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Cobalt-mediated Reduction of C=N Bond. Synthesis of Methyl *N*-*p*-Toluenesulfonyl-1-phenylglycinate Catalyzed by Bis(dioximato)cobalt-Quinine Complexes

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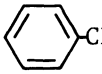
Reduction of C=N bond mediated by cobalt complxes was facilitated by the electron withdrawing substituents on the substrate. Catalytic hydrogenation of methyl *N*-*p*-toluenesulfonyl-1-imino-1-phenylacetate in the presence of quininiun salt afforded the corresponding *N*-tosyl amino ester in good yields.

As an important unit process in organic synthesis, homogeneous catalytic hydrogenation of unsaturated compounds attracted attention, especially in relevance to asymmetric synthesis. Although many catalyst systems have been developed for reduction of C=C or C=O bond, some of which attained nearly quantitative enantioselectivity[1] by the use of a small amount of chiral catalyst, many of these catalysts were ineffective for the hydrogenation of C=N bond and this field of research has been left relatively unexplored.[2] Nevertheless, importance of this reaction has increased recently since a facile process for the synthesis of derivatives of α-keto acid was developed by palladium-catalyzed double carbonylation of organic halides,[3] which brings forth a strategy for the synthesis of chiral α-amino acid by imination of α-keto acid and subsequent asymmetric hydrogenation of the resultant C=N bond. In this context, we examined the homogeneous hydrogenation of C=N bond mediated by cobalt complexes, and found a smooth catalytic reaction with methyl *N*-*p*-toluenesulfonyl-1-imino-1-phenylacetate (1) as the substrate under atmospheric pressure of hydrogen.

Because the catalytic reduction did not proceed smoothly with every C=N compound, the effect of substituents on the reduction of C=N bond was examined first by using a stoichiometric amount of bis(dimethylglyoximato)pyridinecobaltate(I), $Na[Co(DH)_2(py)]$ (2). In a typical procedure, the imino compound was added to the solution of Co(I) prepared by BH_4^- reduction of Co(III) complex under Argon. After stirring the solution under hydrogen overnight, the product was separated over silica-gel column. The results summarized in Table 1 indicate that the reaction was facilitated with the electron withdrawing substituent on both the C and N sides of C=N bond and *N*-tosyliminoester 1 was the most reactive substrate examined. Use of *p*-toluenesulfonyl group as the substituent is preferred[4] also from the other respect that, as a well known

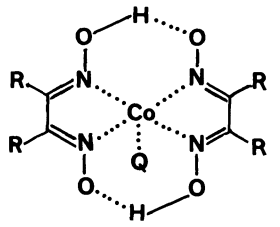
Table 1. Stoichiometric Reduction of C=N Bond with Na[Co(DH)$_2$(py)] (2)[a]

R^1-C(=NR^3)-R^2			Solvent	R^1-CH(NHR^3)-R^2
R^1	R^2	R^3		Yield/%[b]
Phenyl	H	Phenyl	THF/MeOH (5/2)	12
Phenyl	H	OMe	THF/MeOH (5/2)	0
Phenyl	H	Tosyl	CH_2Cl_2/MeOH (5/2)	52
Phenyl	H	Tosyl	THF/MeOH (5/2)	60
Phenyl	Me	Tosyl	CH_2Cl_2/MeOH (5/2)	24
Phenyl	Et	Tosyl	THF/MeOH (5/2)	42
 CH=CH-	H	Tosyl	THF/MeOH (5/2)	53
Phenyl	COOMe	Tosyl	THF/MeOH (5/2)	74

a) Na[Co(DH)$_2$(py)]/Substrate = 1.1; Addition of 2 at -10 °C under Ar. Stirring under H_2 at -10 °C-room temperature for 17 h. b) Isolated yield.

protecting group of amino acids, it can be easily removed from the hydrogenation product for generating free amino acid.[5]

