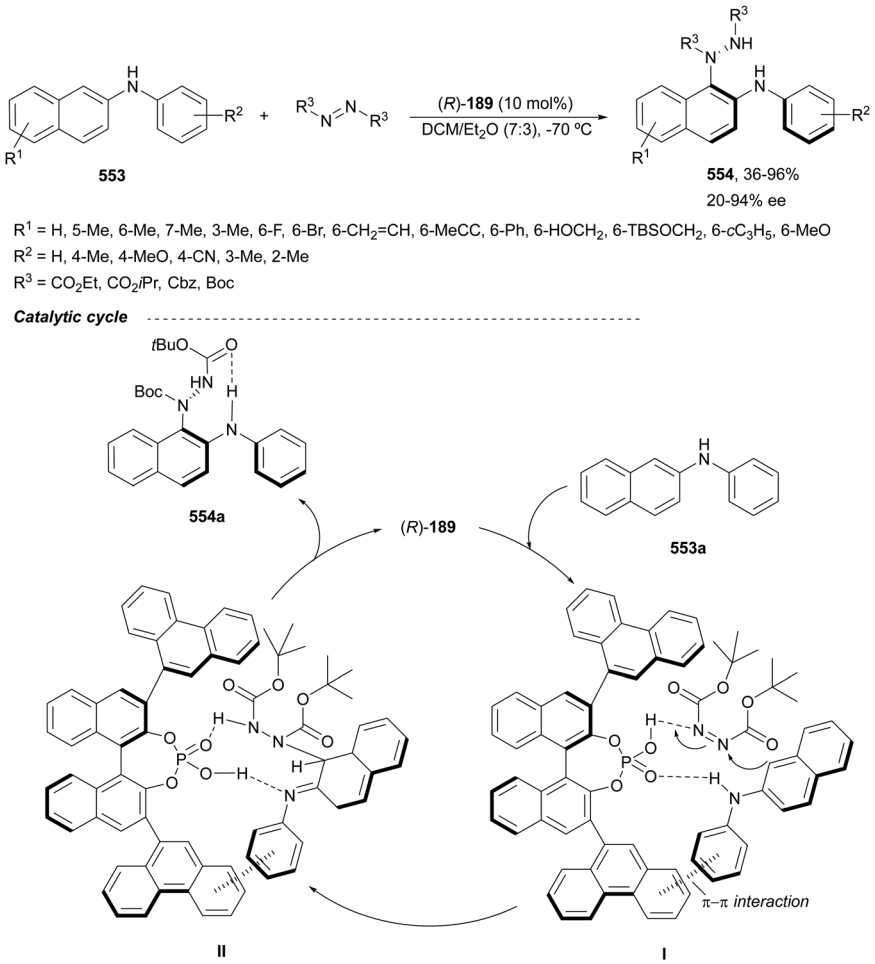


Scheme 166 Asymmetric radical C–H amination of *N*-benzoyloxy ureas **550** under Ru(II) complex **551** catalysis.

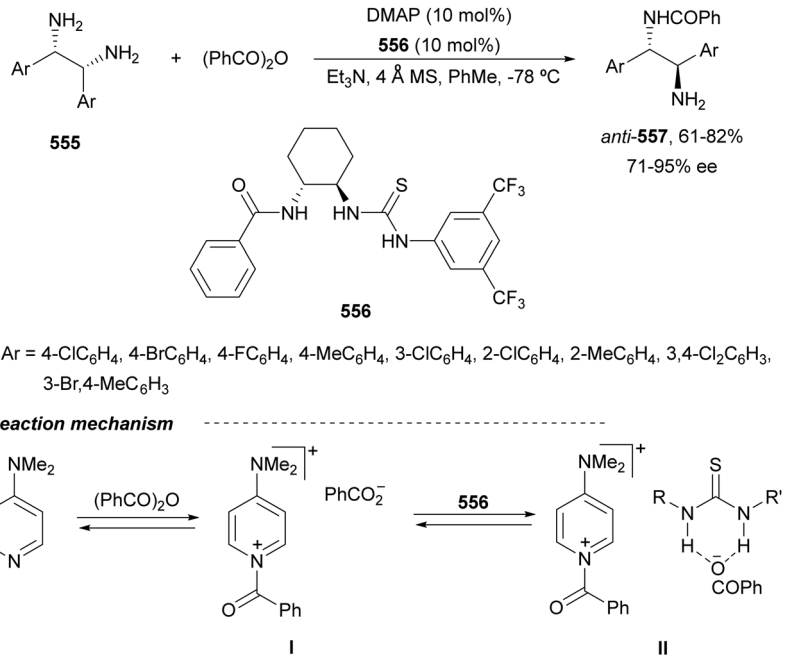
from the bottom face favoring the formation of the *endo*-**579** through approaching from the top face. Nitro group reduction of cycloadduct **579a** with RANEY® Ni and deprotection of phthalyl by methylamine provided *trans*-3,4-diaminopyrrolidine **580**.

