Metal-Free Enantioselective Hydroxyamination of Aldehydes with Nitrosocarbonyl Compounds Catalyzed by an Axially Chiral Amine

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S *Supporting Information*

ABSTRACT: The first example of a highly regio- and enantioselective hydroxyamination of aldehydes with in situ generated nitrosocarbonyl compounds from hydroxamic acid derivatives was realized by combined use of TEMPO and BPO as the oxidant in the presence of a binaphthyl-modified amine catalyst.

Nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in synthetic organic chemistry.[1−3] Among them, nitrosocarbonyl compounds, which can be generated in situ by oxidation of hydroxamic acid derivatives, are highly unstable transient species and have long been employed mainly in hetero-Diels−Alder reactions[2] and ene reactions,[3] despite their high synthetic potential (Scheme 1).[4,5]

**Scheme 1. Typical Reactions of Nitrosocarbonyl Compounds**
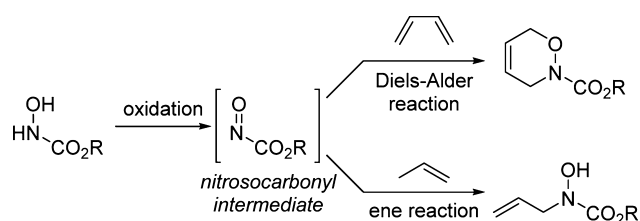
Very recently, both aminoxylation[6] and hydroxyamination[7] of β-ketoesters with in situ generated nitrosocarbonyl compounds were reported as new entries to the reaction of nitrosocarbonyl compounds (Scheme 2). The asymmetric aminoxylation is only one example of the catalytic asymmetric reaction of nitro-

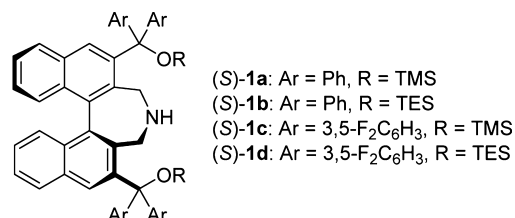**Scheme 2. Addition Reactions to in Situ Generated Nitrosocarbonyl Compounds**
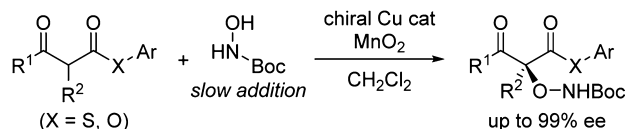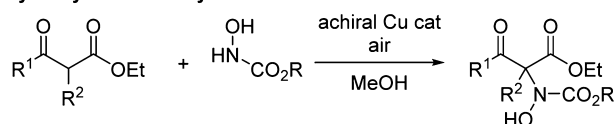
socarbonyl compounds to date,[6] while a number of catalytic asymmetric transformations using relatively stable and easily handled nitrosobenzene have been developed.[8−10] The difficulty in developing the catalytic asymmetric reaction of nitrosocarbonyl compounds can be attributed to their high reactivity as well as instability. Indeed, the development of the catalytic asymmetric hydroxyamination with nitrosocarbonyl compounds still remains challenging. In this context, we have been interested in the possibility of developing such an asymmetric transformation, which introduces a nitrogen atom bearing a readily removable protecting group. Herein, we wish to report a highly regio- and enantioselective hydroxyamination of aldehydes with in situ generated nitrosocarbonyl compounds by using a binaphthyl-modified amine catalyst of type **1**.[11]

(S)-**1a**: Ar = Ph, R = TMS
(S)-**1b**: Ar = Ph, R = TES
(S)-**1c**: Ar = 3,5-F$_2$C$_6$H$_3$, R = TMS
(S)-**1d**: Ar = 3,5-F$_2$C$_6$H$_3$, R = TES

We chose *tert*-butyl *N*-hydroxycarbamate (**2a**) as a precursor of the nitrosocarbonyl intermediate because of the synthetic utility of the *N*-Boc group. In the presence of the binaphthyl-modified amine catalyst (S)-**1a**,[12] various oxidants were screened to generate the nitrosocarbonyl intermediate in the reaction of 3-phenylpropanal with **2a** (Table 1). When standard oxidants such as PhI(OAc)$_2$ and CuCl−pyridine−air for this purpose were used, the undesired aminoxylated product **4a** was obtained in low yield (entries 1 and 3).[2,3,5] While MnO$_2$ gave only a small amount of the desired hydroxyamination product **3a**,[6] the aminoxylation product **4a** was still the major product (entry 4). On the other hand, a combination of 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) and benzoyl peroxide (BPO), which is known to generate the corresponding oxoammonium salt,[12a] gave the desired **3a** as a major product in good yield and enantioselectivity (entry 5).[13] Since use of either TEMPO or BPO afforded neither **3a** nor **4a** (entries 6 and 7), the oxoammonium salt generated from TEMPO and BPO would be the actual oxidant of **2a**.[12a]

