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

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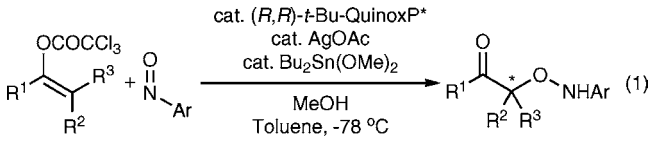
The asymmetric nitroso aldol reaction is a convenient method for the preparation of nonracemic α-aminooxy and/or α-hydroxyamino carbonyl compounds.[1−3] We have recently found that dibutyltin dimethoxide catalyzes the *N*-nitroso aldol reaction between alkenyl trichloroacetates and nitrosobenzene in 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).



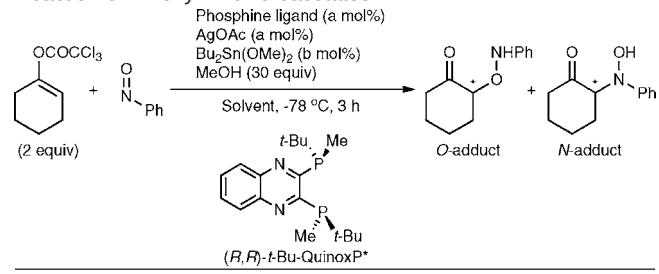
(1)

First, we tested the catalytic activity of BINAP·AgX complexes that have been shown by Momiyama and Yamamoto[5] 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 $Bu_2Sn(OMe)_2$ (20 mol %) in the presence of MeOH (30 equiv) in toluene at −78 °C for 3 h, an 87:13 mixture of the α-aminooxy 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 $Bu_2Sn(OMe)_2$ 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-aminooxylation, as shown in Table 3. Both cyclopentanone and

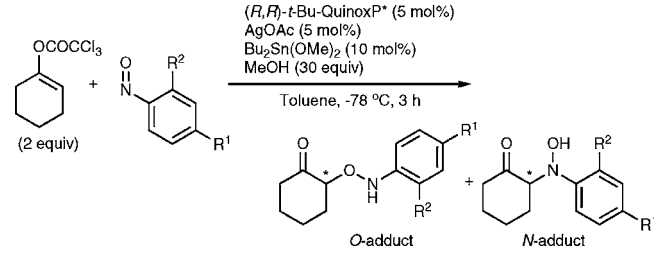
Table 1. Optimization of Catalytic Asymmetric Nitroso Aldol Reaction of Alkenyl Trichloroacetates[a]



entry	phosphine ligand	a	b	solvent	yield, %[b]	*O*/*N*	ee, % (*O*-adduct)[c]
1[d]	(*S*,*S*)-CHIRAPHOS	10	20	toluene	55	72/28	<1
2[d]	(*S*)-BINAP	10	20	toluene	73	87/13	85 (*R*)
3[d]	(*S*)-Tol-BINAP	10	20	toluene	68	90/10	92 (*R*)
4	(*R*)-MOP	10	20	toluene	29	39/61	22 (*S*)
5[d]	(*S*)-SEGPHOS	10	20	toluene	68	79/21	93 (*R*)
6	(*R*,*R*)-*t*-Bu-QuinoxP*	10	20	toluene	70	91/9	98 (*S*)
7	(*R*,*R*)-*t*-Bu-QuinoxP*	10	20	CH_2Cl_2	45	78/22	96 (*S*)
8	(*R*,*R*)-*t*-Bu-QuinoxP*	10	20	Et_2O	68	88/12	98 (*S*)
9	(*R*,*R*)-*t*-Bu-QuinoxP*	10	20	THF	68	73/27	94 (*S*)
10	(*R*,*R*)-*t*-Bu-QuinoxP*	10	20	MeOH	64	92/8	95 (*S*)
11	(*R*,*R*)-*t*-Bu-QuinoxP*	5	10	toluene	65	89/11	99 (*S*)
12	(*R*,*R*)-*t*-Bu-QuinoxP*	2	4	toluene	26	79/21	98 (*S*)

[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 °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]	*O*/*N*	ee, % (*O*-adduct)[c]
1	H	H	65	89/11	99 (*S*)[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 °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.

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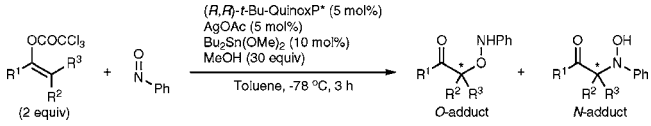
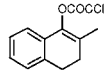
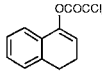
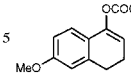
cycloheptanone derivatives gave high optical purities similar to that of the cyclohexanone derivative (entries 1−3). In regard to 1-tetralone derivatives, nearly exclusive O-selectivity in addition to excellent enantioselectivity was observed, although the 2-methyl-1-tetralone derivative afforded a low 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]	*O*/*N*	ee, %[c]	entry	alkenyl ester	yield, %[b]	*O*/*N*	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	 (*E*/*Z* = 1/4)	8	51/49	92
5		90	96/4	97	10	 (*E*/*Z* = 1/4)	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, $Bu_2Sn(OMe)_2$ 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·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-aminooxy ketone **4** and the regeneration of $Bu_2Sn(OMe)_2$. 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*·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, aminooxylation occurs selectively at the *Si* face of the tin enolate to afford the (*S*)-α-aminooxy ketone.

In conclusion, we have developed a novel catalytic asymmetric aminooxylation system. The use of the *t*-Bu-QuinoxP*·AgOAc complex as the chiral catalyst and $Bu_2Sn(OMe)_2$ as the achiral cocatalyst allows the synthesis of various nonracemic α-aminooxy ketones with enantioselectivities of up to 99% ee.

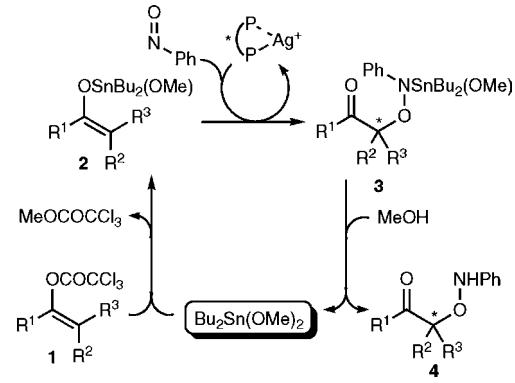


Figure 1. Plausible catalytic cycle for the asymmetric *O*-nitroso aldol reaction.

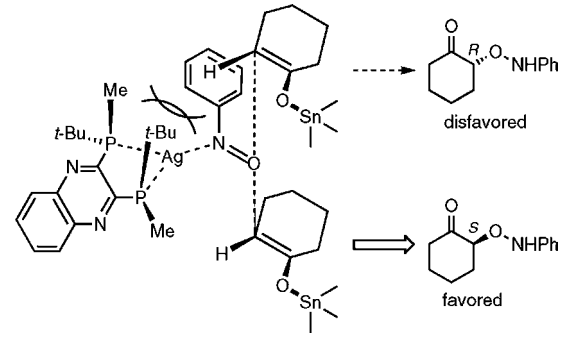


Figure 2. Proposed transition states for the asymmetric *O*-nitroso aldol reaction.

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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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