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Pd-Catalyzed Asymmetric Allylic Substitution Cascade via Desymmetrization for the Construction of Chiral Polyheterocycles

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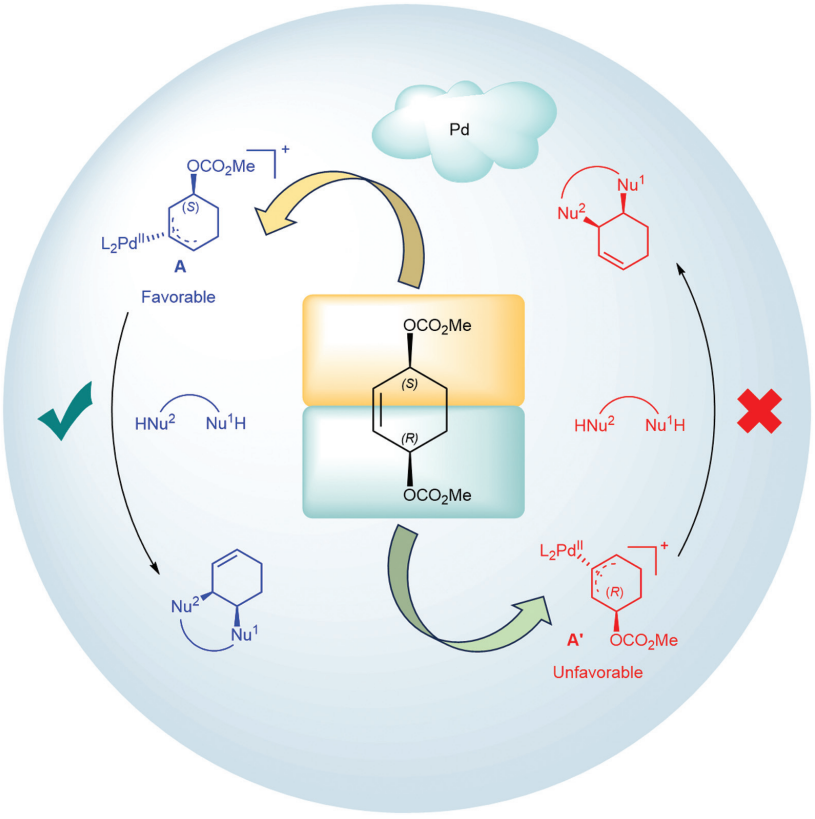

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Abstract

Chiral polyheterocycles represent an important class of compounds because of their prevalence in bioactive natural products and chiral drugs. Pd-catalyzed allylic substitution is a powerful synthetic tool for forming C–C and C–X bonds (X = N, O, S, etc.). Naturally, asymmetric cascade reactions that utilize allylic substitution are undoubtedly efficient pathways to construct heterocycles. In this article, we reviewed the Pd-catalyzed asymmetric allylic substitution cascade via the desymmetrization of *meso*-diol diesters of cycloolefins, for the construction of chiral polyheterocycles and their derivatives.

Keywords

- Pd-catalyst
- asymmetric cascade allylic substitution
- desymmetrization
- chiral polyheterocycles
- synthesis

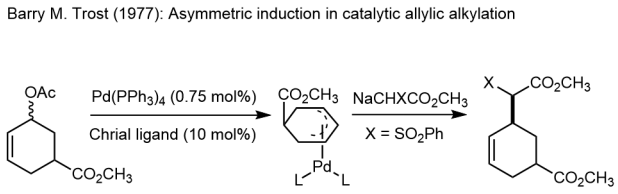
Introduction

Since the pioneering work reported by Tsuji et al in 1965, who disclosed the first allylic alkylation of carbanions attacking the carbon atom of the palladium complex to give allyl derivatives in high yield,[1] the Pd-promoted allylic alkylation reaction has received more attention, particularly from Barry M. Trost.[2–11] His group introduced phosphine ligands in 1973, suggesting that the main intermediate in the reaction should be a cationic diphosphine η^3-allylpalladium complex, and a soft nucleophilic anion favors the complex.[12] In the same year, asymmetric induction in allylic alkylations was achieved through the optically active ligands,[13] and the development of asymmetric induction in catalytic allylic alkylation followed 4 years later (►**Scheme 1**).[14] Since then, the asymmetric Pd-catalyzed Tsuji–Trost allylic substitution reaction has become a powerful method for constructing various chiral compounds due to its strong ability to form C–C and C–X bonds (X = B, O, N, S, etc.).[2–11,15–25]

Chiral polyheterocycles are widely found in natural products with interesting biological properties.[26–30] Cascade catalysis allows for multistep reactions in one pot without the time-consuming, waste-generating, and increased cost due to the isolation of intermediates, thus being a green and useful tool for sustainable chemical synthesis.[31–41] Naturally, asymmetric cascade reactions using allylic substitutions provide an efficient pathway to construct chiral heterocyclic compounds.[15,42–45] Two or more chemical bonds, including C–C, C–N, or C–O bonds, may be formed sequentially under the same catalyst system, and the resulting products can be further transformed by taking advantage of the alkene functionality (►**Fig. 1**, top) or ring-breaking (►**Fig. 1**, bottom) to provide other functionally useful molecules. Therefore, developing a powerful Pd-catalyzed asymmetric allylic substitution cascade is very important.

Pd-catalyzed asymmetric allylic substitution cascade via desymmetrization of *meso*-diol diesters of cycloolefins is an attractive strategy for the construction of polyheterocycles. The general reaction pathway is described as follows (►**Scheme 2**). First, *cis*-**1** binds to L_2Pd^0 to generate the allyl–Pd complex **A** via an asymmetric desymmetrization process. Then, complex **A** reacts with a bis-nucleophile to generate the alkylated intermediate **B**. Finally, **B** takes part in the intramolecular allylic substitution, generating a terminal fused heterocycle product via the allyl–Pd complex **C**, and regenerating the original catalyst system L_2Pd^0. This approach provides an efficient and direct route for the synthesis of chiral polyheterocycles using suitable substrates.

Despite extensive efforts dedicated to the field of Pd-catalyzed asymmetric allylic substitution, the existing general reviews mainly cover a somewhat broad substrate scope or a single reaction model.[17,46–49] This article reviews Pd-catalyzed asymmetric allylic substitution cascades for the



Scheme 1 The asymmetric Pd-catalyzed Tsuji–Trost allylic substitution.

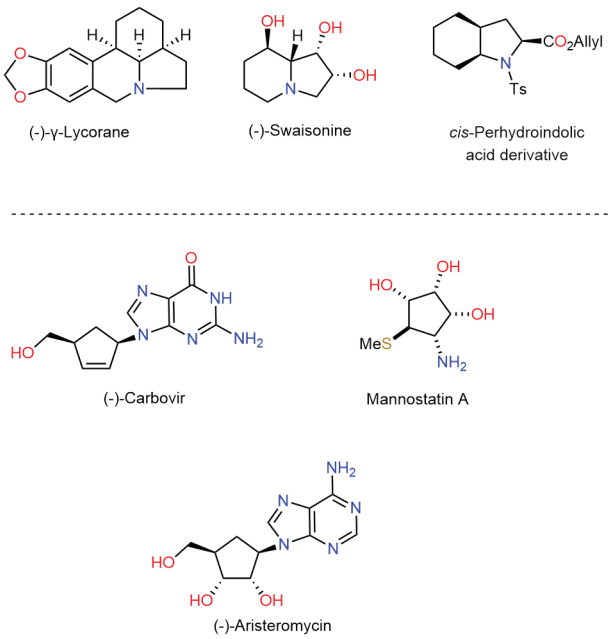
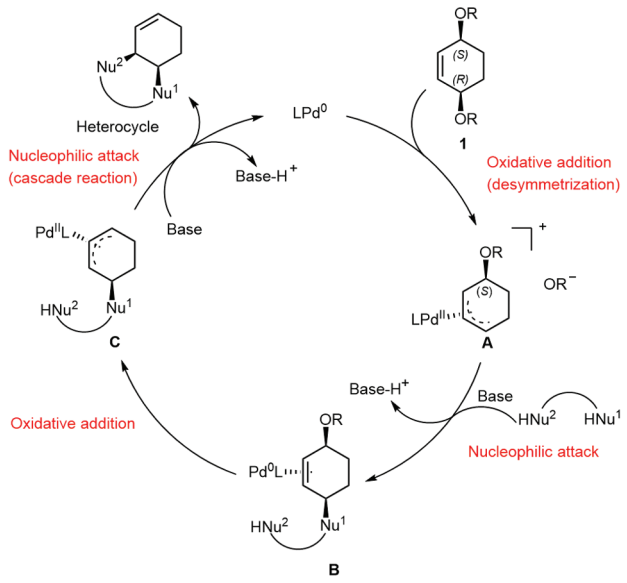
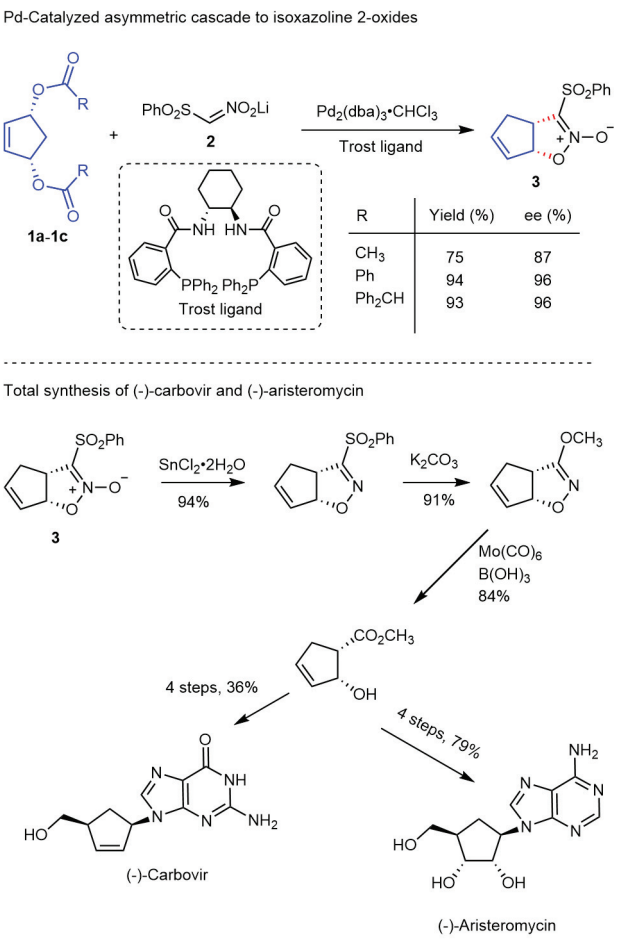


