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Published on Web 01/12/2007

# Diastereo- and Enantioselective Synthesis of Nitroso Diels−Alder-Type Bicycloketones Using Dienamine: Mechanistic Insight into Sequential Nitroso Aldol/Michael Reaction and Application for Optically Pure 1-Amino-3,4-diol Synthesis

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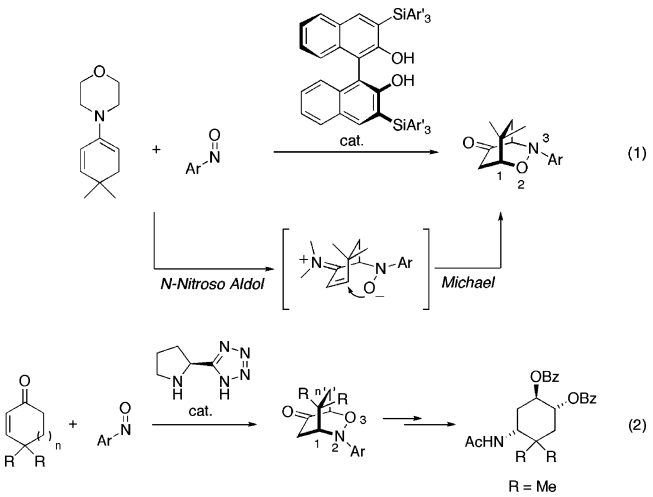
***Abstract:*** This article presents complete diastereo- and highly enantioselective synthesis of nitroso Diels−Alder-type bicycloketones using dienamine. With the hydrogen bonding of two hydroxyls in the bulky binaphthol **1c**, high enantioselectivities and complete diastereoselectivity are realized in 2-oxa-3-aza-bicycloketone synthesis. On the other hand, $\alpha,\beta$-unsaturated ketone can be employed as diene precursor, utilizing readily available tetrazole catalyst **3b**, to provide the 3-oxa-2-aza-bicycloketones in moderate yields with complete enantioselectivities. Investigation into the reaction utilizing 2-morpholino-4,4-diphenylcyclohexadiene **2d** clearly indicated that cyclization with the bulky binaphthol **1c** is involved in the sequential process, the *N*-nitroso aldol reaction, followed by Michael addition. In addition, optically pure 1-amino-3,4-diol is synthesized from 2-oxa-3-aza-bicycloketones. Use of *p*-phenoxynitrosobenzene allows access to protected amino diol via cleavage of the N−Ph bond.

## Introduction

Development of enantioselective addition of carbon nucleophile to nitroso compounds (nitroso aldol (NA) reaction) has been a topic of continued interest during recent years.[1] Extension of this reaction to unsaturated ketone nucleophiles opened a practical and stereoselective route to aza oxa bicycloketone synthesis.[2] In this article, completely diastereo- and highly enantioselective synthesis of nitroso Diels−Alder-type bicycloketones is presented including mechanistic insight into sequential NA−Michael reaction and application for amino diol synthesis (eqs 1 and 2). This system offers not only a new comprehensive perspective of diastereoselection in nitroso Diels−Alder-type bicycloketone synthesis but also new aspects in the effective design of the enantioselective process mediated by hydrogen bonding.

In previous studies, we documented that both the appropriate amine framework of enamine and the proper choice of acidity of Brønsted acid catalyst play contributing roles in O/N regioselectivities in NA reaction. In *N*-NA reaction, the chiral alcohol exhibits complete N-selection and a high enantioselection with piperidine or morpholine enamine (eq 3).[3] For N═O group, alcoholic proton reinforces coordination to the mutually preferred nitroso oxygen.[4] In contrast, the chiral carboxylic acid catalysts or their analogs exhibit uniformly high O selectivity and enantioselectivity depending on the amine structure of enamine (eqs 4 and 5). For instance, the reaction of pre-[3a] or in




(1) For reviews of nitroso aldol reaction, see: (a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995−2997. (b) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292−4300. (c) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514−3525. (d) Plietker, B. *Tetrahedron: Asymmetry* **2005**, *16*, 3453−3459.