We then optimized the reaction conditions and the catalyst as shown in Table 2. Among the solvents tested, 1,2-dichloroethane was found to be the best in terms of the

Table 1. Screening of Oxidant[a]
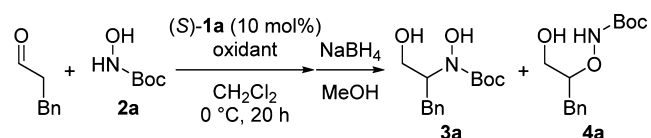
entry	oxidant (equiv)	yield (%)[b]	3a/4a[c]	ee (%)[d]
1	PhI(OAc)$_2$ (2.0)	20	1/>20	–
2	DMP (2.0)	nd	–	–
3	CuCl (0.1), pyridine (0.025), air	10	1/>20	–
4	MnO$_2$ (2.0)	26	1/2.4	–
5	TEMPO (2.0), BPO (1.0)	71	2.5/1	70
6[e]	TEMPO (3.0)	nd	–	–
7[e]	BPO (2.0)	nd	–	–

[a]The reaction of 3-phenylpropanal (0.050 mmol) with **2a** (0.10 mmol) in CH$_2$Cl$_2$ (1.0 mL) was carried out in the presence of (S)-**1a** (0.005 mmol) and an oxidant. [b]Combined yield of **3a** and **4a**. [c]Determined by ^{1}H NMR analysis. [d]The ee of **3a** was determined by HPLC using a chiral column. [e]Using 3.0 equiv of **2a**.

Table 2. Screening of Reaction Conditions[a]
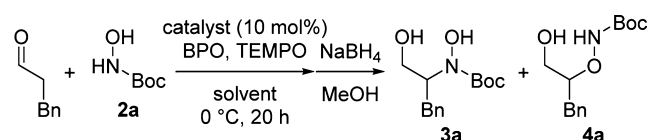
entry	solvent	catalyst	yield (%)[b]	3a/4a[c]	ee (%)[d]
1	THF	(S)-**1a**	20	1/>20	–
2	toluene	(S)-**1a**	25	1/>20	–
3	CH$_2$Cl$_2$	(S)-**1a**	71	2.5/1	70
4	CHCl$_3$	(S)-**1a**	69	1.0/1	61
5[e]	(CH$_2$Cl)$_2$	(S)-**1a**	70	3.7/1	75
6	(CH$_2$Cl)$_2$	(S)-**1b**	60	1.4/1	90
7	(CH$_2$Cl)$_2$	(S)-**1c**	47	>20/1	95
8	(CH$_2$Cl)$_2$	(S)-**1d**	77	>20/1	98

[a]The reaction of 3-phenylpropanal (0.050 mmol) with **2a** (0.10 mmol) in a solvent (1.0 mL) was carried out in the presence of a catalyst (0.005 mmol), BPO (0.050 mmol), and TEMPO (0.10 mmol). [b]Combined yield of **3a** and **4a**. [c]Determined by ^{1}H NMR analysis. [d]The ee of **3a** was determined by HPLC using a chiral column. [e]Aminoxylation product (R)-**4a** was obtained as a major enantiomer (47% ee).

regio- and enantioselectivity (entry 5). Replacing TMS groups in the catalyst (S)-**1a** with TES groups resulted in an increase in enantioselectivity (entry 6). When the catalysts having 3,5-difluorophenyl groups instead of phenyl groups were used, a significant improvement in both regio- and enantioselectivity was observed and thus led to the formation of **3a** exclusively (entries 7 and 8).[14] Introduction of fluorine groups to phenyl groups of the catalyst might change the conformation of the catalyst and increase selectivities.

