



Transition-metal-free chiral Brønsted/Lewis acid-catalyzed asymmetric diazo nucleophile-imine reactions

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Received: April 05, 2026 **Accepted:** May 11, 2026 **Published:** May 12, 2026

Cite this article: Xie PR, Luo YP, Xie ZY, Pan C, Xuan J. Transition-metal-free chiral Brønsted/Lewis acid-catalyzed asymmetric diazo nucleophile-imine reactions. *Chiral Chem.* 2026;2:202620. <https://doi.org/10.70401/cc.2026.0026>

Abstract

Over the past few decades, transition-metal-free chiral Brønsted acid or Lewis acid-catalyzed asymmetric reactions between diazo nucleophiles and imines have emerged as a pivotal strategy for constructing chiral aziridines or β -amino α -diazo derivatives, achieving remarkable synthetic progress. This review summarizes the research advances in asymmetric aza-Darzens reactions and asymmetric Mannich-type reactions of diazo nucleophiles with imines. It encompasses diverse catalytic systems, including chiral boroxinates, chiral dicarboxylic acids, chiral phosphoric acids, chiral *N*-triflylphosphoramides, and chiral Lewis acids, with an emphasis on the effects of substrate and catalyst on chemoselectivity. Remaining challenges and future perspectives are presented in this review.

Keywords: Chiral Brønsted acid, chiral Lewis acid, diazo compound, aza-Darzens reaction, Mannich-type reaction

1. Introduction

Diazo compounds serve as useful and versatile synthons in organic synthesis due to their diverse reactivity, acting as nucleophiles, carbene precursors, or radical precursors^[1-3]. Over the past decades, the transition-metal-free chiral Brønsted acid or Lewis acid-catalyzed asymmetric reactions of diazo nucleophiles with imines have emerged as an important method for the synthesis of chiral aziridines or β -amino α -diazo derivatives. In contrast to the metal carbene-involved mechanism^[4-6], these reactions generally proceed via the initial nucleophilic addition of diazo acetate to the activated imine carbon, generating a chiral diazo zwitterionic intermediate bearing two stereocenters. This key intermediate can then undergo a subsequent asymmetric aza-Darzens reaction or Mannich-type process, to afford chiral aziridines (Figure 1, path A) or β -amino α -diazo derivatives (path B), respectively. Concurrently, the same zwitterionic intermediate may also participate in competitive 1,2-H or 1,2-carbon migration steps, variably leading to achiral enamine byproducts (paths C and D). While existing reviews have summarized aspects of aziridine synthesis via the condensation of imines with diazo compounds, there remains an urgent need for a comprehensive and updated overview focusing on asymmetric diazo nucleophile-imine reactions^[7,8]. In this review, we summarize the advances in transition-metal-free chiral Brønsted/Lewis acid-catalyzed asymmetric diazo nucleophile-imine reactions. We systematically summarize these two types of reactions classified by catalyst type. This review aims to distinguish between the generation of chiral aziridines and chiral β -amino α -diazo derivatives, with a particular focus on the effects of substrate substituents and catalysts on chemoselectivity.

2. Asymmetric Aza-Darzens Reaction

Aziridines are privileged structural motifs in organic synthesis, attributed to their inherent ring strain and versatile reactivity profiles^[9]. In this context, the chiral Brønsted acid-catalyzed asymmetric aza-Darzens reaction of imines with diazo compounds represents an efficient approach to access enantioenriched aziridines. Mechanistically, this reaction proceeds via initial nucleophilic



attack of the diazo compound onto the catalyst-activated imine carbonyl, generating a chiral diazo zwitterionic intermediate. Subsequent intramolecular S_N2 cyclization occurs, wherein the antiperiplanar nitrogen executes nucleophilic displacement at the diazonium carbon with concomitant expulsion of N_2 to afford chiral aziridines (Figure 2).

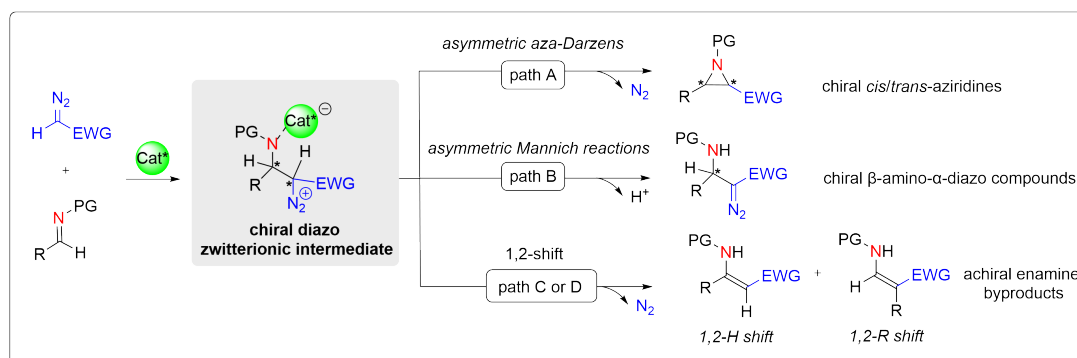


Figure 1. Chiral Brønsted/Lewis acid-catalyzed asymmetric diazo nucleophile-imine reactions.

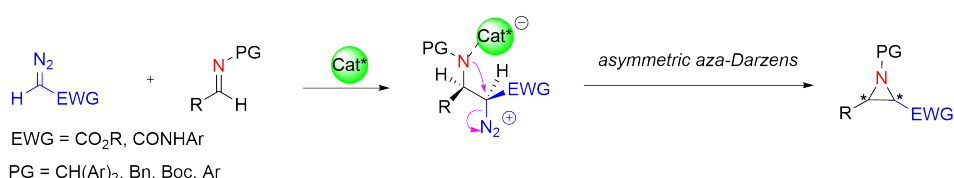


Figure 2. Chiral Brønsted/Lewis acid-catalyzed asymmetric aza-Darzens reaction of diazo nucleophile with imine.

2.1 Chiral boroxinate-catalyzed asymmetric aza-Darzens reaction

In a pioneering 1999 report, the Wulff group described a boroxinate (BOROX) Brønsted acid catalyst derived from (S)-2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol (VAPOL) and a borane-tetrahydrofuran (THF) complex (for relevant structural studies of BOROX catalysts, see Figure 3). This catalyst enabled, for the first time, the asymmetric reaction of *N*-diphenylmethyl aldimines **2.2** with ethyl α -diazoacetate **2.1** to afford chiral *cis*-aziridine compounds **2.3** (Figure 4)^[10]. Achiral enamine byproducts **2.4** and **2.5** could be detected in this reaction. Notably, VAPOL proved superior to the more common 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) in inducing chirality. Phenyl, 2-naphthyl, 2-furyl, and cyclohexyl groups are all compatible in this reaction system. In 2000, the team further revealed that the BOROX Brønsted acid catalyst prepared from triphenyl borate exhibited enhanced catalytic performance compared to other analogues^[11].

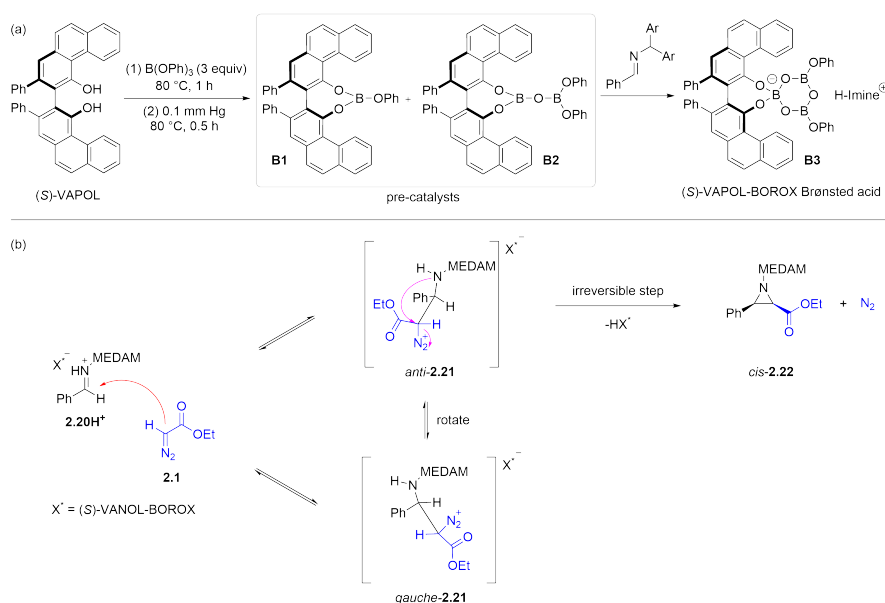
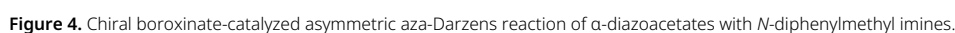


Figure 3. Mechanism of chiral BOROX-catalyzed asymmetric aza-Darzens reaction. BOROX: boroxinate.



2.6 + **2.1** $\xrightarrow[\text{CCl}_4, 25^\circ\text{C}, 24\text{ h}]{\text{(S)-VANOL, B(OPh)}_3}$ **2.7** + **2.8 (2.9)**

up to 98% yields
97% ee

2-19% yields

2.7 $\xrightarrow[\text{anisole}]{\text{TfOH}}$ **2.10**

92-100% yields

(S)-VAPOL

Figure 5. Chiral BOROX-catalyzed asymmetric aza-Darzens reaction of α -diazoacetates with *N*-DAM-imines. BOROX: boroxinate; DAM: dianisylmethyl.

Reaction scheme showing the asymmetric synthesis of **2.12** from **2.1** and **2.11** using (S)-VANOL or (S)-VAPOL and $B(OPh)_3$ in toluene at 25 °C for 24 h. The reaction yields **2.12** in up to 99% yield and 99% ee. The structure of **BUDAM** is shown in a dashed box.

