Asymmetric Catalysis

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Dynamic Kinetic Resolution Allows a Highly Enantioselective Synthesis of *cis*-α-Aminocycloalkanols by Ruthenium-Catalyzed Asymmetric Hydrogenation**

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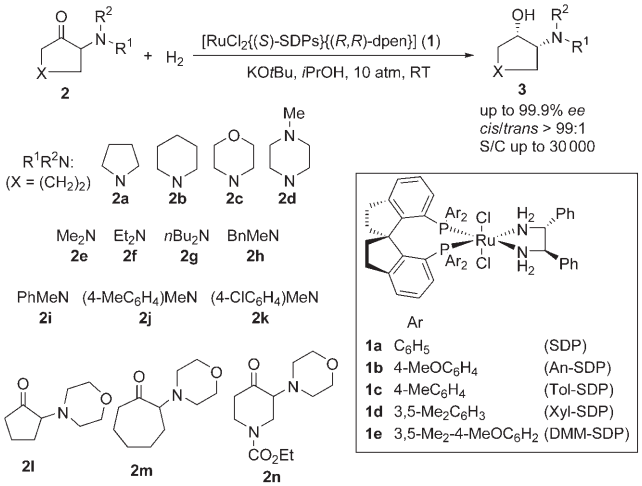
Chiral amino alcohols are essential structural units in natural products and key functional groups in biologically active molecules, and optically pure amino alcohols have been used as chiral ligands and auxiliaries in asymmetric synthesis.[1] The synthesis of enantiomerically enriched chiral amino alcohols has attracted considerable attention in the past few decades and various methods for the enantio- and diastereoselective preparation of these compounds have been reported.[2]

The asymmetric hydrogenation of amino ketones is without doubt one of the most efficient methods for synthesizing chiral amino alcohols.[3] Kumada and co-workers reported the first asymmetric hydrogenation of amino ketones with Rh complexes of ferrocenylphosphanes as catalysts in 1979,[4] and since then many other catalysts, including Rh[5] and Ru complexes,[6] have been developed. The hydrogenation of amino ketones by dynamic kinetic resolution (DKR) has also been achieved,[7] although the scope of this reaction is limited to the use of acyclic amino ketones as substrates.

To our knowledge, the only example of the asymmetric hydrogenation of cyclic amino ketones was reported in 2000 by Noyori, Ohkuma, and co-workers who used [$RuCl_2$((*S*)-Xyl-binap)((*R*)-daipen)] (Xyl-binap = 2,2′-bis[di(3,5-xylyl)-phosphino]-1,1′-binaphthyl; daipen = 1,1-bis[4-methoxyphenyl)-3-methyl-1,2-butanediamine) as a catalyst to hydrogenate racemic 2-(*tert*-butoxycarbonylamino)cyclohexanone by DKR, with a substrate to catalyst (S/C) ratio of 300, to provide the corresponding amino alcohol with 82% *ee* and 98% *cis* selectivity.[7e] In light of the importance of the products and the need for an improvement in the enantioselectivity and the substrate scope, an efficient asymmetric hydrogenation of cyclic amino ketones is therefore still required.

We have recently synthesized a series of [$RuCl_2$(SDPs)-(diamine)] (SDP = 7,7-bis(diarylphosphino)-1,1′-spirobiindane) complexes[8] that give high enantioselectivities and diastereoselectivities in the asymmetric hydrogenation of α-aryl-substituted ketones and aldehydes by DKR.[9] Herein we focus on the asymmetric hydrogenation of racemic α-aminocycloalkanones because the corresponding products, *cis*-α-aminocycloalkanols, are of great interest for the synthesis of various biologically active compounds.[1,10] Existing methods for the enantioselective synthesis of *N*,*N*-disubstituted *cis*-α-aminocycloalkanols are rather difficult and tedious.[11] We describe a simple and highly efficient method for preparing optically active *N*,*N*-disubstituted *cis*-α-aminocycloalkanols by the ruthenium-catalyzed asymmetric hydrogenation of racemic α-aminocycloalkanones by DKR. The enantioselectivities (up to 99.9% *ee*) and *cis* diastereoselectivities (*cis*/*trans* > 99:1) obtained are excellent with S/C ratios up to 30000 (Scheme 1).



Scheme 1. [$RuCl_2$(SDPs)(dpen)]-catalyzed asymmetric hydrogenation of racemic dialkylaminocycloalkanones by DKR. dpen = *trans*-1,2-diphenylethylenediamine.

