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Rh-Catalyzed One-Pot Sequential Asymmetric Hydrogenation of α-Dehydroamino Ketones for the Synthesis of Chiral Cyclic *trans*-β-Amino Alcohols

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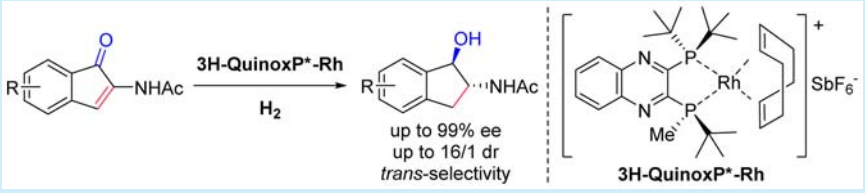
Supporting Information

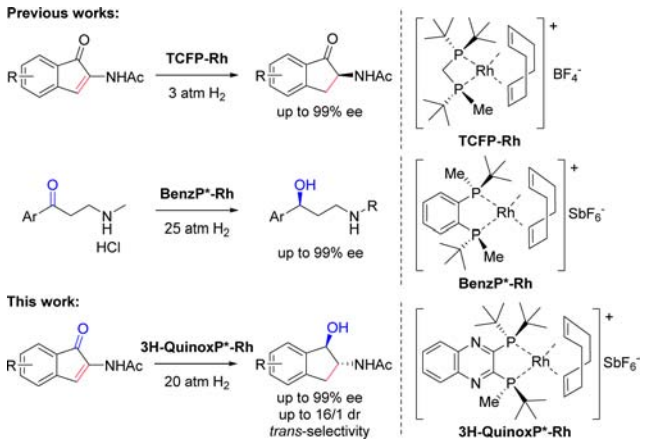


ABSTRACT: Catalyzed by a rhodium complex of P-stereogenic diphosphine ligand (*R*)-2-*tert*-butylmethylphosphino-3-(di-*tert*-butylphosphino)quinoxaline ((*R*)-**3H-QuinoxP***), five-membered cyclic α-dehydroamino ketones bearing endocyclic vinyl and endocyclic keto-carbonyl groups were sequentially hydrogenated to give chiral cyclic *trans*-β-amino alcohols with two contiguous stereocenters in quantitative conversions, excellent enantioselectivities and good diastereoselectivities.

Chiral cyclic β-amino alcohols with contiguous stereocenters are important building blocks for the synthesis of many biologically active molecules and chiral catalysts.[1] Therefore, considerable effort has been devoted to developing methodologies for the asymmetric synthesis of such compounds. Previously, optically active cyclic β-amino alcohols were generally synthesized by ring-opening of *meso*-epoxides or aziridines via asymmetric desymmetrization or acylation of the racemic β-amino alcohols via kinetic resolution.[2−4] Recently, asymmetric hydrogenation,[5] which is considered to be more practical and efficient, was applied to the preparation of the target compounds from racemic α-amino ketones using an unusual strategy of dynamic kinetic resolution[6] or via tetrasubstituted alkenes in a one-step process.[7] However, chiral cyclic *cis*-β-amino alcohols were the predominant products due to the simultaneous formation of the two stereocenters. An efficient method for the synthesis of cyclic *trans*-β-amino alcohols by asymmetric hydrogenation remains elusive and thus highly desired.

Over the duration of our research concerning asymmetric hydrogenations,[8] our laboratory has reported a highly chemo- and enantioselective hydrogenation of α-dehydroamino ketones catalyzed by a rhodium complex derived from a P-stereogenic diphosphine ligand[9] trichickenfootphos (**TCFP**) (Scheme 1).[8g] The readily prepared chiral cyclic α-amino ketones can be further converted to cyclic *cis*-β-amino alcohols using a four-step process. Related studies showed that a similar rhodium complex of P-stereogenic diphosphine ligand 1,2-bis(*tert*-butylmethylphosphino)benzene (**BenzP***) could be successfully applied to the asymmetric hydrogenation of ketones with the help of a coordinating amino group (Scheme 1).[8e] Herein, we reported the rhodium-catalyzed preparation of chiral cyclic

Scheme 1. P-Stereogenic Diphosphine-Rh-Catalyzed Asymmetric Hydrogenation in Our Lab