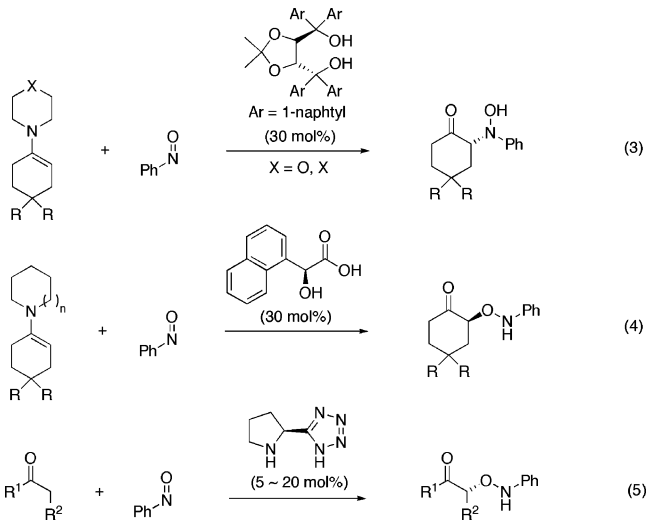
(2) (a) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962−5963. For examples reported by other groups, see: (b) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Mitsuru, S.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435−1439. (c) Sunden, H.; Dahlin, N.; Ibrahem, I.; Adolfsson, H.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3385−3389.

(3) (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080−1081. For examples reported by other groups, see: (b) Guo, H. M.; Cheng, L.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Chem. Commun.* **2006**, 429−431. (c) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046−6047.

(4) a) Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Połoński, T. *Chem. Commun.* **1999**, 1385−1386. (b) Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Małszynska, H.; Połoński, T. J. *Org. Chem.* **2001**, *66*, 501−506.


**10.1021/ja066037m CCC: $37.00** 

situ[5] formed pyrrolidine or piperidine enamines provided excellent enantioselectivities of the *O*-NA product.

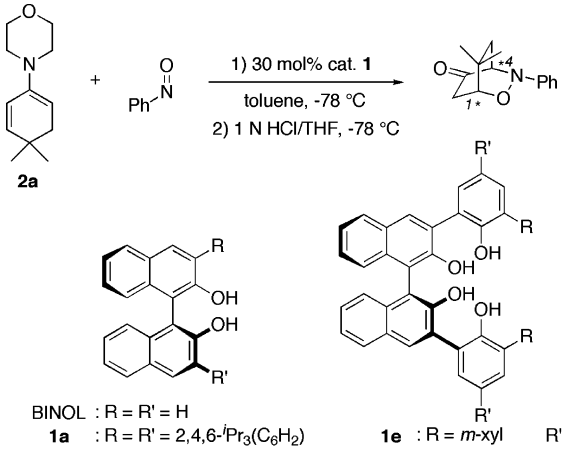



The goal of this investigation is to realize complete diastereo- and enantioselective nitroso Diels−Alder-type bicycloketone synthesis. Despite development of a number of chiral auxiliary-mediated asymmetric nitroso Diels−Alder reactions,[6] the catalytic enantioselective version of this process has not been fully reported.[7] The underlying premise for this study is that good levels of asymmetric induction as well as regioselection might be anticipated in the sequential NA/Michael process using dienamine derived from α, β-unsaturated ketones.

## Results and Discussion

**Diastereo- and Enantioselective Synthesis of 2-Oxa-3-aza Bicycloketone.** Considering the data profile in *N*-NA reaction,[3a] our preliminary investigation for an enantioselective 2-oxa-3-aza bicycloketone synthesis rested on finding a suitable hydrogen-bonding catalyst capable of facilitating reaction of 2-morpholino-4,4-dimethyl-1,3-cyclohexadiene without protonation or hydration. The (4*S*)-*trans*-1-naphthyl TADDOL was initially evaluated as a catalyst in the addition of 2-morpholino-1,3-diene to nitrosobenzene. Dropwise addition of dienamine to a cooled solution (−78 °C) of nitrosobenzene with (4*S*)-*trans*-1-naphthyl TADDOL followed by brief treatment of 1 N HCl in THF produced the expected nitroso Diels−Alder adduct in 36% yield with 52 % ee.

***Table 1.*** Modification of BINOL Derivatives in Reaction of Dienamine **2a**[a]




| entry | cat. | yield, %[b] | ee, %[c] | config. |
|---|---|---|---|---|
| 1 | BINOL | 78 | 28 | (1*S*,4*R*) |
| 2 | **1a** | 31 | 46 | (1*S*,4*R*) |
| 3 | **1b** | 45 | 52 | (1*S*,4*R*) |
| 4 | **1c** | 57 | 90 | (1*S*,4*R*) |
| 5 | **1d** | 74 | 25 | (1*S*,4*R*) |
| 6 | **1e** | 41 | 17 | (1*S*,4*R*) |
| 7 | **1f** | 63 | 70 | (1*R*,4*S*) |
| 8 | **1g** | 80 | 43 | (1*R*,4*S*) |
| 9 | **1h** | 60 | 20 | (1*R*,4*S*) |

[a] Reactions were conducted with 30 mol % of catalyst, 1.0 equiv of nitrosobenzene, and 1.5 equiv of dienamine in toluene at −78 °C. [b] Isolated yield. [c] Determined by HPLC (see Supporting Information).

