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Direct Proline-Catalyzed Asymmetric α-Aminoxylation of Aldehydes and Ketones

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The direct proline-catalyzed asymmetric α-aminoxylation of aldehydes and ketones has been developed using nitrosobenzene as an oxygen source, affording α-anilinoxy-aldehydes and -ketones with excellent enantioselectivity. Reaction conditions have been optimized, and low temperature (−20 °C) was found to be a key for the successful α-aminoxylation of aldehydes, while slow addition of nitrosobenzene is essential for that of ketones. The scope of the reaction is presented.

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis, and because of this utility many methods have been developed for their preparation. For the synthesis of optically active α-hydroxyaldehydes, transformations from chiral natural sources such as amino acids,[1] sugars,[2] and chiral α-hydroxy acids[3] are widely used. Diastereoselective reactions such as nucleophilic addition to chiral glyoxal derivatives[4] or alkylation of chiral hydrazones[5] are other useful synthetic methods. Asymmetric hydrocyanation[6] and enzymatic resolution[7] have also been employed as a key step in their synthesis. Optically active α-hydroxyketones, on the other hand, can be prepared by several methods such as the electrophilic α-hydroxylation of enolates using chiral oxaziridines as the oxidizing agent.[8] Several methods using asymmetric catalytic reactions are known, including the asymmetric dihydroxylation of enol ethers developed by Sharpless et al.,[9] the asymmetric epoxidation of silyl enol ethers with a chiral dioxirane,[10] and the asymmetric epoxidation of enol ethers with a chiral Mn-Salen catalyst.[11] Most of these preparations, however, require multiple manipulations, and no direct method from the corresponding aldehyde or ketone has been available.

On the other hand, proline[12] has been found to be an excellent asymmetric catalyst of the aldol reaction[13] and Mannich reaction,[14] for α-amination of carbonyl compounds,[15] and for intramolecular alkylation.[16] Recently, Momiyama and Yamamoto have reported an excellent catalytic asymmetric nitroso-aldol reaction, in which the tin enolate of a ketone reacts with nitrosobenzene in the presence of a catalytic amount of BINAP−AgOTf complex, affording an α-aminoxy ketone in high enantioselectivity, which is easily converted into the corresponding α-hydroxy ketone.[17] Inspired by the notion that nitrosobenzene acts as an electrophilic aminoxylating reagent, we examined the reaction between nitrosobenzene and an aldehyde or a ketone in the presence of L-proline and have discovered the direct, L-proline-catalyzed, asymmetric α-aminoxylation of aldehydes and

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ketones.[18] At the same time Zhong[19] and MacMillan et al.[20] have reported the α-aminoxylation of aldehydes, and Cordova et al.[21] have discovered the α-aminoxylation of ketones independently. Just recently Yamamoto and co-workers have reported the α-aminoxylation of aldehydes and ketones catalyzed by pyrrolidine-2-yl-1*H*-tetrazole.[22]

The conditions employed by Zhong,[19] MacMillan et al.,[20] and ourselves[18a] for this α-aminoxylation reaction of aldehydes are slightly different: Zhong employed 1.2 equiv of the aldehyde to nitrosobenzene in the presence of 20 mol % of proline in DMSO at room temperature for 10−20 min,[19] whereas MacMillan and co-workers used 2−3 equiv of the aldehyde in the presence of 5 mol % of proline in $CHCl_3$ at 4 °C for 2−4 h and a catalyst loading that can be reduced as low as 0.5 mol %.[20] In our reported procedure,[18a] 3 equiv of an aldehyde was used in the presence of 30 mol % of proline in CH_3CN at −20 °C for 24 h, and we proposed that use of a low temperature (−20 °C) is suitable for suppressing the self-aldol reaction of aldehydes, which is known to proceed at 4 °C.[13m] Although we can reproduce the excellent enantioselectivity they obtained using Zhong and MacMillan's procedures, we have been unable to obtain a high yield at room temperature or under low catalyst loading. To clarify the discrepancy between the work performed by other groups and our own work and to propose robust, easily reproducible reaction conditions, we have carried out several detailed experiments at various temperatures and under several different catalyst loadings, which will be described in this full paper.