Reaction scheme showing the asymmetric synthesis of **2.12a** through **2.12e** from **2.1** and **2.11** using (S)-VANOL or (S)-VAPOL and $B(OPh)_3$ in toluene at 25 °C for 24 h. The reaction yields **2.12a** through **2.12e** in the following yields and ee values:

- 2.12a**: 97%, 98% ee
- 2.12b**: 96%, 98% ee
- 2.12c**: 57%, 87% ee
- 2.12d**: 87%, 84% ee
- 2.12e**: 76%, 80% ee

Figure 6. Chiral BOROX-catalyzed asymmetric aza-Darzens reaction of α -diazoacetates with *N*-BUDAM-imines. BOROX: boroxinate; BUDAM: tetra-*tert*-butyldianisylmethyl.

In terms of innovation in reaction substrates, in 2007, Wulff and colleagues achieved the synthesis of *cis*-aziridine ketones from the reaction of diphenylmethyl aldimines **2.2** with vinyl diazoketones **2.13**, catalyzed by chiral BOROX generated *in situ* from chiral (S)-VAPOL with triphenylborate (Figure 7)^[14]. Notably, the *syn*, *anti*-aminodiols **2.14a-I** and *syn*, *syn*-aminodiols **2.14a-II** can be obtained from compound **2.14a** by reduction with $\text{Zn}(\text{BH}_4)_2$ or L-Selectride, respectively, followed by hydrolysis.

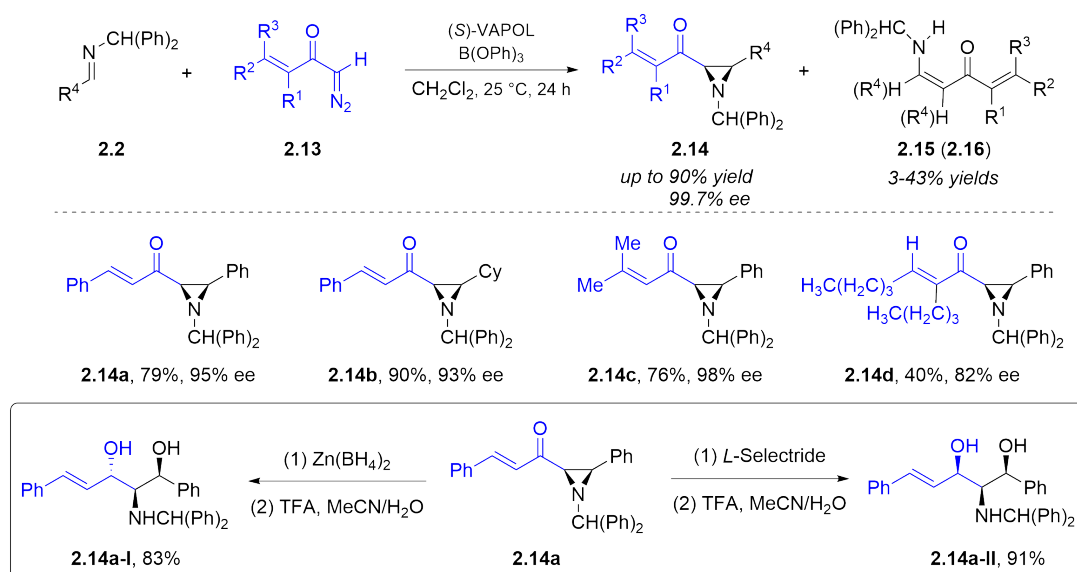


Figure 7. Chiral BOROX-catalyzed asymmetric aza-Darzens reaction of vinyl diazoketones with diphenylmethyl imines. BOROX: boroxinate.

In 2011, the Wulff group achieved a three-component asymmetric aza-Darzens reaction under this BOROX catalysis. Aldehydes **2.17** and amines **2.18** bearing a bis(dimethylanisyl)methyl group (MEDAM) generated imines *in situ* in the reaction system, which were then immediately captured by the catalyst and reacted with ethyl α -diazooacetate **2.1** to produce chiral *cis*-aziridine compounds **2.19** (Figure 8)^[15]. Notably, aryl, heteroaryl, and aliphatic aldehydes were compatible with this reaction, overcoming the previous limitation where imines derived from aliphatic aldehydes were unstable and caused reaction failure.

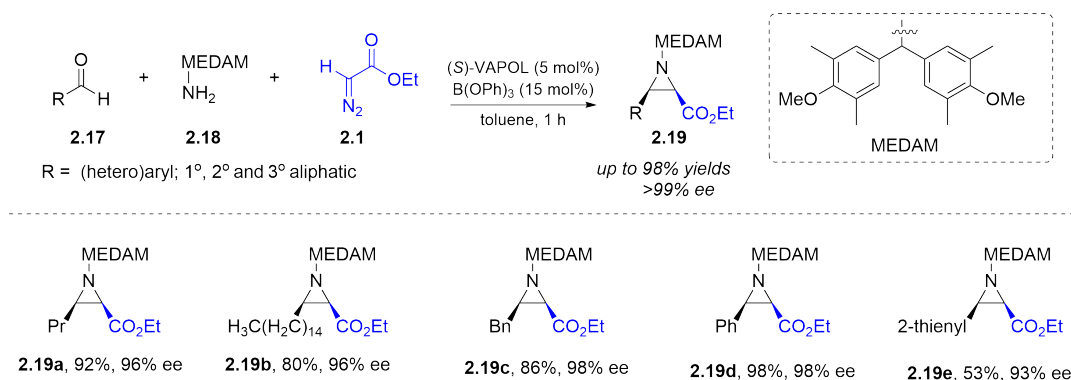


Figure 8. A three-component asymmetric aza-Darzens reaction under chiral BOROX catalysis. BOROX: boroxinate.

In 2012, the Wulff group demonstrated that the mesoborate (**B1**) and pyroborate (**B2**) generated from VAPOL and triphenyl borate act as precatalysts. The actual catalytic species is the boroxinate (**B3**) formed upon reaction of these precatalysts with imines^[16]. Furthermore, the mechanism of the chiral BOROX Brønsted acid catalyzed aziridination reaction of imines and ethyl α -diazooacetate **2.1** was investigated using a combination of experimental kinetic isotope effects and theoretical calculations. Specifically, the process initiates with reversible nucleophilic addition of ethyl α -diazooacetate **2.1** to the intermediate **2.20H'** activated by the catalyst, generating a chiral diazonium intermediate **2.21**. The *gauche*-**2.21** can undergo rotation around the C-C bond to give the *anti*-**2.21**. An intramolecular irreversible $\text{S}_{\text{N}}2$ -like ring-closure step then occurs, accompanied by nitrogen extrusion, ultimately yielding the *cis*-aziridine product **2.22** (Figure 3)^[17].

2.2 Chiral dicarboxylic acid-catalyzed asymmetric aza-Darzens reaction

In contrast to the well-developed asymmetric *cis*-aziridination of diazo compounds with imines, the *trans*-selective variant has

remained largely elusive. In 2008, the Maruoka group reported the *trans*-selective asymmetric aziridination of diazoacetamides **2.24** and *N*-Boc aldimines **2.23** catalyzed by axially chiral dicarboxylic acids (Figure 9)^[18]. α -Diazoacetamide is critical for selective *trans*-aziridination. Its weakly acidic amide α -H prevents the occurrence of asymmetric Mannich-type side reactions. Moreover, in the anti-periplanar diazonium zwitterionic intermediate, hydrogen bonding between the amide N-H and the Boc group stabilizes the transition state, favoring *trans*-aziridine formation.

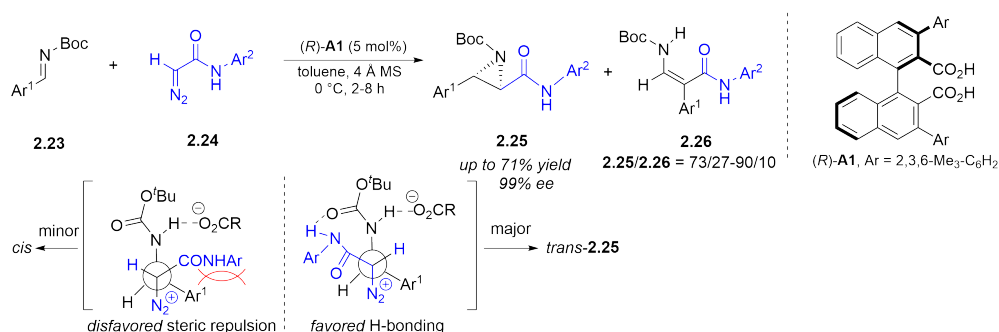


Figure 9. Chiral dicarboxylic acid-catalyzed asymmetric aza-Darzens reaction of α -diazoacetamides with *N*-Boc-imines.

2.3 Chiral phosphoric acid/*N*-triflylphosphoramidate-catalyzed asymmetric aza-Darzens reaction

Chiral phosphoric acid could lower the lowest unoccupied molecular orbital (LUMO) energy of the C=N bond to activate an imine group. In 2009, the Akiyama group reported a chiral phosphoric acid-catalyzed asymmetric aza-Darzens reaction of ethyl diazoacetate **2.1** and *N*-*p*-methoxybenzyl (PMB) aldimines derived from aryl glyoxals **2.27**, which furnished *cis*-aziridine carboxylates **2.29** (Figure 10)^[19]. Phenyl, 4-biphenyl, 1-naphthyl, and 2-thienyl groups are all compatible in this catalytic reaction system.