Fig. 1 Natural product constructed by cascade Tsuji–Trost reaction.



Scheme 2 General pathway of cascade reaction via desymmetrization.



Scheme 3 Pd-catalyzed asymmetric cascade to isoxazoline 2-oxides.

construction of chiral polyheterocycles through the desymmetrization of *meso*-diol diesters of cycloolefins. It also describes examples of their application in the synthesis of more functionalized molecules and includes sections discussing the key mechanistic aspects of the desymmetrization process and stereoselectivity.

Critical Issues in Reaction Cascades

Three sections are included in this article: (1) desymmetrization cycloaddition via C–C and C–O bond formation cascade; (2) desymmetrization cycloaddition via C–C and C–N bond formation cascade; (3) desymmetrization cycloaddition via two C–X bond formation cascade.

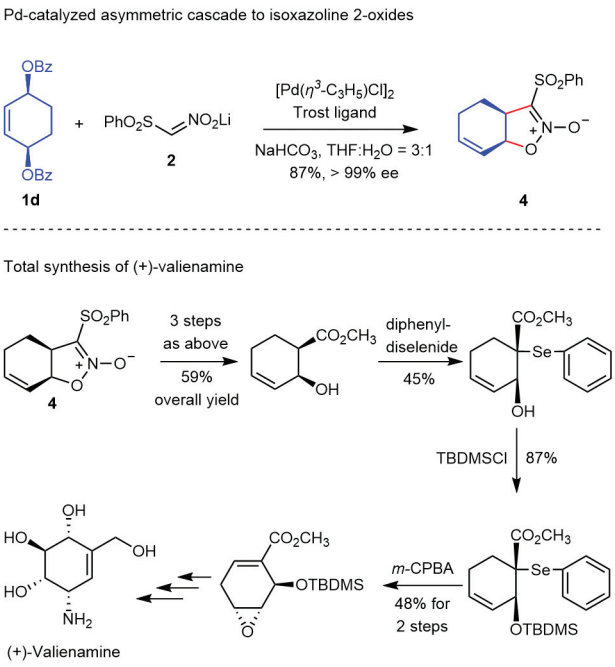
Cycloaddition via C–C and C–O Bond Formation

The ambident nature of nitro-stabilized anions allows for both C- and O-alkylation to afford chiral fused heterocycles via asymmetric cascade reactions. As early as 1991, Trost had developed Pd-catalyzed asymmetric allylic substitution cascades of lithium [(phenylsulfonyl)methylene]nitronate **2** with *cis*-1,4-diacetoxycyclopent-2-ene (**1a–1c**), giving the corresponding fused heterocycle isoxazoline-*N*-oxide **3** in high yields with up to 96% ee. No further increase in ee was observed when the steric bulk of the leaving group was increased by using diphenylacetate (Ph_2CH) instead of a phenyl ring (►**Scheme 3**, top).[49]

Compound **3** is a useful chiral building block for the synthesis of the important antiviral carbanucleosides. For example, **3** is deoxidized with $SnCl_2{\cdot}2H_2O$ to give isoxazoline in 94% yield, which is converted to its methoxy analogue by nucleophilic substitution of the sulfone in basic methanol in 91% yield. The resulting methoxyisoxazoline is reduced to the *cis*-hydroxy ester with $Mo(CO)_6$ in the presence of boric acid and methanol (84% yield). By a simple conversion, carbovir and aristeromycin, candidates as potential antiretroviral agents for the treatment of acquired immunodeficiency syndrome, have been synthesized with high selectivities (►**Scheme 3**, bottom).[49]

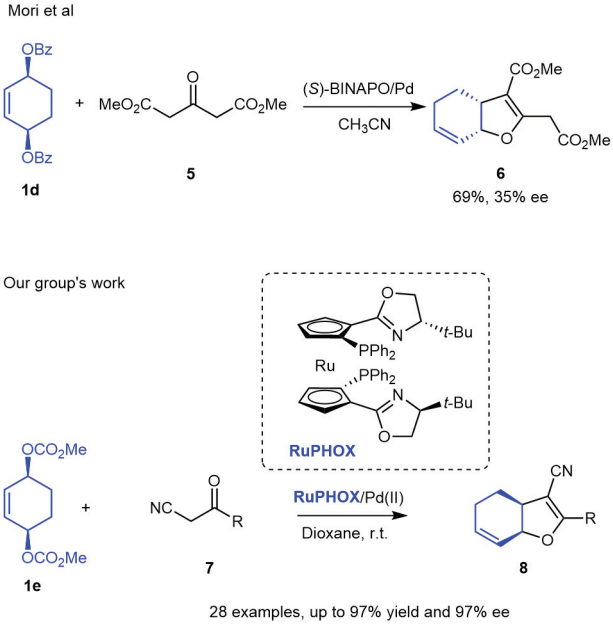
The importance of pseudo-oligosaccharides in myriad cellular functions makes their synthesis an interesting target for the design and development of therapeutic agents. Common to all of these pseudo-oligosaccharides is the presence of aminocyclitol unit valienamine in their structure.[50,51] In 1998, dibenzoate **1d** derived from cyclohexa-1,3-diene was applied to the above reaction to give isoxazoline-*N*-oxide **4** in 87% yield and with ee >99% (►**Scheme 4**, top), which could be transformed to several potent glycosidase inhibitors.[52] **4** was obtained following the similar pathways mentioned above (►**Scheme 3**, bottom), and converted to enantiomerically pure *cis*-hydroxy ester in 59% overall yield (►**Scheme 4**, bottom). Treatment of the *cis*-hydroxy ester with diphenyldiselenide under strong basic conditions yielded the corresponding selenide ether in 45% yield, which was converted to its *tert*-butyl dimethyl silyl (TBDMS) ether to protect the free hydroxyl group. The epoxidation reaction of the TBDMS ether with *m*-CPBA afforded the key scalemic epoxide, which yields valienamine according to a known synthetic route (►**Scheme 4**, bottom).[49]

Chiral compounds containing bicyclic dihydrofuran cores are widely distributed in pharmaceuticals, diverse synthetic

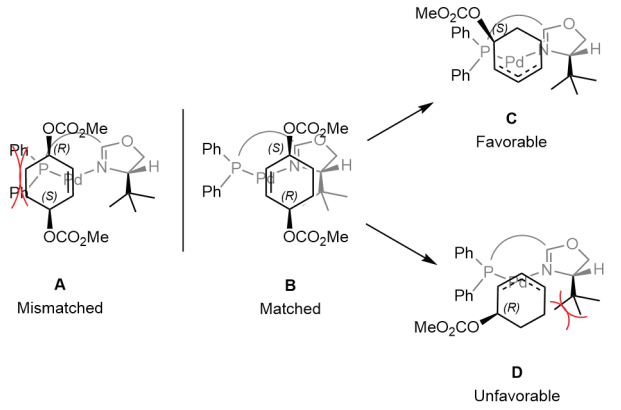


Scheme 4 (+)-Valienamine total synthesis.

intermediates, biologically active compounds, and natural products.[53–56] In 1995, Mori and colleagues reported the synthesis of bicyclic furans from *meso*-dibenzoylate and acetone-1,3-dicarboxylic acid ester **5** to obtain such chiral skeletons (►**Scheme 5**).[57] Although both chiral furans and bicyclic furans were obtained, only one example (**6**) has been reported and catalytic activity is poor. Our group has held a longstanding interest in Pd-catalyzed asymmetric allylic substitution reactions.[58–61] Recently, we employed a



Scheme 5 Alkylation of allylic *meso*-dicarbonate (**1e**) with 3-oxo-nitriles (**7**).