Concerning the α-aminoxylation of ketones, the reaction conditions of Cordova and co-workers[21] are also different from ours:[18b] Cordova used a large excess of ketone (10 equiv) to nitrosobenzene in the presence of 20 mol % of proline in DMSO at room temperature for 2−3 h, with one example of a cyclic ketone,[21] whereas we used 2 equiv of ketones in the presence of considerably lower catalyst loading (10 mol %) in DMF at 0 °C, using slow addition of the nitrosobenzene, and with several examples of cyclic ketones including asymmetric desymmetrization.[18b] As chiral α-hydroxyketones are synthetically useful building blocks, the generality of the present reaction has been investigated in detail, and these results will also be presented here. In this paper we will disclose the full details of our direct asymmetric α-aminoxylation of aldehydes and ketones using nitrosobenzene as oxidant and proline as catalyst.[23]

Asymmetric α-Aminoxylation of Aldehydes. The reaction of propanal and nitrosobenzene was selected as a model, and the effect of solvent was examined with the results summarized in Table 1. As the α-aminoxy aldehyde product **1** is rather labile, isolation and characterization was performed after conversion to the corresponding α-aminoxy alcohol **2** by treatment of the reaction mixture with $NaBH_4$. Although the α-aminoxylation reaction is readily accomplished with very high enantioselectivity in most of the solvents employed, the yield is dependent on the solvent. Acetonitrile was the best of the solvents examined, the reaction proceeding at −20 °C, to afford the α-aminoxylated aldehyde quantitatively in 98% ee.[24] In this reaction, no α-hydroxyamino aldehyde was formed at all, and α-hydroxyamino ketones are major

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(24) Though $CHCl_3$ is reported to be a suitable solvent by MacMillan et al.,[20] CH_3CN is found to be superior in our hands.

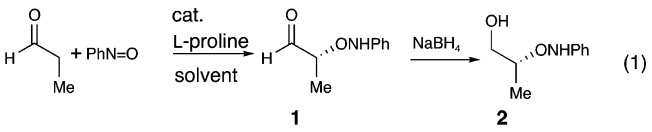
TABLE 1. Solvent and Temperature Effects on the α-Aminoxylation of Propanal[a]

entry	solvent	catalyst (mol %)	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	THF	30	−20	24	18	99
2	NMP	30	−20	24	34	98
3	CH_3NO_2	30	−20	24	43	98
4	$CHCl_3$	30	−20	24	43	98
5	DMF	30	−20	24	49	98
6	CH_2Cl_2	30	−20	24	63	98
7	CH_3CN	30	−20	24	quant	98
8	CH_3CN	30	0	24	80	98
9	CH_3CN	30	23	10 min	29	nd[d]
10	CH_3CN	10	−20	24	quant	98
11	CH_3CN	5	−20	24	81	98

[a] Reaction conditions: 3.0 equiv of propanal and 1.0 equiv of nitrosobenzene were employed. [b] Isolated yield of the alcohol (2 steps). [c] Determined by chiral HPLC with a Chiralpak AD-H column. [d] Not determined.

products in the reaction of nitrosobenzene with a variety of alkali metal or tin enolates of ketones.[25]

Next, reaction temperature was investigated. Whereas the reaction proceeds quantitatively with excellent enantioselectivity at −20 °C, the yield decreases to 80% although maintaining the excellent enantioselectivity when the reaction is conducted at 0 °C (entries 7 and 8). Side reactions at 0 °C are the generation of azoxybenzene from nitrosobenzene, and the self-aldol reaction of propanal, which is known to proceed at 4 °C[13m] (vide infra). Though the reaction is complete within 10 min at room temperature, the yield is low (29%) (entry 9). The catalyst loading can be reduced to 5 mol % without significant loss in yield or enantioselectivity (entry 11), but the reproducibility of the reaction is found to be poor with low catalyst loading (5 and 10 mol %) owing to the low solubility of proline in the solvent. This problem can be solved by forming a saturated proline solution using ultrasound radiation before addition of the aldehyde and nitrosobenzene.[26]



The generality of the reaction was examined under four reaction conditions, which differ in catalyst loading and reaction temperature, with the results summarized in Table 2. The best reaction conditions were found to vary with the aldehyde, and the following features were observed: (1) Excellent enantioselectivity was attained at both −20 °C and 0 °C. (2) In the reactions of reactive aldehydes such as propanal and *n*-butanal, the lower reaction temperature (−20 °C) is preferable to 0 °C, and 10 mol % loading of the catalyst is enough for efficient promotion of the reaction (entries 1 and 2). (3) A catalyst loading of 30 mol % at −20 °C gave a good result in the case of *n*-pentanal (entry 3). (4) In the reaction of 3-methylbutanal, nearly identical results are obtained under all four reaction conditions (entry 4). (5) In the reaction of 3-phenylpropanal, the reaction does not

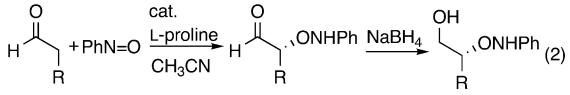
TABLE 2. Proline-Catalyzed Direct Asymmetric α-Aminoxylation of Various Aldehydes[a]