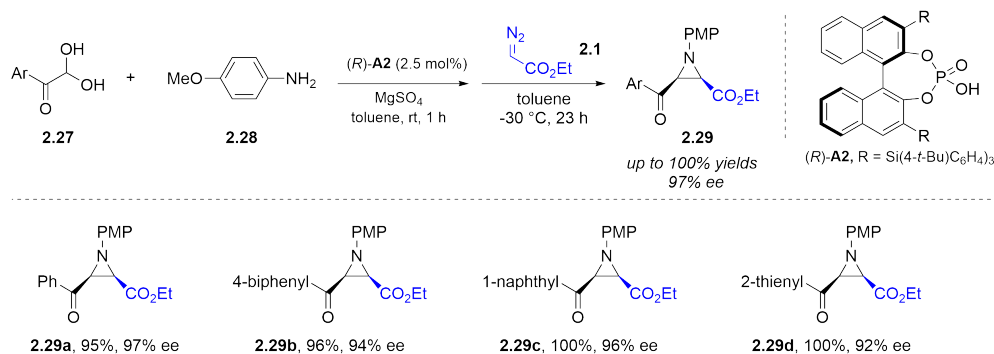


Figure 10. Chiral phosphoric acid-catalyzed asymmetric three-component aziridination reaction of α -ethyl diazoacetate with aryl glyoxals and 4-methoxyaniline.

In the same year, the Zhong group reported a chiral phosphoric acid-catalyzed asymmetric aza-Darzens reaction of diazoacetamides **2.24** and *N*-Boc aldimines **2.23** (Figure 11)^[20]. Both the reaction yields and chemoselectivities were improved significantly compared with those obtained using the axially chiral dicarboxylic acid [(*R*)-A1] shown in Figure 9. A wide range of aryl-substituted substrates afford satisfactory results in this catalytic reaction.

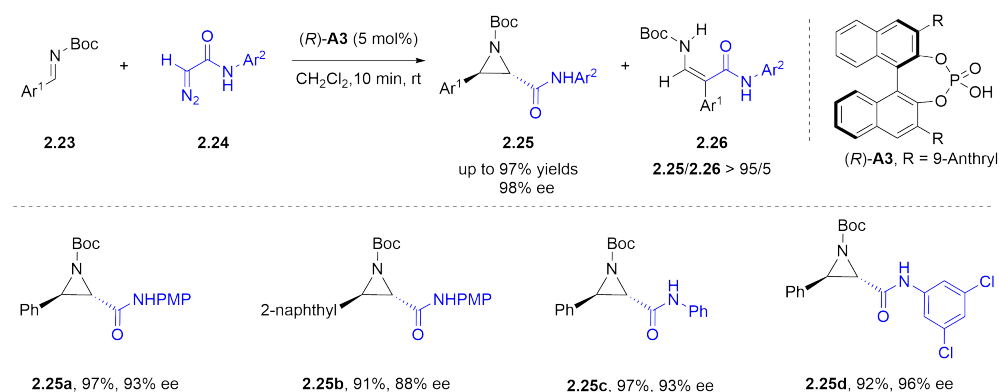


Figure 11. Chiral phosphoric acid-catalyzed asymmetric aza-Darzens reaction of α -diazoacetamides with *N*-Boc-imines.

Regarding the expansion of new types of diazo substrates for such asymmetric aza-Darzens reactions, the Cahard group in 2012 achieved the diastereo- and enantioselective synthesis of CF₃-substituted aziridines **2.31** catalyzed by chiral phosphoric acids (Figure 12)^[21]. Trifluoromethyl diazomethane **2.30** was generated in situ from the reaction of trifluoroethylamine hydrochloride with sodium nitrite, thereby avoiding the deactivation of the chiral phosphoric acid catalyst, as the chiral phosphoric acid catalyst (*S*)-**A4** can react with excess trifluoromethyl diazomethane to form an ester compound. Treatment of *cis*-**2.31f** with phenylmethanethiol as the nucleophile afforded the *syn*-β-CF₃ isocysteine derivative **2.31f-I** in good yield. The 4-methoxyphenyl (PMP) protecting group can also be removed using CAN as the oxidant.

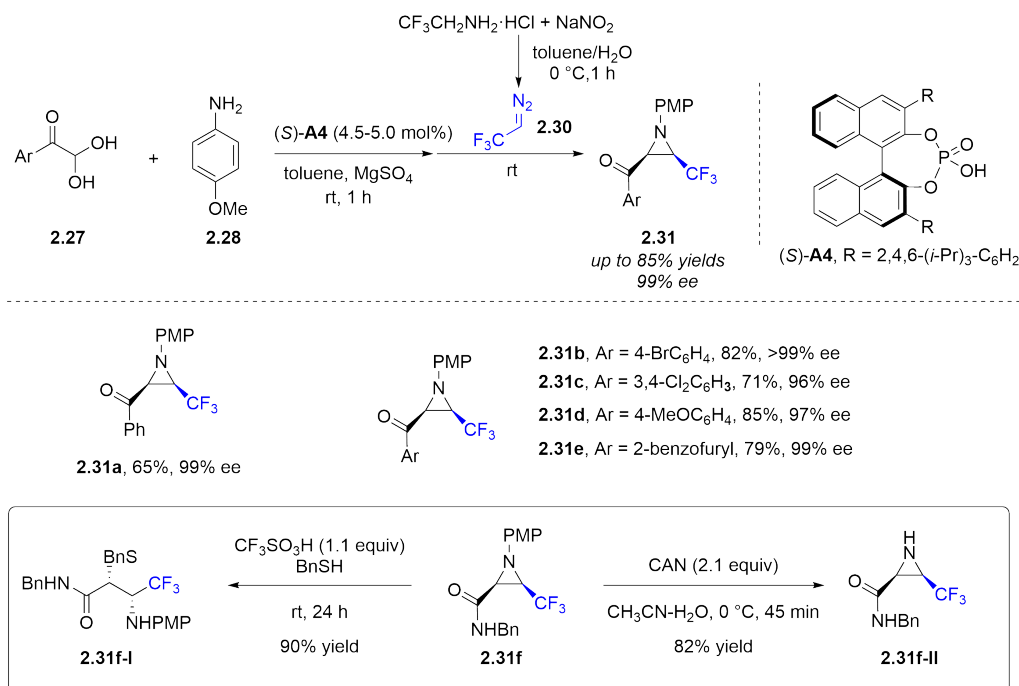


Figure 12. Chiral phosphoric acid-catalyzed asymmetric multicompartment aza-Darzens reaction of in situ generated CF₃CHN₂ with aryl glyoxal-derived *N*-PMB imines.

Despite significant advances in chiral Brønsted acid-catalyzed asymmetric aza-Darzens reactions between imines and diazo nucleophiles for aziridine synthesis, these transformations have been largely restricted to acyclic imine substrates, leaving cyclic imines virtually unexplored. In 2026, the Xuan group reported a chiral phosphoric acid-catalyzed asymmetric aza-Darzens reaction of quinoxalin-2(1*H*)-ones **2.32** with α-diazoacetates **2.33** (Figure 13)^[22]. A proposed mechanism for this catalytic asymmetric aza-Darzens reaction was shown in Figure 13a. First, protonation of quinoxalin-2(1*H*)-one **2.32a** with chiral phosphoric acid (*R*)-**A5** affords the activated iminium INT I with a H-bonding interaction between the amidic hydrogen and an oxygen atom of the chiral counterion. Then, an enantio- and diastereo determining nucleophilic addition of diazo acetate **2.33a** to the iminium carbon occurs, generating the chiral *anti*-diazonium intermediate INT II. Finally, an intramolecular S_N2 cyclization between the antiperiplanar amine and diazonium group, affords *cis*-aziridine carboxylate **2.34a** with N₂ release. The stereochemical outcome can be rationalized by the approach of the diazo nucleophile **2.33a** through its *Si* face (**2.33a**_{Si}) toward the *Re* face of the activated iminium intermediate INT I. This trajectory minimizes steric clashes between the bulky anthracen-9-yl substituent of the CPA catalyst [(*R*)-**A5**] and the *tert*-butyl ester moiety of **2.33a**_{Si} (Figure 13b).

Compared with chiral phosphoric acids, chiral *N*-triflylphosphoramides are more acidic. In 2017, the Bew group reported a chiral *N*-triflylphosphoramide-catalyzed three-component asymmetric aza-Darzens reaction of (hetero)aryl aldehydes **2.35** with 2-(*tert*-butoxy)aniline **2.36** and *tert*-butyl 2-diazoacetate **2.33a** (Figure 14)^[23]. This work extends the substrate scope from "activated" aryl glyoxals to various heteroaryl aldehyde starting materials. The catalytic cycle begins with *N*-protonation of an imine substrate with chiral *N*-triflylphosphoramide (*S*)-**A6**, generating the iminium INT IV. The stereochemical outcome is governed by the approach of **2.33a** through its *Re* face to the *Si* face of INT-IV, a pathway that alleviates steric congestion between the *ortho-tert*-butylphenyl ether moiety and the *tert*-butyl ester of the diazo nucleophile (Path A). Intramolecular S_N2 cyclization of the antiperiplanar amine and diazonium group then furnishes *cis*-aziridines **2.37a**.

2.4 Combined strong Brønsted acid-catalyzed asymmetric aza-Darzens reaction

Typical chiral Brønsted acids comprise a proton and a chiral conjugate base. As the proton is structurally invariant, the catalyst acidity, reactivity, and chirality are governed solely by the conjugate base. In 2013, the Maruoka group developed a new chiral Brønsted acid catalyst composed of two independent organic molecules, a chiral diol as a ligand and 2-boronobenzoic acid as an

achiral Brønsted acid^[24]. This in situ assembled catalyst proved efficient in an asymmetric aza-Darzens reaction of *N*-Boc and *N*-benzyl aldimines with *N*-phenyldiazoacetamide, affording *trans*-aziridines **2.39** (Figure 15).

