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Ir-Catalyzed Double Asymmetric Hydrogenation of 3,6-Dialkylidene-2,5-diketopiperazines for Enantioselective Synthesis of Cyclic Dipeptides

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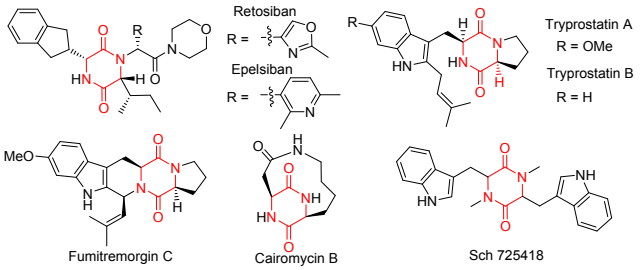
ABSTRACT: An Ir/SpinPHOX complex catalyzed double asymmetric hydrogenation of 3,6-dialkylidene-1,4-dimethylpiperazine-2,5-dione has been developed, providing an efficient and practical access to a wide variety of chiral 3,6-disubstituted-2,5-diketopiperazines in high yields with exclusive *cis*-diastereo- and excellent enantioselectivities (>99% de, up to 98 % ee). The synthetic utilities of the protocol have been demonstrated in a gram scale synthesis of **6a**, and efficient construction of chiral products **8**, **14** and **17** as well as a 2-butenyl-bridged bicyclic diketopiperazine **10** and hydroxydiketopiperazine **11**. With an analogous achiral Ir catalyst, the hydrogenation of enantiopure mono-hydrogenated intermediate **7a** gave *cis*-**6a** as the only product, indicating that stereochemistry of the second-step hydrogenation of the titled transformation is a chiral substrate controlled process. Reaction profile study for AH of **5a** revealed that the concentration of the monohydrogenation intermediate **7a** remianed at a low level (<8%) during the course of hydrogenation. The double hydrogenation of **5a** to **6a** proceeded significantly faster than that of its half-hydrogenated intermediate (*S*)-**7a**, indicating that the double AH reaction involves primarily a processive mechanism, in which a single catalyst molecule performs consecutive hydrogenation of the two C=C double bonds in substrate **5a** without dissociation of the partially reduced **7a**. The present protocol represents a rare example of asymmetric catalytic consecutive hydrogenation of heterocycles and provides an alternative way for efficient construction of cyclic dipeptides.

INTRODUCTION

Substances containing a conformationally rigid 2,5-diketopiperazine subunit, known as cyclic dipeptides, represent a large class of biologically interesting molecules with high stability and protease resistance.[1] The features of the scaffold allow the binding affinity and specificity of the molecules with biological targets to be enhanced, which is particularly attractive for drug discovery.[2,3] For examples, retosiban and epelsiban are highly potent oxytocin antagonists and retosiban has been approved as an oral drug for treatment of preterm labor.[2a, 3a] Tryprostatin A and Fumitremorgin C are inhibitors of the multidrug-resistance protein (BCRP/ABCG2) that mediate resistance to chemotherapeutics in breast cancer treatment (Chart 1).[3b,c] Moreover, some compounds containing a chiral piperazine motif, which can be obtained from 2,5-diketopiperazines by carbonyl reduction, display interesting activity in many biological systems.[4] On the other hand, some chiral 3,6-disubstituted-2,5-diketopiperazine derivatives have also been used in asymmetric synthesis as organocatalysts or auxiliaries.[5]

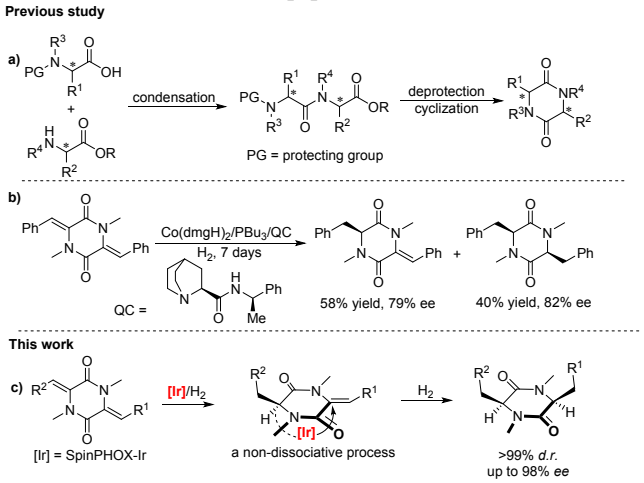
Chart 1. Representative bioactive molecules with 3,6-disubstituted-2,5-diketopiperazine core



The importance of this type of molecules has stimulated extensive research on the development of methodologies for their syntheses.[2a,6] Some type of 3,6-disubstituted-2,5-diketopiperazines have been produced by microorganisms in nature.[1d,f,7] However, the limited productivity hindered extensive screening of biological activities, and many of these naturally occurring structures do not have the expected bioactivity or physicochemical properties. The chemical synthesis of 3,6-disubstituted-2,5-diketopiperazines generally involves amide formation via condensation cyclization of linear dipeptides, which are derived from protected chiral α-amino acids (Scheme 1a).[6]