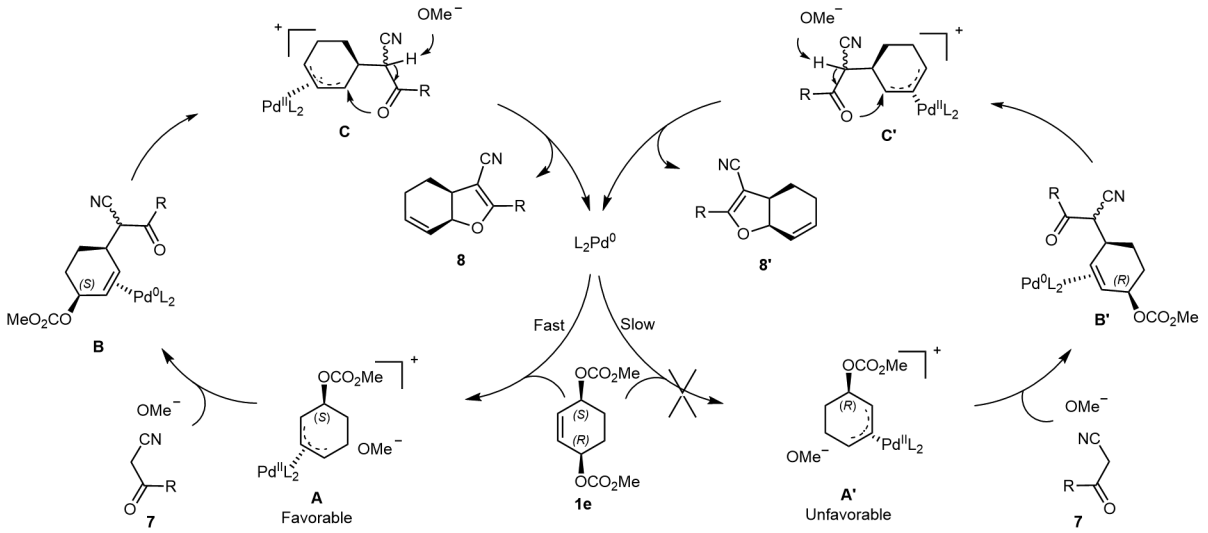
Scheme 6 Proposed desymmetrization process.

RuPHOX/Pd catalyzed asymmetric allylic substitution cascade of allylic dicarbonate (**1e**) with 3-oxo-nitriles **7** to synthesize chiral bicyclic dihydrofurans **8** in high yields and with ee up to 97% (►**Scheme 5**; ee values up to 97% among 28 substrates).[62]

An asymmetric desymmetrization process is involved in the reaction, and the chiral RuPHOX/Pd complex plays a key role in the process. That is, the two allylic positions should react at significantly different rates. As is shown in ►**Scheme 6**[7,63] the RuPHOX/Pd complex first coordinates with the C = C double bond from the back of the two OCO_2Me groups of *cis*-**1e**. Due to the strong steric hindrance between the sp^3 C and the large PPh_2 group of **A**, the right complex **B** is the matched state. Next, the allylic complex **C** is formed as the most favorable configuration because of the weaker steric hindrance between the sp^2 C and *t*-Bu group compared with that of complex **D**. Complex **C** is readily available, resulting in high yields as well as excellent dr values of the desired bicyclic dihydrofuran products.

A plausible catalytic cycle is then depicted in ►**Scheme 7**. The position of the C = C double bond of **8** suggested that the reaction may proceed via an allylic alkylation followed by an intramolecular *O*-allylic alkylation. First, *cis*-**1e** binds to L_2Pd^0 to provide allyl-Pd complex **A**. The process represents an asymmetric desymmetrization of *cis*-**1e** because L_2Pd^0 prefers to attack the *R*-chiral carbon of **1e** in the presence of a chiral catalyst, as shown in the above section (►**Scheme 6**). Then, complex **A** reacts with nucleophile **7** to give alkylated intermediate **B**, which takes part in the next intramolecular *O*-allylic alkylation, giving the chiral bicyclic dihydrofuran **8** in high yield as well as excellent dr via allyl–Pd complex **C**.

Our group expanded the above reaction by using both (*Z*)- and (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonates (**1f** and **1g**) with α-substituted cyano ketones (**7**) considering the cyano group cannot be readily introduced and is a very important functional group that is widely encountered in both natural products and pharmaceuticals (►**Scheme 8**). This enabled the preparation of chiral 2,3-dihydrofurans (**9**) in up to 97% yield and 98% ee with the best results being achieved when a hydrogenated phosphoramidite ligand was used as the chiral ligand.[64]

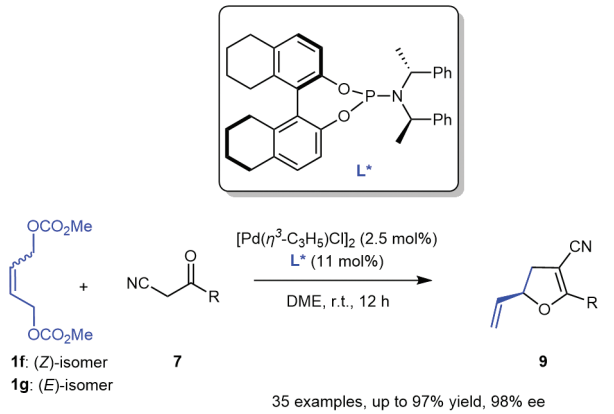


Scheme 7 Proposed reaction mechanism for the formation of compound **8** form **1e**.

Polyheterocycles containing furo[3,2-*c*]pyrans units are widely distributed in pharmaceuticals and biologically active compounds.[65–67] Yoshida et al performed a Pd-catalyzed asymmetric allylic substitution cascade of 4-hydroxy-2*H*-pyrones (**10**) with a *meso*-allyl bisacetate (**1h**) under reflux conditions and the bridged products 2-oxabicyclo[3.3.1]nonanes *rac*-**11** were formed regioselectively in 65 to 87% yield (►**Scheme 9**).[68] When the reaction was performed at room temperature, a sole product, the fused-ring tetrahydro-1*H*-pyrano[4,3-*b*]benzofuran-1-ones *rac*-**12**, could be obtained in 58% yield. However, an efficient synthetic protocol, particularly an asymmetrically catalyzed version of the aforementioned reaction, has not yet been realized.

Our group has successfully achieved the selective synthesis of chiral (*S,S*)-**12**, kinetic products, in up to 87% yield and 99% ee, by a temperature-controlled RuPHOX/Pd-catalyzed asymmetric allylic substitution cascade reaction of substituted **10** with *meso*-allyl dicarbonates **1e**. The bridged product·*rac*-**11** (R = H) also obtained an 84% yield when the above reaction was performed at room temperature overnight (►**Scheme 9**).[69] The results revealed that chiral fused-ring products **12** are kinetic products, which could be transformed to their thermodynamically stable isomer, the racemic bridged products **11**, at room temperature.

