Asymmetric α-Aminoxylations of Stoichiometric Ketones Using 2-Nitrosotoluene

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Abstract: Asymmetric aminoxylations of a stoichiometric amount of ketones were accomplished through *O*-nitrosoaldol reactions of 2-nitrosotoluene catalyzed by a proline-based tetrazole. The advantages of 2-nitrosotoluene and the tetrazole over nitrosobenzene and proline, respectively, were demonstrated.

Key words: aminoxylations, *O*-nitrosoaldol reactions, α-aminoxy cyclic ketones, proline-based tetrazole, nitrosotoluene

Chiral α-hydroxy aldehydes and ketones are important intermediates in organic synthesis. Catalytic asymmetric preparation of α-hydroxy carbonyl compounds has been realized by dihydroxylation and epoxidation of silyl enol ethers.[1–3] BINAP–AgOTf complex catalyzed nucleophilic addition of tin enolates to nitrosobenzene is the first example of asymmetric O-selective nitrosoaldol (O-NA) reaction, affording α-aminoxy ketones in excellent ee, which are easily converted to α-hydroxy ketones.[4] Silyl enolates can also be used for the same purpose in the presence of a chiral phosphite ligand and $AgBF_4$.[5] In these methods, the preformed enolates of carbonyl compounds are used as substrates for the enantioselective introduction of an α-oxy group. Direct α-oxidation of a carbonyl compound is obviously more attractive with respect to its ease of manipulation. Sibi et al. used TEMPO (2 equiv) for the asymmetric α-aminoxylations of aldehydes through a radical procedure.[6] O-NA reactions of nitrosobenzene catalyzed by proline or proline-based tetrazole also give α-aminoxylated aldehydes and ketones.[7,8] Although these O-NA reactions give the products in excellent ee, excess (2–3 equiv) carbonyl substrates are required to secure a good yield. This drawback restricts the wide application of these O-NA reactions, especially when the carbonyl compound is very important. In our recent paper, we noted that 2-nitrosotoluene is superior to nitrosobenzene for the aminoxylations of carbonyl compounds.[9] Herein we further investigate the advantage of 2-nitrosotoluene in the aminoxylations of a stoichiometric amount of ketones.

The reaction of cyclohexanone with 2-nitrosotoluene was conducted under various conditions, and the results are shown in Table 1. With the tetrazole as the catalyst, the reaction of one equivalent cyclohexanone in DMSO at room temperature gave the monoaminoxylation product in 74% yield and the bisaminoxylation product in 8% yield (entry 1). When the reaction was carried out in a 1:1 mixture of DMSO and DMF at 0 °C, the monoaminoxylation product was obtained in 82% yield (entry 3). In DMF at 0 °C, the monoaminoxylation product was obtained in 81% yield (entry 4). Further decrease of the temperature to –10 °C did not increase the yield (entry 5). For comparison, proline was used instead of the tetrazole under otherwise identical conditions: the yield of the monoaminoxylation product was 59%, and the yield of the bisaminoxylation product increased to 12% (entry 6). With proline as the catalyst, $CHCl_3$ (entry 7) or MeCN was also examined as the solvent. Very low conversions of 2-nitrosotoluene were observed in these cases. When 2 equivalents cyclohexanone were reacted with 2-nitrosotoluene, the monoaminoxylation product was obtained in quantitative yield, and the formation of the bisaminoxylation product was sufficiently suppressed (entry 8). Nitrosobenzene gave lower yield (89%) than 2-nitrosotoluene under the same conditions (entry 9). When 2 equivalents nitrosotoluene were used, the bisaminoxylation product became the major one (entry 10). It is clear from these results that slow addition of 2-nitrosotoluene, low temperature (0 °C), and the tetrazole catalyst are essential for good yields of the monoaminoxylation products.

Under optimized conditions, aminoxylations of several six-membered cyclic ketones were examined (Table 2).[10] In all the cases, the monoaminoxylation products were obtained in >75% yield and excellent ee. These yields are comparable to those obtained using excess ketones and proline as the catalyst. 4-Piperidone (X = N) was also reacted with 2-nitrosotoluene. However, the conversion was very low. In order to further improve the yields of the monoaminoxylation products, 2-isopropylnitrosobenzene[11] was used instead of 2-nitrosotoluene. However, similar selectivities were observed (entries 1, 3, and 4). Cyclopentanone or cyclododecanone did not react with 2-nitrosotoluene. Cycloheptanone gave the aminoxylation product in <10% yield.