		10 mol %, 0 °C		30 mol %, 0 °C		10 mol %, −20 °C		30 mol %, −20 °C	
entry	R	yield[b] (%)	ee (%)	yield[b] (%)	ee (%)	yield[b] (%)	ee (%)	yield[b] (%)	ee (%)
1	Me	81	98[c]	80	98[c]	quant	98[c]	quant	98[c]
2	Et	64	98[c]	64	98[c]	88	98[c]	87	99[c]
3	*n*-Pr	55	98[c]	71	97[c]	53	97[c]	81	98[c]
4	*i*-Pr	72	98[c]	77	97[c]	77	99[c]	77	99[c]
5	CH_2Ph	67	98[c]	72	99[c]	<5		70	99[c]
6	Ph	20		44	99[d]	<5		62	99[d]

[a] Reactions were conducted with 1.0 equiv of nitrosobenzene and 3.0 equiv of aldehyde in CH_3CN for 24 h in the presence of 10 or 30 mol % of L-proline at 0 or −20 °C. [b] Isolated yield of the alcohol (2 steps). [c] Determined by chiral HPLC with a Chiralpak AD-H column. [d] Determined by chiral HPLC with a Chiralpak OD-H column.

proceed in the presence of 10 mol % of the catalyst at −20 °C but does at 0 °C, which is a suitable reaction temperature (entry 5). (6) A catalyst loading of 30 mol % has to be employed for an unreactive aldehyde such as phenylacetaldehyde, and good results are obtained in this case when the reaction is performed in the presence of 30 mol % of the catalyst at −20 °C (entry 6).

Side reactions in the α-aminoxylation of aldehydes are the self-aldol reaction, which is known to proceed at 4 °C,[13m] and the formation of azoxybenzene. In the reaction of reactive aldehydes, α-aminoxylation with nitrosobenzene can proceed at −20 °C, at which temperature the self-aldol reaction is suppressed. This is why good results are obtained. When an unreactive aldehyde was employed, not only the α-aminoxylation but also the self-aldol reaction slowed, and a substantial amount of azoxybenzene side-product was formed. The generation of azoxybenzene is known from the reaction of benzaldehyde with nitrosobenzene in the presence of a triazonium salt and triethylamine in $MeOH-H_2O$, generating azoxybenzene and methyl benzoate.[27] In the reaction of unreactive aldehydes, it is preferable that the catalyst loading is increased to 30 mol % in order to accelerate the desired aminoxylation.



Asymmetric α-Aminoxylation of Ketones. As an effective method for the asymmetric α-aminoxylation of aldehydes had been developed, the same methodology was applied to the α-aminoxylation of ketones. Cyclohexanone was selected as a model ketone, and its reaction (2 equiv) with nitrosobenzene (1 equiv) was conducted in DMSO at room temperature in the presence of 30 mol % of L-proline, in which the yield was based on nitrosobenzene. Because of the lower reactivity of ketones compared with that of aldehydes, ketone α-aminoxylation does not proceed at −20 °C, which is a suitable temperature for the reaction of more reactive aldehydes. When the reaction was performed at room temperature, the desired α-aminoxylated cyclohexanone **3** was obtained in 31% yield, along with α,α′-diaminoxylated product **4** in

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(26) See Supporting Information for experimental details.
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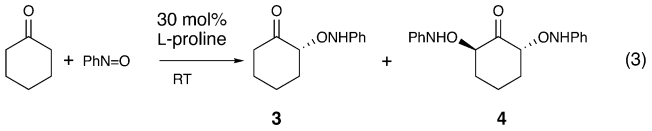
TABLE 3. Solvent Effect on the α-Aminoxylation of Cyclohexanone[a]

entry	solvent	yield[b] (%) 3	yield[b] (%) 4	(%) ee of 3[c]
1	THF	0	0	
2	CH_2Cl_2	11	0	>99
3	CH_3CN	26	2	>99
4	NMP	29	6	>99
5	DMSO	31	11[d]	>99
6	CH_3NO_2	34	2	>99
7	DMF	37	7[d]	>99
8[e]	DMF	58	5	>99

[a] Reactions were conducted with 30 mol % catalyst, 1.0 equiv of nitrosobenzene, and 2.0 equiv of cyclohexanone at room temperature, to which nitrosobenzene was added in one portion. The reaction time is 1 h. [b] Isolated yield. [c] Determined by chiral HPLC with a Chiralpak AD-H column. [d] Optical purity of **4** is over 99% ee. [e] Cyclohexanone (10 equiv) was employed.

11% yield and also azoxybenzene. The solvent effect for ketone α-aminoxylation was found to be rather different from that of aldehydes. Though yield is dependent on solvent in the α-aminoxylation of aldehydes, with the best result obtained in CH_3CN, polarized solvents such as DMF, DMSO, CH_3NO_2, *N*-methylpyrrolidinone (NMP), and CH_3CN are all suitable for the α-aminoxylation of ketones, affording the α-aminoxylated product **3** in 26−37% yield with excellent enantioselectivity (>99% ee, Table 3), while α,α′-diaminoxylated cyclohexanone **4** is also obtained optically pure. As the best yield was obtained in DMF, further investigations were performed using this solvent.