Despite the versatility of the approach, however, meticulous control of reaction conditions (e.g., pH values) is obligatory to prevent the racemization and/or epimerization of chiral carbon centers. Several other methods[8] such as substrate-induced asymmetric alkylation of 2,5-diketopiperazines[8e-g] or Pd/C catalyzed hydrogenation of enantioenriched dehydrophenylalanine[8h] have also been developed. In 1990, Takeuchi and co-workers reported the synthesis of a piperazine alkaloid via a Co-catalyzed asymmetric hydrogenation (AH) of 3,6-dibenzylidene-2,5-diketopiperazine as the key step, albeit 3,6-dibenzyl-2,5-diketopiperazine was obtained with 40% yield and moderate enantioselectivity (Scheme 1b).[9] In the present work, we report an Ir-catalyzed double hydrogenation of 3,6-dialkylidene-2,5-diketopiperazines for asymmetric synthesis of cyclic dipeptides with excellent stereoselectivity (Scheme 1c). The synthetic utilities of the protocol in facile construction of biologically important molecules, and the underlying non-dissociative pathway involved in the catalysis will also be disclosed.

Scheme 1. Asymmetric catalytic synthesis of 3,6-disubstituted-2,5-diketopiperazines

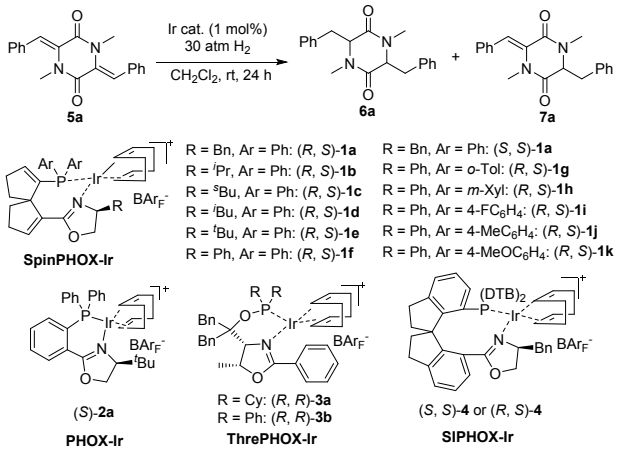


RESULTS AND DISCUSSION

Catalyst optimization for Ir-catalyzed enantioselective hydrogenation of cyclic dehydropeptides. Although some chiral catalysts based on iridium, rhodium and ruthenium have been documented to be effective in asymmetric hydrogenation of exocyclic α, β-unsaturated lactams,[10] the examples on consecutive AH of two or more C=C double bonds in a cyclic dehydropeptide are quite rare.[11] We previously reported a class of chiral iridium(I) complexes with spiro[4,4]-1,6-nonadiene-based phosphine-oxazoline ligands, SpinPHOX/Ir(I), for AH of ketimines and several types of α,β-unsaturated carbonyl compounds, including α,α'-bis-(arylidene)cyclohexanones, cyclic α-alkylidene carbonyl compounds, and 3-alkylidenephthalides.[10f,12] Given the importance of optically active 2,5-diketopiperazine cyclic dipeptides, we were intrigued by the feasibility of using SpinPHOX/Ir(I) complexes for the catalysis of asymmetric hydrogenation of 3,6-dialkylidene-2,5-diketopiperazines, which would provide a direct access to the corresponding chiral cyclic dipeptides.