For the enantioselective synthesis of chiral *cis*-3,4-diaminopyrrolidine derivatives **583**, Nájera, Sansano and co-workers[328] recently reported the 1,3-DC of azomethine ylides with (*Z*)-2-amido-1-nitroethenes **581a** and **581b**.[329] Imino esters **166** reacted with (*Z*)-amidonitroethenes **581a** and **581b** using $AgClO_4$ or Ag_2CO_3 and phosphoramidite (S_a,*R*,*R*)-**180** as a catalyst to furnish pyrrolidines *endo*-**582** (Scheme 174). In the case of cycloadduct *endo*-**582b**, the reduction with Zn and concentrated HCl under reflux afforded the *cis*-3,4-diamine derivative **583** in 90% yield and with the same enantiomeric excess.

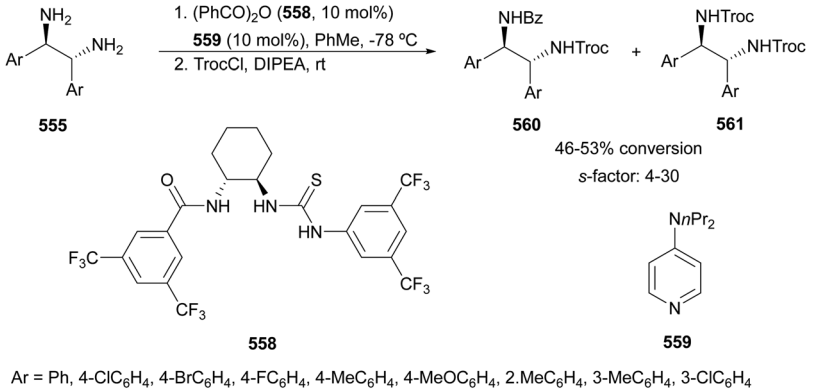
Desymmetrization of *meso*-1,2-diamines by acylation under thiourea catalysis and *meso*-diaminocyclopropane by Friede-Crafts alkylation of indoles under Cu/bis(oxazoline) catalysis were efficient strategies for the asymmetric synthesis of 1,2-diamines and 4,5-disubstituted imidazolidinones, respectively. Alternatively, KR of 1,2-diamines by acylation under thiourea catalysis has been employed. Electrophilic amination of *N*-aryl-1,2-diamines with azodicarboxylate under CPA catalysis allowed the KR of these compounds. DYKAT of allylic trichloroacetamidates with aromatic amines has been accomplished under Rh/chiral diene complexes to obtain 1,2-diamines. 1,3-DC of imino esters with β-nitroaminoethenes under Cu or Ag catalysis have been applied to the synthesis of *trans*- or *cis*-3,4-diaminoprolinates, respectively.



Scheme 167 Asymmetric atroposelective C–H amination of *N*-aryl-2-naphthylamines **553** with azodicarboxylates under CPA (*R*)-**189** catalysis.



Scheme 168 Enantioselective desymmetrization of *meso*-diamines **555** with benzoic anhydride under cooperative DMPA and thiourea **556** catalysis.



Ar = Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2.MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-ClC$_6$H$_4$

Scheme 169 Kinetic resolution of 1,2-diaryl-1,2-diaminoethanes **555** under amide-thiourea **558** and 4-(di-*n*-propylamino)pyridine (**559**) dual catalysis.