When a large excess (10 equiv) of cyclohexanone was employed instead of 2 equiv, the generation of α,α′-diaminoxylated product **4** was suppressed and the yield of α-aminoxylated cyclohexanone **3** was increased to 58%, though this is still not synthetically satisfactory (Table 3, entry 8). Slow addition of nitrosobenzene, however, 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 (2 equiv) and 10 mol % of proline at 0 °C effectively suppressed both α,α′-diaminoxylation and the generation of azoxybenzene (vide infra), affording **3** in 77% yield with >99% ee (Table 4, entry 2). No α-hydroxyamino ketone, a major product in the reaction of nitrosobenzene with a variety of alkali metals or tin enolates,[25] was formed at all.

As the optimal reaction conditions had been established, the generality of the reaction was examined using various six-membered cyclic ketones, with the results summarized in Table 4. 1,4-Cyclohexanedione monoethylene ketal and 4,4-dimethylcyclohexanone were transformed into α-aminoxylated cyclohexanones **5** and **6**, respectively, in good yield with very high enantioselectivity, indicating that the mild reaction conditions do not affect the acetal functional group (entries 3−7). Not only cyclohexanones but also tetrahydro-4*H*-pyran-4-one, *N*-methyl-, *N*-benzyl-, and *N*-Boc-4-piperidinone, and tetrahydrothiopyran-4-one were successfully employed in this reaction, affording α-aminoxylated compounds with moderate yield and excellent enantioselectivity (entries 8−12). In the reaction of *N*-methyl-4-piperidinone, CH_3NO_2 was used as solvent instead of DMF, owing to the difficulty of separating the product from the latter solvent (entry 9). It is noteworthy that the basic tertiary amine moiety has no detrimental effect on the proline catalyst and that the oxidatively labile thioether is not affected under these oxidizing conditions.

TABLE 4. Asymmetric α-Aminoxylation of Various Ketones[a]

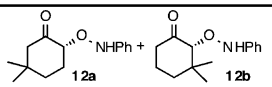
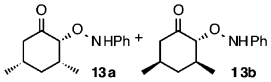
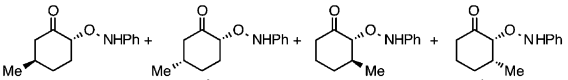
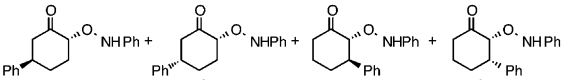
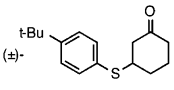
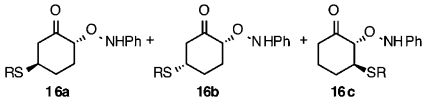
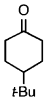
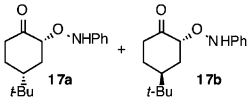
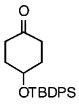
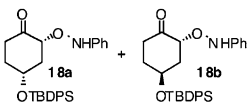
entry	ketone	product	catalyst /mol%	addition time/h	yield /%[b]	ee/%
1		 **3**	30	5.5	79	>99[d]
2			10	5.5	77	>99[d]
3		 **5**	30	12	96	>99[e]
4			10	24	93	>99[e]
5[c]			10	30	90	>99[e]
6			5	60	86	>99[e]
7		 **6**	10	24	84	>99[e]
8		 **7**	10	24	53	96[d]
9[g]		 **8**	10	24	44	99[d]
10		 **9**	10	60	45	>99[e]
11		 **10**	10	24	41	>99[f]
12		 **11**	10	25	69	>99[f]

[a] Unless otherwise shown, reactions were conducted with a catalytic amount of L-proline, 1.0 equiv of nitrosobenzene, and 2.0 equiv of ketone in DMF at 0 °C with slow addition of nitrosobenzene. [b] Isolated yield. [c] An equivalent amount of ketone was employed. [d] Determined by HPLC using a Chiralpak AD-H column. [e] Determined by HPLC using a Chiralpak OD-H column. [f] Determined by HPLC using a Chiralpak AS-H column. [g] CH_3NO_2 was used as solvent.

Though the optimum addition time for nitrosobenzene varies according to the ketone, a good yield is generally obtained using addition over 24 h when 10 mol % of proline is employed. The catalyst loading can be reduced to 5 mol % without significant loss in yield or enantioselectivity, but a longer reaction time is required (entry 6).