(3*Z*, 6*Z*)-3,6-Dibenzylidene-1,4-dimethylpiperazine-2,5-dione (**5a**), a cyclic dehydropeptide, was taken as a model substrate for catalyst screening and condition optimization in the asymmetric hydrogenation. The reaction was typically carried out in CH_2Cl_2 under 30 atm H_2 for 12 h at room temperature, with 1 mol% SpinPHOX/Ir(I) complex **1a-k** as the catalyst (entries 1-14, Table 1). Under these conditions, the reaction using (*R*, *S*)-**1a** gave the double AH product (*S*, *S*)-**6a** as a single diastereomer with 92% ee, albeit in 41% yield along with the co-generation of a small amount of mono-reduced product (*S*)-**7a** (5% yield, 15% ee) (entry 1). In contrast, the reaction catalyzed by complex (*S*, *S*)-**1a**, diastereomeric isomer of (*R*, *S*)-**1a**, afforded (*R*, *R*)-**6a** as the major product in only moderate enantioselectivity (45% ee), indicating a mismatched combination of ligand chirality in this case (entry 2). Further survey of (*R*, *S*)-SpinPHOX/Ir(I) catalyst series (*R*, *S*)-**1a-k** revealed that (*R*, *S*)-**1k**, with a phenyl group on the oxazoline ring and two 4-methoxyphenyl groups on the P atom, afforded the optimal reactivity to give (*S*, *S*)-**6a** in 95% yield with 92% ee (entry 13). Elevation of the initial hydrogen pressure to 40 atm resulted in full conversion of **5a**, and (*S*, *S*)-**6a** was obtained in quantitative yield with 94% ee (entry 14). Under otherwise identical conditions, several types of well-established Ir(I) complexes with privileged chiral phosphino-oxazoline ligands, including PHOX ((*S*)-**2a**),[13] ThrePHOX ((*R*, *R*)-**3a**-**b**)[14] and SIPHOX ((*S*, *S*)-**4** and (*R*, *S*)-**4**),[15] demonstrated no activity or less satisfactory enantioselectivity (entries 15-19), thus underscoring the unique performance of SpinPHOX/Ir(I) catalysts in AH of this type of challenging substrates. The impact of diketopiperazine *N*-substituents on the catalysis has also been examined. While the reaction of **5a** with *N*-methyl groups delivered the optimal results, similar diketopiperazines with *N*-Ac or *N*-Bn protecting groups, or with naked N-H moieties demonstrated no hydrogenation activities under otherwise identical conditions (30 atm H_2, 1 mol% (*R*, *S*)-**1f**, CH_2Cl_2 solvent, rt, 12 h. For details, see Table S1 in SI). In the case of the diketopiperazine substrate containing both exocyclic alkylidenyl C=C bonds and *N*-allyl groups, ^{1}H NMR indicated that only the terminal C=C bonds were reduced (see SI). Though the exact reason for these intriguing reactivity behaviors is unclear at the present stage, it seems likely that the reluctance to hydrogenation might be a result of competitive coordination (*N*-Ac), steric hindrance (*N*-Bn), and/or poor solubility (*N*-H) of the corresponding diketopiperazines, which can eventually prevent coordination of the proximal C=C bond to Ir and hence inhibit the substrate activation by the catalyst. A variety of solvents have also been screened in the reaction, and dichloromethane turns out to be optimal (see Table S2 in SI).

Table 1. Ir(I)-catalyzed AH of (3*Z*,6*Z*)-3,6-dibenzylidene-1,4-dimethylpiperazine-2,5-dione 5a[a]

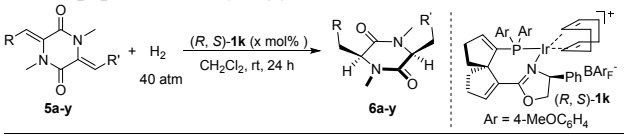


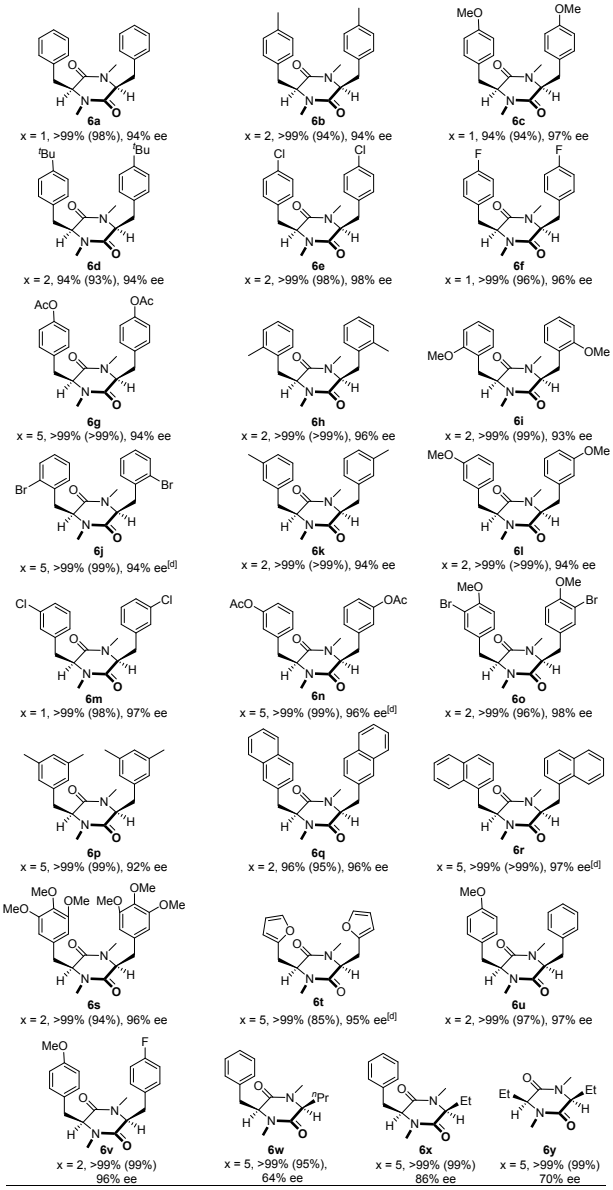
Entry	Ir cat.	yield of **6a** (%)[b]	*ee* of **6a** (%)[c]	yield of **7a** (%)[b]	*ee* of **7a** (%)[c]
1	(*R*, *S*)-**1a**	41	92(*S*, *S*)	5	15(*S*)
2	(*S*, S)-**1a**	37	45(*R*, *R*)	8	7(*S*)
3	(*R*, *S*)-**1b**	30	94(*S*, *S*)	6	77(*S*)
4	(*R*, *S*)-**1c**	48	92(*S*, *S*)	4	11(*S*)
5	(*R*, *S*)-**1d**	40	94(*S*, *S*)	5	26(*S*)
6	(*R*, *S*)-**1e**	18	97(*S*, *S*)	5	62(*S*)
7	(*R*, *S*)-**1f**	93	90(*S*, *S*)	3	66(*R*)
8	(*R*, *S*)-**1f**	94	90(*S*, *S*)	2	67(*R*)
9	(*R*, *S*)-**1g**	82	96(*S*, *S*)	2	66(*R*)
10	(*R*, *S*)-**1h**	69	92(*S*, *S*)	3	26(*R*)
11	(*R*, *S*)-**1i**	85	96(*S*, *S*)	3	26(*R*)
12	(*R*, *S*)-**1j**	90	92(*S*, *S*)	2	54(*R*)
13	(*R*, *S*)-**1k**	95	92(*S*, *S*)	2	76(*R*)
14[d]	(*R*, *S*)-**1k**	>99	94(*S*, *S*)	0	-
15	(*S*)-**2a**	41	79(*S*, *S*)	6	7(*S*)
16	(*R*, *R*)-**3a**	0	-	0	-
17	(*R*, *R*)-**3b**	0	-	0	-
18	(*R*, *S*)-**4**	0	-	0	-
19	(*S*, *S*)-**4**	0	-	0	-

