

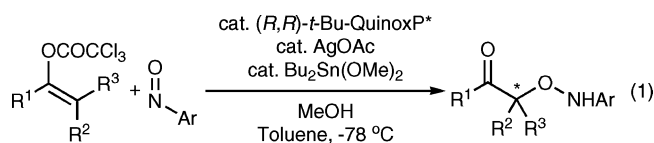
Enantioselective Nitroso Aldol Reaction Catalyzed by QuinoxP*·Silver(I) Complex and Tin Methoxide

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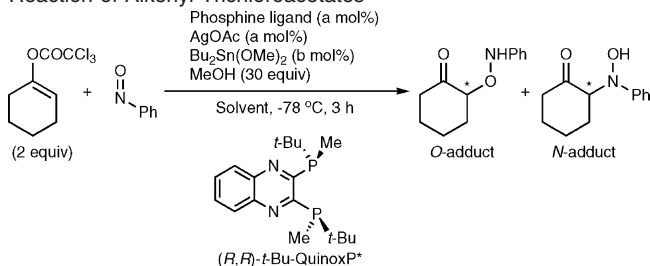
The asymmetric nitroso aldol reaction is a convenient method for the preparation of nonracemic α -aminoxy and/or α -hydroxyamino carbonyl compounds.^{1–3} We have recently found that dibutyltin dimethoxide catalyzes the *N*-nitroso aldol reaction between alkenyl trichloroacetates and nitrosobenzene in the presence of methanol.⁴ The reaction proceeds via a tin enolate, and the tin methoxide is regenerated with the assistance of MeOH. We envisaged that if an appropriate chiral Lewis acid could activate the nitrosoarene without disturbing the tin-promoted catalysis, the asymmetric version of the nitroso aldol reaction would be achieved. We report here a novel example of the enantioselective nitroso aldol reaction using QuinoxP*·silver(I) complex as the chiral catalyst (eq 1).



First, we tested the catalytic activity of BINAP·AgX complexes that have been shown by Momiyama and Yamamoto⁵ to be efficient chiral catalysts for asymmetric nitroso aldol reactions. When a 1:2 mixture of nitrosobenzene and 1-trichloroacetoxycyclohexene was treated with (*S*)-BINAP·AgOAc (10 mol %) and Bu₂Sn(OMe)₂ (20 mol %) in the presence of MeOH (30 equiv) in toluene at $-78\text{ }^{\circ}\text{C}$ for 3 h, an 87:13 mixture of the α -aminoxy ketone (*O*-adduct) and α -hydroxyamino ketone (*N*-adduct) was obtained in 73% combined yield (Table 1, entry 2). The *O*-adduct had 85% ee (*R*). Next, we further examined the catalytic activity of chiral phosphines other than BINAP and found that *t*-Bu-QuinoxP* was the chiral ligand of choice (entry 6 vs entries 1–5).⁶ The enantioselectivity of the reaction reached 98% ee (entry 6). In order to get better results, we attempted to optimize the reaction conditions. Among the solvents investigated, toluene gave the highest yield and ee (entry 6 vs entries 7–10). Reducing the amounts of *t*-Bu-QuinoxP*·AgOAc and Bu₂Sn(OMe)₂ to 5 and 10 mol %, respectively, did not affect the chemical yield, the *O*/*N* ratio, or the enantioselectivity (entry 11).

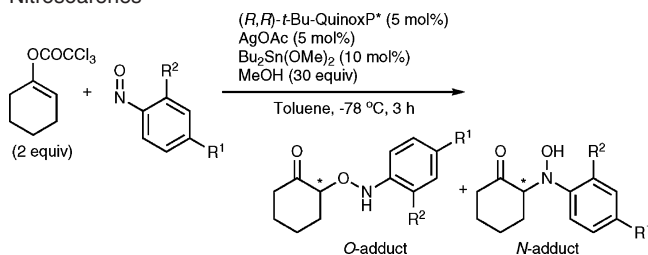
With the optimized reaction conditions in hand, we studied the catalytic asymmetric *O*-nitroso aldol reaction employing substituted nitrosobenzenes (Table 2). An obvious decrease in the ee as well as the yield and the *O*/*N* ratio was observed for a substrate that had an electron-withdrawing group at the para position (entry 2). In contrast, the introduction of a methyl group at the ortho or para position promoted the reaction, affording the *O*-adduct with 99% ee without significant loss of reactivity or regioselectivity (entries 3 and 4). However, use of 1-methoxy-4-nitrosobenzene resulted in no yield of adducts because of their instability.