Asymmetric aminoxylations of a stoichiometric amount of aldehydes using 2-nitrosotoluene or 2-isopropylnitrosobenzene were also investigated (Scheme 1). With slow addition (3 h) of nitrosotoluene, hydrocinnamaldehyde, and isovaleraldehyde gave the aminoxylation products in 53% and 61% yield, respectively. 4-Pentenal and phenylacetaldehyde gave the products in 38% and 44% yield, respectively, at –20 °C. In these two cases, the con-

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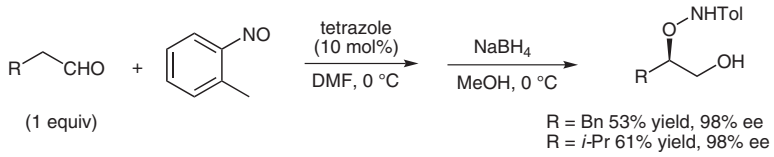
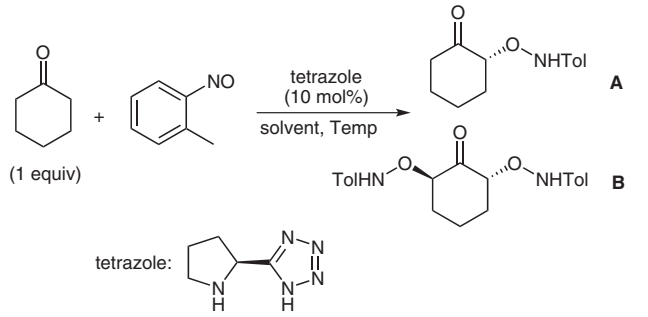


Scheme 1 Aminoxylations of aldehydes

Table 1 Optimization of Reaction Conditions



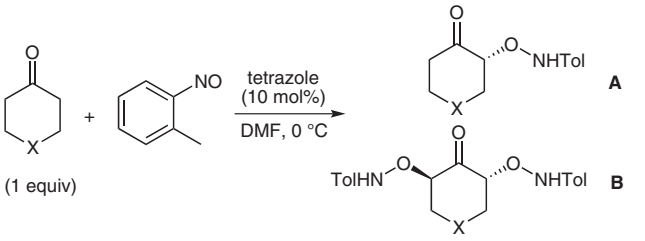
Entry	Ketone (equiv)	TolNO (equiv)	Solvent	Temp (°C)	Time (h)[a]	Yield (%)[b]	
						A	**B**
1	1	1	DMSO	r.t.	5	74	8
2	1	1	DMSO–DME	0	3	79	4
3	1	1	DMSO–DMF	0	3	82	9
4	1	1	DMF	0	3	81	9
5	1	1	DMF	–10	5	77	6
6[c]	1	1	DMF	0	3	59	12
7[c]	1	1	$CHCl_3$	0	3	3	0
8	2	1	DMF	0	3	98	2
9[d]	2	1	DMF	0	3	89	1
10	1	2	DMF	0	6	32	47

[a] Addition time of TolNO or PhNO.
[b] **A** and **B** isolated as a mixture. Yields calculated from the ratio determined by ^{1}H NMR.
[c] The amount of 10 mol% L-proline was used.
[d] Nitrosobenzene used.

version of 2-nitrosotoluene was 70%, even after a long reaction time (24 h).

In summary, we have demonstrated that the combination of 2-nitrosotoluene and the proline-based tetrazole is effective for asymmetric aminoxylations of a stoichiometric amount of cyclic ketones. The addition time of nitrosotoluene is greatly reduced in comparison with that for proline-catalyzed procedures. The present procedure avoids the use of excess ketone substrate, which is difficult to separate from the aminoxylation product.

Table 2 Aminoxylations of Cyclic Ketones[a]



Entry	Ketone X	Yield (%)[b]		ee (%)[c]
		A	**B**	
1	CH_2	81 (81)	9 (9)	>99
2	CMe_2	86	3	>99
3	CH*t*-Bu	84 (88)	16 (12)	>99[d], >99[e]
4	O	75 (71)	11 (12)	>99

[a] TolNO added over 3 h.
[b] **A** and **B** isolated as a mixture. Yields calculated from the ratio determined by ^{1}H NMR. Yields in parentheses obtained from 2-isopropylnitrosobenzene.
[c] Determined by chiral HPLC.
[d] The ee of 2*R*,4*R*-isomer.
[e] The ee of 2*R*,4*S*-isomer.

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(10) **Typical Experimental Procedure**
2-Nitrosotoluene (1.0 mmol, 121 mg) in DMF (1 mL) was added over 3 h via syringe pump to a solution of the tetrazole catalyst (0.1 mmol, 14 mg) and the cyclic ketone (1.0 mmol) in DMF (1 mL) cooled to 0 °C. After completion of the addition, the mixture was stirred at 0 °C for a further 5 h. Saturated aq $NHCl_4$ was added and the mixture extracted with AcOEt. The crude product was chromatographed on silica gel to give a mixture of the mono- and bisaminoxylation products.

(11) 2-Isopropylnitrosobenzene was prepared in high purity by oxidation of 2-isopropylaniline with Oxone in H_2O at 0 °C.