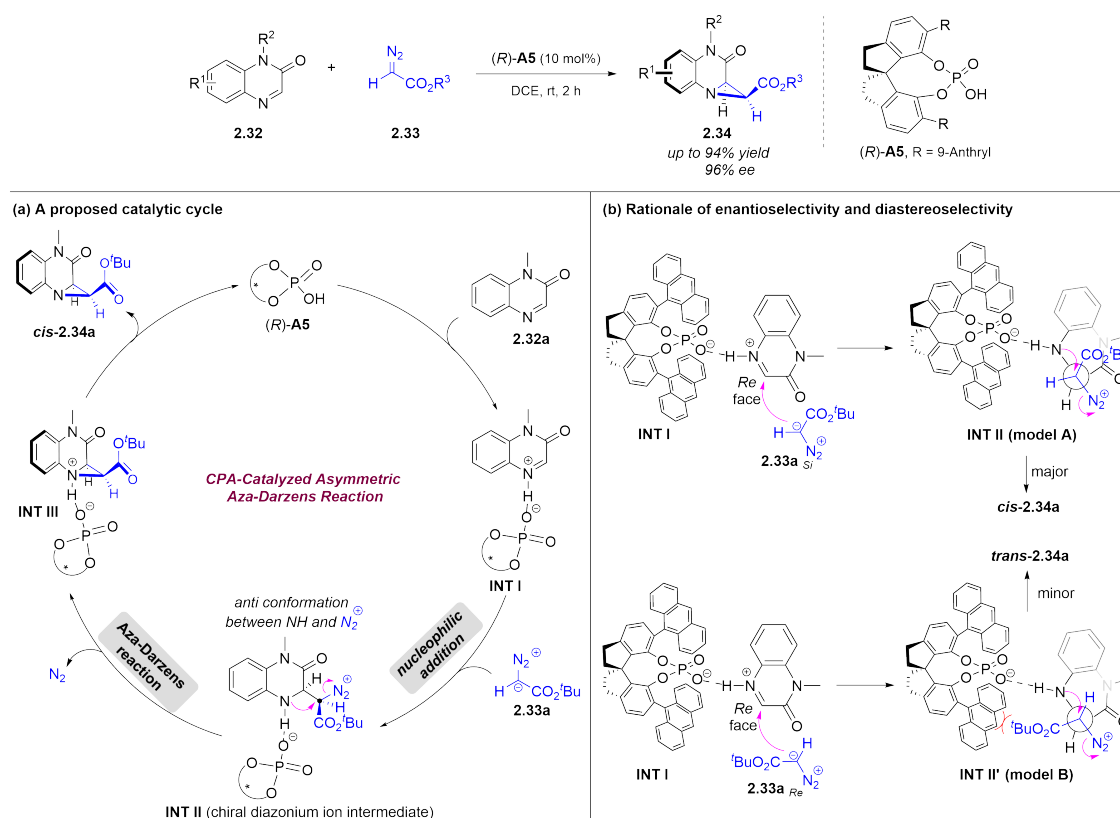


Figure 13. Chiral phosphoric acid-catalyzed asymmetric aza-Darzens reaction of quinoxalin-2(1*H*)-ones with α -diazoacetates.

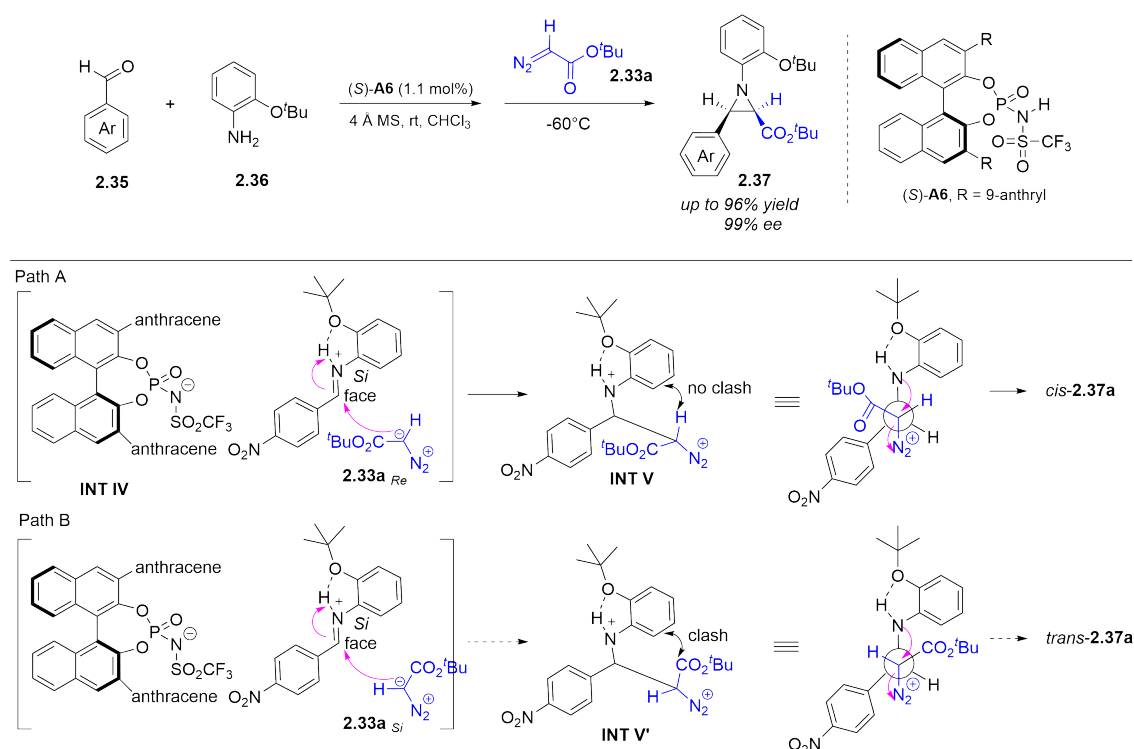


Figure 14. Chiral *N*-triflylphosphoramidate-catalyzed three component asymmetric aza-Darzens reaction of (hetero)aryl aldehydes with 2-(*tert*-butoxy)aniline and *tert*-butyl 2-diazoacetate.

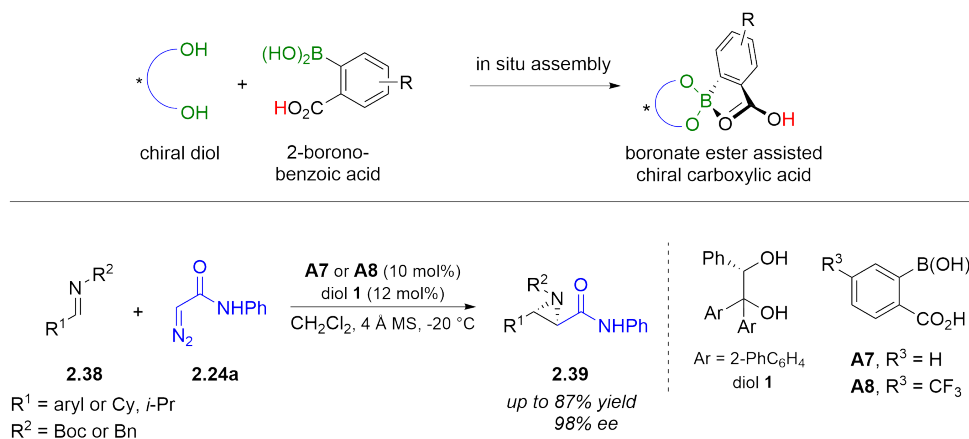


Figure 15. In-situ-assembled boronate ester assisted chiral carboxylic acid-catalyzed asymmetric aza-Darzens reaction.

Inspired by prior studies of arylboronic acid in combination with chiral diols or chiral aminoalcohols, in 2020, the Ma/Zhang group further achieved the synthesis of chiral CF₂-functionalized aziridines **2.40** in the three-component asymmetric aza-Darzens reaction of aryl glyoxals **2.27** and 4-methoxyaniline **2.28** with difluorodiaoethyl phenyl sulfone **2.40**, using a combined strong Brønsted acid system comprising a chiral disulfonimide (*S*)-**A9** and 2-carboxyphenylboronic acid **A7** (Figure 16)^[25]. A series of derivatization experiments were conducted to demonstrate the synthetic utility of this method. For example, selective oxidative cleavage of the PMP protecting group in **2.41a** using ceric ammonium nitrate proceeded smoothly, affording the unprotected aziridine **2.41a-I** in 81% yield. Reduction of the ketone functionality with either sodium borohydride or lithium aluminum hydride furnished the hydroxy-bearing CF₂-aziridine **2.41a-II** in excellent yield. Moreover, acid-mediated ring-opening of **2.41a** occurred efficiently to generate the CF₂-containing α-chloro-β-amino ketone **2.41a-III**.

