Organic LETTERS

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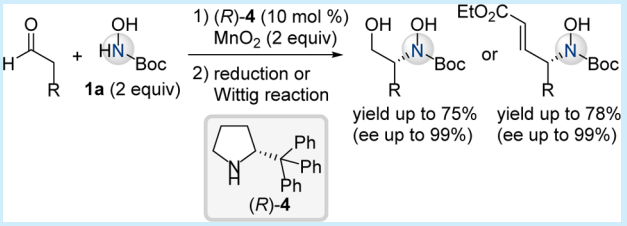
Practical Approach for Asymmetric Hydroxyamination of Aldehydes with *in Situ* Generated Nitrosocarbonyl Compounds: Application to One-Pot Synthesis of Chiral Allylamines

Taichi Kano, Fumitaka Shirozu, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

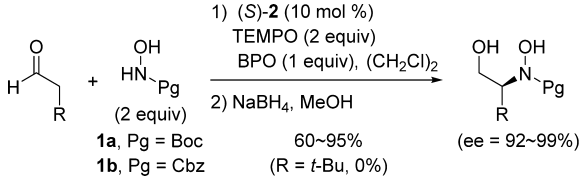
Supporting Information

ABSTRACT: The highly regio- and enantioselective hydroxyamination of aldehydes with *in situ* generated nitrosocarbonyl compounds from a hydroxamic acid derivative was realized by simple and readily available chiral amine catalysts. The resulting hydroxyamination products were readily converted to the corresponding chiral 1,2-aminoalcohol or allylamine derivatives in one pot.

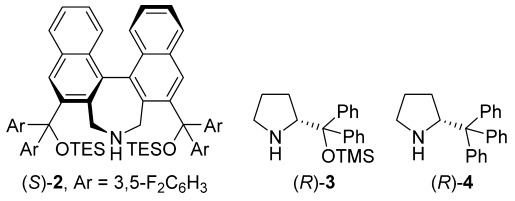


The electrophilic α-amination of carbonyl compounds is one of the most straightforward methods for the synthesis of α-amino carbonyl compounds including α-amino acids.[1] In the area of organocatalysis, enamines, which are *in situ* generated from carbonyl compounds and chiral amine catalysts, are known to react with electrophilic aminating agents, and a number of chiral amine catalyzed α-aminations of aldehydes and ketones have been reported to date.[2] In such reactions, azodicarboxylates are the most frequently used aminating agents;[3] however, transformation of the reaction products to *N*-protected α-amino carbonyl compounds by the N−N bond cleavage requires harsh conditions.[4] In enamine catalysis, nitrosoarenes such as nitrosobenzene have also served as electrophilic aminating agents.[5,6] However, the synthetic utility of products bearing an aryl group on the nitrogen atom is quite limited due to the difficulty in removal of the aromatic *N*-substituent. On the other hand, nitrosocarbonyl compounds are ideal aminating agents, giving α-amino carbonyl compounds having easily removable *N*-substituents such as *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).[7,8] In contrast to relatively stable nitrosobenzene, nitrosocarbonyl compounds are highly reactive and transient species, which are generated *in situ* by oxidation of hydroxamic acids or *N*-hydroxycarbamates. While groups of Read de Alaniz and Yamamoto independently reported the first example of the Cu(II)-catalyzed α-amination of β-ketoesters with *in situ* generated nitrosocarbonyl compounds,[9] their use in asymmetric amination was not achieved. In this context, we have previously developed a metal-free asymmetric hydroxyamination of aldehyde with nitrosocarbonyl intermediates using the binaphthyl-based secondary amine catalyst (*S*)-**2** and a combination of benzoyl peroxide (BPO) and TEMPO as oxidants (Scheme 1).[10] Despite the potential of this organocatalytic transformation, however, the substrate scope of the present system is limited to the sterically less hindered aldehydes, and replacement of the catalyst with a readily available chiral amine and reduction of the amounts of

Scheme 1. Previous Asymmetric Hydroxyamination with *in Situ* Generated Nitrosocarbonyl Compounds



reagents and byproducts are required to improve the utility of this methodology. Thus we investigated a chiral pyrrolidine-catalyzed hydroxyamination of aldehydes with *in situ* generated nitrosocarbonyl compounds by standard oxidants and the application to the one-pot synthesis of chiral allylamine derivatives.