β-amino alcohols with two contiguous stereocenters via a one-pot sequential asymmetric hydrogenation of C═C and C═O bonds (Scheme 1).[10,11] To the best of our knowledge, this procedure represents the first example for the construction of two contiguous stereocenters in a cyclic structure using such a strategy.[10] Besides overcoming the challenges posed by the rigid and sterically demanding structures of cyclic substrates in achieving high enantioselectivities, it is worth noting that our catalytic system afforded unusual *trans*-β-amino alcohols with

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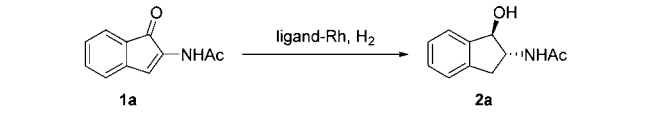
high diastereoselectivities, in part due to its unique stepwise process.

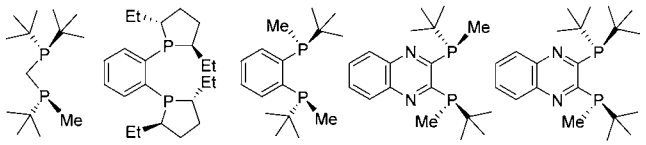
Initially, **TCFP**−Rh complex, which has provided excellent chemo- and enantioselectivities for the hydrogenation of α-dehydroamino ketones to α-amino ketones under a hydrogen pressure of 3 atm (Table 1, entry 1), was used as a catalyst in a model sequential asymmetric hydrogenation. As expected, after sequential hydrogenation of C═C and C═O bonds at 30 atm H_2 and in EtOH solvent, the starting material **1a** was converted to the desired 2-amino-indanol **2a** in quantitative yield and with 99% ee for both diastereoisomers but with a poor diastereoselectivity (entry 2). Subsequently, other rhodium complexes bearing electron-rich P-stereogenic diphosphine ligands were screened. The C_2-symmetric ligands (**Duphos**, **BenzP***, and **QuinoxP***) showed poorer enantioselectivities and similar diastereoselectivities (entries 3−5). A stable C_1-symmetric ligand **3H-QuinoxP***, which was recently developed by Imamoto et al. and can be easily prepared via a one-step reaction,[8h] also gave the desired product with excellent ee (97%) and with an unexpected *trans*-selectivity (entry 6). The absolute configuration of the hydrogenated product was assigned by H−H Noesy (see Supporting Information) and HPLC spectra according to the literature.[8g] Following studies showed a dramatic and interesting solvent effect (see Supporting Information for details). For example, EtOH and *i*PrOH gave opposite diastereoselectivities for reactions carried out using **BenzP***−Rh (entry 7 vs 4), and EtOH and DCM provided the main products with different *trans*/*cis*-configurations in **QuinoxP***−Rh-catalyzed reactions (entry 8 vs 5). Using **3H-QuinoxP***−Rh as the catalyst, we found that dioxane afforded the best diastereoselectivity (93/7) with 93% ee (entries 9−14). Reducing the hydrogen pressure to 20 atm increased the ee to 94% and had no effect on dr (entry 15). Further reducing the hydrogen pressure to 10 atm was detrimental to selectivity (entry 16).

Various substrates with different substituents were studied in the **3H-QuinoxP***−Rh-catalyzed sequential asymmetric hydrogenation under a hydrogen pressure of 20 atm in dioxane at room temperature (Scheme 2). All substrates were reduced smoothly with excellent enantioselectivities (89−99% ee) and satisfactory diastereoselectivities (3/1 to 16/1 dr). Only the 7-Me-substituted substrate **2e** and 6-COOMe-substituted **2h** gave lower enantioselectivities of 90% and 89% ee's, respectively. Substrates **2b**−**2f** bearing electron-donating substituents on the phenyl ring gave the desired products with higher diastereoselectivities (9/1 to 16/1 dr). Substrates **2g**−**2p** bearing electron-withdrawing groups provided lower diastereoselectivities (3/1 to 7/1 dr).