7. Conclusions

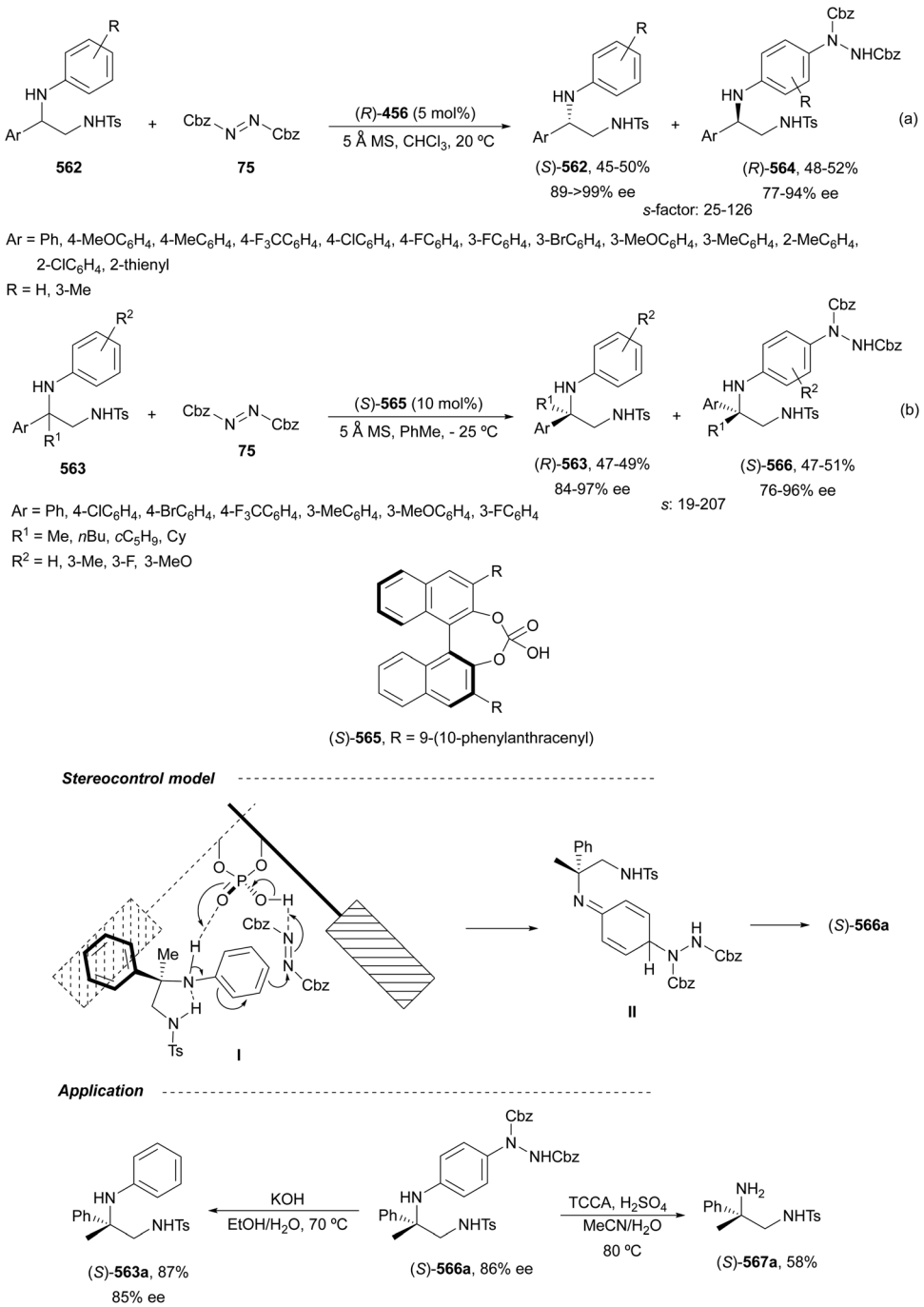
Particular conclusions are included at the end of each section in this review article. We report now general conclusions of this subject. With respect to asymmetric C–N bond-forming reactions detailed in Section 2, classical ring opening of aziridines was accomplished with trimethylsilyl azide using metal-catalyzed methods or Brønsted acids such as CPA, whereas desymmetrization of *meso*-aziridines with aromatic amines has been mainly accomplished with binol–metal complexes derived from Nb, Ti and Mg, and aliphatic amines were able to open aziridines under Ag/diphosphine catalysis. Other nitrogenated compounds such as hydroxylamines, tetrazoles and pyrazoles were also employed for desymmetrization of *meso*-aziridines by Mg complexes. Desymmetrization of azabenzonorbornadienes with amines has to be carried out under transition-metal catalysis to obtain *anti*-diamines, whereas using amides as nucleophiles *syn*-diamino derivatives were mainly formed.