With the optimized conditions in hand, we examined the substrate scope, and the results are shown in Table 3. In the presence of 10 mol % of (S)-**1d**, 2 equiv of TEMPO, and 1 equiv of BPO, the reactions of various aldehydes with **2a** gave the corresponding hydroxyamination products **3** in moderate to good yields with excellent regio- and enantioselectivities (entries 1–9). Unfortunately, the reactions of the sterically hindered 3,3-dimethylbutanal and phenylacetaldehyde did not afford the desired product (entries 10 and 11). Benzyl N-hydroxycarbamate (**2b**) was also applicable to the present

Table 3. Enantioselective Hydroxyamination of Various Aldehydes[a]
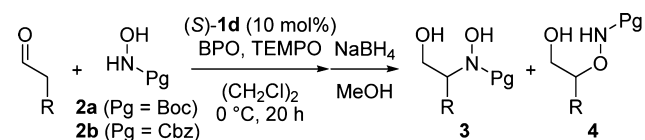

entry	R	Pg	yield (%)[b]	3/4[c]	ee (%)[d]
1	Me	Boc	66	>20/1	98
2	Bu	Boc	80	>20/1	99
3	Bn	Boc	77	>20/1	98
4	allyl	Boc	67	>20/1	94
5	CH$_2$Cy	Boc	56	>20/1	99
6	(CH$_2$)$_3$OBn	Boc	95	>20/1	99
7[e]	CH$_2$CO$_2$Me	Boc	56	>20/1	92
8	i-Pr	Boc	75	>20/1	99
9	Cy	Boc	65	>20/1	99
10	t-Bu	Boc	nd	–	–
11	Ph	Boc	nd	–	–
12	Bn	Cbz	60	>20/1	99

[a]The reaction of an aldehyde (0.050 mmol) with **2** (0.10 mmol) in 1,2-dichloroethane (1.0 mL) was carried out in the presence of (S)-**1d** (0.005 mmol), BPO (0.050 mmol), and TEMPO (0.10 mmol). [b]Isolated yield of **3**. [c]Determined by ^{1}H NMR analysis. [d]The ee of **3** was determined by HPLC using a chiral column. [e]Use of **2a** (0.15 mmol), BPO (0.075 mmol), and TEMPO (0.15 mmol).

hydroxyamination, and the corresponding product with a Cbz protecting group was obtained with virtually perfect regio- and enantioselectivity (entry 12). In all cases, the aminoxylation products **4** were not observed by TLC and ^{1}H NMR analysis.

The obtained hydroxyamination product was a useful intermediate in organic synthesis and readily converted to the corresponding 1,2-hydroxyamino alcohol and N-Boc-protected 1,2-amino alcohol, respectively (Scheme 3). When a solution of

**Scheme 3. Transformations of Hydroxyamination Product**
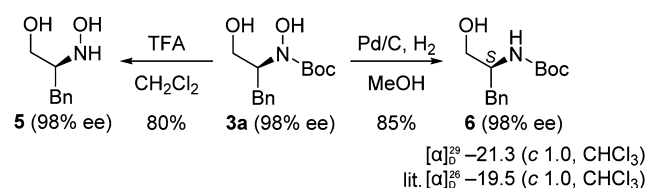
3a in CH$_2$Cl$_2$ was treated with TFA at room temperature, 1,2-hydroxyamino alcohol **5** was obtained in good yield with complete retention of stereochemistry. On the other hand, reduction of **3a** with Pd/C under a hydrogen atmosphere at room temperature gave the N-Boc-protected 1,2-amino alcohol **6** in good yield without loss of optical purity. The absolute configurations of **3a** and **6** were determined to be S by comparing the optical rotation of **6** with the literature value.[15]

We have previously reported that the direct asymmetric aminoxylation of aldehydes with the in situ generated oxoammonium salt **8** from TEMPO and BPO was catalyzed by (S)-**1a**, giving the aminoxylation product **7** with R configuration (Scheme 4).[12a,16] Interestingly, the present hydroxyamination did not afford **7** under similar conditions (Scheme 5), and therefore, the oxidation of **2a** with **8** must be significantly faster than the aminoxylation of aldehydes with **8**. Additionally, when the reaction was performed under identical conditions for the present hydroxyamination, but in the

Scheme 4. Previous Aminoxylation Using TEMPO and BPO

7
99%, 95% ee
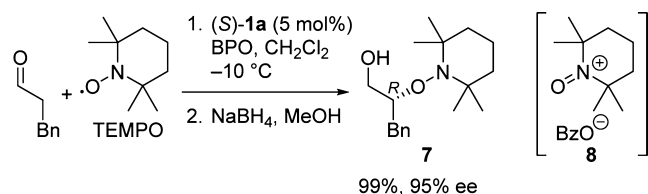
Scheme 5. Hydroxyamination vs Aminoxylation