To gain a better understanding of the reaction mechanism, control experiments were performed (Scheme 3). First, the hydrogenation reaction was conducted under a hydrogen pressure of 3 atm in dioxane, and the α-amino ketone was solely obtained in quantitative yield with 92% ee. Another reaction was set up under a hydrogen pressure of 20 atm. After 0.5 h, ^{1}H NMR spectra indicated that both α-amino ketone (89% yield) and β-amino alcohol (11% yield) were formed,

Table 1. Ligand and Solvent Screening[a]

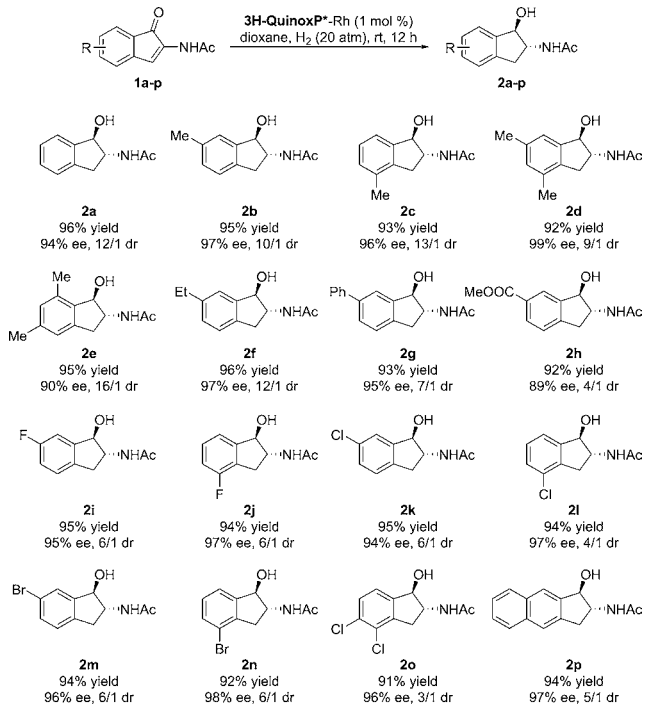




entry	ligand	solvent	conv [%] (*trans*/*cis*)[b]	ee [%] (*trans*)[c]
1[d]	**TCFP**	EtOH	99	99
2	**TCFP**	EtOH	34/66	−99
3	**Duphos**	EtOH	39/61	−49
4	**BenzP***	EtOH	12/88	−33
5	**QuinoxP***	EtOH	23/77	39
6	**3H-QuinoxP***	EtOH	65/35	97
7	**BenzP***	*i*PrOH	78/22	15
8	**QuinoxP***	DCM	75/25	84
9	**3H-QuinoxP***	DCM	79/21	67
10	**3H-QuinoxP***	EtOAc	82/18	98
11[e]	**3H-QuinoxP***	MeOH	35/20	93
12	**3H-QuinoxP***	THF	83/17	90
13	**3H-QuinoxP***	toluene	81/19	95
14	**3H-QuinoxP***	dioxane	93/7	93
15[f]	**3H-QuinoxP***	dioxane	93/7	94
16[g]	**3H-QuinoxP***	dioxane	92/8	82

[a]Conditions: **1a** (0.2 mmol), ligand−Rh (1 mol %), H_2 (30 atm), solvent (2 mL), rt, 12 h. [b]Conversions were calculated from ^{1}H NMR spectra. [c]The ee values were determined by HPLC using chiral columns. [d]Under a hydrogen pressure of 3 atm, only α-amino ketone was obtained in 99% conversion and 99% ee. [e]Product **2a** was obtained in yield of 55% with α-amino ketone in yield of 45%. [f]Under a hydrogen pressure of 20 atm. [g]Under a hydrogen pressure of 10 atm.

Scheme 2. Substrate Scope[a]



[a]Conditions: **1** (0.2 mmol), **3H-QuinoxP***−Rh (1 mol %), H_2 (20 atm), dioxane (2 mL), rt, 12 h. The dr and ee values were determined by HPLC using chiral columns. The yields were for the mixture of *trans*- and *cis*-products isolated by flash chromatography.