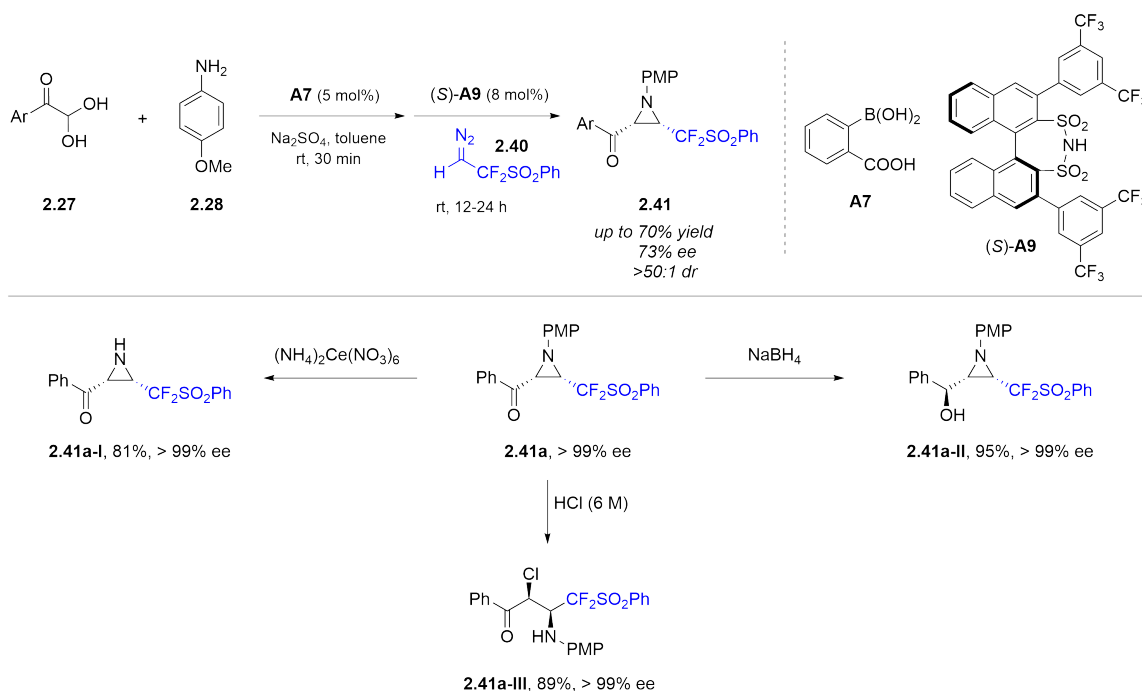


Figure 16. Asymmetric synthesis of CF₂-functionalized aziridines by combined strong Brønsted acid catalysis.

3. Asymmetric Mannich-Type Reaction

The diverse reactivity of diazo groups renders their incorporation into molecular core skeletons highly advantageous for subsequent functionalization and structural elaboration^[26-29]. Chiral Brønsted/Lewis acid-catalyzed asymmetric Mannich-type reactions provide an efficient strategy for introducing diazo groups into organic molecules. Mechanistically, nucleophilic addition of diazo compounds to the catalyst-activated imine carbon generates a chiral diazo zwitterionic intermediate. Subsequent intramolecular deprotonation of this intermediate by the basic moiety of the catalyst delivers chiral β-amino α-diazo compounds (Figure 17).

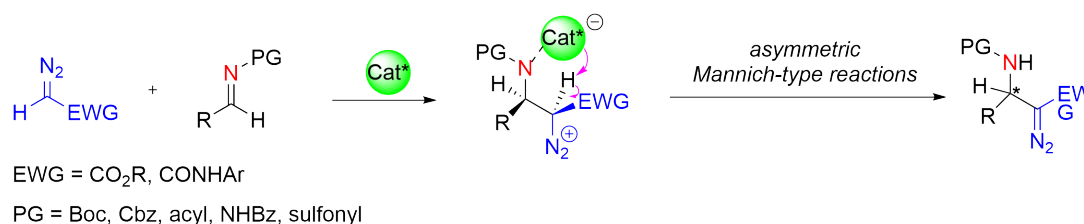


Figure 17. Chiral Brønsted/Lewis acid-catalyzed asymmetric Mannich-type reaction of diazo nucleophile with imine.

3.1 Chiral Brønsted acid-catalyzed asymmetric Mannich-type reaction

In 2005, the Terada group reported the first chiral phosphoric acid-catalyzed asymmetric Mannich-type reaction of ethyl diazoacetate **2.33** and *N*-acyl aldimines **3.1**, affording chiral β-amino-α-diazo esters **3.2** (Figure 18)^[30]. The key process was proposed to involve the intracomplex deprotonation of the chiral diazo zwitterionic intermediate by the phosphoryl oxygen through C-H bond cleavage.

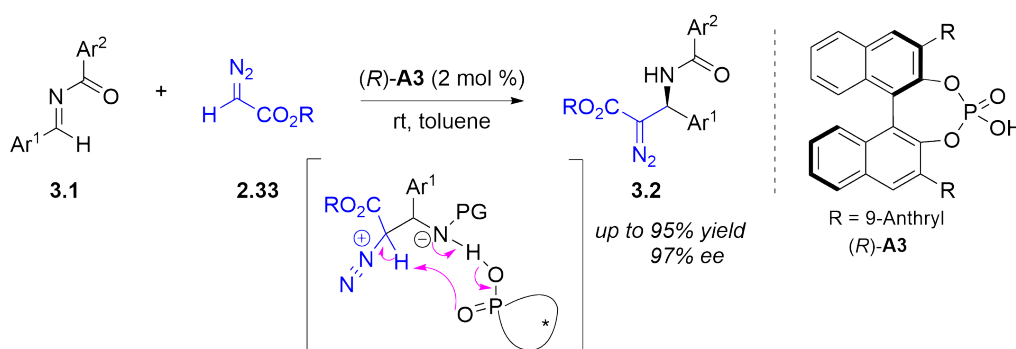


Figure 18. Chiral phosphoric acid-catalyzed asymmetric Mannich-type reaction of α-diazo esters with *N*-acyl imines.

In contrast to the well-established α-diazo carbonyl chemistry, α-diazomethylphosphonates generally exhibit lower reactivity, which can be attributed to both electronic effects and the greater steric bulk of the phosphonate group. In 2012, the Peng group first applied chiral phosphoric acids to the asymmetric Mannich-type reaction of dialkyl diazomethylphosphonates **3.4** with *N*-carbamoyl aldimines **3.3** (Figure 19)^[31]. The reaction afforded β-*N*-Boc amino-α-diazophosphonates **3.5** with good yields, diastereoselectivities, and enantioselectivities at a catalyst loading as low as 0.1 mol%. A reasonable transition state model was established to illustrate the catalytic pathway. Phenyl, 2-naphthyl and 2-thienyl are all compatible in this catalytic reaction. The chiral phosphoric acid (R)-A4 serves as a bifunctional Brønsted acid–base catalyst: its acidic proton activates the imine nitrogen via hydrogen bonding, and the nucleophilic carbon of diazomethylphosphonate attacks the imine from the *Si*-face. The phosphoryl oxygen then acts as a Brønsted basic site to mediate intramolecular deprotonation.

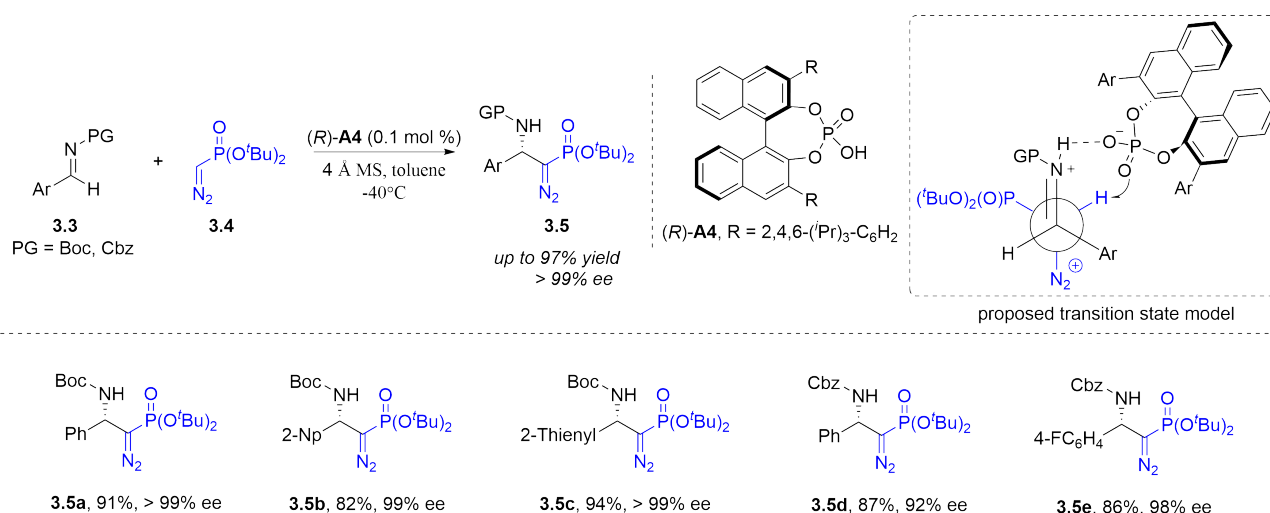


Figure 19. Chiral phosphoric acid-catalyzed asymmetric Mannich-type reaction of dialkyl diazomethylphosphonates with *N*-carbamoyl imines.

In 2019, the Singh group reported a chiral phosphoric acid-catalyzed tandem Mannich–lactamization reaction (Figure 20)^[32]. A reasonable transition-state model was proposed based on experimental results to explain the stereochemical outcome. Chiral phosphoric acid acts as a bifunctional catalyst with both Brønsted acid and Brønsted base sites. In this process, acidic protons activate the in situ generated imines and ester groups via hydrogen bonding. Nucleophilic α -diazo esters **2.33** then attack the *Si* face of the imines. The α -diazo esters are subsequently deprotonated by the phosphoryloxy group, which serves as the Brønsted base site. The desired products are finally obtained through intramolecular lactamization.