It is also noteworthy that slow addition of nitrosobenzene makes it unnecessary to use a large excess of ketone[21] and that only 2 equiv of ketone is enough. In fact, as for the reactive substrate such as 1,4-cyclohex-

TABLE 5. Asymmetric α-Aminoxylation of 3- or 4-Substituted Cyclohexanones[a]

entry	substrate	addition time/h	yield /%[b]	products
1		38	43	 **12a** : **12b** = 88 : 12 >99% ee[c] >99% ee[c]
2		26	60	 **13a** : **13b** = 70 : 30 >99% ee[c] >99% ee[c]
3		24	70	 **14a** : **14b** : **14c** : **14d** = 34 : 40 : 18 : 8
4		29	72	 **15a** : **15b** : **15c** : **15d** = 32 : 32 : 32 : 4 >99% ee[d]
5		13	61	 **16a** : **16b** : **16c** = 46 : 21 : 33 >99% ee[e] >99% ee[e] 97% ee[c] R=*p*-*tert*-butylphenyl
6		32	62	 **17a** : **17b** = 50 : 50 >99% ee[c] 94% ee[e]
7		32	69	 **18a** : **18b** = 67 : 33 >99% ee[c] 94% ee[e]

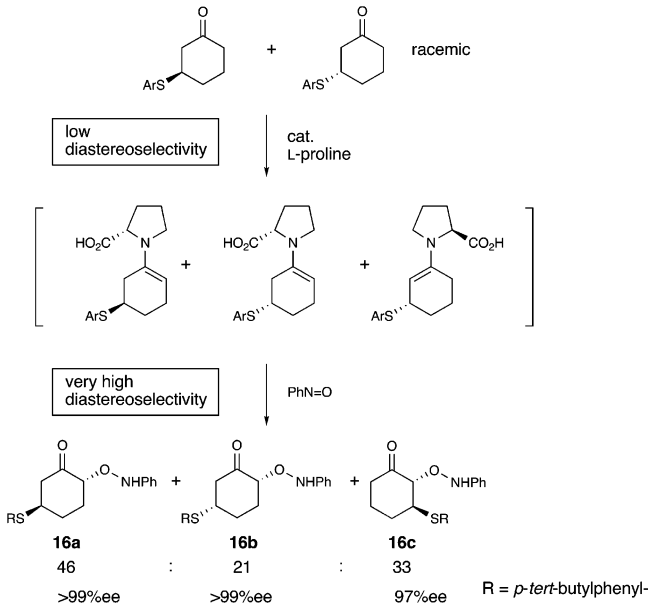
[a] Reactions were conducted with 0.1 equiv of L-proline, 1.0 equiv of nitrosobenzene, and 2.0 equiv of ketone in DMF at 0 °C with slow addition of nitrosobenzene. [b] Isolated yield. [c] Determined by HPLC using a Chiralpak AD-H column. [d] Determined by HPLC using a Chiralpak AD-I column. [e] Determined by HPLC using a Chiralpak OD-H column.

anedione mono-ethylene ketal, good results are also obtained even when only 1 equiv of cyclohexanone derivative is employed (entry 5).

Despite these successful results, 2-substituted cyclohexanones such as 2-methylcyclohexanone, 2-chlorocyclohexanone, 2-benzoyloxycyclohexanone, and 2-benzyloxycyclohexanone do not react efficiently in the presence of 30 mol % of proline with slow addition of nitrosobenzene and afford the α-aminoxylated products in less than 10% yield in our hands, although Cordova and co-workers have obtained α-aminoxylated product from 2-methylcyclohexanone in moderate yield.[21] Cyclopentanone, cycloheptanone, cyclooctanone, and α- and β-tetralones are also unreactive under these conditions.

α-Aminoxylation of 3- or 4-Substituted Cyclohexanone. The reaction of 3- or 4-substituted cyclohexanones was investigated, with the results summarized in Table 5. 3,3-Dimethylcyclohexanone was also a suitable substrate, affording 2-anilinoxy-5,5-dimethylcyclohexanone (**12a**) and 2-anilinoxy-3,3-dimethylcyclohexanone (**12b**) in 38% yield and >99% ee and 5% yield and >99% ee, respectively. Owing to steric hindrance due to

SCHEME 1. Resolution of 3-Arylthiocyclohexanone



the two methyl groups, the former isomer **12a** predominated over the latter **12b** (entry 1). α-Aminoxylation also proceeded in the reaction of *cis*-3,5-dimethylcyclohexanone, affording (2*R*,3*R*,5*S*)-2-anilinoxy-3,5-dimethylcyclohexanone (**13a**) and (2*R*,3*S*,5*R*)-isomer **13b** in 42% yield and >99% ee and 18% yield and >99% ee, respectively, with the creation of three chiral centers with excellent enantioselectivity in a single operation (entry 2).

