Asymmetric Catalysis

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Enantioselective O-Nitroso Aldol Reaction of Silyl Enol Ethers**

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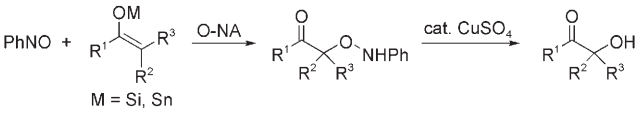
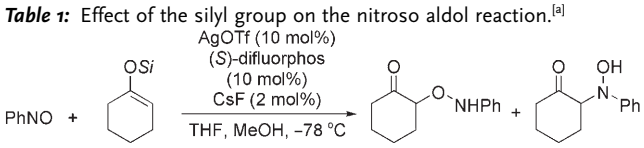
The regio- and stereoselective introduction of a hydroxy group at the α position to a carbonyl group is an important transformation in organic synthesis.[1] Recently, we reported that the asymmetric nitroso aldol (NA) reaction is a powerful method for this endeavor.[2,3] Although NA reactions of nitrosobenzene with tin enolates in the presence of silver catalysts proceeded with excellent regio- and enantioselectivities, this reaction has a drawback: The use of tin enolates is unfavorable for the environment. Enantioselective O-nitroso aldol reactions in the presence of an organocatalyst or with enamines have also been developed. However, the regioselective formation of highly substituted enamines is a problematic issue. As the silyl group is environmentally benign and the regioselective formation of silyl enol ethers is well known, we focused on the use of silyl enol ethers as nucleophiles. Herein, we describe the enantioselective O-NA reaction of silyl enol ethers (Scheme 1).



Scheme 1. The O-nitroso aldol reaction.

On the basis of the successful NA reaction of tin enolates,[3c,e] we first attempted the reaction of PhNO (**1**) with the silyl enol ether **2aa** in the presence of a chiral silver catalyst (Table 1). In the absence of a fluoride source, the reaction did not proceed at all (Table 1, entry 1). To improve the reactivity of the silyl enol ether, CsF was used as an additive. Under these conditions, **3a** and **4a** were obtained as an approximately 1:1 mixture in up to 44% yield (Table 1, entry 2). When **1** was treated with the bulky silyl enol ethers **2ab** and **2ac** under the same conditions, the desired products were not formed (Table 1, entries 3 and 4). However, we found that the disilanyl enol ether **2ad**, which has a Si–Si bond, was an excellent nucleophile.[4] Thus, the reaction of **1** with **2ad** afforded **3a** and **4a** in 69% combined yield (Table 1, entry 5).[5] The disilanyl enol ether was used for further studies as a result of its high reactivity and stability.[6]

Table 1: Effect of the silyl group on the nitroso aldol reaction.[a]



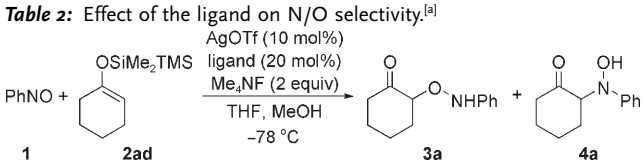
1 **2aa–2ad** **3a** **4a**

Entry	Silyl enol ether	**3a**/**4a**	Yield [%][b]	*ee* [%][c] **3a**/**4a**
1[d]	**2aa**: *Si* = TMS	–	NR[e]	–
2	**2aa**: *Si* = TMS	44:56	23–44	76/17
3	**2ab**: *Si* = TBS	–	NR[e]	–
4	**2ac**: *Si* = TIPS	–	NR[e]	–
5	**2ad**: *Si* = $SiMe_2$TMS	61:39	69	73/19

[a] Nitrosobenzene (**1**): 1 equivalent, **2**: 1 equivalent. [b] Combined yield of **3a** and **4a**. [c] The *ee* values were determined by HPLC analysis on a chiral phase. [d] The reaction was conducted without CsF. [e] No reaction. Difluorphos = [4,4′-bi(2,2-difluoro-1,3-benzodioxol)-5,5′-diyl]-bis(diphenylphosphane), TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

