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Highly Enantioselective and Diastereoselective Synthesis of Chiral Amino Alcohols by Ruthenium-Catalyzed Asymmetric Hydrogenation of α-Amino Aliphatic Ketones

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Transition metal catalyzed asymmetric hydrogenation holds a venerable position in organic synthesis.[1] The catalytic asymmetric hydrogenation of configurationally labile substrates containing carbon−oxygen double bonds via dynamic kinetic resolution (DKR) is a highly efficient method to create simultaneously two or more stereogenic centers in a single synthetic step.[2] Initiated by Noyori[3] and Genêt[4] in the asymmetric hydrogenation of α-substituted β-ketoesters, the Ru-catalyzed asymmetric hydrogenation via DKR has become a useful synthetic method.[5] Recently, [$RuCl_2$(diphosphine)(diamine)] complexes have been proven to be the most efficient catalysts for this transformation.[6] In the hydrogenation of racemic α-substituted cycloalkanones, [$RuCl_2$(diphosphine)(diamine)] catalysts provided the chiral cycloalkanols in excellent enantio- and diastereoselectivities.[6c−6e] Good results have also been achieved by the same catalysts in the asymmetric hydrogenation of racemic α-substituted aromatic ketones such as α-amidopropiophenones.[6f] However, the asymmetric hydrogenation of the conformationally flexible substrates such as acyclic α-substituted aliphatic ketones has been far from successful.[6g]

Asymmetric hydrogenation of α-amino ketones represents one of the most elegant approaches to chiral 1,2-amino alcohols,[1,7] one of the prevailing structural motifs found in a vast array of biologically active molecules.[8] Recently, we demonstrated that the [$RuCl_2$((*S*)-SDPs)((*R*,*R*)-diamine)][9] complexes were efficient catalysts for the asymmetric hydrogenation of racemic α-dialkylamino cycloalkanones via DKR, providing a highly enantio- and diastereoselective method for preparing optically active *cis*-β-amino cycloalkanols.[6e] Encouraged by this result, we therefore intend to study the asymmetric hydrogenation of more difficult acyclic substrates, racemic α-amino aliphatic ketones with [$RuCl_2$(SDPs)(diamine)] catalysts (Scheme 1).

Initially, we chose [$RuCl_2$((*S*)-SDP)((*R*,*R*)-DPEN)] ((*S*,*RR*)-**1a**) as the catalyst, which has been proven to be very efficient for asymmetric hydrogenation of racemic α-amino cycloalkanones,[6e] and the α-pyrrolidinyl-1-arylpropan-2-one (**2a**) as the standard substrate. When the hydrogenation was performed in 2-propanol in the presence of ^{t}BuOK (S/C = 1000, [**2a**] = 0.2 M, [^{t}BuOK] = 0.04 M) under 10 atm of H_2 at room temperature for 5 h, the substrate **2a** was fully converted and the hydrogenation product (1*R*,2*S*)-**3a** was obtained in 94% yield with 98% ee and high diastereoselectivity (*anti*/*syn* 97:3). However, when the hydrogen pressure was increased to 50 atm, the enantioselectivity and *anti*/*syn* selectivity were improved to 99.9% ee and 99:1 (Table 1, entry 1). Ligand comparison showed that the substituents on the *P*-phenyls of the SDPs ligands **1** have no apparent effect on the enantioselectivity (98−99.9% ee) and diastereoselectivity (98:2− 99:1) or on the reactivity of reaction. The high efficiency of the catalyst (*S*,*R*,*R*)-**1a** was further demonstrated in an experiment with a low catalyst loading (0.01 mol%, S/C = 10 000), giving identical ee and dr values of product, albeit the reaction required a longer time (24 h).

Scheme 1. [$RuCl_2$-((*S*)-SDPs)((*R*,*R*)-DPEN)] Catalyzed Asymmetric Hydrogenation of Racemic α-Amino Aliphatic Ketones via DKR