A possible mechanism of selective synthesis of kinetic product **12** and thermodynamically stable **11** via the temperature-controlled pathway is shown in ►**Scheme 10**.[7,68,69] First, the treatment of **1e** with Pd-complex L_2Pd^0 forms a π-allylpalladium complex **A**, which is reacted with nucleophile **10** to give the monosubstituted intermediate **B**. Then, **B** is converted into π-allylpalladium intermediate **C**, the key intermediate of the whole reaction, which undergoes two different reaction pathways according to the reaction environment, particularly the reaction temperature. If the reaction is conducted at a lower temperature, such as 0°C, kinetic product **12** is obtained as the major product, releasing the activated Pd complex L_2Pd^0. This step is a reversible process because when the temperature is increased, **12** is converted to intermediate **C** in the presence

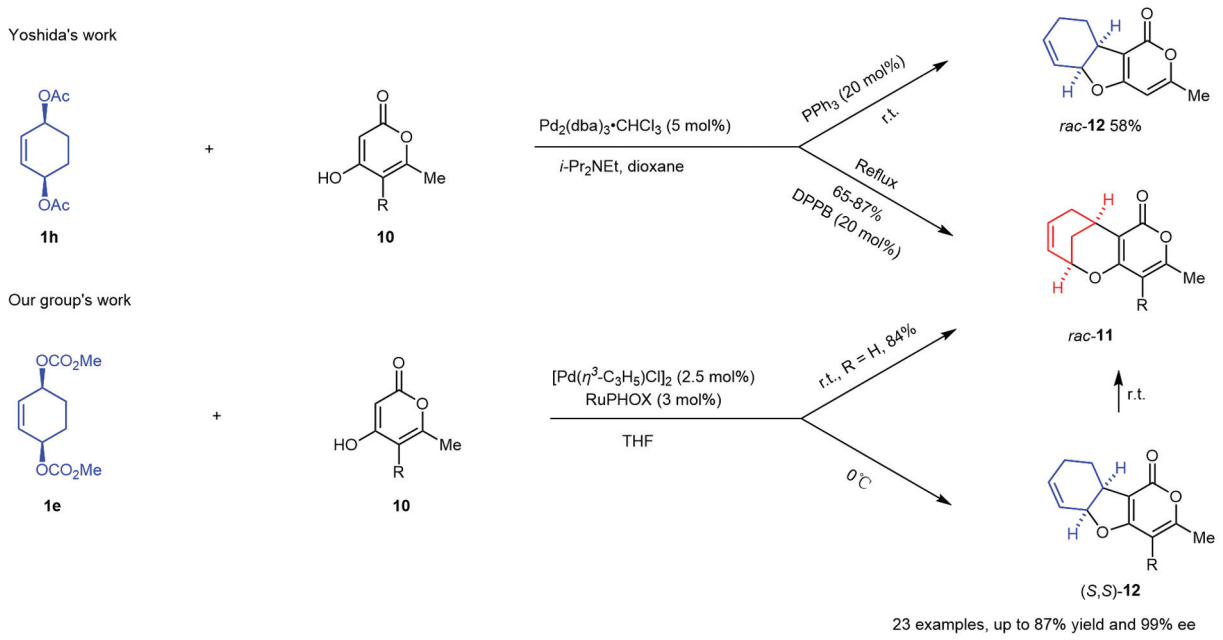


Scheme 8 Cascade reaction of but-2-ene-1,4-diyl dimethyl dicarbonates (**1f** and **1 g**) with α-substituted cyano ketones (**7**).

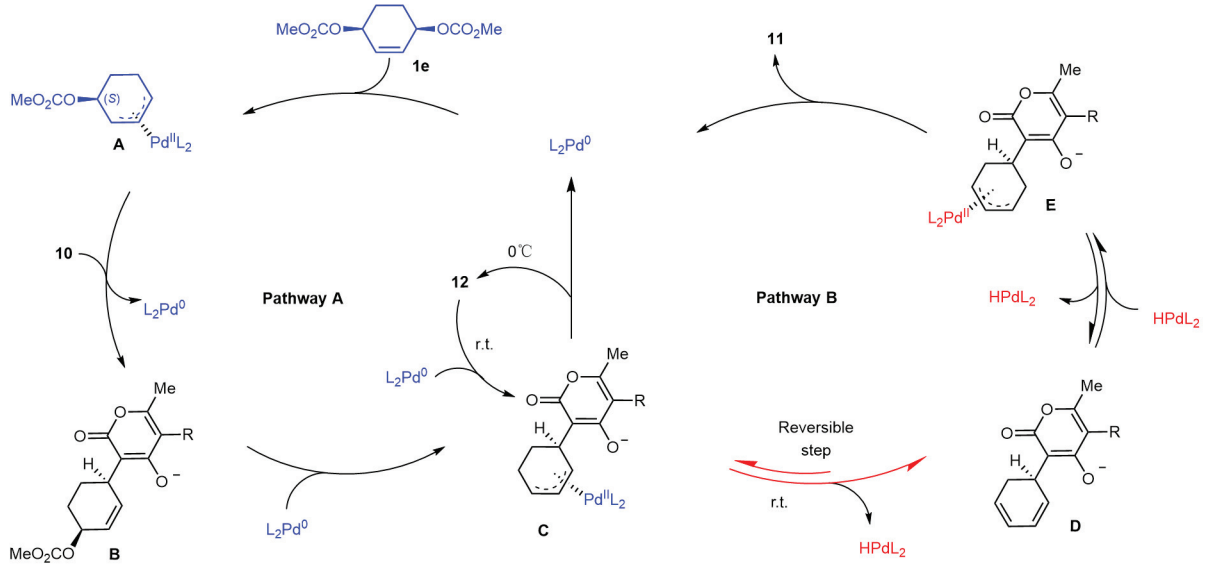
of the activated Pd complexes (**Pathway A**). Alternatively, intermediate **C** is converted to intermediate **D** via the elimination of the PdH species from **C** when the reaction is performed at room temperature. This step is also a reversible process but mainly proceeds from **C** to **D** because the ee values of **12** are slightly decreased in the presence of a nonchiral 1,4-bis (diphenylphosphino)butane (DPPB)/Pd catalyst (**Pathway B**). Then, **D** undergoes a PdH insertion to afford intermediate **E**, which furnishes thermodynamically stable **11** after intramolecular allylic substitution cyclization and releases the activated Pd complex L_2Pd^0.

Cycloaddition via C–C and C–N Bond Formation

Chiral fused azabicycles represent an important class of compounds because of their prevalence in bioactive natural products and chiral drugs.[70–73] Our group has developed the Pd-catalyzed asymmetric allylic substitution cascade of *meso*-allyl dicarbonates (**1h**) with cyclic *N*-sulfonylimines (**13**) via an accompanying asymmetric desymmetrization for the construction of fused tetrahydroindole derivatives bearing two chiral



Scheme 9 Cascade reaction of **1e** and **1h** with 4-hydroxy-2*H*-pyrones (**10**).



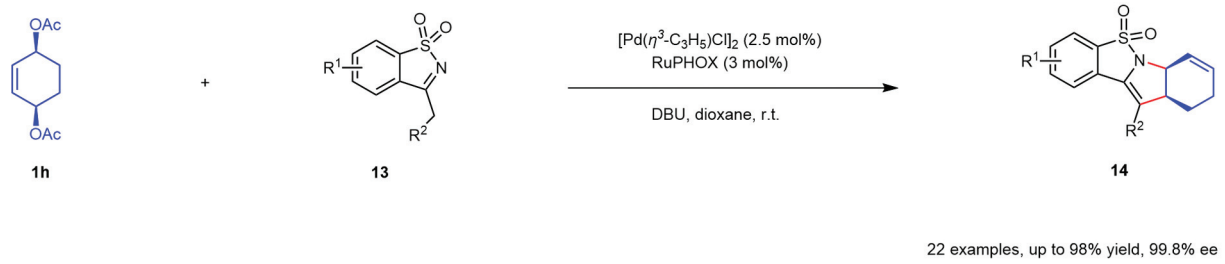
Scheme 10 Proposed reaction mechanism for the formation of compounds **11** and **12** from **1e**.

centers. Under the optimal reaction conditions, a series of cyclic *N*-sulfonylimines **14** can be employed to give the desired products in high yields with up to 99.8% ee (►**Scheme 11**).[74]

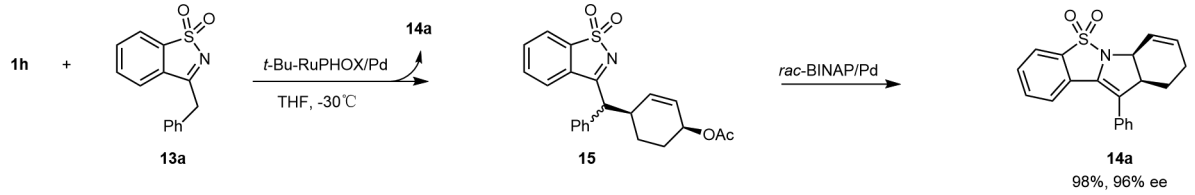
To determine the reaction pathway, an asymmetric allylic substitution cascade of **1h** and **13a** was performed using the above optimal reaction conditions in tetrahydrofuran at −30°C over 24 hours (►**Scheme 12**). The major product was a mixture of diastereomers **15**, and only a trace amount of **14a** and the remaining starting material were recovered. Without further isolation, the mixture of **15** was further converted to the desired product **14a** in 98% yield and with 96% ee using racemic BINAP as a ligand.[74]

The results showed that the fused azacycle **14a** is constructed via an allylic alkylation followed by an allylic amination (►**Scheme 13**). First, the binding of *cis*-**1h** with L_2Pd^0 provides the allyl–Pd complex **A** via an asymmetric desymmetrization of *cis*-**1h**. Complex **A** reacts with nucleophile **13a** to give the alkylated intermediate **B**, which takes part in the next allylic amination, giving the terminal fused heterocycle **14a** via allyl–Pd complex **C**. The original catalyst system, L_2Pd^0, is subsequently regenerated. It is clear that the asymmetric desymmetrization is a chirality-control step, and the chirality of **14a** is determined by intermediate **B**.