[a] Unless otherwise noted, all reactions were conducted in dichloromethane with [**5a**] = 0.1 M and Ir cat. = 1.0 mM (1 mol%) under 30 atm of H_2 at rt for 12 h (entries 1-7) or 24 h (entries 8-19). [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was conducted under 40 atm of H_2.

Substrate Scope of the Catalytic Hydrogenation Protocol. Having established complex (*R*, *S*)-**1k** as the optimal catalyst, the substrate scope of this catalytic protocol was subsequently investigated. As shown in Table 2, various symmetric 3,6-dibenzylidene-1,4-dimethylpiperazine-2,5-diones **5b**-**n** containing different *ortho*-, *meta*-, or *para*- substituents on the phenyl rings were smoonthly hydrogenated, affording the corresponding (*S*, *S*)-3,6-dibenzyl-1,4-dimethylpiperazine-2,5-diones **6b**-**n** in high yields (94~99%), excellent enantioselectivities (93~98% ee) and complete *cis*-diastereoselectivity, irrespective of the position and electronic nature of the substituents on the phenyl rings. Moreover, AH of substrates **5o**-**s**, bearing multi-substituted phenyl rings or naphthyl groups, also worked well to give the correspongding products (*S*, *S*)-**6o**-**s** in nearly quantative yields with 92~98% ee. AH of substrate **5t**, with 2-furanyl groups on the two exocyclic C=C bonds, afforded **6t** in 85% yield with 95% ee under a catalyst loading of 5 mol%. Substrates with two different benzylidene substituentents (**5u** and **5v**) were reduced in excellent yields (97~99%) and enantioselectivities (96~97% ee). The hydrogenation of aliphatic group containing substrates **5w**-**y** also proceeded smoothly, furnishing the corresponding diketopiperazines **6w**-**y** in quantantive yields with moderate to good ee values.

Table 2. AH of the 3,6-dialkylidene-2,5-diketopiperazines (5a-y)[a-c]





[a] Unless otherwise noted, all reactions were performed with **5** (0.04-0.2 mmol) in CH_2Cl_2 (2.0 mL) in the presence of (*R*, *S*)-**1k** (0.002 mmol) under hydrogen atmosphere (40 atm) at 25 °C for 24 h. [b] The conversions of **5** were determined by ^1H NMR spectroscopy. Data in the parentheses are the yields for isolated products **6a-y**. [c] The ee values were determined by HPLC analysis on a chiral stationary phase. [d] Under a hydrogen pressure of 80 atm.