|	3a	7
2a (2 eq.)	77%, 98% ee	not detected
2a (0 eq.)	-	52%, 88% ee
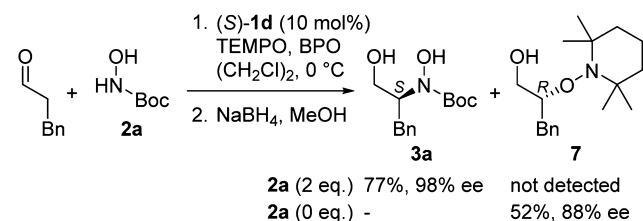
absence of **2a**, the aminoxylation product **7** with an *R* configuration was obtained as the major enantiomer (Scheme 5). Since the enantiofacial selectivity was inversed depending on the electrophile used,[17] we have then examined another electrophile to clarify the unique behavior of our catalyst. When *tert*-butyl glyoxylate was employed instead of the in situ generated nitrosocarbonyl compounds in the presence of (*S*)-**1d**, the aldol reaction proceeded to give *syn*-**9** with (2*R*,3*R*) configuration as a major stereoisomer (Scheme 6).

Scheme 6. Aldol Reaction of *tert*-Butyl Glyoxylate

syn-**9**	*anti*-**9**
35%, 47% ee	9%, 25% ee
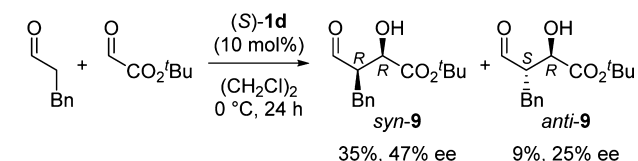
Based on the observed stereochemistry, transition state models can be proposed, as shown in Figure 1. In the present hydroxyamination and the aldol reaction, both the in situ generated nitrosocarbonyl intermediate and *tert*-butyl glyoxylate gain access to the sterically more congested *Si* face of the enamine compared to the *Re* face (**TS1** and **TS2**). Both electrophiles might approach the *Si* face with the aid of a CH/π interaction between the *tert*-butyl group of the electrophiles and the aryl substituent of the catalyst[18] and/or a hydrogen bonding between Ar−H of the catalyst aryl substituent and electrophiles.[19] In the aminoxylation with either the in situ generated nitrosocarbonyl compound (Table 2, entry 5) or **8** (Scheme 5), on the other hand, the *Si* face of the enamine intermediate is effectively shielded by the right-hand bulky substituent of (*S*)-**1** (**TS3** and **TS4**). Consequently, the reaction of an aldehyde with the nitrosocarbonyl intermediate or **8** catalyzed by (*S*)-**1** provides the *R* isomers predominantly.

In summary, we have realized a highly regio- and enantioselective hydroxyamination of aldehydes with hydroxamic acid derivatives by using a combination of TEMPO and BPO as the oxidant and the binaphthyl-modified amine catalyst. This method represents the first example of using the in situ generated nitrosocarbonyl compounds for the catalytic asymmetric hydroxyamination, which provides a new entry to the enantioselective introduction of a nitrogen functionality in

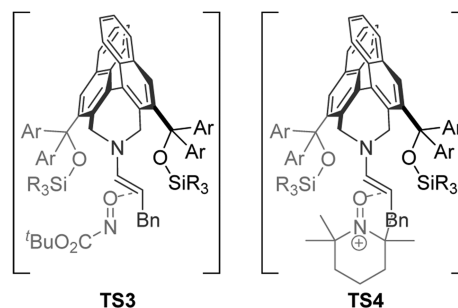**Hydroxyamination/Aldol Reaction**
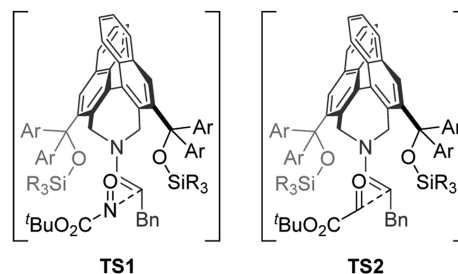
Aminoxylation

Figure 1. Plausible transition state models.

organic synthesis. Further study is underway to ascertain mechanistic details of the present hydroxyamination.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Use of a catalytic amount of TEMPO resulted in a significant decrease in yield.

(14) When TMS ether of diphenylprolinol was used as the catalyst under identical conditions, **3a** was obtained exclusively, albeit in low yield (30% yield, 94% ee).

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(17) In the presence of (*S*)-**1d**, the nucleophilic substitution by **2a** at the α-position of the α-aminoxy aldehyde, which was obtained from the reaction between 3-phenylpropanal and **8**, did not proceed. This result suggests that the in situ generated α-aminoxy aldehyde is not a precursor of the desired hydroxyamination product. See Supporting Information for details.

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