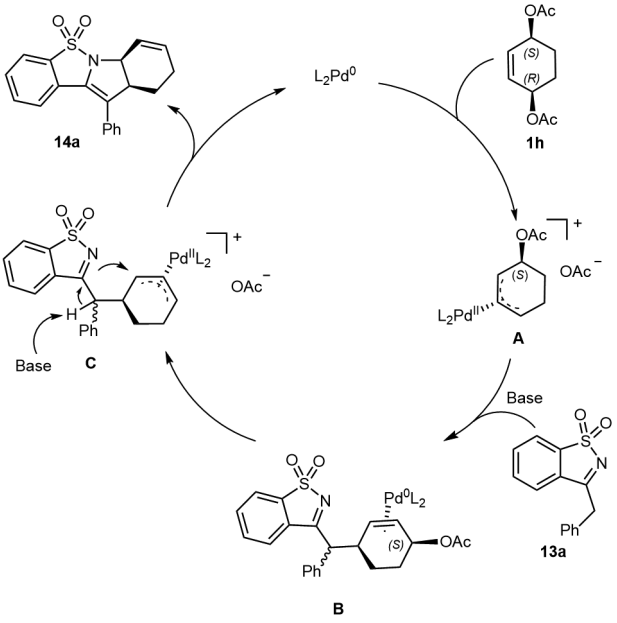
The reaction of simple ketones with amines gives simple ketimines **16**, which can be used in the asymmetric synthesis described above, compensating for the disadvantage of reacting with cyclic *N*-sulfonylimines as nucleophiles. Therefore, we have developed an efficient RuPHOX/Pd-catalyzed



Scheme 11 Construction of fused tetrahydroindole (**14**) from the reaction of **1h** with cyclic *N*-sulfonylimines (**13**).



Scheme 12 Reaction pathway of the asymmetric allylic substitution cascade.

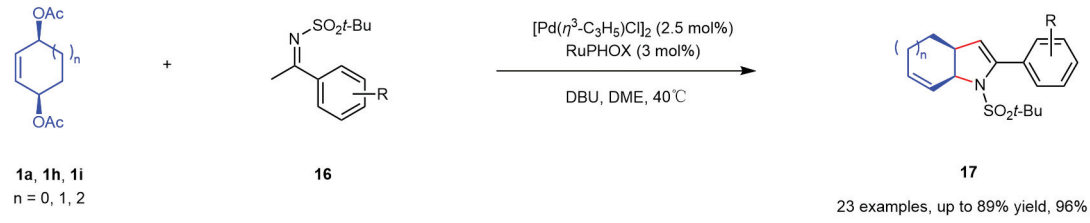


Scheme 13 Proposed reaction mechanism for the formation of compounds **14a** from **1h**.

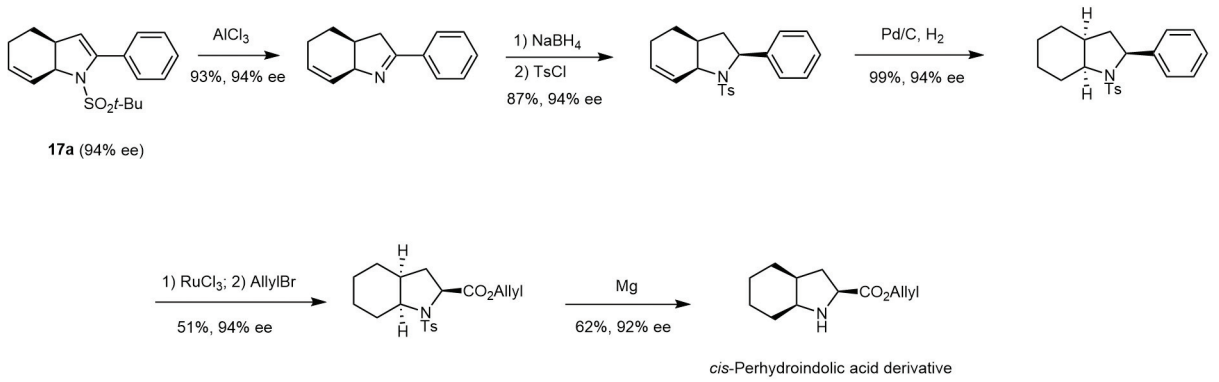
asymmetric allylic substitution cascade of unstable simple ketimines with *meso*-diacetatecycloalkenes (**1a**, **1h**, and **1i**) to construct chiral tetrahydroindoles (►**Scheme 14**). With the optimal reaction conditions in hand, a series of unstable simple ketimines were employed to generate the desired products in moderate to high yields (up to 89%) and with excellent enantioselectivities (up to 96% ee).[75]

The above product **17a** allowed the synthesis of a chiral *cis*-perhydroindolic acid derivative (►**Scheme 15**). Thus, cleavage of the *N*-SO_2t-Bu bond in dry dichloromethane with excess $AlCl_3$ gave a deprotected product in high yield and with ee up to 94%. The product was reduced with $NaBH_4$, followed by *N*-tosylation with TsCl to give a hydrogenated product with dr > 20:1. The reduction of the double bond of the six-membered ring gave a *cis*-perhydroindole derivative in quantitative yield under 40 bar H_2 and using Pd/C as a catalyst. Then, a Ru-catalyzed oxidative degradation of the phenyl moiety to a carboxylic acid, which was subsequently protected with an allyl group *in situ*, provided a *cis*-perhydroindolic acid derivative in 51% yield. Finally, reductive detosylation with magnesium in methanol was performed to afford terminal *cis*-perhydroindolic acid derivative in 62% yield with excellent diastereoselectivity.[75]

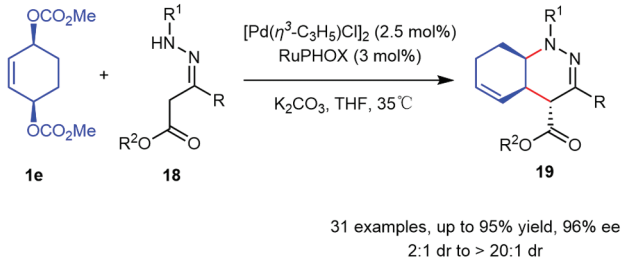
Chiral hydrocinnolines are significant structural motifs found in numerous compounds with medicinal importance and remain relatively unknown in modern-day organic chemistry. Their construction has not been widely explored.[76–81] Encouragingly, our group has developed a RuPHOX/Pd-catalyzed allylic substitution cascade involving a desymmetrization of *meso*-dicarbonatecycloalkene **1e** with β-hydrazino carboxylic esters **18**, providing chiral hexahydrocinnoline derivatives **19** in up to 95% yield and 96% ee



Scheme 14 The construction of chiral tetrahydroindoles from the reaction of *meso*-diacetatecycloalkenes (**1a**, **1h**, and **1i**) with ketimines (**16**).



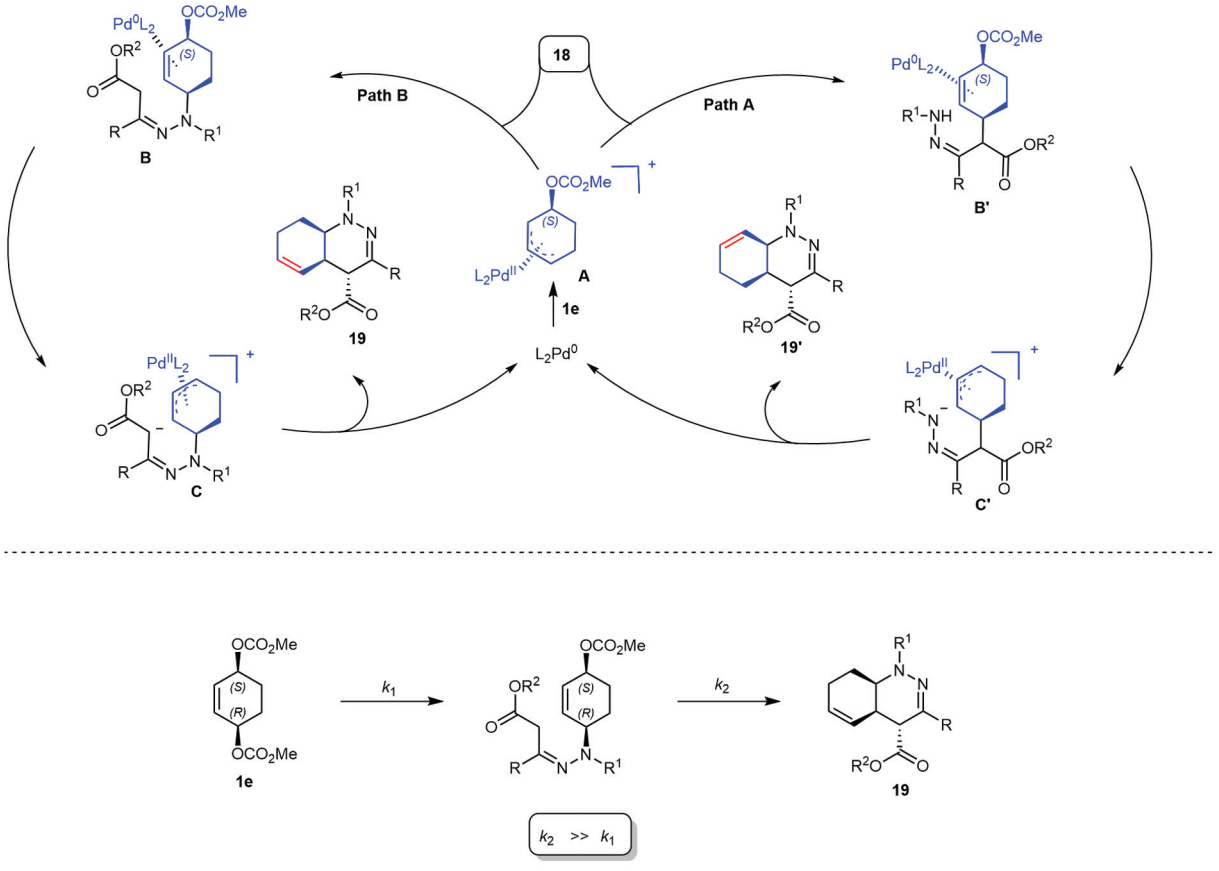
Scheme 15 The construction of *cis*-perhydroindolic acid derivative.