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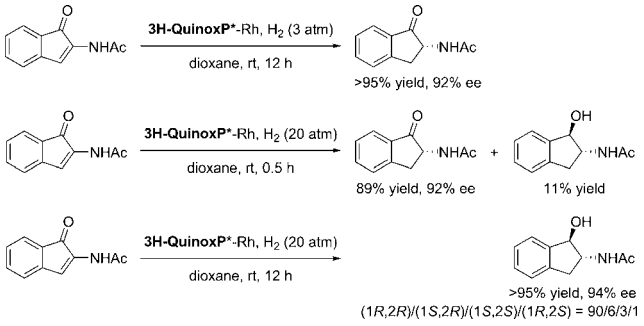
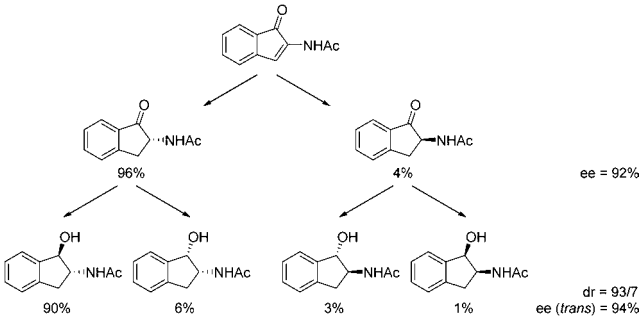
Scheme 3. Control Experiments



with the ee of the α-amino ketone (92%) being consistent with that obtained under a lower hydrogen pressure. A third reaction, also carried out under a hydrogen pressure of 20 atm for 12 h, gave the four isomers of β-amino alcohols in a ratio of 90/6/3/1. A detailed conversion process is described in Scheme 4. These results reveal that the one-pot synthesis of

Scheme 4. Detailed Conversion Process for the Synthesis of the Four Isomers of β-Amino Alcohols

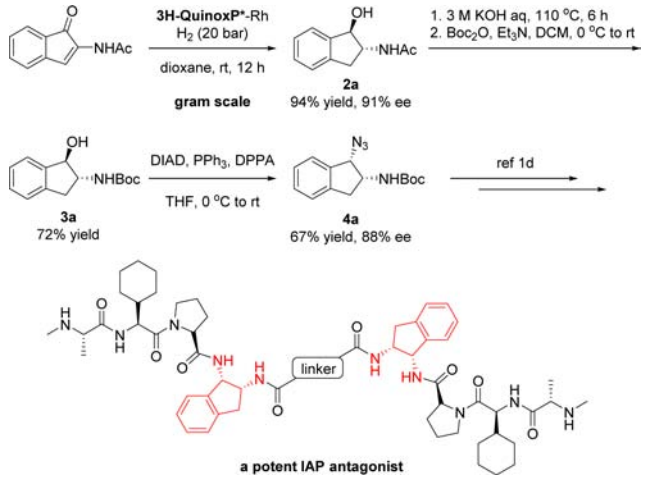


cyclic *trans*-β-amino alcohols includes two sequential asymmetric hydrogenation steps with the C=C bond being reduced more rapidly than the C=O bond. The high enantioselectivity can be mainly attributed to the hydrogenation of the C=C bond and is further enriched during hydrogenation of the C=O bond. The diastereoselectivity is influenced by a "match/mismatch" relationship between the catalyst and the α-amino ketone (see Supporting Information for details).

To further demonstrate the usage of this highly efficient catalytic system, the asymmetric hydrogenation was carried out on a gram scale and further applied to the synthesis of important bioactive compounds (Scheme 5). The desired product **2a** was obtained in 94% yield with a slight decrease in the enantiomeric excess (91%) and diastereoselectivity (9/1 dr). The protecting Ac substituent on the amino group of **2a** was easily removed under reflux conditions in a 3 M KOH aqueous solution followed by reprotection with a Boc group. Finally, the hydroxyl group of compound **3a** was converted to an azide group via a Mitsunobu reaction to give compound **4a**, an important intermediate used for the synthesis of a potent inhibitor of apoptosis (IAP) antagonist.[1d]

In summary, a highly efficient synthesis of chiral cyclic *trans*-β-amino alcohols was developed via a one-pot sequential asymmetric hydrogenation of α-dehydroamino ketones with excellent enantioselectivities and diastereoselectivities. A special P-stereogenic diphosphine ligand, **3H-QuinoxP***, which possesses a rigid and sterically hindered structural motif, was sufficient for the hydrogenation. This methodology represents

Scheme 5. Application for the Preparation of an Important Intermediate of IAP Antagonist



the first example of the construction of two contiguous stereocenters in a cyclic structure using such a strategy. The reaction could be carried out on a gram scale and was further applied to an asymmetric synthesis of a key intermediate required for the preparation of a potent IAP antagonist.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00212.

Synthetic details for substrates, procedures for hydrogenation reactions, spectra of NMR and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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