Various achiral ligands were surveyed in an attempt to create a silver catalyst that would promote the selective formation of **3a** over **4a** in the reaction of PhNO (**1**) with **2ad** (Table 2). A series of reactions with phosphine ligands showed clearly that electron-deficient phosphine ligands gave the O adduct **3a** preferentially (Table 2, entries 1–4). Encouraged by these results, we tested other electron-deficient ligands and found that $PPh(OPh)_2$ and $P(OPh)_3$ gave **3a** with good selectivity (Table 2, entries 5, 6, and 8). Moreover, when 10 mol% of $P(OPh)_3$ was used, **3a** was obtained almost exclusively (Table 2, entry 9). On the other

Table 2: Effect of the ligand on N/O selectivity.[a]



1 **2ad** **3a** **4a**

Entry	Ligand	**3a**/**4a**[b]	Entry	Ligand	**3a**/**4a**[b]
1	PPh_3	62:38	6	$PPh(OPh)_2$	93:7
2	$P(c\text{-Hex})_3$	55:45	7[c]	$PPh(OPh)_2$	95:5
3	$P(2\text{-furyl})_3$	66:34	8	$P(OPh)_3$	90:10
4	$P(C_6F_5)_3$	84:16	9[c]	$P(OPh)_3$	97:3
5	$PPh_2(OPh)$	87:13	10	$P(OEt)_3$	84:16

[a] Nitrosobenzene (**1**): 1 equivalent, **2**: 1 equivalent. [b] The ratio was determined by ^{1}H NMR spectroscopy of the crude product mixture. [c] Ligand: 10 mol%.

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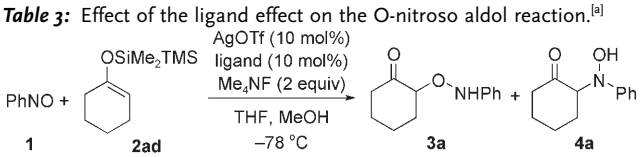
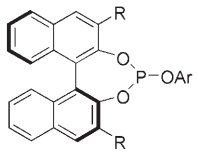
hand, the selectivity of the reaction decreased significantly with $P(OEt)_3$ (Table 2, entry 10).

On the basis of these results, which clearly indicate that electron-deficient ligands provide highly active catalysts with high O selectivity, we examined the chiral phosphite ligands **5a–g** derived from (*S*)-1,1′-binaphthalene-2,2′-diol ((*S*)-binol; Table 3).[7] Generally, the reaction afforded **3a** selectively in

Table 3: Effect of the ligand effect on the O-nitroso aldol reaction.[a]





5a: Ar = 1-naphthyl, R = H
5b: Ar = 2-naphthyl, R = H
5c: Ar = 2,6-*t*Bu$_2$-4-MeC$_6$H$_2$, R = H
5d: Ar = 1-naphthyl, R = Ph
5e: Ar = 1-naphthyl, R = 2,4,6-Me$_3$C$_6$H$_2$
5f : Ar = Ph, R = 2,4,6-*i*Pr$_3$C$_6$H$_2$
5g: Ar = Ph, R = Ph

Entry	Ligand	Yield of **3a** [%]	*ee* (**3a**) [%][b]	**3a**/**4a**[c]
1	**5a**	63	44	95:5
2	**5b**	40	35	>99:1
3	**5c**	38	18	93:7
4	**5d**	59	90	97:3
5	**5e**	52	86	>99:1
6[d]	**5f**	49	28	97:3
7	**5g**	49	94	98:2

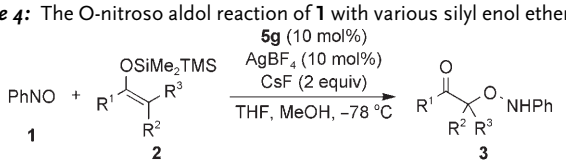
[a] Nitrosobenzene (**1**): 1 equivalent, **2**: 1 equivalent. [b] The *ee* value was determined by HPLC analysis on a chiral phase. [c] The ratio was determined by ^{1}H NMR spectroscopy of the crude product mixture. [d] CsF was used instead of Me_4NF.