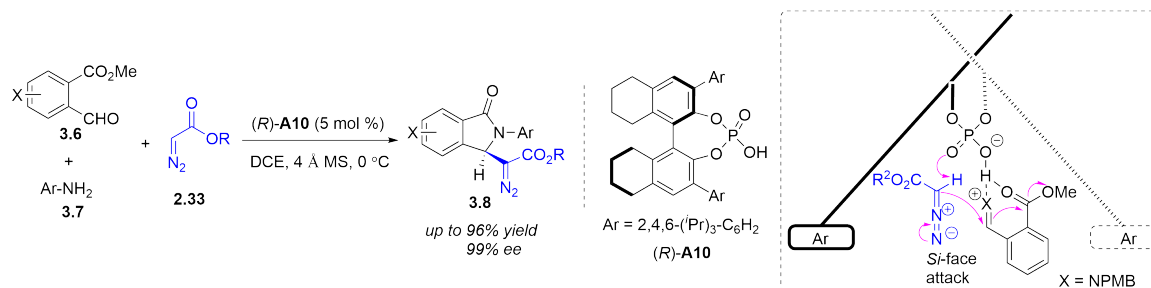


Figure 20. Chiral phosphoric acid-catalyzed Tandem Mannich–lactamization reactions.

In 2019, Ma *et al.* developed a facile, and chemodivergent, and stereoselective reaction of *N*-Boc aldimines with $\text{PhSO}_2\text{CF}_2\text{CHN}_2$ (Figure 21)^[33]. The reaction proceeded via a Mannich-type pathway when employing (*S*)-A4 as the catalyst, whereas the use of ($\pm$)-BPA selectively afforded *E*-configured enamine products **3.11**. Mechanistic studies showed that TEMPO (3 equiv) could form a hydrogen-bonded ion pair ($\text{O}^-\cdots\text{H}-\text{N}^+$) with chiral phosphoric acid to suppress the rearrangement, and diazo-Mannich adducts were identified as key intermediates en route to enamines.

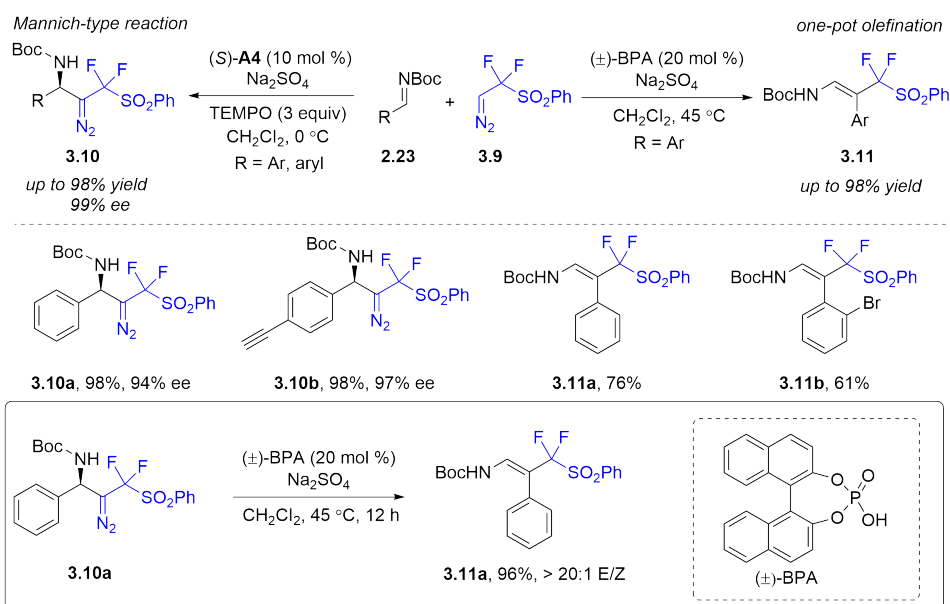


Figure 21. Chiral phosphoric acid-catalyzed chemodivergent and stereoselective reaction of *N*-Boc aldimines with $\text{PhSO}_2\text{CF}_2\text{CHN}_2$.

In 2020, the Peng group reported a chiral phosphoric acid-catalyzed asymmetric acyl-Mannich reaction of (diazomethyl)phosphonate **3.14** or ethyl α -diazoacetate **2.1** with isoquinolines (Figure 22)^[34]. This highly atom-economical reaction begins with the isoquinoline reacting with diethyl dicarbonate **3.13** to generate intermediate **3.16**. Protonation of the 1-ethoxy group in **3.16** by chiral phosphoric acid, followed by loss of EtOH, furnishes a 2-ethoxycarbonylisoquinolinium ion. This cation forms an ion pair with the chiral phosphate anion, which directs the enantioselective nucleophilic addition of **3.14** to the *Si*-face of the iminium. Finally, the phosphoryl oxygen acts as a Brønsted base to abstract the α -hydrogen from the α -(diazomethyl)phosphonate, affording product **3.15**.

In 2018, the Singh group reported a chiral phosphoric acid-catalyzed asymmetric Mannich-type reaction of α -diazoacetate with in situ generated *N*-acyl ketimines, derived from 3-hydroxyisoindolinones^[35]. Inspired by this work, the Zhao group further expanded the substrate scope from 3-hydroxyisoindolinones to 2-aryl-3*H*-indol-3-ones in 2025 (Figure 23)^[36]. The reaction is initiated by the interaction of ethyl diazoacetate **2.1** and 2-aryl-3*H*-indol-3-one **3.17a** with chiral phosphoric acid via hydrogen bonding to generate intermediate INT VI. In INT VI, the hydroxyl group of the chiral phosphoric acid protonates the imine unit of **3.17a** through hydrogen

bonding, forming a chiral indolin-3-one iminium ion. Simultaneously, the α -hydrogen of diazoacetate **2.1** interacts with the phosphoryl oxygen of the chiral phosphoric acid, enhancing its nucleophilicity. Subsequently, nucleophilic attack of the activated **2.1** onto the *Si*-face of the indolin-3-one iminium ion occurs via transition state **TS-2**, affording intermediate **INT VII**. Finally, intramolecular deprotonation of **INT VII** yields the final product **3.18a**.

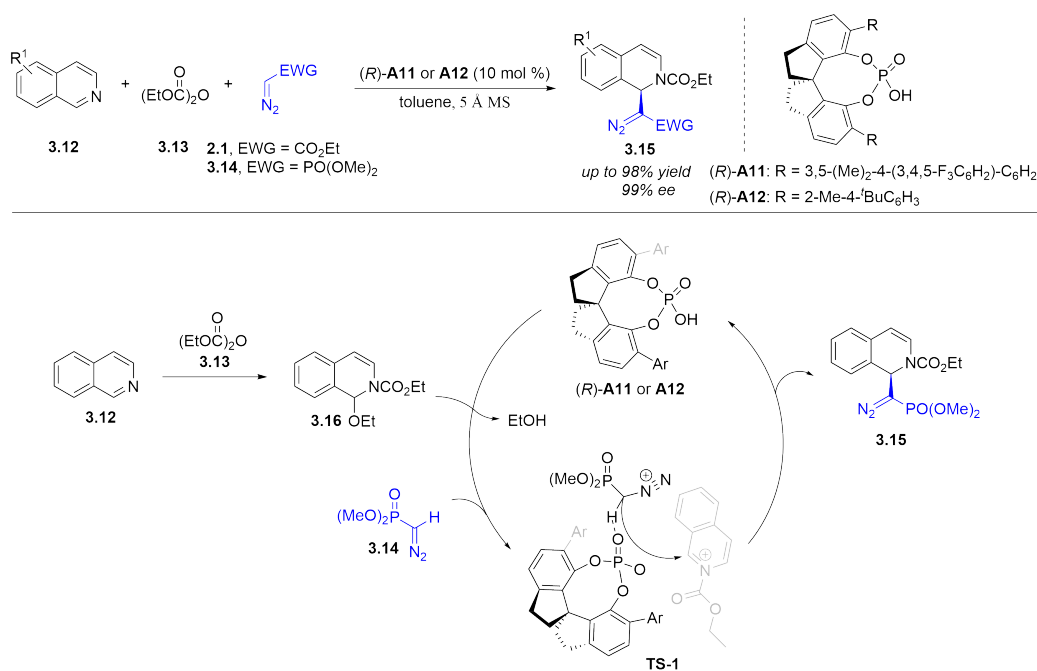


Figure 22. Chiral phosphoric acid-catalyzed asymmetric acyl-Mannich reaction of isoquinolines with α -diazoethylphosphonate and ethyl α -diazoacetate.

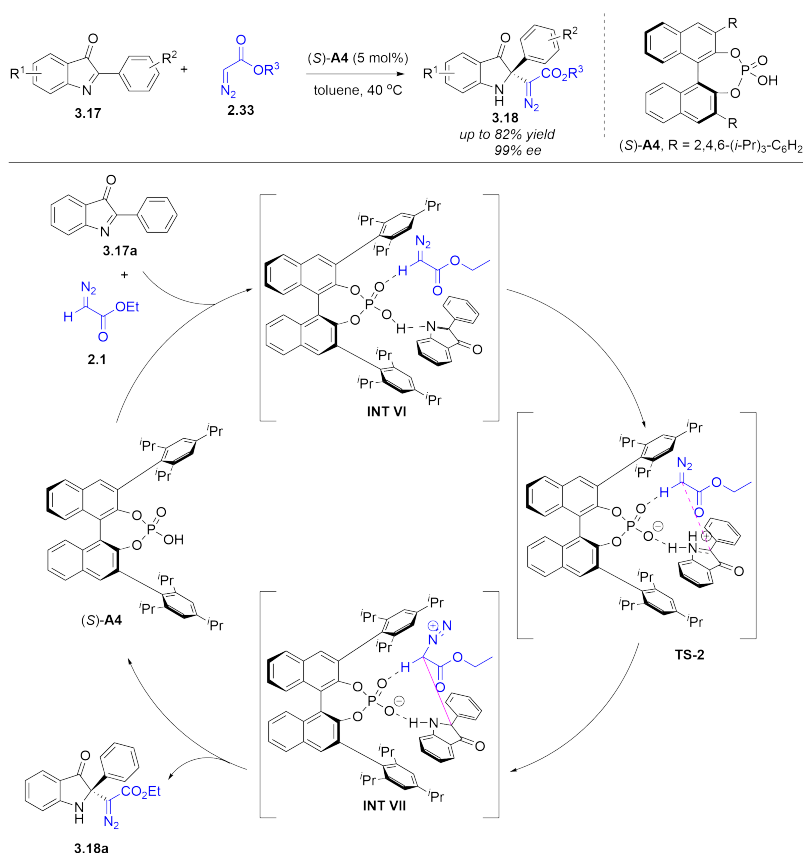


Figure 23. Chiral phosphoric acid-catalyzed asymmetric Mannich-type reaction of α -diazoacetate with 2-aryl-3H-indol-3-ones.