Next, the reactions of racemic 3-methyl- and 3-phenylcyclohexanones were investigated, in the expectation that a kinetic resolution could be achieved (entries 3 and 4). When racemic 3-methyl- and 3-phenyl-cyclohexanones (2 equiv) were treated with nitrosobenzene in the presence of 10 mol % of L-proline, four isomeric α-aminoxylated cyclohexanones were obtained. The 2-aminoxy-5-methyl and 2-aminoxy-5-phenyl isomers were obtained predominantly over the 2-aminoxy-3-methyl and 2-aminoxy-3-phenyl isomers owing to steric effects and with low *trans*/*cis* diastereoselectivity. The optical purity of the products obtained was not determined, except for that of (2*R*,5*R*)-2-anilinoxy-5-phenylcyclohexanone (**15a**), which was >99% ee.

3-Arylthiocyclohexanones, however, gave a synthetically useful result. The reaction of 3-(*p*-*tert*-butylphenylthio)-cyclohexanone afforded three isomers, and the diastereoselectivity was low (**16a**:**16b**:**16c** = 46:21:33, entry 5). The 2-anilinoxy-5-(*p*-*tert*-butylphenylthio)-cyclohexanones were generated predominantly over the 3-arylthio isomers. Though the diastereoselectivity is low, both 5-arylthio isomers **16a** and **16b** can be converted to the same (*R*)-2-anilinoxy-5-cyclohexene-1-one (**19**), a useful chiral synthetic intermediate, by oxidation and elimination. In fact (*R*)-2-anilinoxy-5-cyclohexene-1-one (**19**) can be prepared in 44% yield in two steps without separation of the α-anilinoxylated diastereomers **16a**, **16b**, as shown in eq 4.

In the reaction of 3-substituted cyclohexanones, the 4-isomers were obtained with excellent enantioselectivity but low diastereoselectivity. This reaction is composed

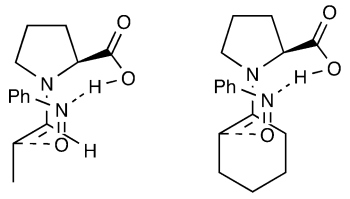


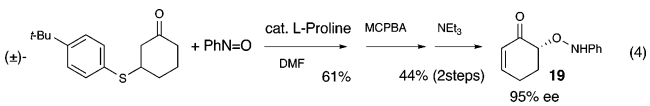
FIGURE 1. Transition state model of the α-aminoxylation of aldehydes and ketones.

of two successive steps: formation of the two diastereomers of an enamine and subsequent diastereoselective α-aminoxylation of that enamine. The 3-substituent on the cyclohexanone induces little diastereoselectivity during formation of the enamine, whereas excellent diastereoselectivity is achieved in the following reaction with nitrosobenzene. Thus, a highly efficient asymmetric resolution can be realized (Scheme 1).

Next, this asymmetric α-aminoxylation has been applied to the asymmetric desymmetrization of 4-substituted cyclohexanones. When 4-*tert*-butylcyclohexanone was treated with nitrosobenzene in the presence of L-proline, (2*R*,4*R*)-2-anilinoxy-4-*tert*-butylcyclohexanone (**17a**) and the (2*R*,4*S*)-isomer **17b** were obtained in 31% yield and >99% ee and 31% yield and 94% ee, respectively (entry 6). 4-*tert*-Butyldiphenylsilyloxycyclohexanone gave almost identical results, affording (2*R*,4*R*)-2-anilinoxy-4-*tert*-butyldiphenylsilyloxycyclohexanone (**18a**)and the (2*R*,4*S*)-isomer **18b** in 46% yield and >99% ee and 23% yield and 96% ee, respectively (entry 7).

In the reactions of 4-substituted cyclohexanones and of *cis*-3,5-dimethylcyclohexanone, efficient asymmetric desymmetrization can be achieved with excellent enantioselectivity despite the low *trans*/*cis* diastereoselectivity, generating two and three chiral centers, respectively, in a single operation. This reaction is also composed of two successive steps, an asymmetric desymmetrization for the enamine formation and diastereoselective α-aminoxylation of the enamine generated. Asymmetric induction in the initial enamine formation is not high, whereas the diastereoselectivity of the second α-aminoxylation is excellent.

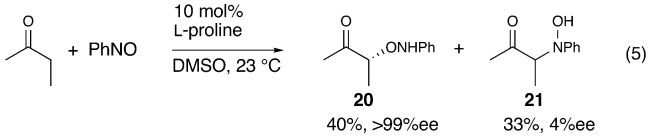
In this proline-mediated α-aminoxylation of cyclohexanone derivatives, substituents at the 3-, 4-, or 5-positions have little effect on the formation of the enamine, and the high enantioselectivity can be attributed to the nearly perfect diastereoselectivity of the subsequent reaction with nitrosobenzene through a fixed transition state described in the model shown in Figure 1 (vide infra). The present reaction is a powerful method for introducing an aminoxy group into the α-position of cyclohexanone derivatives, irrespective of any substituents at the 3-, 4-, or 5-positions, in which a *pro-S* proton at the α-position of cyclohexanone is enantioselectively replaced with an anilinoxy group.



