Asymmetric Catalysis

Direct Proline-Catalyzed Asymmetric α-Aminoxylation of Ketones**

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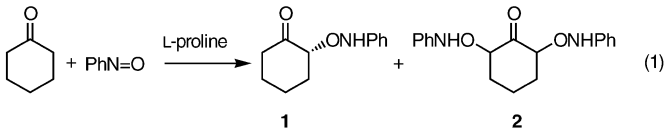
Optically active α-hydroxy carbonyl compounds, important building blocks in organic synthesis, can be prepared by several methods such as the electrophilic α-hydroxylation of enolates using chiral oxaziridines as the oxidizing agent.[1] As for methods based on asymmetric catalytic reactions, there are several, including the asymmetric dihydroxylation of enol ethers developed by Sharpless et al.,[2] the asymmetric epoxidation of silyl enol ethers with a chiral dioxirane,[3] and the asymmetric epoxidation of enol ether with a chiral Mn–salen catalyst.[4] Recently Yamamoto et al. have developed an excellent asymmetric, catalytic nitroso-aldol reaction:[5] a catalytic amount of a binap–AgOTf complex promotes the reaction of tin enolate and nitrosobenzene, affording an α-aminoxy ketone, which is easily converted into the α-hydroxy ketone. In most of these reactions, however, the ketones must be converted into isolable enolate or enol derivatives, and there is as yet no direct catalytic method for the synthesis of chiral α-hydroxy ketones from the corresponding ketones. In this communication, we disclose the direct catalytic enantioselective α-aminoxylation of ketones, which is complementary to the recent asymmetric α-aminoxylation of aldehydes.[6]

Proline[7] has been found to be an excellent catalyst of asymmetric aldol[8] and Mannich reactions[9] and of the asymmetric α-amination of carbonyl compounds.[10] In our continuing research on asymmetric reactions catalyzed by proline,[6c,9c,11] we have found the asymmetric α-aminoxylation of a ketone: The reaction of cyclohexanone and nitrosobenzene was conducted in dimethyl sulfoxide (DMSO) at room temperature in the presence of a catalytic amount of L-proline. The desired α-aminoxylated cyclohexanone **1** was obtained in 31% yield, along with the α,α′-diaminoxylated product **2** in 11% yield [Eq. (1)]. Dimerized nitrosobenzene



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[**] This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Prof. K. Tachibana and Dr. S. Fukuzawa, The University of Tokyo, for measurement of CD spectra and T. HASEGAWA Co., LTD. for chiral GC analysis.

  DOI: 10.1002/anie.200353085

was also generated. This α-aminoxylation is readily accomplished in highly polarized solvents such as DMSO, dimethylformamide (DMF), CH_3NO_2, *N*-methylpyrrolidinone (NMP), and CH_3CN, affording the α-aminoxylated product in 26–37% yield with excellent enantioselectivity (>99% *ee*, Table 1). As the best yield was obtained for the reaction in DMF, further investigations were performed with this solvent.

Slow addition of nitrosobenzene was found to be crucial for obtaining a high yield without affecting the enantioselectivity. That is, addition of nitrosobenzene by syringe pump to a solution of cyclohexanone and 10 mol% proline effectively suppresses both homodimerization of nitrosobenzene and α,α′-diaminoxylation, affording **1** in 77% yield with >99% *ee* (Table 2, entry 2). No α-hydroxyamino ketone, a major product in the reaction of nitrosobenzene with a variety of alkali metals or tin enolates,[12] is formed at all.

As the best reaction conditions had been established, the generality of the reaction was examined (Table 2). 1,4-Cyclohexanedione monoethylene ketal and 4,4-dimethylcyclohexanone were transformed into the α-aminoxylated cyclohexanones in good yield with very high enantioselectivity (entries 4–6).[13] Not only cyclohexanones, but also tetrahydro-4*H*-pyran-4-one and 1-methyl-4-piperidinone were successfully employed in this reaction, affording α-aminoxylated compounds with moderate yield and excellent enantioselectivity (entries 7 and 8). In the reaction of 1-methyl-4-piperidinone, CH_3NO_2 was used as solvent instead of DMF, owing to the difficulty of separating the product from the solvent. It is noteworthy that the basic tertiary amine moiety has no detrimental effect on the proline catalyst. Though the reactivity of acyclic ketones is different from that of cyclic ketones under our conditions, the aminoxylated product is generated in moderate yield: 2-Butanone reacts with nitrosobenzene in DMSO at room temperature, affording 2-aminoxy-3-butanone in 40% yield with >99% *ee*, together with the hydroxyaminated product in 33% yield with 4% *ee* (entry 9). It is noteworthy that hydroxyaminated product is racemic and that the possible regioisomer, 1-aminoxy-2-butanone, was not formed at all.