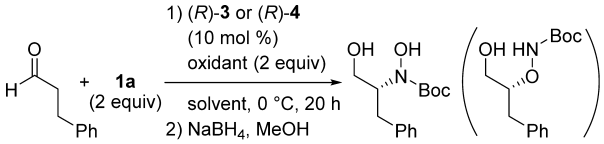


In view of catalyst accessibility, we first chose the secondary amine catalyst (*R*)-**3**,[11] which is commercially available and also readily prepared from L-proline, for the asymmetric hydroxyamination of aldehydes with *in situ* generated nitrosocarbonyl compounds. In the presence of 10 mol % of (*R*)-**3**, various oxidants were screened to generate a nitrosocarbonyl intermediate in the reaction of 3-phenylpropanal with *tert*-butyl *N*-hydroxycarbamate (**1a**) (Table 1). Use of $PhI(OAc)_2$ afforded the desired hydroxyamination product **5a** in low yield albeit with high enantioselectivity (Table 1, entry 1). A slightly

Received: January 9, 2014
Published: February 19, 2014

dx.doi.org/10.1021/ol5000742 | *Org. Lett.* 2014, 16, 1530−1532

Table 1. Asymmetric Hydroxyamination of 3-Phenylpropanal with 1a[a]



entry	catalyst	oxidant	solvent	yield (%)[b]	ee (%)[c]
1	(*R*)-**3**	$PhI(OAc)_2$	CH_2Cl_2	5	95
2[d]	(*R*)-**3**	BPO, TEMPO	CH_2Cl_2	30	93
3	(*R*)-**3**	MnO_2	CH_2Cl_2	52	90
4	(*R*)-**4**	$PhI(OAc)_2$	CH_2Cl_2	5	97
5[d]	(*R*)-**4**	BPO, TEMPO	CH_2Cl_2	56	99
6	(*R*)-**4**	MnO_2	CH_2Cl_2	69	99
7	(*R*)-**4**	MnO_2	$CHCl_3$	50	98
8	(*R*)-**4**	MnO_2	$(CH_2Cl)_2$	23	98
9	(*R*)-**4**	MnO_2	toluene	30	99
10	(*R*)-**4**	MnO_2	THF	n.d.	–

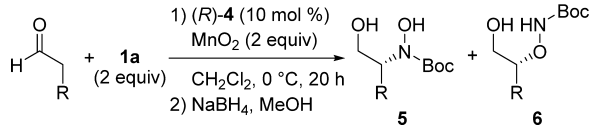
[a]The reaction of 3-phenylpropanal (0.10 mmol) with **1a** (0.20 mmol) was carried out in the presence of an oxidant (0.20 mmol) and a catalyst (0.010 mmol) in a solvent (2.0 mL) at 0 °C for 20 h. [b]Isolated yield of **5a**. Aminoxylation product **6a** was not observed. [c]Enantiomeric excess of **5a** was determined by HPLC using a chiral column. [d]Use of BPO (0.10 mmol) and TEMPO (0.20 mmol).

improved yield was obtained by using the combination of BPO and TEMPO, which generates the corresponding oxoammonium salt (Table 1, entry 2).[12] Finally, MnO_2 was found to be the optimal oxidant and the desired hydroxyamination product was obtained in moderate yield with high enantioselectivity (Table 1, entry 3).[9a] Under these conditions using MnO_2 the formation of organic wastes was significantly reduced. When the readily accessible secondary amine catalyst (*R*)-**4**[13] having a trityl group was used instead of (*R*)-**3**, both yield and enantioselectivity were improved (Table 1, entry 6). Among the solvents tested, dichloromethane provided the highest level of yield (Table 1, entries 6−10). In all cases, the aminoxylation product **6a** was not detected.

With the optimized conditions in hand, we examined the substrate scope, and the results are shown in Table 2. In the presence of 10 mol % of (*R*)-**4** and 2.0 equiv of MnO_2, the reactions of various aldehydes with **1a** gave the corresponding hydroxyamination products **5** in moderate to good yields with excellent regio- and enantioselectivities. The reaction of sterically hindered 3,3-dimethylbutanal, which did not give the product under our previously reported conditions (10 mol % of (*S*)-**2**, 2.0 equiv of TEMPO, 1.0 equiv of BPO), proceeded smoothly to give the desired product (Table 2, entry 9). On the other hand, only a trace amount of product was obtained in the reaction of phenylacetaldehyde (Table 2, entry 10). Use of benzyl *N*-hydroxycarbamate instead of *tert*-butyl *N*-hydroxycarbamate gave the Cbz-protected hydroxyamination product **7** with excellent enantioselectivity albeit in low yield (Scheme 2).

We then examined the one-pot synthesis of chiral allylamine **9** by the present asymmetric hydroxyamination and the subsequent Wittig reaction. The *in situ* treatment of the hydroxyamination products with (ethoxycarbonylmethylene)-triphenylphosphorane (**8**) gave the corresponding (*E*)-allylamines **9** in good yield with high regio- and stereoselectivity (Table 3).