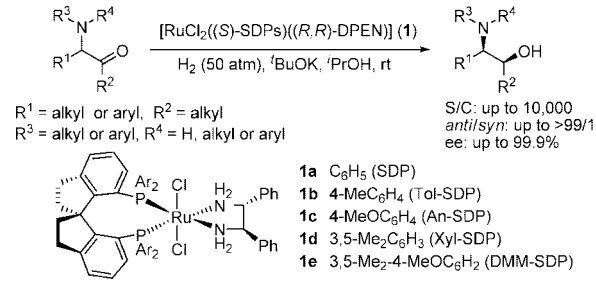

Table 1. Asymmetric Hydrogenation of Racemic α-Dialkylamino Aliphatic Ketones **2** Catalyzed by (*S*,*R*,*R*)-**1a**[a]

entry	R^1	R^2	R^3, R^4	prod.	*anti*/*syn*[b]	ee (%)[c]
1	C_6H_5	Me	$(CH_2)_4$	**3a**	>99:1	99.9
2	C_6H_5	Me	$(CH_2)_5$	**3b**	95:5	99
3	C_6H_5	Me	$C_2H_4OC_2H_4$	**3c**	96:4	99.9
4	C_6H_5	Me	$C_2H_4N(Me)C_2H_4$	**3d**	>99:1	99
5	C_6H_5	Me	Me, Me	**3e**	>99:1	99.9
6[d]	C_6H_5	Me	Et, Et	**3f**	71:29	99.9
7	C_6H_5	Et	$(CH_2)_4$	**3g**	96:4	99.3
8	4-$MeOC_6H_4$	Me	$(CH_2)_4$	**3h**	95:5	99.9
9	4-ClC_6H_4	Me	$(CH_2)_4$	**3i**	>99:1	99
10[e]	4-BrC_6H_4	Me	$(CH_2)_4$	**3j**	>99:1	99.2
11	3-$MeOC_6H_4$	Me	$(CH_2)_4$	**3k**	95:5	98
12	3-MeC_6H_4	Me	$(CH_2)_4$	**3l**	>99:1	99.4
13	2-$MeOC_6H_4$	Me	$(CH_2)_4$	**3m**	99:1	99.6
14	2-ClC_6H_4	Me	$(CH_2)_4$	**3n**	92:8	99.9
15	2-BrC_6H_4	Me	$(CH_2)_4$	**3o**	94:6	99.6
16	2,3-$(CH)_4C_6H_3$	Me	$(CH_2)_4$	**3p**	>99:1	98
17	3.4-$(OCH_2O)C_6H_3$	Me	$C_2H_4OC_2H_4$	**3q**	95:5	99
18	Me	Me	$(CH_2)_4$	**3r**	97:3	97
19	Me	Et	$C_2H_4OC_2H_4$	**3s**	89:11	93

[a] Reaction conditions: (*S*,*R*,*R*)-**1a**/**2**/^{t}BuOK=1/1000/200, 5 h, 100% conv. >90% isolated yield. [b] Determined by GC or HPLC. [c] Ee of *anti*-isomer determined by HPLC. [d] 57% ee for *syn*-isomer. [e] The configuration of the product **3j** is (1*R*,2*S*) determined by X-ray analysis.

A variety of racemic acyclic α-*N*,*N*-dialkylamino aliphatic ketones **2** can be hydrogenated under the optimal conditions, and complete conversions and excellent enantioselectivities were obtained in all reactions (Table 1). The α-dialkylamino group of the substrates imposed a significant influence on the diastereoselectivity of the reaction. Generally, the ketones **2** having a small dialkylamino group such as dimethylamino or pyrrolidinyl provided high diastereoselectivities. However, when a bulkier diethylamino group was introduced into the substrate the reaction produced a low diastereoselectivity (entry 6). The diastereoselectivity of the hydrogenation of ketones **2s** (R^1 = Me, R^2 = Et) was also lower (entry 19). It is worth mentioning that the product **3q** can serve as a novel analgesic (Filenadol)[10] and the current hydrogenation reaction provides a practical and enantioselective approach to this important compound.

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Table 2. Asymmetric Hydrogenation of Racemic α-*N*-Alkyl/Arylamino Aliphatic Ketones **4** (R^4 = H)[a]

entry	R^1	R^2	R^3	prod.	time (h)	*anti/syn*[b]	ee (%)[b]
1	C_6H_5	Me	C_6H_5	**5a**	10	97:3	96
2	C_6H_5	Me	^{i}Pr	**5b**	1	>99:1	99
3[c]	Me	Me	C_6H_5	**5c**	2	>99:1	96
4	Me	Me	$C_6H_5CH_2$	**5d**	8	92:8	92
5	Me	Me	*c*-C_6H_{11}	**5e**	2	99:1	96
6	Me	Et	*c*-C_6H_{11}	**5f**	6	91:9	90
7	Et	Me	C_6H_5	**5g**	4	95:5	95
8	Et	Me	$C_6H_5CH_2$	**5h**	10	95:5	97

[a] Reaction conditions are the same as those in Table 1. 100% conv. >90% isolated yield. [b] For analyses, see Supporting Information. [c] Catalyst [$RuCl_2$((*S*)-BINAP)((*S*,*S*)-DPEN)] gave product **5c** with 85% ee and 92:8 of *anti*/*syn* selectivity in 6 h.