Racemic 2-(pyrrolidin-1-yl)cyclohexanone (**2a**) was first hydrogenated in *i*PrOH containing (*S*,*RR*)-**1a** and KO*t*Bu (S/C = 1000, [**2a**] = 0.6 M, [KO*t*Bu] = 0.06 M) under H_2 (10 atm) at room temperature for 2 h. This substrate was fully converted and the hydrogenation product (1*S*,2*R*)-**3a** was obtained in 90% yield with extremely high enantioselectivity (99.8% *ee*) and *cis* diastereoselectivity (*cis*/*trans* > 99:1; Table 1, entry 1). Complexes (*S*,*RR*)-**1b**–**e** are also good catalysts for this transformation, although (*S*,*RR*)-**1e**, which has 4-methoxy-3,5-dimethylphenyl groups on the phosphorus

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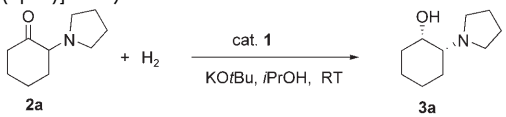
Table 1: Asymmetric hydrogenation of racemic **2a** with the [$RuCl_2$(SDPs)(dpen)] catalysts **1**.[a]



Entry	Catalyst	Diphosphine	*t* [h]	*cis*/*trans*[b]	*ee* [%][c]
1	(*S*,*RR*)-**1a**	(*S*)-SDP	2	>99:1	99.8
2	(*S*,*RR*)-**1b**	(*S*)-Tol-SDP	2	>99:1	99.5
3	(*S*,*RR*)-**1c**	(*S*)-An-SDP	2	>99:1	99.9
4	(*S*,*RR*)-**1d**	(*S*)-Xyl-SDP	2	>99:1	99.7
5	(*S*,*RR*)-**1e**	(*S*)-DMM-SDP	2	96:4	96
6[d]	(*S*,*RR*)-**1a**	(*S*)-SDP	24	>99:1	99.8
7[e]	(*S*,*RR*)-**1a**	(*S*)-SDP	48	>99:1	99.8

[a] Reaction conditions: S/C = 1000, [**2a**] = 0.6 M, [KO*t*Bu] = 0.06 M, P_{H_2} = 10 atm, *i*PrOH, 18–25 °C; 100% conversion. [b] Determined by GC. [c] Determined by chiral GC (Supelco α-DEX 120 column). The absolute configuration is (1*S*,2*R*). [d] S/C = 10000, 50 atm of H_2. [e] S/C = 30000, 50 atm of H_2.

atoms of the SDP ligand, gave a slightly lower enantioselectivity (96% *ee*) and *cis* diastereoselectivity (*cis*/*trans* = 96:4; Table 1, entry 5). Complex (*S*,*RR*)-**1a** is highly active and allows the reaction to be performed at a very low catalyst loading (S/C = 30000; Table 1, entry 7).

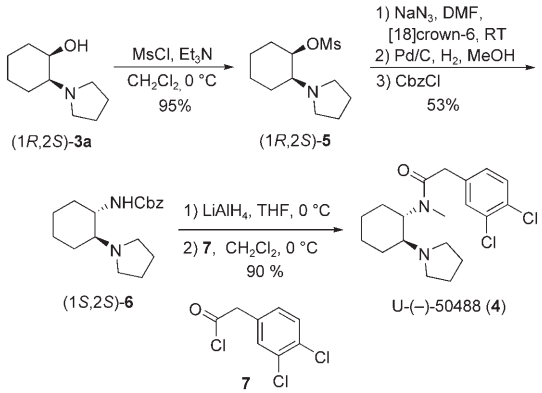
The reactivity of a series of racemic α-dialkylaminocycloalkanones **2a**–**h** was then explored with (*S*,*RR*)-**1a** as catalyst. Hydrogenation of all these substrates yielded the corresponding *cis*-α-dialkylaminocycloalkanols **3a**–**h** with excellent enantioselectivities and *cis* diastereoselectivities (Table 2). This result indicates a high tolerance of the reaction for different substituents on the dialkylamino group in terms of both enantioselectivity and diastereoselectivity. The reaction rate, however, is sensitive to the dialkylamino group of the substrates. Thus, with a benzylmethylamino group (BnMeN, **2h**), the hydrogenation required 72 h at a pressure of 50 atm for complete conversion (Table 2, entry 8). Changing the dialkylamino groups for arylalkylamino groups also lowered the reaction rate (Table 2, entries 9–11). The enantioselectivity of this hydrogenation decreased slightly when the ring of the substrate contained more or fewer atoms, such as in **2l** and **2m** (Table 2, entries 12 and 13, respectively), while the aza analogue **2n** of α-dialkylaminocyclohexanone provided the corresponding hydrogenation product with excellent enantioselectivity and *cis* diastereoselectivity (Table 2, entry 14).