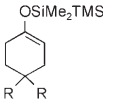
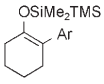
the presence of the silver–phosphite catalysts. First, we tested the simple binol-derived ligands **5a–c**. The reactions in the presence of **5a** and **5b** gave **3a** with moderate enantioselectivity (Table 3, entries 1 and 2). However, when **5c**, which has a bulky OAr moiety, was used as the ligand, the *ee* value of **3a** decreased significantly (Table 3, entry 3). Encouraged by these results, we prepared the 3,3′-disubstituted binol-derived ligands **5d–g**. When **5d** was used, the *ee* value of **3a** increased dramatically (Table 3, entry 4). Although the reaction with **5e** gave **3a** with 86% *ee*, the enantioselectivity decreased with **5f** (Table 3, entries 5 and 6). Finally, we found that **5g** was the optimal ligand: In the presence of this binol derivative, **3a** was formed with 94% *ee* (Table 3, entry 7).

Next, we optimized the reaction conditions (see the Supporting Information for details). We found that the reaction in the presence of $AgBF_4$ (10 mol%) and **5g** afforded **3a** with 95% *ee* in 85% yield when CsF was used as the fluoride source. Furthermore, when the quantity of $AgBF_4$ was decreased to 5 mol%, **3a** was formed with 95% *ee* in 76% yield in the presence of **5g** and CsF.

The generality of this reaction was studied with various silyl enol ethers (Table 4). PhNO (**1**) reacted with the six-membered-ring enol ethers **2ad**, **2b**, and **2c** to provide the corresponding products **3a–c** with 95–98% *ee* (Table 4, entries 1–3). Moreover, the tetrahydropyran derivative **2d** is a suitable substrate, the reaction of which with **1** gave the

Table 4: The O-nitroso aldol reaction of **1** with various silyl enol ethers.[a]



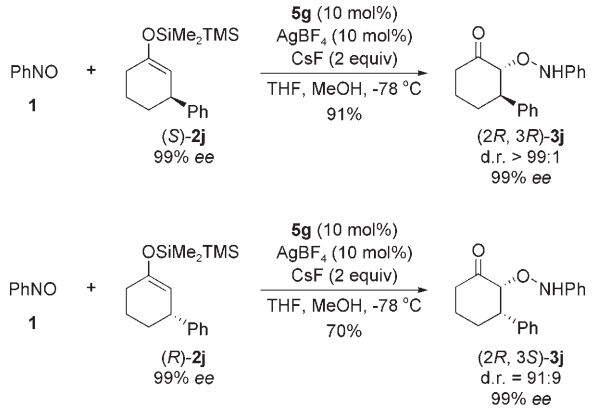
Entry	Silyl enol ether		Yield [%]	*ee* [%][b]
1		**2ad**: R = H	85	95
2		**2b**: R = Me	72	98
3		**2c**: R = OCH_2CH_2O	85	96
4		**2d**	6	97
5		**2e**: *n* = 1	41[c]	90
6		**2f**: *n* = 3	37[d]	64
7		**2g**	84	92
8		**2h**: Ar = Ph	99	79
9		**2i**: Ar = 2-naphthyl	80	76

[a] Nitrosobenzene (**1**): 1 equivalent, **2**: 1 equivalent. [b] The *ee* value was determined by HPLC analysis on a chiral phase. [c] The corresponding N adduct was obtained in 20% yield. [d] The corresponding N adduct was obtained in 27% yield.