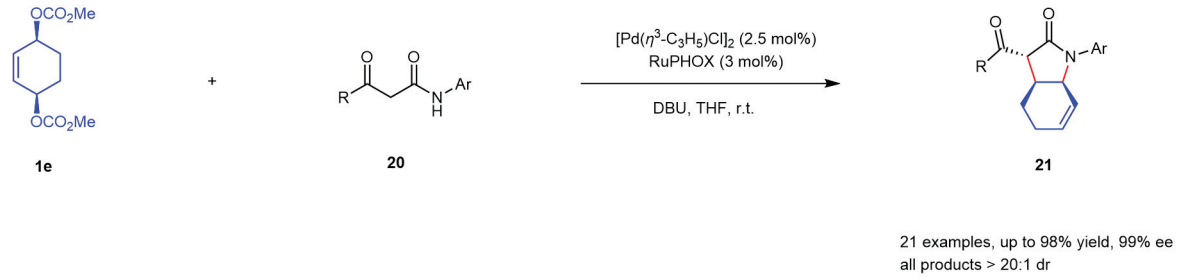
Scheme 16 The construction of chiral hexahydrocinnoline derivatives (**19**).

(►**Scheme 16**).[82] Unfortunately, the dr values are poor, with only one example providing 20:1 dr.

A catalytic cycle for the formation of chiral hexahydrocinnolines has been proposed (►**Scheme 17**, top). First, the RuPHOX/Pd complex forms an allyl Pd-complex **A** intermediate via an enantioselective desymmetrization by coordinating with the C=C double bond from the back of the two OCO_2Me groups of *cis*-**1e**. Next, intermediate **A** reacts with β-hydrazino carboxylic ester **18** to produce **B'** via carbon nucleophilic substitution. The terminal chiral hexahydrocinnoline product (**19'**) is obtained via an



Scheme 17 Proposed reaction mechanism for the formation of chiral hexahydrocinnoline derivatives (**19**).



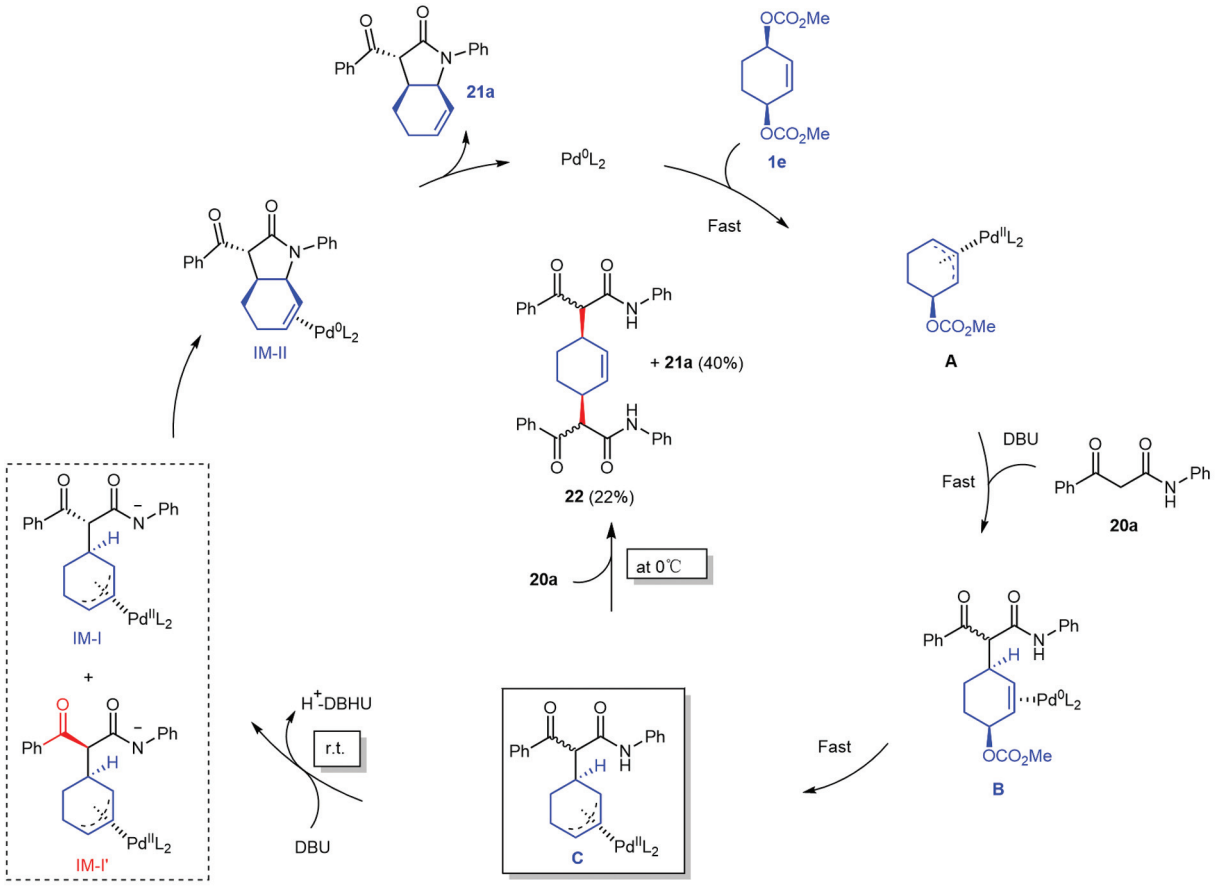
Scheme 18 Construction of chiral 3-acyl bicyclolactams (**21**) from the reaction of **1e** with α-carbonyl amides (**20**).

intramolecular nitrogen nucleophilic substitution cascade reaction (**Path A**). However, the position of its C=C bond is not identical to that of the desired product **19**, suggesting that the sequence of the carbon and nitrogen nucleophilic substitutions may proceed via a different pathway compared with the reaction we previously reported (**Path B**).[75] That is, after the formation of intermediate **A**, the cascade process involves nucleophilic substitution with the nitrogen before carbon nucleophilic substitution via the intermediates **B** and **C**. The strong acidic nature of the NH in **18** must be responsible for the reversal of the nucleophilic pathway.

We attempted to obtain nucleophilic nitrogen intermediate by lowering the reaction temperature or shortening the reaction time. However, only the desired product **19** was obtained, with the starting materials **1e** and **18** being recovered. This suggests that the second intramolecular carbon nucleophilic substitution is much faster than the first intermolecular nitrogen nucleophilic substitution, illustrating that the first nitrogen nucleophilic process is the rate-determining step in the cascade reaction process (►**Scheme 17**, bottom).

Unsatisfactory dr values have been an unsolved challenge in the above work. However, this problem was solved by our group by using α-carbonylamides **20** as nucleophiles to provide chiral 3-acyl bicyclolactams bearing three vicinal carbon stereocenters (**21**) in high yields and with up to 99% ee and >20 : 1 dr (►**Scheme 18**).[83]

According to the control experiments and density functional theory (DFT) calculations, a possible mechanism has been outlined to illustrate the highly efficient synthesis of **21a** via a dynamic kinetic resolution (DKR) pathway (►**Scheme 19**).