Synthetic Application of the Protocol for Efficient Construction of Biologically Interesting Molecules. As shown in Figure 1, in the molecular structure of product (*S*, *S*)-**6a** the two benzyl moeities are orientated *cis* to each other at the same side of the quasi-planar six-membered dipeptide ring. Such a structural feature of the prepared cyclic dipeptides would provide an interesting molecular platform for the design of chiral organocatalysts[5a,b] and as useful intermediates for the synthesis of biologically important molecules.[16] To showcase the practicality of this protocol, substrate **5a** was hydrogenated on a gram-scale in the presence of catalyst (*R*, *S*)-**1k** (1 mol %) in CH_2Cl_2 under 50 atm of hydrogen pressure to afford (*S*, *S*)-**6a** in 95% yield with 94% ee (Scheme 2a). The enantiopurity of **6a** was readily upgraded to >99% ee by a simple recrystallization (75% yield). To exemplify the utility of the hydrogenation products, (*S*, *S*)-**6a** was reduced with $LiAlH_4$ to afford (2*S*, 5*S*)-2,5-dibenzyl-l,4-dimethylpiperazine **8**, an alkaloid isolated from Zanthoxylurn arborescens Rose[17], in 80% yield without loss of enantiopurity (Scheme 2b). Moreover, double allylation of (*S*, *S*)-**6a** with allyl bromide proceeded cleanly in the presence of NaHMDS as the base, to give **9** in almost quantitative yield with nearly perfect stereoselectivity (>99% ee). Such a stereospecificity can be rationalized by consecutive allylations via stepwise formation of two distinct chiral sodium enolates, wherein the bulkier Bn group on the remaining chiral center would effectively steer the incoming allyl electrophile to the opposite face of the nearby enolate moiety. Subsequent ring closure olefin metathesis[18] of **9** furnished 2-butenyl-bridged bicyclic diketopiperazine derivative **10** in >99% ee (Scheme 2c). Hydroxylation of (*S*, *S*)-**6a** with oxygen as the oxidant afforded enantiomeric pure *C*-hydroxydiketopiperazine **11**, an analog of Thaxtomin A (a potential pesticides) [19], in 65% yield (Scheme 2d). Finally, AH of **12** and **15** using (*R*, *S*)-**1k** as the catalyst provides key chiral precursors for the synthesis of calpain inhibitor (*S*, *S*)-**14**[20] and Sch725418 **17**[21], respectively, in high yields with excellent ee values (Scheme 2e-f).

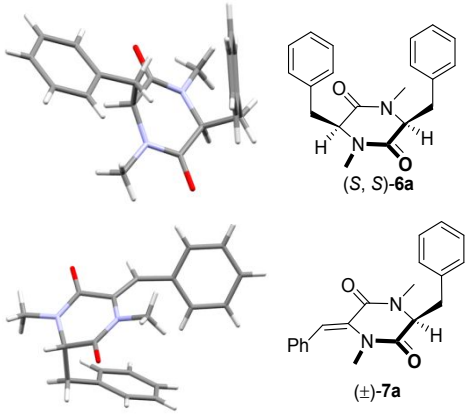
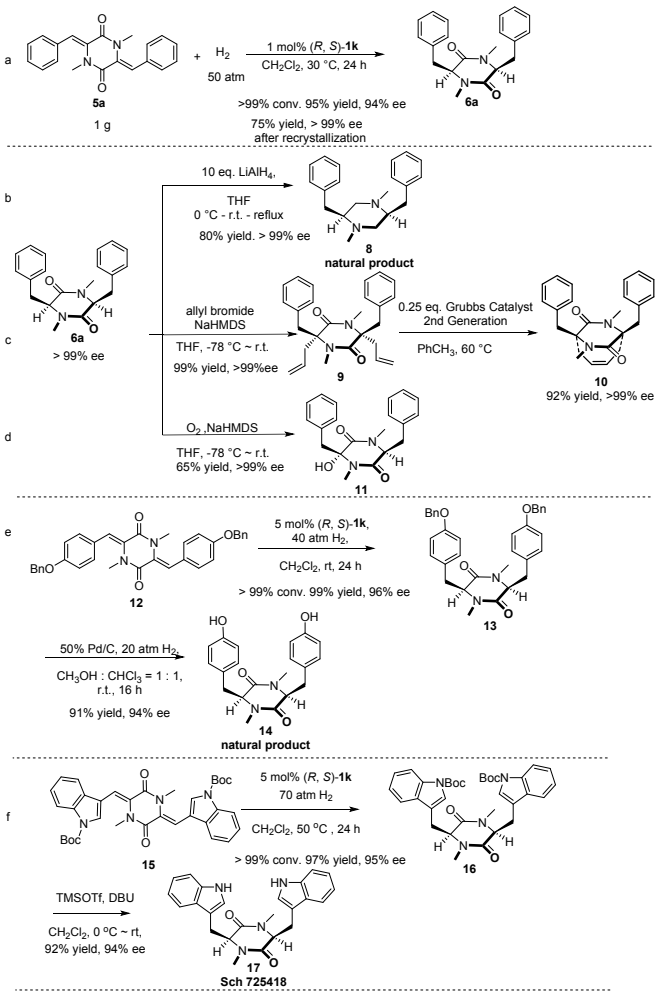


Figure 1. Molecular structure of double and mono-hydrogenated cyclic dipeptides (*S*, *S*)-**6a** and (±)-**7a**.

Scheme 2. Gram-scale AH of 5a and Utilities of the Hydrogenation Products in the Synthesis of Biologically Interesting Molecules



Reaction Pathway Study. While some mechanistic details remain controversial, the reaction pathways for Ir-catalyzed asymmetric hydrogenation of monoenes have been intensively studied both experimentally and theoretically in recent years.[22] On the other hand, Ir-mediated AH of dienes remains much less explored so far, and the mechanism relevant informations are scarce. In this context, Burgess and coworkers reported elegant studies on Ir-carbene-oxazoline catalyzed AH of conjugated dienes, whereby the reduction was suggested to occur in mechanistically different phases.[23] Andersson et al recently described an efficient regio- and enantioselective monohydrogenation of 1,4-cyclohexadienes, arguably a type of isolated dienes, using an iridium catalyst with a chiral N,P-ligand.[24] However, no mechanistic information was available in this report. Given the excellent performance of SpinPHOX/Ir catalyst (*R*, *S*)-**1k** in the AH of the 3,6-dialkylidene-2,5-diketopiperazines, we were intrigued by the mechanistic events in the hydrogenation of this particular type of functionalized dienes.