Intermolecular hydroamination of allyl amines has been achieved under Rh catalysis. On the other hand, asymmetric hydrocupration allowed inter and intramolecular hydroaminations. Intramolecular carboamination of allylic ureas and sulfamides has been carried out under Pd catalysis with concomitant cross-coupling with aryl or alkenyl halides at the terminal position. Hydroamination of enamines has been performed by hydrocupration with *O*-acyl hydroxylamines and by Cu or Ca catalyzed amination by azodicarboxylates, alternatively CPAs can also be used as a catalyst.

Diamination of olefins can be carried out by a two-electron redox pathway using Pd(0)/Pd(II) or Pd(II)/Pd(IV) catalysis under I(I)/I(III) or Se(II)/Se(IV), and by one-electron radical mechanism under Cu or Fe catalysis. 1,3-Dienes and enynes were diaminated with urea under Pd(0)/Pd(II) catalysis, whereas intramolecular diamination of tethered double bonds has been performed under Pd(II)/Pd(IV) catalysis as well as by chiral λ^3-iodane reagents. Intermolecular *syn*-diamination of alkenes was achieved using Se(II) reagents. In the case of one-electron mechanism, intermolecular diamination of 1,3-dienes was accomplished with di-*tert*-butylaziridinone under Cu catalysis. Intramolecular radical diamination was also achieved under Cu catalysis. Recently, an enantioselective radical aminoazidation of styrenes has been carried out successfully under Fe(II) catalysis. Section 3 discussed C–C bond-forming reactions, such as classical asymmetric aza-Mannich and aza-Henry reactions, which have been widely used for the synthesis of 1,2-diamines.

For the direct aza-Mannich reaction, different nucleophiles such as imino esters, imino nitriles, azlactones, isocyano acetates and isothiocyanates were reacted with imines to obtain α,β-diamino acid derivatives. For imino esters, Cu and Ag catalysis gave mainly *syn*-α,β-diamino acids. Moreover, organocatalytic methods using asymmetric PTC also gave *syn*-α,β-diamino acid derivatives. For *anti*-α,β-diamino acids a biomimetic strategy using a chiral aldehyde as catalyst has been described. Imino nitriles needed activated aldimines and ketimines under Cu or Pd catalysis. Azlactones were specially useful for the synthesis of α,β-diamino acids bearing quaternary stereocenters. Isocyano acetates reacted with aldimines and ketimines under metal salt catalysis and a *Cinchona*-derived alkaloid as a chiral base as well as thioureas and squaramides to provide imidazolines that can be easily transformed into α,β-diamino acid derivatives. Isothiocyanates reacted with aldimines and activated ketimines under Mg or Sr catalysis but also with *Cinchona*-derived alkaloids, guanidines and thioureas as chiral organocatalysts. Other nucleophiles such as α-azido carbonyl compounds or amides, as well as α-amino acetaldehydes have been employed under organocatalysis. Recently, *N*-aryl glycines and hydrazones were reacted under Cu/bis(oxazoline) and visible light-induced photoredox catalysis to obtain 1,2-diamine derivatives.

Asymmetric aza-Henry reactions were considered in Section 3.2 either under metal complexes or mainly under organocatalysis. Recent examples used Ir(III), Cu(II) and Zn(II) complexes to obtain *anti*-β-nitroamine derivatives. As organocatalysts, chiral thioureas and squaramides derived from *Cinchona* alkaloids have been efficiently used for acyclic and cyclic aldimines and ketimines. PTC mainly with *Cinchona*-derived ammonium salts has been widely used in the aza-Henry reaction for aldimines, which can be generated *in situ* from α-amido sulfones. Ketimines can also be employed with simple nitroalkanes. Recently, chiral bases have been extensively used for the addition of nitroalkanes to aldimines and ketimines, specially mono and bis(amidine)-derived catalysts. This strategy has been employed for the