(4)

Acyclic Ketones. An acyclic ketone showed reactivity different from that of the cyclic ketones. Though most highly polarized solvents can be employed in the reaction of cyclohexanones, the reaction of 2-butanone proceeded

more efficiently in DMSO than in DMF, with no reaction at all in CH_3NO_2 and CH_3CN. While slow addition (over 5 h) is essential in the reaction of cyclohexanones, a much shorter addition time (2 h) is enough for that of 2-butanone. Though only the 2-anilinoxylated product **3** was isolated in the reaction of cyclohexanone, both the α-aminoxylated product **20** and also the α-hydroxyaminated product **21** were obtained with 2-butanone, and while the former anilinoxylated product **20** was produced with excellent enantioselectivity, the latter hydroxyamino derivative **21** was almost racemic.

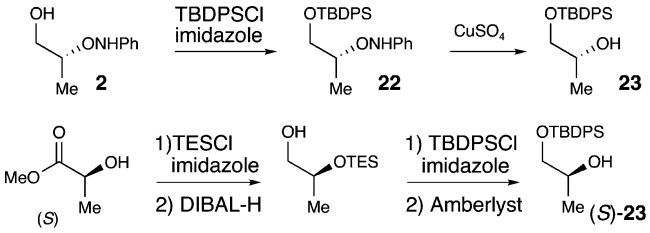


(5)

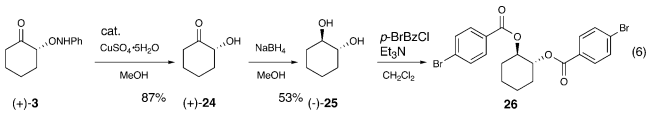
We also examined the reaction of 3-pentanone, which was very slow, affording 2-anilinoxy-3-pentanone and 2-(*N*-hydroxyanilino)-3-pentanone in only 7% and 9% yield, respectively.

Determination of Absolute Configurations. The absolute configuration of 2-anilinoxypropanal was determined as follows. 2-Anilinoxypropanol **2** was converted into *tert*-butyldiphenylsilyl (TBDPS) ether **22** by treatment with TBDPSCl and imidazole. Transformation of the anilinoxy moiety into a hydroxy group can be successfully carried out by treatment with a catalytic amount of copper sulfate under the conditions developed by Yamamoto,[17a] affording alcohol **23**. The absolute stereochemistry of alcohol **23** was unambiguously determined to be (*R*) on the basis of chiral HPLC analysis and comparison of the optical rotation with that of authentic (*S*)-**23** prepared from (*S*)-methyl lactate as shown in Scheme 2.

SCHEME 2. Determination of the Absolute Configuration of 2-Anilinoxypropanal



The conversion of 2-anilinoxycyclohexanone (**3**) into 2-hydroxycyclohexanone (**24**)[28] was successfully carried out in 87% yield with only partial racemization (>99% ee ⟹ 96% ee[29]) by treatment with $CuSO_4$.[17a] This 2-hydroxycyclohexanone was reduced to the corresponding diol, from which *trans*-1,2-cyclohexanediol **25** was isolated in 53% yield along with *cis*-isomer in 31% yield. The optical rotation of **25** is in good agreement with that of (1*R*,2*R*)-1,2-cyclohexanediol with respect to both its sign and absolute value.[30] The absolute configuration of **25** shown is further supported by the CD-chirality method[31] after conversion into (1*R*,2*R*)-1,2-bis(*p*-bromobenzoyloxy)cyclohexane (**26**).



(6)

The absolute stereochemistry of bisaminoxylated cyclohexanone **4** was determined after conversion into (−)-1,2,3-trihydroxycyclohexane.[32]

The relative stereochemistry of 2-anilinoxy-3,5-dimethylcyclohexanones **13a**, **13b** was determined from their ^{1}H NMR coupling constants, and the absolute stereochemistry of **13a** was deduced by the CD-chirality method[31] after conversion into 1,2-bis(*p*-bromobenzoyloxy)-3,5-dimethylcyclohexane.

The relative stereochemistries of 2-anilioxy-5-(*p*-*tert*-butylphenylthio)-cyclohexanones **16a**, **16b** and 2-anilinoxy-3-(*p*-*tert*-butylphenylthio)-cyclohexanones **16c** were determined from their ^{1}H NMR coupling constants, and the absolute stereochemistries of **16a**, **16b** and 2-anilinoxy-5-cyclohexen-1-one (**19**) were determined after conversion into (−)-1,2-dihydroxycyclohexane (**25**).