The aforementioned results further encouraged us to use various alkenyl trichloroacetates of cyclic ketones in the asymmetric α -aminoxylation, as shown in Table 3. Both cyclopentanone and

Table 1. Optimization of Catalytic Asymmetric Nitroso Aldol Reaction of Alkenyl Trichloroacetates^a

entry	phosphine ligand	a	b	solvent	yield, % ^b	<i>O</i> / <i>N</i>	ee, % (<i>O</i> -adduct) ^c
1 ^d	(<i>S,S</i>)-CHIRAPHOS	10	20	toluene	55	72/28	<1
2 ^d	(<i>S</i>)-BINAP	10	20	toluene	73	87/13	85 (<i>R</i>)
3 ^d	(<i>S</i>)-Tol-BINAP	10	20	toluene	68	90/10	92 (<i>R</i>)
4	(<i>R</i>)-MOP	10	20	toluene	29	39/61	22 (<i>S</i>)
5 ^d	(<i>S</i>)-SEGPPOS	10	20	toluene	68	79/21	93 (<i>R</i>)
6	(<i>R,R</i>)- <i>t</i> -Bu-QuinoxP*	10	20	toluene	70	91/9	98 (<i>S</i>)
7	(<i>R,R</i>)- <i>t</i> -Bu-QuinoxP*	10	20	CH ₂ Cl ₂	45	78/22	96 (<i>S</i>)
8	(<i>R,R</i>)- <i>t</i> -Bu-QuinoxP*	10	20	Et ₂ O	68	88/12	98 (<i>S</i>)
9	(<i>R,R</i>)- <i>t</i> -Bu-QuinoxP*	10	20	THF	68	73/27	94 (<i>S</i>)
10	(<i>R,R</i>)- <i>t</i> -Bu-QuinoxP*	10	20	MeOH	64	92/8	95 (<i>S</i>)
11	(<i>R,R</i>)- <i>t</i> -Bu-QuinoxP*	5	10	toluene	65	89/11	99 (<i>S</i>)
12	(<i>R,R</i>)- <i>t</i> -Bu-QuinoxP*	2	4	toluene	26	79/21	98 (<i>S</i>)

^a Unless otherwise specified, the reaction was carried out using chiral phosphine (2–10 mol %), silver acetate (2–10 mol %), dibutyltin dimethoxide (4–20 mol %), alkenyl trichloroacetate (2 equiv), nitrosobenzene (1 equiv), and methanol (30 equiv) in the specified solvent at $-78\text{ }^{\circ}\text{C}$ for 3 h. ^b Isolated yield. ^c The value is for the *O*-adduct and was determined by HPLC analysis. The absolute configuration of the *O*-adduct is shown in parentheses. ^d The reaction time was 2 h.

Table 2. Catalytic Asymmetric *O*-Nitroso Aldol Reaction of Diverse Nitrosoarenes^a

entry	R ¹	R ²	yield, % ^b	<i>O</i> / <i>N</i>	ee, % (<i>O</i> -adduct) ^c
1	H	H	65	89/11	99 (<i>S</i>) ^d
2	Br	H	28	63/37	90
3	Me	H	40	90/10	99
4	H	Me	67	76/24	99

^a Unless otherwise specified, the reaction was carried out using (*R,R*)-*t*-Bu-QuinoxP* (5 mol %), silver acetate (5 mol %), dibutyltin dimethoxide (10 mol %), alkenyl trichloroacetate (2 equiv), nitrosoarene (1 equiv), and methanol (30 equiv) in toluene at $-78\text{ }^{\circ}\text{C}$ for 3 h. ^b Isolated yield. ^c The value is for the *O*-adduct and was determined by HPLC analysis. ^d The absolute configuration is shown in parentheses.

cycloheptanone derivatives gave high optical purities similar to that of the cyclohexanone derivative (entries 1–3). In regard to 1-tetralone derivatives, nearly exclusive *O*-selectivity in addition to excellent enantioselectivity was observed, although the 2-methyl-1-tetralone derivative afforded a low yield because of steric bulkiness (entries 4–6). The existence of two methyl groups at either the 4- or 6-position of the cyclohexanone-derived alkenyl trichloroacetate effectively improved the *O/N* ratio (entries 7 and 8). In the case of acyclic alkenyl trichloroacetates, a significant amount of *N*-adduct was formed (entries 9 and 10).