Table 2: Asymmetric hydrogenation of racemic *N*,*N*-disubstituted α-aminocycloalkanones **2** catalyzed by (*S*,*RR*)-**1a**.[a]

Entry	Substrate	*t* [h]	Product	*cis*/*trans*[b]	*ee* [%][c]
1	**2a**	2	**3a**	>99:1	99.8
2	**2b**	2	**3b**	>99:1	99
3	**2c**	2	**3c**	>99:1	99.9
4	**2d**	3	**3d**	>99:1	99.6
5	**2e**	2.5	**3e**	>99:1	99.9
6	**2f**	3	**3f**	>99:1	99
7	**2g**	5	**3g**	>99:1	99.6
8[d]	**2h**	72	**3h**	>99:1	99
9	**2i**	10	**3i**	>99:1	99.3
10	**2j**	10	**3j**	>99:1	99.6
11	**2k**	10	**3k**	>99:1	99.6
12	**2l**	4	**3l**	>99:1	98
13	**2m**	6	**3m**	>99:1	97
14	**2n**	6	**3n**	>99:1	99.9

[a] The reaction conditions are the same as those in Table 1, entry 1; 100% conversion was obtained for all reactions. [b] Determined by GC or HPLC. [c] Determined by chiral GC, HPLC, or SFC (see the Supporting Information). [d] 50 atm of H_2.

The enantioselective synthesis of *N*,*N*-disubstituted *trans*-cycloalkane-1,2-diamines, an important class of chiral compounds in the pharmaceutical industry, is a challenging task.[12] For example, in their synthesis of U-(−)-50488 (**4**), which is a highly selective κ-opioid agonist, Gotor, Rebolledo, and González-Sabín attempted to convert optically pure *trans*-2-(pyrrolidin-1-yl)cyclohexanol into *trans*-2-(pyrrolidin-1-yl)cyclohexanamine but obtained a racemic product. Optically pure (1*S*,2*S*)-*trans*-2-(pyrrolidin-1-yl)cyclohexanamine was finally achieved by enzymatic resolution.[12b] We found that (1*R*,2*S*)-**3a** (99.8% *ee*), which we obtained by hydrogenating the corresponding ketone in the presence of catalyst (*R*,*SS*)-**1a**, is a convenient starting material for the synthesis of **4** (Scheme 2). The synthetic route begins with the reaction



Scheme 2. Enantioselective synthesis of U-(−)-50488 (**4**).

of (1*R*,2*S*)-**3a** with MsCl in the presence of Et_3N to provide mesylate (1*R*,2*S*)-**5** in 95% yield. Nucleophilic substitution of the mesyl group of (1*R*,2*S*)-**5** with NaN_3, followed by hydrogenation with Pd/C under H_2 (3 atm) and protection with benzyl chloroformate (CbzCl), produced the *trans*-1,2-diamine (1*S*,2*S*)-**6** in 53% yield with 99.5% ee.[13] This result shows that substitution of the mesyl group in (1*R*,2*S*)-**5** proceeds by a simple S_N2 mechanism with no formation of an aziridinium ion.[12b] This outcome can be attributed to the positioning of the pyrrolidino group in compound (1*R*,2*S*)-**5** on the same side as the mesyl group, a configuration which is unfavorable for the formation of an aziridinium ion. Compound (1*S*,2*S*)-**6** was then reduced with $LiAlH_4$ and the reduction product treated with 2-(3,4-dichlorophenyl)acetyl chloride (**7**) to furnish U-(−)-50488 (**4**) in 90% yield.

In summary, we have reported a highly enantioselective and diastereoselective synthesis of *N*,*N*-disubstituted *cis*-α-aminocycloalkanols that involves the ruthenium-catalyzed asymmetric hydrogenation of racemic α-aminocycloalka-

nones and DKR. Additionally, we have developed a practical approach to U-(−)-50488 starting from an asymmetric hydrogenation product, namely a *cis*-2-aminocycloalkanol.

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[13] $[\alpha]_D^{20} = +50.2$ ($c = 1.05$, $CHCl_3$) for (1*S*,2*S*)-**6**. Ref. [12b]: $[\alpha]_D^{20} = +49.2$ ($c = 1.05$, $CHCl_3$) for 99% *ee*.