The absolute stereochemistry of *cis*-2-anilinoxy-4-*tert*-butylcyclohexanone (**17a**) was determined to be (2*R*,4*R*) after conversion into the corresponding hydroxycyclohexanone,[33] and that of *trans*-isomer **17b** was determined to be (2*R*,4*S*) by the CD-chirality method after conversion into (1*S*,2*R*,4*S*)-4-*tert*-butyl-1,2-dibenzoyloxycyclohexane.

The absolute stereochemistry of 3-anilinoxy-2-butanone **20** was determined after conversion to (+)-2,3-bis(*p*-toluenesulfoxy)-butane[34] by the sequence of $NaBH_4$ reduction, tosylation, and separation of the *dl*-isomer from the *meso*-isomer.

Reaction Mechanism. The transition state model (Figure 1), which is similar to that proposed for the aldol reaction[13e−g,j,r,s,z] by List, Houk, and Barbas and for the α-amination of aldehydes,[15] explains the absolute stereochemistry of the α-aminoxylated aldehydes and ketones, though two reaction mechanisms have been proposed for the nitroso-aldol reaction of ketones, one proceeding via a nitrosobenzene-monomer and the other a nitrosobenzene-dimer.[17,25]

The reaction mechanism for cyclohexanone is shown in Scheme 3. Proline reacts with cyclohexanone to generate a chiral enamine, which reacts with nitrosobenzene, affording an iminium ion intermediate. The α-aminoxylated cyclohexanone is formed on hydrolysis with regeneration of proline.

(28) (a) Lee, L. G.; Whitesides, G. M. *J. Org. Chem.* **1986**, *51*, 25. (b) Bortolini, O.; Casanova, E.; Fantin, G.; Medici, A.; Poli, S.; Hanau, S. *Tetrahedron*: *Asymmetry* **1988**, *9*, 647. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 7823. (c) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, *58*, 3600. (d) Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Rosa, A. *Tetrahedron Lett.* **1996**, *37*, 115. (e) Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4389. (f) Sugimura, T.; Iguchi, H.; Tsuchida, R.; Tai, A.; Nishiyama, N.; Hakushi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1007.

(29) The enantiomeric excess of 2-hydroxycyclohexanone (96% ee) was determined by chiral GC analysis using a CHIRAMIX column (0.25 mm i.d./df = 0.25 mm). Column temp 60−160 °C (0.7 °C/min); column flow rate 1.2 mL/min. (*S*)-isomer, t_R = 70.81 min, (*R*)-isomer, t_R = 71.68 min. CHIRAMIX is licensed by T. HASEGAWA CO., Ltd.

(30) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Guerrini, A.; Medici, A. *J. Org. Chem.* **1997**, *62*, 1854.

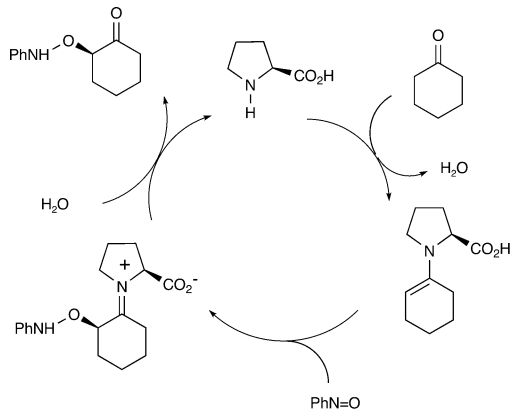
(31) Harada, N.; Nakanishi, K. In *Circular Dichroic Spectroscopy. Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(32) (a) Paulsen, H.; Brauer, O. *Chem. Ber.* **1977**, *110*, 331. (b) Kim, K. S.; Park, J. I.; Moon, H. K.; Yi, H. *Chem. Commun.* **1998**, 1945.

(33) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.

(34) Kottner, J.; Greber, G. *Chem. Ber.* **1980**, *113*, 2323.

SCHEME 3. Reaction Mechanism



Conclusion

In summary, the direct catalytic enantioselective α-aminoxylation of aldehydes and ketones has been developed by using nitrosobenzene as an oxygen source and L-proline as a catalyst. There are several noteworthy features to this reaction: The reaction proceeds with moderate to high yield and excellent enantioselectivity. This α-aminoxylation can be successfully applied not only to a variety of aldehydes and cyclohexanone derivatives but also to 4-monosubstituted cyclohexanones with asymmetric desymmetrization, affording both α-aminoxylated products with very high enantioselectivities. As α-aminoxylated aldehydes and ketones can easily be converted into α-hydroxy aldehydes and ketones and because of its operational simplicity and the ready availability and low cost of the catalyst, the present method is one practical approach to the preparation of optically active α-hydroxy carbonyl compounds.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^{1}H and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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