As discussed in the introduction, Co catalyzed AH of cyclic dehydropeptide **5a** reported previously by Takeuchi afforded the double-hydrogenated *cis*-**6a** as minor product (40%), along with mono-hydrogenated **7a** as the major (58%) and *meso*-isomer in trace amount (1% yield) (Scheme 1b),[9] implying that in this case the hydrogenation of second C=C double bond in the substrate is somehow slower than AH of first C=C double bond. In sharp contrast, AH of **5a** using SpinPHOX/Ir(I)-type catalysts (**1a-k**) generally gave the double-hydrogenated **6a** as the major product with exclusive *cis*-configuration (entries 1-13, Table 1), and mono-hydrogenated intermediate **7a** was only detected as a minor product in less than 8% yield irrespective of the conversion of substrate **5a**. A close examination of reaction profile for AH of **5a** (**Figure 2**) [1 mol% of (*R*, *S*)-**1k**] revealed that (*S*, *S*)-**6a** remains the major product throughout the whole reaction course with **7a** being kept at a consistently low level (<8%), further verifying the observation in Table 1. It is also noteworthy that over the reaction course no *meso*-isomer of **6a** was detected, indicating the complete *cis*-selectivity for the relative stereochemistry in the tandem AH process. During the reaction course, the ee values of the double-hydrogenation product (*S*, *S*)-**6a** decreased slightly from the initial >99% at 5 min to a final 94% at 12 h. Concomitantly, the ee value of **7a** also gradually diminished, and eventually shifted its absolute configuration from *S* to *R*. This intriguing behavior might be caused by the kinetic resolution in the AH of enantioenriched **7a** by (*R*, *S*)-**1k**-derived Ir catalyst, which by chiral discrimination led to preferential AH of (*S*)-**7a** and a gradual enrichment of (*R*)-**7a** in the reaction mixture (*vide infra*).

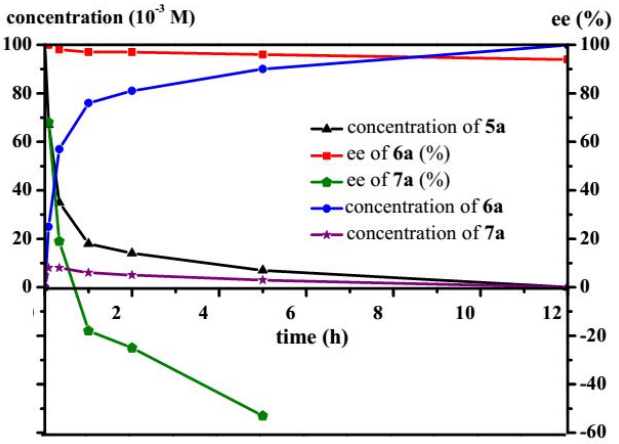
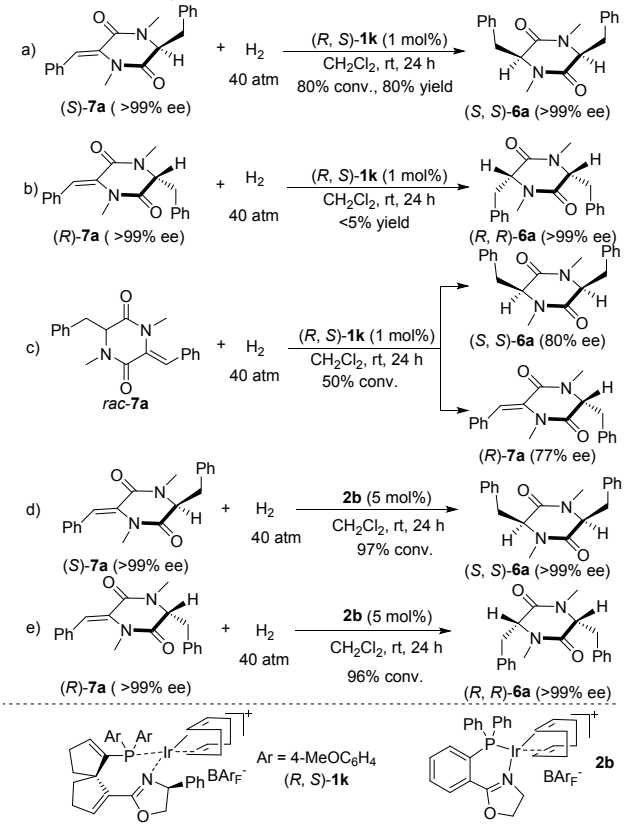


Figure 2. Reaction profile of hydrogenation of **5a** in the presence of *(R, S)*-**1k** under the optimized reaction conditions: 1 mol % of (*R, S*)-**1k**, 40 atm of H_2 in CH_2Cl_2 with an initial [**5a**] = 0.1 M.