Scheme 19 Proposed mechanism for the formation of **21a**.

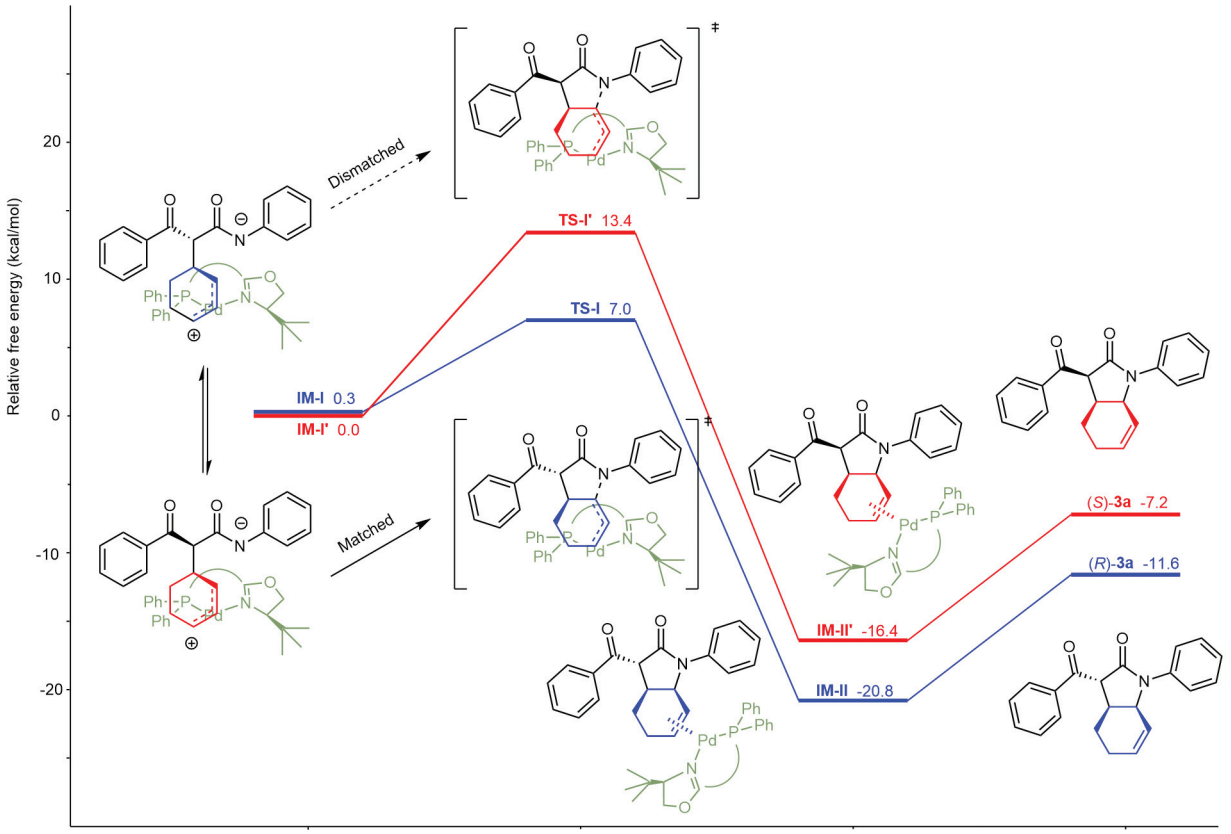


Fig. 2 DFT calculations. Free energy profile (ΔG_{298}) of general base catalytic mechanism calculated at ωB97XD/6–31G(d,p) level of theory. DFT, density functional theory.

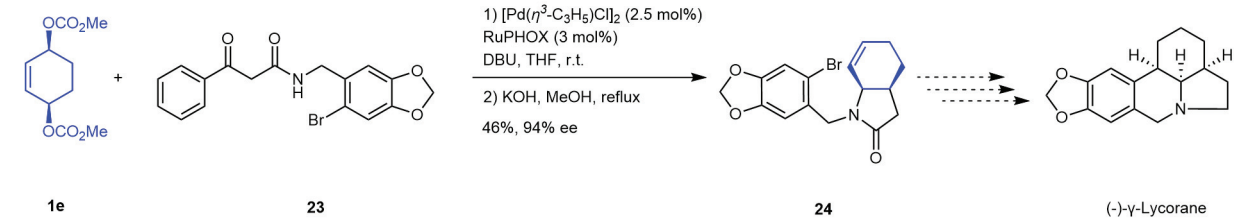
Treatment of activated Pd-complex L_2Pd^0 with **1e** first generates the π-allylpalladium complex **A** rapidly, which then reacts with **20a** to give the mono-substituted intermediate **B**, indicating that the C-nucleophilic process is faster than the corresponding N-nucleophilic process during asymmetric allylic substitution. Subsequently, the oxidative addition of **B** rapidly generates intermediate **C**, which is the key intermediate of the reaction because complex **C** can be converted to final product **21a** and/or the by-product **22** at a different reaction temperature. When the reaction is conducted at room temperature, the H atom on the NH group of complex **C** can be removed at a suitable basic concentration and/or strength to afford intermediates **IM-I** and **IM-I′**. The former **IM-I** then undergoes the second allylic substitution smoothly to afford the terminal product **21a** via intermediate **IM-II**, releasing the activated Pd-complex L_2Pd^0. At this stage, intermediate **IM-I′** can be converted to **IM-I** easily via racemization in a basic environment. It appears that a DKR process occurs during the second step of the cascade reaction which is responsible for the excellent diastereoselectivity of the desired product (►**Scheme 19**).

DFT calculations were conducted to further elucidate the DKR process. As shown in ►**Fig. 2**, the energy difference between **IM-I** and **IM-I′** is only 0.3 kcal·mol^{-1}, and between **TS-I** and **TS-I′** is 6.4 kcal·mol^{-1}, indicating that the second step proceeds more easily via **TS-I** since it has a low activation energy. Therefore, the transformation of **IM-I** to **IM-II** via **TS-I** is energetically favorable, from which the final product **21a** is obtained after the dissociation of the chiral Pd-complex. On the other hand, **IM-I′** is converted to **IM-I** by racemization because the latter is consumed during the reaction. A DKR likely occurs during the second step of the cascade reaction.

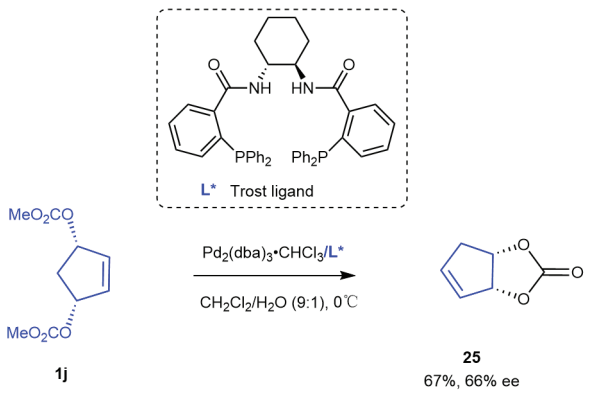
In 1995, Mori and colleagues disclosed a Pd-catalyzed asymmetric allylic substitution to synthesize a chiral 3-methoxycarbonyl bicyclolactam during the total synthesis of (+)-γ-lycorane.[57] The desired product was obtained via two steps with an overall yield of 53% but with unsatisfactory stereoselectivity. The above two-step protocol was improved by Ojima and colleagues using a $Pd(OAc)_2$/phosphoramidite catalytic system instead of Mori's $Pd(OAc)_2$/BINAPO, providing excellent enantioselectivity (99% ee).[84] Interestingly, the key intermediate **24** of (−)-γ-lycorane can be easily obtained in a moderate yield (46%) and with high ee (94%) using our cascade reaction followed by debenzoylation; it can then be transformed to (−)-γ-lycorane according to a reported method (►**Scheme 20**).[57]

Cycloaddition via Two C–X Bond Formation

Optically active diols are useful and valuable chiral synthetics in preparing pharmaceuticals, agrochemicals, and natural compounds. The oxidation of olefins to 1,2-diols is of importance in the fine chemical industry and is industrially manufactured by a two-step process. However, the chiral diols can be synthesized by a one-pot procedure using asymmetric cascades, which is undoubtedly an efficient pathway.



Scheme 20 Synthesis of (−)-γ-lycorane.