3.2 Chiral dicarboxylic acid-catalyzed asymmetric Mannich-type reaction

By combining two carboxylic acids and an axially chiral binaphthyl moiety, the Maruoka group designed a new type of axially chiral binaphthalenedicarboxylic acid catalyst in 2007, which was designed to address the issues of poor reactivity of carboxylic acid and difficulty in building an effective chiral recognition site around them. It was successfully applied to the asymmetric Mannich-type reaction of arylaldehyde *N*-Boc imines **2.23** with *tert*-butyl 2-diazoacetate **2.33a** or dimethyl diazomethylphosphonate **3.14** (Figure 24)^[37]. The use of 4 Å molecular sieves could inhibit the hydrolysis of imines and improve the yield. In 2011, they expanded the substrate scope to include tolyl (diazomethyl)sulfone **3.19**^[38]. A transition state model was proposed in which *N*-Boc aldimines coordinated to axially chiral dicarboxylic acid to form a reactive complex, while the steric bulk of 3,3'-aryl groups and the binaphthyl unit control the orientation of *N*-Boc aldimine by sterically preventing the formation of conformational isomers arising from the rotation of the *N*-H...O hydrogen bond. Nucleophilic *tert*-butyl 2-diazoacetate **2.33a** approached from the side of the inward oxygen, which acted as a Lewis base by forming a hydrogen bond with the α -hydrogen of the diazoacetate.

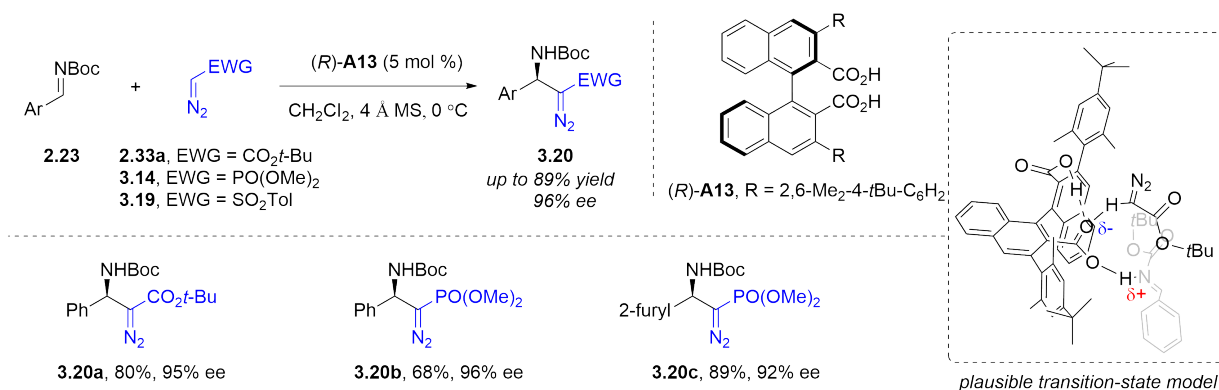


Figure 24. Chiral dicarboxylic acid-catalyzed asymmetric Mannich-type reaction of aromatic aldehyde *N*-Boc imines with diazo compounds.

While cyclic azomethine imines were widely utilized in asymmetric additions, acyclic azomethine imines remained underdeveloped. In 2011, the Maruoka group employed acyclic azomethine imines as novel prochiral electrophiles, which were generated in situ from the reaction of aldehydes **3.21** with *N*'-benzylbenzoylhydrazide **3.22** (Figure 25)^[39]. Using an axially chiral dicarboxylic acid catalyst (*R*)-**A14**, a variety of chiral α -diazo- β -hydrazino esters and phosphonates **3.25** were obtained in the reaction of 2,4-dimethylpentan-3-yl 2-diazoacetate **3.23** or dimethyl diazomethylphosphonate **3.14** with aldehydes and *N*'-benzylbenzoylhydrazide. Alkyl, aryl, and alkynyl aldehydes were suitable for this three-component asymmetric Mannich-type reaction. Furthermore, *trans*- α -amino- β -hydrazinoester **3.25a-I** could be obtained via a reductive treatment with samarium iodide in good yield and with moderate diastereoselectivity, without erosion of the enantiomeric excess.

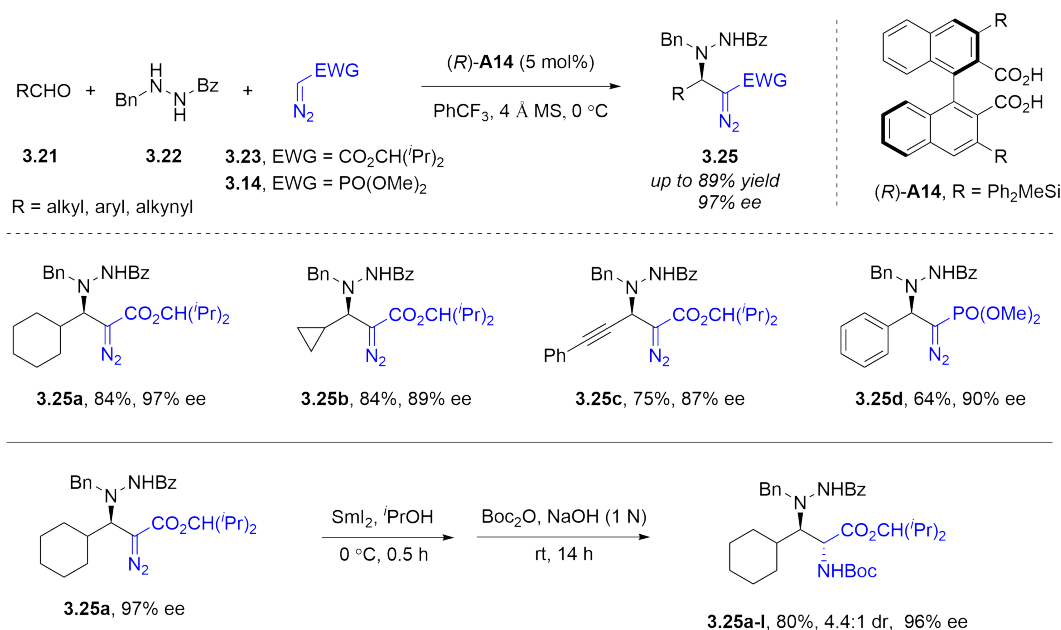


Figure 25. Chiral dicarboxylic acid-catalyzed asymmetric three-component Mannich-type reaction of aldehydes and *N*'-benzylbenzoylhydrazide with diazo compounds.

3.3 Chiral Lewis acid-catalyzed asymmetric Mannich-type reaction

The lower reactivity of α -diazomethylphosphonates has largely confined asymmetric Mannich-type reactions to aldimines. Their reactions with less reactive ketimines remain highly challenging. In 2016, the Peng group reported a chiral silver phosphate-catalyzed asymmetric Mannich-type reaction of isatin-derived ketimines **3.26** with α -diazomethylphosphonates **3.27** (Figure 26)^[40]. A broad range of isatin ketimines bearing electron-withdrawing or electron-donating groups gave good to excellent yields and enantioselectivities. Rearrangement products **3.29** were observed in the reaction.

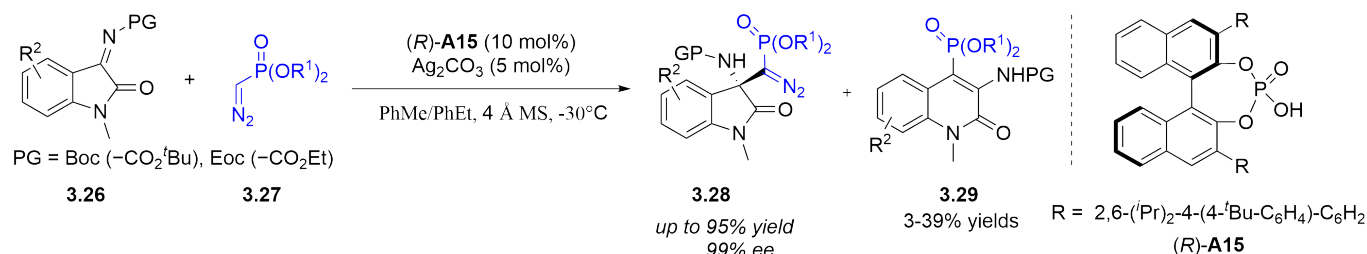


Figure 26. Chiral silver phosphate-catalyzed asymmetric Mannich-type reaction of isatin-derived ketimines with α -diazomethylphosphonates.

In 2018, the Wang/He group reported a Lewis acidic gold(I)-catalyzed asymmetric Mannich-type reaction of α -diazoacetates **2.33** with *N*-sulfonyl cyclic ketimines **3.30** (Figure 27)^[41]. This reaction was catalyzed by a chiral phosphine ligand [(*S*)-BINAP] with an achiral PPh_3AuCl complex. A plausible mechanism is depicted in Figure 27. The (*S*)-BINAP ligand (**L1**) coordinates to PPh_3AuCl in the presence of AgOTf to generate a chiral cationic Au(I) complex. This complex then promotes the enolization of ethyl α -diazoacetate **2.1**, while *N*-sulfonyl cyclic ketimine **3.30** coordinates to Au(I) from the sterically favored face. Subsequent nucleophilic attack of the enolate intermediate at the *Si*-face of **3.30a**, directed by the chiral **L1**- Au(I) environment, delivers the product (*S*)-**3.31a**.