Table 3. Catalytic Asymmetric *O*-Nitroso Aldol Reaction of Various Alkenyl Trichloroacetates^a

entry	alkenyl ester	yield, % ^b	<i>O/N</i>	ee, % ^c	entry	alkenyl ester	yield, % ^b	<i>O/N</i>	ee, % ^c
1		81	76/24	97	6 ^e		24	82/18	95
2		65	89/11	99 (S) ^d	7		71	97/3	97
3		72	68/32	96	8		68	91/9	97
4		92	>99/1	99	9		8	51/49	92
5		90	96/4	97	10		21	<1/99	3 ^f

^a Unless otherwise specified, the reaction was carried out using (*R,R*)-*t*-Bu-QuinoxP* (5 mol %), silver acetate (5 mol %), dibutyltin dimethoxide (10 mol %), alkenyl trichloroacetate (2 equiv), nitrosobenzene (1 equiv), and methanol (30 equiv) in toluene at -78°C for 3 h. ^b Isolated yield. ^c The value is for the *O*-adduct and was determined by HPLC analysis. ^d The absolute configuration is shown in parentheses. ^e The reaction was performed at -40°C . ^f The value is for the *N*-adduct.

A plausible catalytic cycle is shown in Figure 1. First of all, $\text{Bu}_2\text{Sn}(\text{OMe})_2$ reacts with alkenyl trichloroacetate **1** to yield tin enolate **2** accompanied by methyl trichloroacetate. Next, enolate **2** is allowed to add to nitrosobenzene enantioselectively in the presence of the chiral phosphine $\cdot\text{silver(I)}$ complex, affording the tin amide of α -aminooxy ketone **3**. Finally, protonation of tin amide **3** with MeOH results in the formation of optically active α -aminoxy ketone **4** and the regeneration of $\text{Bu}_2\text{Sn}(\text{OMe})_2$. The rapid methanolysis of tin amide **3** promotes the catalytic cycle.

The proposed transition state structures of this *O*-nitroso aldol reaction are shown in Figure 2. Initially, the silver atom of the (*R,R*)-*t*-Bu-QuinoxP* $\cdot\text{AgOAc}$ complex coordinates to the nitrogen atom of nitrosobenzene. A tin enolate then approaches the oxygen atom of nitrosobenzene while avoiding steric repulsion from a *tert*-butyl group of the chiral phosphine ligand. Thus, aminoxylation occurs selectively at the *Si* face of the tin enolate to afford the (*S*)- α -aminoxy ketone.

In conclusion, we have developed a novel catalytic asymmetric aminoxylation system. The use of the *t*-Bu-QuinoxP* $\cdot\text{AgOAc}$ complex as the chiral catalyst and $\text{Bu}_2\text{Sn}(\text{OMe})_2$ as the achiral cocatalyst allows the synthesis of various nonracemic α -aminoxy ketones with enantioselectivities of up to 99% ee.

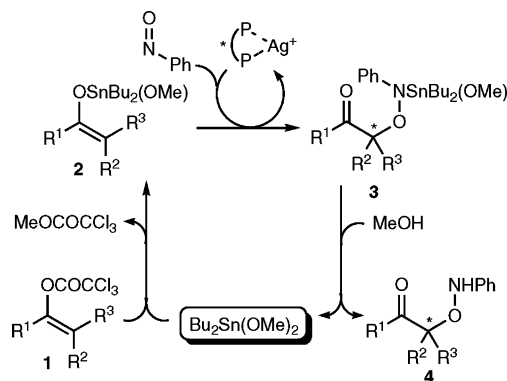


Figure 1. Plausible catalytic cycle for the asymmetric *O*-nitroso aldol reaction.

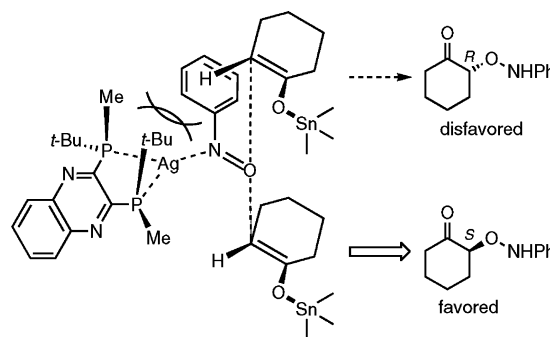


Figure 2. Proposed transition states for the asymmetric *O*-nitroso aldol reaction.

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Supporting Information Available: Experimental procedures and spectral data for the products in Tables 1–3. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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