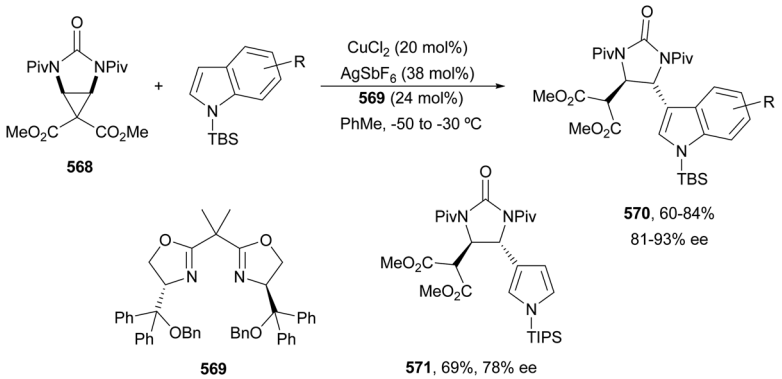


Scheme 170 Kinetic resolution of 1,2-diamines **562** and **563** *via* electrophilic reaction with dibenzyl azodicarboxylate (**75**) under CPA (*R*)-**456** and (*S*)-**565** catalysis, respectively.

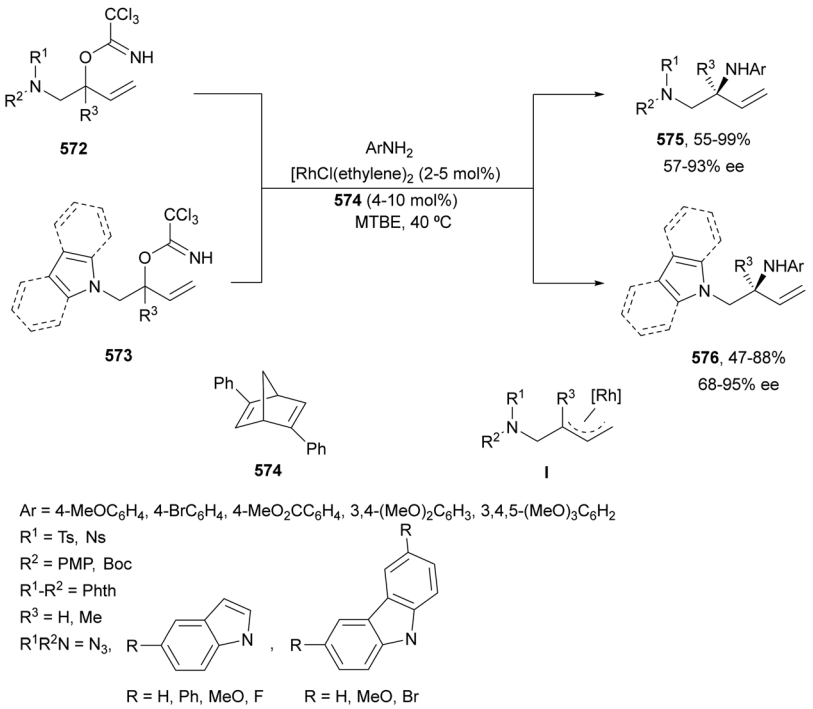
synthesis of 1,2-diamine precursors of (−)-nutlin-3, azetidine (−)-441 and (+)-VNI therapeutics.

In Section 3.3, imine–imine coupling such as aza-pinacol promoted by chiral diboron compounds allowed the synthesis of non-substituted 1,2-diamines. For the coupling of imines with hydrazones, a CPA has been employed. In the second strategy, azaallyl anions acted as nucleophiles with imines and chiral guanidines, thioureas and squaramides were used as catalysts or PTC conditions to obtain *syn*-diamines. In Section 3.5, 1,3-DC of azomethine ylides or 5-vinyloxazolidinones with imines to obtain imidazolidines were described. CPAs as well as chiral Ag and Cu complexes gave by *endo*-selectivity *cis*-imidazolidines. In the case of [2+2] cycloaddition of allenamides under Rh(I)/Binap (**53**) catalysis, bis(methylene)-1,2-diamines were formed.

Section 4 considered C–H bond-forming reactions by C=N asymmetric hydrogenation reactions to obtain saturated *N*-containing heterocyclic systems such as piperazines, dihydro-2,2′-bisquinolines, quinoxalines and tetrahydroquinolines.



Scheme 171 Enantioselective desymmetrization of *meso*-diaminocyclopropane **568** by Friedel–Crafts alkylation of indoles and a pyrrole under Cu(II)/bis(oxazoline) **569** catalysis.