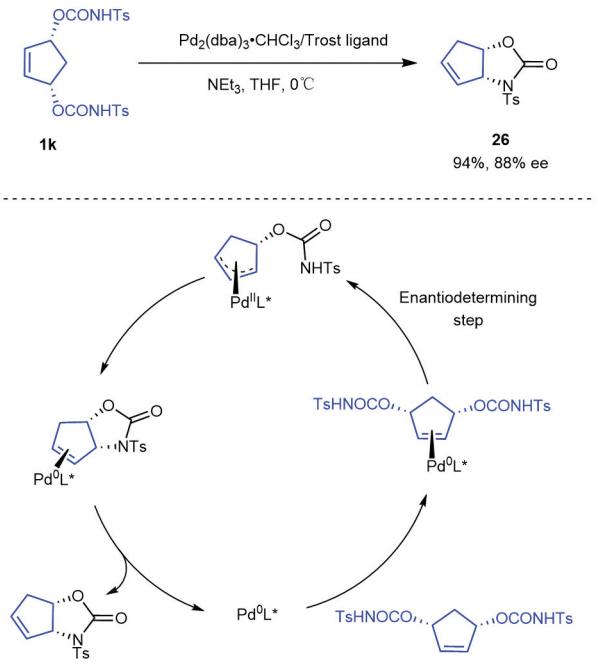


Scheme 21 Formation of bicyclic carbonate from the reaction of **1j** with H_2O.

In 2005, Gais et al reported the synthesis of several unsymmetrical and symmetrical allylic alcohols by the Pd-catalyzed asymmetric reaction via the desymmetrization of *meso*-cycloalkene-1,4-biscarbonates **1j** with H_2O. The reaction was performed at 0°C in a mixed solvent system, giving the carbonate product (**25**) with 66% ee and 67% yield (►**Scheme 21**).[85]

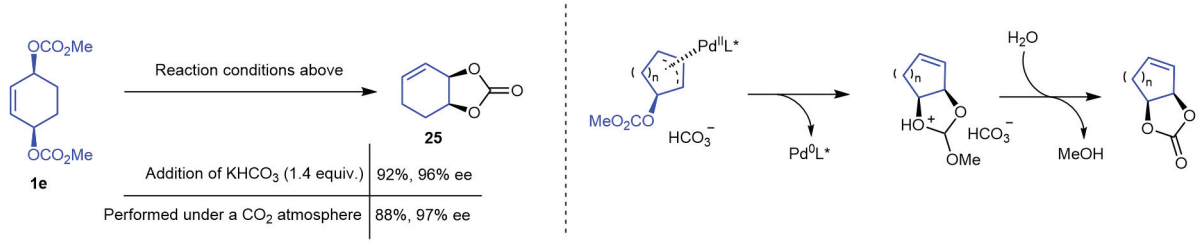
In 2010, Gais et al achieved **25** (92% yield, 96% ee) under the above-mentioned reaction conditions in the presence of $KHCO_3$ using **1e** as the starting material (►**Scheme 22**, left). The reaction pathway was suggested as follows (►**Scheme 22**, right). First, **1e** was substituted with a chiral Pd-catalyst to give the π-allyl–Pd complex via asymmetric dememorization. Intramolecular substitution of the π-allyl–Pd complex occurs, giving the carbenium ion which is hydrolyzed to afford the carbonate enantiomer.[86]

The β-amino alcohol functional motif is one of the most important pharmacophores because of its prevalence in biologically active compounds, such as antibiotics, alkaloids, and enzyme inhibitors.[87–91] It has been successfully used as

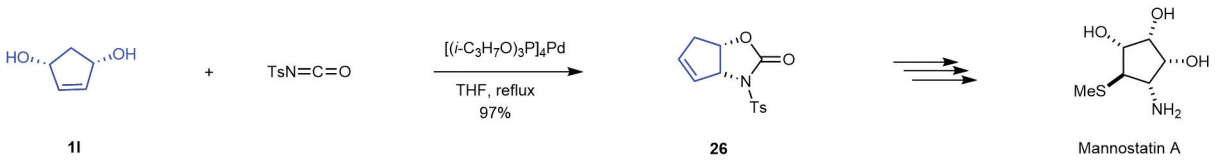


Scheme 23 Synthesis of chiral oxazolidin-2-one (**26**) and the proposed mechanism.

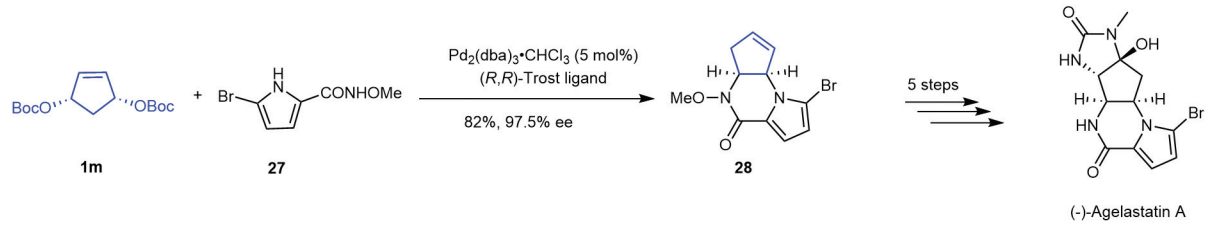
auxiliaries or ligands in asymmetric synthesis.[92–95] Many existing synthetic routes rely on the derivatization of the available pool of amino acids, inherently limiting the number of analogues that can be obtained. Preparation of those chiral skeletons by a one-pot procedure is an alternative and useful strategy. In 1991, Trost et al reported the Pd-catalyzed desymmetrization of bis-urethane substrates **1k** derived from the corresponding *cis*-2-cycloalkene-1,4-diols. This protocol gave chiral oxazolidin-2-one (**26**) in a high yield and 88% ee via intramolecular asymmetric allylic substitution (►**Scheme 23**, top).[96,97]



Scheme 22 Formation of bicyclic carbonate from the reaction of **1e** with $KHCO_3$.



Scheme 24 Synthesis of mannostatin A.



Scheme 25 Synthesis of (−)-agelastatin A.

The proposed reaction pathway is described as follows. The Pd^0L^* catalyst binds to the bis-urethane substrate (**1k**). Then, the allyl–Pd complex forms as one of the urethane group leaves, which is the enantio-determining step in the catalytic cycle and will lead to the formation of the desired chiral product. Then, an intramolecular nucleophilic substitution occurs to give the target product **26** accompanied by the release of the catalyst, which can be involved in the next catalytic cycle. Notably, there are no competing side reactions throughout the reaction process (►**Scheme 23**, bottom).[97,98]

The above reaction can also be performed using *meso*-alkenediols as the starting material. The process involves a one-pot reaction in which bis-urethane is generated *in situ*. In addition, the Pd-catalyzed asymmetric desymmetrization reaction of 2-alkene-1,4-diols (**1l**) yields oxazolidine-2-ones (**26**) with excellent catalytic behavior, which can be further used for the synthesis of compounds containing highly functionalized cyclopentane rings, such as the natural product mannostatin A (►**Scheme 24**).[96,99,100]

In 2009, Trost used a new class of nucleophile, pyrroles (**27**), in the Pd-catalyzed asymmetric allylic amination cascade to generate the corresponding regioisomeric product tricyclic pyrrolopiperazinone (**28**) in 82% yield and 97.5% ee. Starting with **28**, a five-step sequence has been developed for the total synthesis of (−)-agelastatin A (►**Scheme 25**).[101]

Conclusion

The Pd-catalyzed asymmetric allylic substitution reaction provides a simple and popular synthesis method for constructing carbon–carbon and carbon–heteroatom bonds. It is very useful in organic transformation and can be further utilized in the synthesis of functional molecules and biologically active natural products. This review compiles the evolution, mechanistic understanding, and more recent advances in asymmetric Pd-catalyzed asymmetric allylic substitution cascades via the desymmetrization of *meso*-diol diesters of cycloolefins for the construction of chiral polyheterocycles. Three sections are summarized in this review according to the different types of bond formation cascade involved, including desymmetrization cycloaddition via C–C and C–O bond formation cascade, desymmetrization cycloaddition via C–C and C–N bond formation cascade, and desymmetrization cycloaddition via two C–X bond formation cascade.

In the past decade, impressive results, mainly by Trost et al and our group, have been achieved in this field by developing highly efficient catalytic systems that explore new generations of catalysts, substrates, and reaction conditions. The future of this reaction should be focused on new strategies including the development of novel catalytic models, more practical reaction examples, and broader reaction substrates. For example, synergistic dual catalysis (dual Pd/PTC, Pd/organocatalysis, and bimetallic catalysis) could be applied to this asymmetric cascade reaction to afford a more diverse range of functional molecules.[102–105] The employment of an earth-abundant chiral metal catalyst will enable large-scale synthesis of chiral polyheterocycles relatively inexpensively. Further efforts can also be directed toward expanding the scope of substrates and nucleophiles, thereby increasing the possibilities of application to the synthesis of more complex organic molecules. In addition, other cascade reactions could be developed, such as allylic substitutions with ring-closing metathesis or Pauson – Khand reactions, which could be efficiently applied to the preparation of a wide range of chiral (poly)carbo- and heterocyclic compounds.

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Conflict of Interest
None declared.

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