Then the catalytic hydrogenation was examined with catalysts 3a-e by using 1 as the substrate. The reaction proceeded smoothly to yield methyl *N*-*p*-toluenesulfonyl-1-phenylglycinate (4) in good yields under the atmospheric pressure of hydrogen at room temperature in the presence of quininium salts as listed in Table 2. As far as we know, this is the first example of successful synthesis of amnino acid derivative by homogeneous catalytic hydrogenation of C=N bond.[6] The reactivity of catalyst was not influenced much by the substituents in the equatorial ligands. Other substrates in Table 1 were unreactive under the catalytic reaction conditions of atomospheric pressure of hydrogen.[7] Furthermore, the reduction of 1 did not proceed when quininium salt was replaced by quinine. The present reduction could be complementary to the well known



Q = quinine

3

a R = Me
b R = *i*-Bu
c R = Ph
d R,R = $-(CH_2)_4-$
e R,R = 

Table 2. Asymmetric Hydrogenation of 1 by Cobaloxime Quinine Complex[a)]

Entry	Catalyst[b)]	Solvent	Product (4)		
			Chemical yield[c)] %	Optical yield %	Config.
1	3a + Q·HOCOCH$_3$	Methanol	88	14	*R* (-)
2[d)]	3a + Q·HOCOCH$_3$	Dichloromethane	81	5.8	*S* (+)
3	3a + Q·HOCOCH$_3$	Benzene	82	16	*S* (+)
4	3b + Q·HOCOCH$_3$	Benzene	79	19	*S* (+)
5	3c + Q·HOCOCH$_3$	Benzene	76	16	*S* (+)
6	3d + Q·HOCOCH$_3$	Benzene	86	9.1	*S* (+)
7	3a + Q·HCl	Benzene	82	20	*S* (+)
8	3e + Q·HCl + 1-Methylimidazole[e)]	Methanol	75	7.3	*R* (-)

a) Reaction condition: 1, 2.0 mmol; 3, 0.5 mmol (prepared *in situ* from corresponding salts and DH_2); Q, 1.0 mmol; in solvent (10 ml); 40 h under H_2 (1 kg/cm^2) . *b*) Catalyst was prepared from $Co(OCOCH_3)_2$ (entries 1-6) or $CoCl_2$ (entries 7,8). *c*) Isolated yield. *d*) The reaction was run for 17 h. *e*) 1-Methylimidazole (0.5 mmol) was added.

rhodium-catalyzed reduction of C=C bond in amino acid synthesis, since some amino acids such as 1-phenylglycine is not available by the hydrogenation of C=C bond.

As for the asymmetric synthesis, the obtained maximum optical yield was moderate as high as 20%,[8)] but nevertheless the value is near to the highest of the reported asymmetric hydrogenation of C=N bonds.[9)] The optical yield of product around 60% was reported for the reduction of $C_6H_5C(CH_3)=NCH_2C_6H_5$ by the use of [Rh(NBD)Cl] -chiral diphosphine catalyst, but unfortunately, the reproducibility of the result was poor.[10)] As the results in Table 2 show, the optical yield of the product was dependent on the polarity of the solvent under our reaction conditions. While the configuration of the prevailing product was *R*-(-)-4 in methanol, it turned into *S*-(+)-4 in benzene with almost the same absolute value of optical rotation. An intermediate value was observed in dichloromethane. These results are similar to those observed for the Rh(DIOP)-catalyzed hydrogenation of C=C bond in 1-acetylamino-1-phenylethylene.[11)]

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7) The catalytic hydrogenation of *N*-unsubstituted-1-imino acid such as 1-imino-2-phenylpropionic acid (prepared *in situ* by mixing the corresponding keto-acid with aqueous ammonium hydroxide) was unsuccessful under the catalytic influence of 3a, producing only a low yield of amino acid (2%). Reduction of a mixture of methyl benzoylformate and NH_3 in the presence of 3a yielded only methyl 1-hydroxy-1-phenylacetate (59%) instead of an α-amino ester. Substituted imino esters with an electron releasing group on nitrogen such as PhC(=NR)COOCH (Ph=phenyl, R=OH, or O(mesyl)) were all unchanged under the catalytic reaction conditions examined.

8) The authentic sample of methyl *N*-*p*-toluenesulfonyl-(-)-1-phenylglycinate was synthesized by esterification of (-)-1-phenylglycine in methanol followed by the reaction with tosyl chloride in the presence of pyridine, $[\alpha]_D^{25}$ -113.6°C (c 2.33, $CHCl_3$).

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