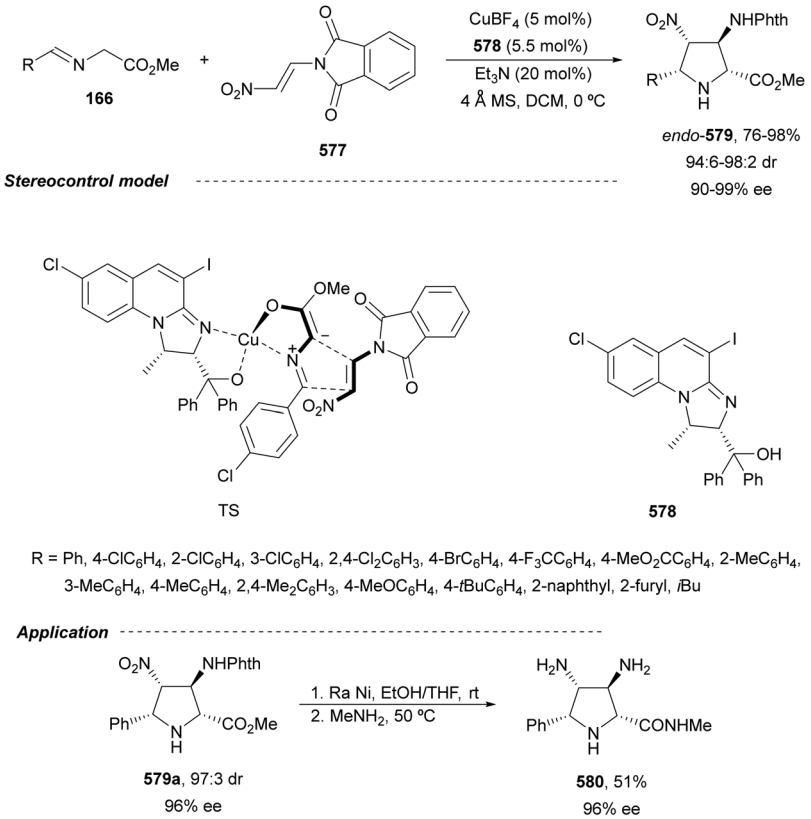
Scheme 172 Enantioselective DYKAT of allylic trichloroacetamidates **572** and **573** with aromatic amines under Rh/diene **574** catalysis.

Asymmetric transfer hydrogenation with RuCl(TsDpen) has been employed for the reduction of thiadiazole-1,1-dioxides to 4-alkylidenthiadiazolines with *cis* and *trans* configurations. Asymmetric hydrogen autotransfer of diols under Ir(I) and (*R*)-TRIP dual catalysis with anilines allowed general synthesis of *N*-arylated 1,2-diamines.

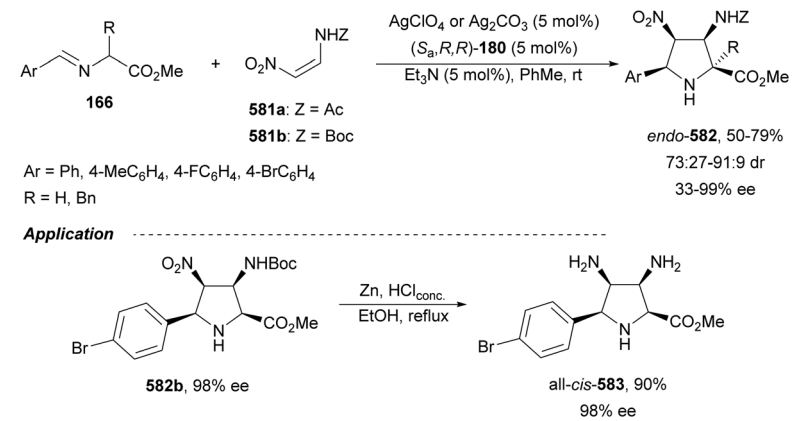
Section 5 included C–H amination reactions such as intramolecular 1,5-radical amination under Co and Ru catalysis of sulfamoyl azides or *N*-benzoyloxyureas to obtain enantioenriched sulfamides or imidazolidinones, respectively. On the other hand, *N*-aryl-2-naphthylamines underwent an asymmetric atroposelective C–H amination with azodicarboxylates under CPA catalysis to give naphthalene-1,2-diamine derivatives.