In order to provide further illuminating insights into the stereochemistry and the kinetic behavior in the titled reaction, control experiments on the AH of mono-hydrogenated intermediate enantiopure (*S*)-**7a**, (*R*)-**7a**, and racemic (±)-**7a**, respectively, were performed with 1 mol% of (*R*, *S*)-**1k** under standard reaction conditions (Scheme 3). The hydogenation of (*S*)-**7a** (Scheme 3a) is obviously much faster than that of (*R*)-**7a** (Scheme 3b), suggesting a strong catalyst–substrate

recognition in the reaction. Either (*S*, *S*)-6**a** or (*R*, *R*)-**6a** (both >99% ee) was obtained in >99% diastereoselectivity but with an opposite asymmetric induction depending on the absolute configuration of **7a**, implying a substrate-control of the relative stereochemistry in the process. Such a distinction in reaction rate between (*S*)-**7a** and (*R*)-**7a** with the same chiral catalyst [(*R*, *S*)-**1k**] is consistent with the presence of a kinetic resolution process of **7a** in its hydrogenation. Indeed, the AH of (±)-**7a** to half conversion in the presence of 1 mol% of (*R*, *S*)-**1k** afforded (*S*, *S*)-**6a** with 80% ee, along with an almost equal amount of the remaining (*R*)-**7a** with 77% ee, without detection of any *meso*-isomer (Scheme 3c).

Scheme 3. Hydrogenation of Mono-Hydrogenated Intermediate 7a in the Presence of (*R, S*)-1k and Achiral Ir Catalyst 2b

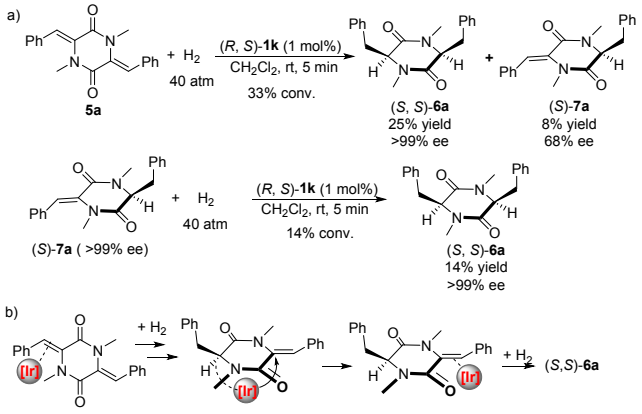


The substrate control of the diastereoselectivity has been further demonstrated by the stereochemical outcomes in the hydrogenation of enantiomers of **7a** with an achiral Pfaltz-type Ir catalyst **2b**, which was used to exclude the otherwise matched or mis-matched catalyst–substrate recognition in the case of a chiral Ir catalyst such as (*R*, *S*)-**1k**. As shown in Schemes 3d-e, the hydrogenations of (*S*)-**7a** or (*R*)-**7a** in the presence of the achiral Ir catalyst **2b** (5 mol%) gave (*S*, *S*)-**6a** or (*R*, *R*)-**6a**, respectively, with >99% ee without the co-production of any *meso*-isomer. These results also clearly confirmed that the stereoselectivity for hydrogenation of **7a** is completely controlled by the chirality of the substrate, irrespective of the Ir catalysts used thereof. The complete *cis*-selectivity for the relative stereochemistry in Scheme 3d and 3e can be rationalized in a way analogous to that discussed above for double allylation of (*S*, *S*)-**6a** (*vide supra* for discussion of Scheme 2c). In this case, **7a** bears a chiral center that is in proximity to its C=C bond. As shown in the molecular structure of **7a** (Figure 1), the reduced benzyl moiety on the chiral carbon center of **7a** can be expected to effectively block one of the prochiral alkene faces, thus preventing the access of Ir catalyst species to the same side of diketopiperazine face. As a result, the catalyst would bind to the C=C bond of **7a** on the opposite side of its Bn group, leading to the formation of *cis*-**6a** via ensuing hydrogenation. Accordingly, it can be deduced that for (*R*, *S*)-**1k** mediated AH of cyclic dehydropeptide **5a**, the enantioselectivity of the whole hydrogenation process is completely determined by the asymmetric induction of the first-step hydrogenation, if intermediate **7a** is completely consumed at the end of reaction.