Though the optimum addition time for nitrosobenzene varies according to the ketone, in the case of cyclic ketones a good yield is generally obtained using addition over 24 h when 10 mol% of proline is employed, while addition over 2 h affords a moderate yield in the reaction of 2-butanone. The catalyst loading can be reduced to 5 mol% without significant loss in yield and enantioselectivity, but a longer reaction time is required (entry 5).

The conversion of **1** into α-hydroxycyclohexanone was successfully carried out in 87% yield with only partial racemization (>99% *ee*→96% *ee*[14]) by treatment with $CuSO_4$,[5] and the stereochemistry of the product was determined to be *R* by comparison with the literature.[15] This was also confirmed after conversion to (−)-1,2-cyclohexanediol[16] by the reduction with $NaBH_4$. The transition state model shown in Figure 1,

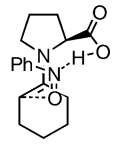
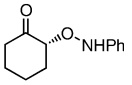
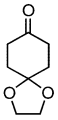
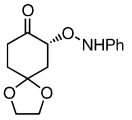
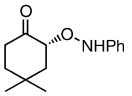
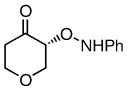
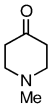
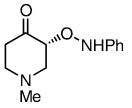
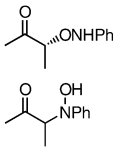


Figure 1. The transition-state model for the L-proline-catalyzed α-aminoxylation of cyclohexanone.

Table 2: Aminoxylation of various ketones.[a]

Entry	Ketone	Product	Cat. [mol%]	Add. time [h]	Yield [%][b]	*ee* [%]
1			30	5.5	79	>99[c]
2			10	5.5	77	>99[c]
3			30	12	96	>99[d]
4			10	24	93	>99[d]
5			5	60	86	>99[d]
6			10	24	84	>99[d]
7			10	24	53	96[c]
8[e]			10	24	44	99[c]
9[f]			10	2[g]	40, 33	>99[d], 4[d]

[a] Unless otherwise shown, reactions were conducted with 10 mol% catalyst, 1.0 equiv nitrosobenzene, and 2.0 equiv ketone in DMF at 0°C with slow addition of nitrosobenzene. [b] Yield of isolated product. [c] Determined by HPLC using a Chiralpak AD-H column. [d] Determined by HPLC using a Chiralpak OD-H column. [e] CH_3NO_2 was used as solvent. [f] The reaction was conducted with 10 mol% catalyst, 1.0 equiv nitrosobenzene, and 10.0 equiv ketone in DMSO at room temperature. [g] After addition of nitrosobenzene, the reaction mixture was stirred for a further 4 h at room temperature.

Table 1: Solvent effect on the α-aminoxylation of cyclohexanone.[a]

Entry	Solvent	Yield [%][b]		*ee* [%] of **1**[c]
		1	**2**	
1	DMSO	31	11	>99
2	DMF	37	7	>99
3	CH_3NO_2	34	2	>99
4	NMP	29	6	>99
5	CH_3CN	26	2	>99
6	CH_2Cl_2	11	0	>99
7	THF	0	0	–

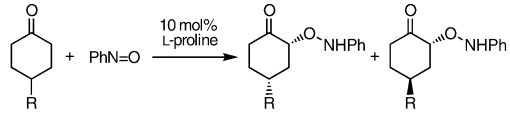
[a] Reactions were conducted with 30 mol% catalyst, 1.0 equiv nitrosobenzene, and 2.0 equiv cyclohexanone at room temperature, and nitrosobenzene was added in one portion. The reaction time was 1 h. [b] Yield of isolated product. [c] Determined by chiral HPLC with a Chiralpak AD-H column.

which is similar to that proposed for the α-aminoxylation of aldehydes,[6] explains the absolute stereochemistry of the α-aminoxylated products.