Table 2. Asymmetric Hydroxyamination of Aldehydes with 1a[a]



entry	R	yield (%)[b]	5/6[c]	ee (%)[d]
1	Me	75	>20/1	99
2	Bu	67	>20/1	99
3	Bn	69	>20/1	99
4	Allyl	51	>20/1	97
5	CH_2Cy	51	>20/1	99
6	$(CH_2)_3OBn$	43	>20/1	99
7	*i*-Pr	64	>20/1	99
8	Cy	59	>20/1	99
9	*t*-Bu	63	>20/1	99
10	Ph	<5	–	–

[a]The reaction of an aldehyde (0.10 mmol) with **1a** (0.20 mmol) was carried out in the presence of MnO_2 (0.20 mmol) and (*R*)-**4** (0.010 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C for 20 h. [b]Isolated yield. [c]Determined by ^1H NMR analysis. [d]Enantiomeric excess of **5** was determined by HPLC using a chiral column.

Scheme 2. Asymmetric Hydroxyamination Using 1b

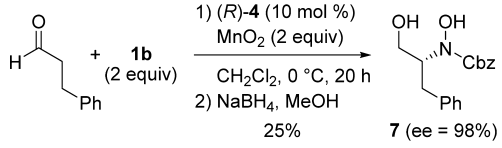
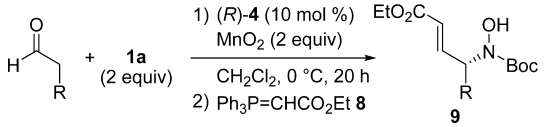


Table 3. One-Pot Synthesis of Allylamine 9[a]



entry	R	yield (%)[b]	*E*/*Z*[c]	ee (%)[d]
1	Me	70	18/1	99
2	Bn	78	11/1	98
3	$(CH_2)_3OBn$	68	14/1	99
4	*i*-Pr	71	15/1	98
5	*t*-Bu	68	10/1	99

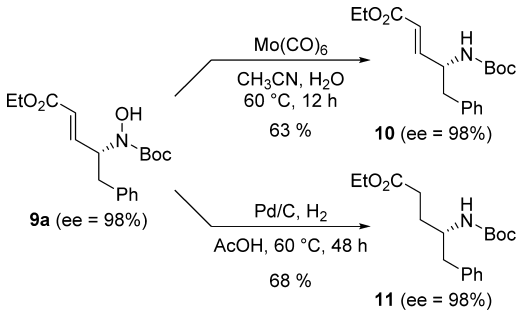
[a]The reaction of an aldehyde (0.16 mmol) with **1a** (0.32 mmol) was carried out in the presence of MnO_2 (0.32 mmol) and (*R*)-**4** (0.016 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C for 20 h. The reaction mixture was then treated with **8** (0.48 mmol). [b]Isolated yield. [c]Determined by ^1H NMR analysis. [d]Determined by HPLC using a chiral column.

The obtained hydroxyamination product was a useful intermediate in organic synthesis and readily converted to the corresponding *N*-Boc-protected allylamine and γ-amino ester, respectively (Scheme 3).[14] When a solution of **9a** in acetonitrile and water was treated with $Mo(CO)_6$ at 60 °C, *N*-Boc-protected allylamine **10** was obtained with complete retention of stereochemistry. On the other hand, reduction of **9a** with Pd/C under a hydrogen atmosphere at 60 °C gave the *N*-Boc-protected γ-amino ester **11** in good yield without loss of optical purity.

The absolute configuration of the products in the asymmetric hydroxyamination catalyzed by (*R*)-**4** was determined to be *R* by comparison of the result of HPLC analysis with the

dx.doi.org/10.1021/ol5000742 | *Org. Lett.* 2014, 16, 1530−1532

Scheme 3. Transformations of Hydroxyamination Product



literature data.[10] Based on the observed stereochemistry, a transition-state model can be proposed as shown in Figure 1. The *Si* face of the enamine intermediate is effectively shielded by the bulky trityl substituent of (*R*)-**4**, and consequently, the reaction of an aldehyde with a nitrosocarbonyl compound provides the *R* isomer predominantly.

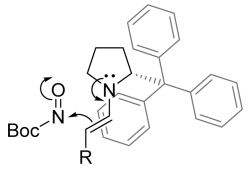


Figure 1. Plausible transition state model.

In summary, we have realized the highly regio- and enantioselective hydroxyamination of aldehydes with *in situ* generated nitrosocarbonyl compounds using readily available pyrrolidine-based amine catalysts and MnO_2 as the oxidant. The resulting optically enriched hydroxyamination products are useful chiral building blocks in the asymmetric synthesis of chiral amines such as amino acid derivatives and an allylamine.

■ 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: maruoka@kuchem.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research from MEXT, Japan.

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(14) The hydroxyamination product **5a** was readily converted to the corresponding 1,2-hydroxyamino alcohol and *N*-Boc-protected 1,2-amino alcohol, respectively (see ref 10).