A notable pattern in both the data of Table 1 and Figure 2 can be found, in that the half-reduced intermediate **7a** was always detected in minor or negligible amount (< 8%) over the course of **5a** hydrogenation. Although this observation might suggest that hydrogenation of **7a** could be somehow faster than that of **5a**, there is an alternative possibility that the hydrogenation of the two C=C bonds in cyclic dehydropeptide **5a** occurs processively. In the latter case, after reduction of the first C=C bond in **5a** the resulting intermediate (*S*)-**7a** can remain bound to the catalyst without dissociation, which can undergo an intramolecular re-organization for the second step of hydrogenation. Such an intramolecular process is expected to be entropically more favorable than the one involving dissociation-reassociation of **7a** from/to the catalyst, thus leading to faster reaction. To shed some light on this mechanistic ambiguity, the initial rate for the hydrogenation of **5a** was compared with that of (*S*)-**7a** by ^{1}H NMR analysis of the reaction mixture. As shown in Scheme 4a, the hydrogenation of **5a** and (*S*)-**7a** (a matched isomer of intermediates) were carried out under otherwise identical reaction conditions (1 mol% of (*R*, *S*)-**1k**, 5 min). It was notable that both the conversion of cyclic dehydropeptide **5a** and yield of (*S*, *S*)-**6a** in the hydrogenation of **5a** are significantly higher than those observed in the hydrogenation of (*S*)-**7a** (Scheme 4a). This indicates for generation of **6a**, the double hydrogenation of two C=C bonds in **5a** is even faster than the hydrogenation of single C=C bond in half-hydrogenated (*S*)-**7a**. Based on these results, we tentatively propose a processive mechanism as the major pathway for Ir-catalyzed double hydrogenation of 3,6-dialkylidene-2,5-diketopiperazines. As shown in Scheme 4b, due to the conformational rigidity of the piperazine-2,5-dione core, the two C=C bonds in diene **5a** are located too far from each other to simultaneously bind to a single Ir center (distance between diene internal carbons: 2.7533(27) Å. for the X-ray structure of **5a**, see Figure S1). After one of C=C bonds in dehydropeptide **5a** is reduced, the mono-hydrogenated (*S*)-**7a** remains bound to the catalyst, and by way of an intramolecular movement is ready for consecutive hydrogenation of second C=C bond. Such a processive double hydrogenation pathway can account for the fact

that no distinct accumulation of mono-hydrogenated imtermediate **7a** is observed (Table 1 and Figure 2), and is consistent with the observation that double-AH of **5a** to **6a** is conspicuously faster than mono-AH of **7a** under otherwise identical reaction conditions, as well as the essentially exclusive *cis*-stereochemistry in the formation of two chiral centers. It is noteworthy that such a pathway features a "walking" model, which is reminiscent of work by Sigman, Ma, and others.[25]

Scheme 4. a) Comparison of the reactivity in (*R*, *S*)-1k catalyzed hydrogenation of 5a and (*S*)-7a, and b) Schematic Illustration of the Major Pathway for the Asymmetric Hydrogenation of 5a



CONCLUSION

In summary, a highly enantioselective hydrogenation reaction of 3,6-dialkylidene-1,4-dimethylpiperazine-2,5-dione has been developed using a SpinPHOX/Ir(I) complex as the catalyst, providing a wide variety of chiral *cis*, *cis*-3,6-disubstituted-2,5-diketopiperazines in high yields with excellent optical purities (up to 98% ee). The perfect diasteroselectivity arised from a very effective chiral substrate controled process. Synthetic utilities of the protocol were demonstrated in the asymmetric synthesis of natural products **8**, **14** and **17** as well as a 2-butenyl-bridged bicyclic diketopiperazine derivative **10** and hydroxyl substituted diketopiperazine derivative **11**. Mechanistic investigation revealed that a partly processive catalysis pathway is present in the reaction course, wherein the two carbon carbon double bonds of the substrate are hydrogenated successively on a single iridium center *via* the formation of an undissociated mono-reduced intermediate. Such kind of processivity is essential in nature,[26] and the present catalytic system represents rare example of artificial catalyst in asymmetric processive hydrogenation of heterocycles.[11] The present protocol might inspire further studies and applications of asymmetric hydrogenation for the synthesis of chiral 2,5-diketopiperazines and their derivatives with biological and medicinal interests.

ASSOCIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at xxxxxx.
Detailed synthetic, crystallographic, and characterization data (PDF)
Crystallographic data for **5a** (CIF)
Crystallographic data for (*S, S*)-**6a** (CIF)
Crystallographic data for (±)-**7a** (CIF)
Crystallographic data (±)-**11** (CIF)

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Notes

The authors declare no competing financial interest.
Crystallographic data (CIF files) for **5a** (CCDC 1877956), (*S*, *S*)-**6a** (CCDC 1877960), (±)-**7a** (CCDC 1877959), (±)-**11** (CCDC 1893145) have been deposited at the Cambridge Crystallographic Data Center

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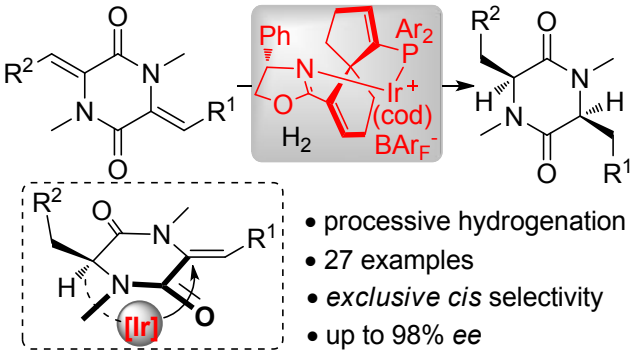
TOC graphic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