Section 6 dealt with other catalytic methods based on desymmetrization reactions for kinetic resolution of 1,2-diamines by acylation under thiourea catalysis. Kinetic resolution of 1,2-diamines *via* an electrophilic reaction at the *N*-aryl group by an azodicarboxylate has been performed under CPA catalysis. DYKAT of racemic allyl trichloroacetamidates with anilines was accomplished under Rh/diene catalysis. Finally, [3+2] cycloadditions of imino esters with β-nitroaminoethanes under Cu or Ag catalysis formed *trans* or *cis*-3,4-diaminopyrrolidines, respectively.

The great importance of asymmetric 1,2-diamines is and will be related to applications of these chiral building blocks to the synthesis of chiral ligands, organocatalysts, biologically active compounds and pharmaceuticals.



Scheme 173 Asymmetric 1,3-DC of imino esters **166** with (*E*)-β-phthalimidonitroethene **577** under $CuBF_4$/ligand **578** catalysis.



Scheme 174 Asymmetric 1,3-DC of imino esters **166** with (*Z*)-amidonitroethenes **581** under Ag/phosphoramidite **180** catalysis.

Abbreviations

Ac	Acetyl
acac	Acetylacetate
Ad	Adamantyl
AH	Asymmetric hydrogenation
AHT	Hydrogen atom transfer
Am	Amyl (2-methyl-2-butyl)
anh	Anhydrous
ATH	Asymmetric transfer hydrogenation
atm	Atmosphere(s)
BAM	Bis(amidine)
BArF	Tetrakis(3,5-bis(trifluoromethyl)-phenyl)borate
Benzhydryl	Diphenylmethyl
Binap	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Binol	1,1′-Bi(2-naphthol)
Binolam	3,3′-Bis(diethylaminomethyl)-1,1′-bi-2-naphthol

Bn	Benzyl
(BNeop)2	Bis(neopentyl glycolato)diboron
Boc	*tert*-Butoxycarbonyl
Bpy	2,2′-Bipirydine
Bz	Benzoyl
C2-ferriphos-tolyl	2,2′-Bis[1-(*N*,*N*-dimethylamino)ethyl]-1,1′-bis(diphenylphosphino)ferrocene
ca.	Circa
cat	Catalyst
Cbz	Benzyloxycarbonyl
CD	Circular dichroism
cod	1,5-Cyclooctadiene
coe	Cyclooctene
conc	Concentrated
CPA	Chiral phosphoric acid
cPr	Cyclopropyl
CuCatMix*	Mixture of Ph3P, (*R*)-DTBM-Segphos and Cu(OAc)2
Cy	Cyclohexyl
CYP51	Catalyst for the demethylation of lanosterol
4CzIPN	1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
D-B	Diboron
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DC	Dipolar cycloaddition
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DCP 083	(*S*,*E*)-6-Chloro-4-(2-cyclopropylvinyl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1*H*)-one
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
Difluorophos	[4-(5-Diphenylphosphanyl-2,2-difluoro-1,3-benzodioxol-4-yl)-2,2-difluoro-1,3-benzodioxol-5-yl]-diphenylphosphine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMB	2,4-Dimethoxybenzyl
DMBQ	2,6-Dimethoxybenzoquinone
DME	Dimethoxyethane
DMF	Dimethylformamide
DMMGarphos	2,2′-Bis[bis(4-methoxy-3,5-di-*t*-butylphenyl)phosphino]-4,4′,6,6′-tetramethoxybiphenyl
DMMS	Dimethoxymethylsilane
DMSO	Dimethyl sulfoxide
DPEN	1,2-Diphenyethane-1,2-diamine
DPP	Diphenylphosphinoyl
dr	Diastereomeric ratio
DTBM-Segphos	5,5′-Bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
DYKAT	Dynamic kinetic asymmetric transformation
ee	Enantiomeric excess
equiv.	Equivalents
Fmoc	Fluorenylmethoxycarbonyl
Fesulphos	2-(*tert*-Butylthio)-1-(diphenylphosphino)-ferrocene
HA	Hydroamination
HAA	H-Atom abstraction
Hex	*n*-Hexyl
HFIP	Hexafluoroisopropanol
HIV	Human immunodeficiency virus
HMDS	Bis(trimethylsilyl)amine
Josiphos	[see, PPF-P(*t*Bu)2]
KR	Kinetic resolution
L	Ligand
LED	Light-emitting diode
LP99	*N*-[(2*R*,3*S*)-2-(4-Chlorophenyl)-1-(1,2-dihydro-1,4-dimethyl-2-oxo-7-quinolinyl)-6-oxo-3-piperidinyl]-2-methyl-1-propane-sulfonamide
M	Metal
MAM	Mono(amidine)
MC-4	Melanocortin-4
MCPBA	*meta*-Chloroperbenzoic acid
MeO-Biphen	2,2′-Bis[di-(2-furyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
N,Nu	Nucleophile
NFSI	*N*-Fluorobenzenesulfonimide
NHC	*N*-Heterocyclic carbene
NIP	*N*-Iodopyrrolidone
NIS	*N*-Iodosuccinimide
NLE	Non-linear effect
NMDA	*N*-Methyl-D-aspartic acid
NMR	Nuclear magnetic resonance
Ns	4-Nitrophenylsulfonyl
OPhen	1,2,3,4,7,8,9,10,-1,10-octahydrophenantroline
PBAM	H,^{4}PyrrolidineQuin-BAM
PG	Protecting group
Phbox	2,2′-Isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline]
Ph-Bpe	2,5-(Diphenylphospholano)ethane
Ph-Dbfox	4,6-Dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)
Ph-Phosferrox	2-(Diphenylphosphino)ferrocenyl-4-isopropyloxazoline
Phth	Phthalimido
Piv	Pivaloyl
PKC	Protein kinase
CPMB	*para*-Methoxybenzyl
PPFOMe	1-[(SP)-2-(Diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
PPF-P(tBu)$_2$	(Josiphos): (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
ppy	2-(2-Pyridyl)phenyl
Pro	Proline