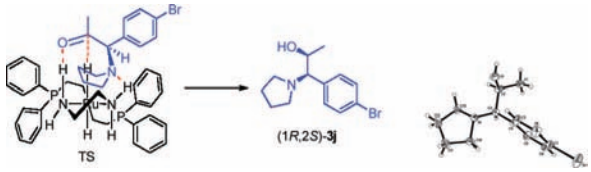

Figure 1. Proposed model for asymmetric hydrogenation of α-aminodialkylketones.

We next evaluated the asymmetric hydrogenation of racemic acyclic α-*N*-alkyl/arylamino aliphatic ketones. To date, no direct preparation of chiral β-amino alcohols from the Ru-catalyzed asymmetric hydrogenation of α-*N*-alkyl/arylamino aliphatic ketones has been reported.[11] The difficulty for this reaction presumably arose from the unprotected amino group, which coordinated to the ruthenium center of the catalyst, resulting in a low catalytic activity.[6a,11a] The great rigidity and steric hindrance of spiro diphosphine ligand may prevent the coordination of the NH group of α-*N*-alkyl/arylamino aliphatic ketones with the metal of the catalyst $RuCl_2$(SDPs)(diamine), thereby making the asymmetric hydrogenation of α-*N*-alkyl/arylamino aliphatic ketones possible. Based on this supposition, we investigated the hydrogenation of racemic α-*N*-alkyl/arylamino aliphatic ketones **4** with catalyst (*S*,*R*,*R*)-**1a**. As illustrated in Table 2, under the established reaction conditions, different types of racemic α-*N*-alkyl/arylamino aliphatic ketones **4** can be hydrogenated to the corresponding amino alcohols **5** in high enantioselectivities (>90% ee) and high *anti*-selectivities (>91:9), showing that the catalyst (*S*,*R*,*R*)-**1a** is effective with a wide scope of substrates.

The products of this hydrogenation reaction, β-*N*,*N*-dialkyl-amino alcohols, can be easily converted to 1,2-diamines, which are also important building blocks for the synthesis of chiral drugs.[12] For example, the reaction of amino alcohol (1*R*,2*S*)-**3a** (99.9% ee) with MsCl in the presence of Et_3N, followed by a treatment with $NH_3 \cdot H_2O$, afforded the diamine (1*S*,2*R*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-amine ((1*S*,2*R*)-**6**) in 80% yield with 99.2% ee. The configuration of (1*S*,2*R*)-**6** was determined by X-ray analysis of a single crystal of its 4-bromobenzenesulfonamide (see Supporting Information, SI), obviously indicating that this transformation took place through an aziridinium intermediate.

It is interesting that both enantio- and diastereoselectivities of the hydrogenation of acyclic α-amino aliphatic ketones are significantly higher than those obtained by the hydrogenations of α-alkyl substituted aliphatic ketones and α-*N*-acylamino aliphatic ketones.[13] To explain the higher selectivity achieved with acyclic α-amino aliphatic ketones, we proposed a transition state model (TS) which undergoes a hydrogen bond formation between the dialkyl-amino group of the substrate and the NH_2 group of the chiral diamine in the catalyst (Figure 1). Based on Noyori's metal−ligand bifunctional mechanism,[14] the hydridic Ru−H and protic $N-H_{ax}$ of the catalyst are simultaneously transferred to the carbon−oxygen double bond *via* a six-membered transition state, and the additional hydrogen bonding between the dialkylamino group of substrate and the protonic $N-H_{eq}$ of catalyst is beneficial to increasing the selectivities.[15] Thus, the hydrogenation favors the formation of the *anti*-isomer with 1*R*,2*S* configuration, which is consistent with the absolute configuration of (1*R*,2*S*)-**3j** determined by X-ray analysis (see SI). The substrate with a bulkier dialkylamino group, such as Et_2N (**3f**), gave a lower diastereoselectivity, perhaps due to its steric hindrance, which impeded the hydrogen-bonding formation.

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Supporting Information Available: Experimental procedures, the characterizations of substrates and products, the analysis of ee values of hydrogenation products, and full ref 6g. This material is available free of charge via the Internet at http://pubs.acs.org.

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