corresponding adduct with 97% *ee* in 66% yield (Table 4, entry 4). The reaction of the five-membered-ring silyl enol ether **2e** gave the adduct **3e** with 90% *ee* in 41% yield; however, the *ee* value of the seven-membered-ring adduct **3f** was significantly lower (Table 4, entries 5 and 6). The α-tetralone derivative **2g** reacted with **1** to afford the corresponding adduct with 92% *ee* in 84% yield (Table 4, entry 7). Furthermore, 2-substituted cyclohexanone derivatives can be used: The reactions of **2h** and **2i** afforded the corresponding adducts, which contain a *tert*-aminoxy group, with 79 and 76% *ee*, respectively (Table 4, entries 8 and 9).

We examined the diastereoselectivity of this reaction with the chiral silyl enol ether substrates (*S*)- and (*R*)-**2j**, which can be prepared selectively from cyclohexenone.[8] The reaction of (*S*)-**2j** with nitrosobenzene (**1**) in the presence of the catalyst afforded (2*R*,3*R*)-**3j** as a single diastereomer in 91% yield (Scheme 2). The enantiomeric substrate (*R*)-**2j** reacted with **1** under same conditions to give (2*R*,3*S*)-**3j** with high diastereoselectivity.[9] These results show that the stereochemical outcome of the O-NA reaction can be controlled by the catalyst regardless of the configuration of the silyl enol ether substrate at C3. Thus, our process provides a new synthetic strategy for controlling 1,2-stereoselectivity in organic synthesis.

In conclusion, we have developed a silver-catalyzed regio- and enantioselective O-nitroso aldol reaction of silyl enol ethers with a new silver–phosphite catalyst system. Disilanyl enol ethers were shown to be excellent nucleophiles, as they are not only more stable but also more reactive than trimethylsilyl enol ethers. Further studies on the use of the silver–phosphite catalyst and synthetic applications of this reaction are currently underway in our laboratory.



Scheme 2. Diastereoselective O-nitroso aldol reaction.

Experimental Section

General procedure: $AgBF_4$ (9.7 mg, 50 μmol) and **5g** (28 mg, 50 μmol) were placed in a Schlenk tube, and the mixture was dried under vacuum for 10 min. Anhydrous THF (2 mL) was then added, and the mixture was stirred under argon at room temperature for 0.5 h. The clear solution was then cooled to −78°C, and PhNO (53.5 mg, 0.50 mmol) dissolved in anhydrous THF (1 mL) was added dropwise. The resulting blue solution was stirred for 5 min, and then the silyl enol ether (0.5 mmol) was added dropwise. CsF (151.9 mg, 1 mmol) dissolved in anhydrous MeOH (1 mL) was added slowly to the resulting solution at −78°C over a period of 16 h. After completion of the addition, the reaction mixture was diluted with hexane and AcOEt (3:1), filtered through short pad of silica gel (elution with hexane/ethyl acetate 3:1), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the O-nitroso aldol adduct.

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[5] Several chiral phosphine ligands, including binap (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl), segphos ((4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphane)), tol-binap (2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl), and xylyl-solphos (7,7′-bis(di-3,5-xylylphosphanyl)-3,3′,4,4′-tetrahydro-4,4′-dimethyl-8,8′-bi(2*H*-1,4-benzoxazine)) were tested; however, mixtures of products were obtained with moderate *ee* values.

[6] Although the pentamethyldisilanyl group is bulky, it makes enol ethers more reactive, because the Si–Si bond donates electrons to the π system by hyperconjugation; for similar examples, see: a) M. Akakura, M. B. Boxer, H. Yamamoto, *ARKIVOC* **2007**, 337; b) H. Yamamoto, M. B. Boxer, *Chimia* **2007**, *61*, 279; c) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 2762; d) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48; e) M. B. Boxer, H. Yamamoto, *Org. Lett.* **2005**, *7*, 3127.

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