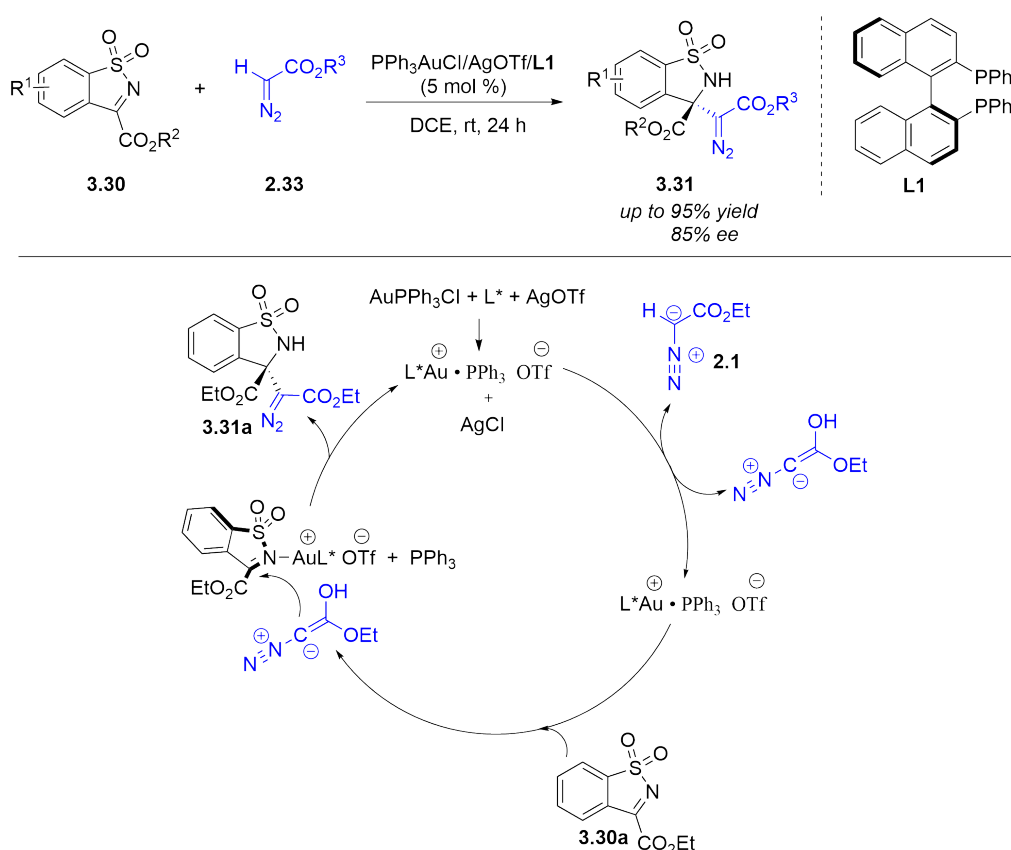


Figure 27. Chiral Au(I) /(*S*)-BINAP asymmetric Mannich-type reaction of *N*-sulfonyl cyclic ketimines with α -diazoacetates. BINAP: 2,2'-diphenylphosphino-1,1'-binaphthyl.

In 2020, the Dixon group reported a silver(I)-catalyzed asymmetric Mannich-type reaction of α -diazoacetates with *N*-Boc aldimines (Figure 28)^[42]. (*R*)-DM-SEGPHOS (**L2**) exhibited remarkable stereocontrol over other chiral ligands. This protocol afforded the chiral β -amino- α -diazo esters **3.32** with high enantioselectivity for imines bearing different substituents on the aromatic ring.

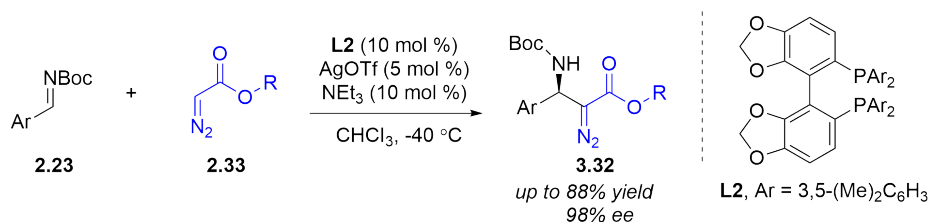


Figure 28. Chiral Ag(I)/(*R*)-DM-SEGPHOS asymmetric Mannich-type reaction of *N*-Boc aldimines with α -diazoacetates.

In 2021, the Wang group reported a chiral silver imidodiphosphate-catalyzed asymmetric tandem reaction of *o*-alkynylbenzaldehydes **3.33**, aromatic amines **3.7**, and ethyl α -diazoacetate **2.1** or α -diazomethylphosphonates **3.14** (Figure 29)^[43]. Various chiral 1,2-dihydroisoquinoline analogues **3.34** have a C1 tertiary stereocenter and substituents at the C3 position were achieved in up to 97% yields and 98% ee. Both electron-withdrawing and electron-donating groups at the para- or meta-positions of the terminal benzene ring were well tolerated.

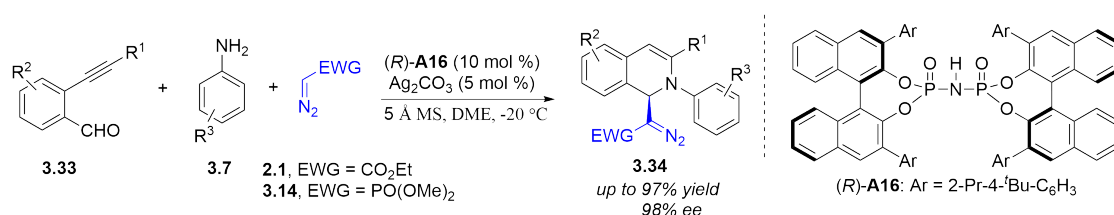


Figure 29. Chiral silver imidodiphosphate-catalyzed asymmetric tandem reaction of *o*-alkynylbenzaldehydes, aromatic amines and diazo compounds.

4. Conclusion and Perspective

In this review, recent developments in transition-metal-free chiral Brønsted/Lewis acid-catalyzed asymmetric diazo nucleophile-imine reactions have been summarized, including asymmetric aza-Darzens reactions and Mannich-type reactions. These approaches have demonstrated exceptional utility in the synthesis of chiral aziridines and β -amino α -diazo compounds. The effects of substrate substituents and catalysts on the chemoselectivity of these asymmetric diazo nucleophile-imine reactions are summarized in Table 1.

Table 1. Summary of chiral Brønsted/Lewis acid-catalyzed asymmetric diazo nucleophile-aldimine reactions.

imine	diazo	<i>cis</i> - aziridine	<i>trans</i> - aziridine	β	catalyst	Refs.
		✓			VANOL/VAPOLB(OPh) ₃	[10-15]
PG = CHPh ₂ , DAM, BUDAM, MEDAM						
			✓		chiral dicarboxylic acid	[18]
					chiral phosphoric acid	[20]
					combination chiral diol with 2-boronobenzoic acid	[24]
				✓	chiral phosphoric acid	[31]
				✓	chiral phosphoric acid	[33]
				✓	chiral dicarboxylic acid	[37,38]

		√	Ag(I)(R)-DM-SEGPPOS	[42]
		√	chiral phosphoric acid	[31]
		√	combination chiral diol with 2-boronobenzoic acid	[24]
		√	chiral phosphoric acid	[21]
		√	chiral phosphoric acid	[19]
		√	combination chiral disulfonimide with 2- boronobenzoic acid	[25]
		√	Chiral phosphoric acid	[22]
		√	chiral <i>N</i> - triflylphosphoramidate	[23]
		√	Chiral phosphoric acid	[30]
		√	Chiral phosphoric acid	[32]
		√	chiral silver imidodiphosphate	[43]

Despite the remarkable progress achieved to date, several critical challenges remain to be addressed. First, the enantioselectivity of products derived from aliphatic imine substrates still needs further improvement. Second, high catalyst loadings (5–10 mol %) are typically needed, and thus catalytic efficiency must be enhanced. Third, chiral Lewis acid catalytic systems remain underdeveloped, with most relying on noble metals such as Au and Ag. Earth-abundant, cost-effective first-row transition metals, including Fe, Ni, Sc, and Cu, offer promising alternatives worthy of systematic exploration in asymmetric diazo nucleophile–imine reactions. Fourth, much attention is currently concentrated on the construction of central chirality, so the design and synthesis of planar, axial, helical, or inherently chiral compounds is in great demand. It is worth mentioning that the enamines generated via 1,2-migration are ubiquitous byproducts across various catalytic systems. Optimizing the catalytic system or rationally designing substrates to achieve controlled synthesis of enamines, particularly chiral enamines, might represent an important direction in this field. It is our hope that

this review will stimulate further investigations to address these outstanding synthetic challenges and foster continued growth in the development of catalytic asymmetric diazo nucleophile-imine reactions.

Declarations

Authors contribution

Xie PR, Luo YP, Xie ZY: Literature search, writing-original draft.

Pan C: Conceptualization, literature search, writing-original draft, writing-review & editing.

Xuan J: Conceptualization, writing-review & editing.

Conflict of interests

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Nos. 22201002, 22571002 and 21971001), the Distinguished Young Research Project of Anhui Higher Education Institution (Grant No. 2023AH020003), and the Natural Science Foundation of Anhui Province (Grant No. 2408085MB041).

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