Next this asymmetric α-aminoxylation was applied to the asymmetric desymmetrization of a 4-substituted cyclohexanone (Table 3). When 4-*tert*-butylcyclohexanone was treated with nitrosobenzene in the presence of L-proline, (2*R*,4*R*)-2-anilinoxy-4-*tert*-butylcyclohexanone and the (2*R*,4*S*) isomer were obtained in 31% yield and >99% *ee* and 31% yield and 94% *ee*, respectively. The absolute stereochemistry of the (2*R*,4*R*) isomer was deduced based on that of the corresponding hydroxycyclohexanone,[17] while that of the (2*R*,4*S*) isomer was determined by the CD-chirality method after conversion into (1*S*,2*R*,4*S*)-4-*tert*-butyl-1,2-dibenzoyloxycyclohexane. 4-*tert*-Butyldiphenylsilyloxycyclohexanone gave almost the same results, affording (2*R*,4*R*)-2-anilinooxy-4-*tert*-butyldiphenylsilyloxycyclohexanone and the (2*R*,4*S*) isomer in 46% yield and >99% *ee*, and 23% yield and 96% *ee*, respectively. These reactions are composed of two successive steps, an asymmetric desymmetrization for the enamine formation, and diastereoselective α-aminoxylation of the generated enamine. These results indicate that the asymmetric induction in the initial enamine formation is not high, while the diastereoselectivity of the second α-aminoxylation is excellent.

In summary, we have developed the direct catalytic enantioselective α-aminoxylation of ketones by using nitrosobenzene as the oxygen source and L-proline as the catalyst. This reaction has several noteworthy features: The reaction proceeds with high yield and excellent enantioselectivity. This α-aminoxylation can be successfully applied not only to cyclohexanone derivatives but also to 4-monosubstituted cyclohexanones with asymmetric desymmetrization, affording both α-aminoxylated products with very high enantioselectivities. Because of the easy conversion of α-aminoxylated ketones into α-hydroxy ketones, operational simplicity, and the availability and low cost of the catalyst, the present method is one practical approach to the preparation of optically active α-hydroxy ketones.

Table 3: Asymmetric desymmetrization of 4-substituted cyclohexanones.[a]



3 **4**

R	Yield [%]		*ee* [%][b]	
	3	**4**	**3**	**4**
*t*Bu	31	31	>99	94
OSi-*t*BuPh$_2$	46	23	>99	96

[a] Reactions were conducted with 10 mol% catalyst, 1.0 equiv nitrosobenzene, and 2.0 equiv ketone in DMF at 0°C with slow addition of nitrosobenzene. [b] Determined by chiral HPLC.

Experimental Section

Typical experimental procedure (Table 2, entry 6): To a solution of 4,4-dimethylcyclohexanone (151.4 mg, 1.2 mmol) and L-proline (6.9 mg, 0.06 mmol) in DMF (2.7 mL) was added a solution of nitrosobenzene (64.2 mg, 0.6 mmol) in DMF (0.9 mL) over 24 h at 0°C by syringe pump, and the mixture was stirred for 30 min at that temperature. The reaction was quenched with phosphate buffer solution (pH 7.0), and the organic materials were extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/hexane 1:10–1:5) gave α-aminoxy ketone (116.7 mg, 0.50 mmol) in 84% yield and >99% *ee*, as determined by chiral HPLC analysis.[18]

Received: October 14, 2003 [Z53085]
Published Online: February 11, 2004

Keywords: asymmetric catalysis · ketones · oxidation · proline

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[13] Cyclopentanone and cycloheptanone do not react under the present reaction conditions.
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[18] HPLC conditions: Chiralcel OD-H column (hexane/2-propanol 40:1), 1.0 mL min^{-1}; $t_R = 9.1$ min (major) and 12.2 min (minor). $[\alpha]_D^{19} = +85.7$ ($c = 0.33$, $CHCl_3$).
[19] Note added in proof (19.1.2004): Please see the preceding communication by Córdova and co-workers, which describes related chemistry: A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109.