psi	Pound-force per square inch
PTC	Phase transfer catalysis
Py	Pyridyl
PyBidine	2,6-Bis[(2*R*,4*S*,5*S*)-1-benzyl-4,5-diphenylimidazolidin-2-yl]pyridine
PYR	6-Chloro-2,5-diphenylpyrimidin-4-yl
Ra	Ni RANEY® nickel
rr	Regioisomeric ratio
RS	Radical substitution
rt	Room temperature
RuPhox	Ruthenocenyl phosphino-oxazoline complex
Segphos	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SES	2-(Trimethylsilyl)ethanesulfonyl
SET	Single electron transfer
Siphos-PE	10,11,12,13-Tetrahydrodiindeno[7,1-*de*:1′,7′-*fg*][1,3,2]dioxaphosphocin-5-bis[(*R*)-1-phenylethyl]amine, *N*-Di[(*R*)-1-phenylethyl]-[(*S*)-1,1′-spirobiindane-7,7′-diyl]-phosphoramidite
SPINOL	12-Hydroxy-1,10-di(phenanthren-9-yl)-4,5,6,7-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBME	*tert*-Butyl methyl ether
TBS	*tert*-Butyldimethylsilyl
Tc	Thiophene-2-carboxylate
TEMPO	2,2,6,6-(Tetramethylpiperidin-1-yl)oxyl
TESH	Triethylsilane
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid, trifluoroacetate
THF	Tetrahydrofuran
THP	Tetrahydropyrane
TMB	2,4,6-Trimethylbenzyl
TMS	Trimethylsilyl
tolyl	Methylphenyl
tosyl, Ts	4-Metylphenylsulfonyl
TPS	*tert*-Butyldiphenylsilyl
TPS-he-Pybox	2,6-Bis(*tert*-butyldiphenylsilyloxyethyl-oxazolinyl)pyridine
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Tro	2,2,2-Trichloroethoxycarbonyl
TS	Transition state
US	Ultrasounds
VNI	Potent inhibitor of CYP51
W	Watts
Xing-Phos	2-[(*R*)-[[(*R*)-(1,1-Dimethylethyl)sulfinyl]-amino](phenyl)methyl]-6-(diphenylphosphino)-*N*,*N*-diisopropylbenzamide
Xylene	Dimethylbenzene
xyl-Segphos	5,5′-Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxol
xylyl	Dimethylphenyl

Conflicts of interest

There are no conflicts to declare.

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