To achieve higher yields and better enantioselectivities, we examined a variety of readily accessible chiral binaphthol derivatives possessing a proper acidity and more flexible chiral scaffold. While unmodified BINOL proved to afford low enantioselectivity (Table 1, entry 1), binaphthol possessing a tris-*m*-xylylsilyl group at the 3,3′ position provided a single regioisomer in high enantioselectivity and moderate yield (Table 1, entry 4). Importantly, the size of steric bulkiness in the triarylsilyl group played an important role in constructing the chiral environment. For instance, in the case of diol, although tris-*m*-xylylsilyl gave the highest enantioselectivity, the more sterically bulky and crowded substituents tri-*o*-tolylsilyl and tris-1-xylylsilyl caused a significant decline of enantioselectivity (Table 1, entry 5). When the reactions were conducted in the presence of tetraol-type catalyst,[8] the best result was obtained in triphenylsilyl substituents (Table 1, entry 7). As the trisaryl group became bulkier and more crowded, the enantioselectivities were significantly diminished (Table 1, entries 8 and 9).

On the basis of high enantioselectivity in tris(*m*-xylyl)silyl binaphthol, we next optimized amino moieties of dienamine and reaction solvents. While the enantioselectivity in the *N*-NA reaction of the piperidine enamine did not differ from that in *N*-NA reaction of morpholine enamine,[3a] the results provided by piperidine dienamine were distinguishable from that obtained using morpholine dienamine in the present reaction. When the

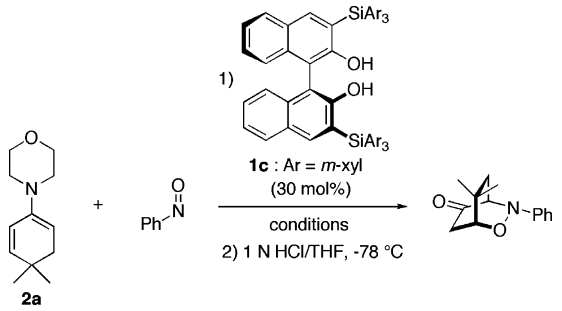
(5) (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247−4250. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808−10809. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293−8296. (d) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109−1112. (e) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112−1115. (f) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374−5378. (g) Córdova, A.; Sundén, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673−3684. (h) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966−5973. (i) Wang, W.; Wang, J.; Li, H.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 7235−7238. (j) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Mitsuru, S.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435−1439. (k) Sunden, H.; Dahlin, N.; Ibrahem, I.; Adolfsson, H.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3385−3389.

(6) For review of nitroso Diels−Alder reactions, see: (a) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107−1117. (b) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348. (c) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031−2043.

(7) (a) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128−4129. (b) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082−7085.

(8) (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310−312. (b) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938−2939. (c) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920−6930.

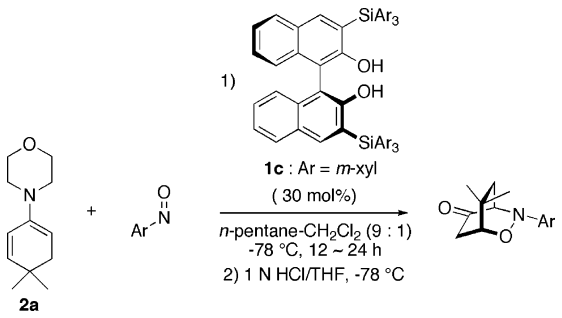
***Table 2.*** Solvent Effect in **1c** Catalyzed Reaction of **2a**[a]




| entry | solvent | conditions | yield, %[b] | ee, %[c] |
|---|---|---|---|---|
| 1 | toluene | −78 °C, 2 h | 57 | 90 |
| 2 | $CH_2Cl_2$ | −78 °C, 2 h | 65 | 28 |
| 3 | THF | −78 °C, 12 h | <5 | 7 |
| 4 | mesitylene | −40 °C, 1 h | 87 | 53 |
| 5 | *n*-hexane-$CH_2Cl_2$ (9/1) | −78 °C, 12 h | 93 | 87 |
| 6 | *n*-pentane-$CH_2Cl_2$ (9/1) | −78 °C, 12 h | 92 | 90 |

[a] Reactions were conducted with 30 mol % of catalyst, 1.0 equiv of nitrosobenzene, and 1.5 equiv of dienamine in corresponding solvent at −78 °C. [b] Isolated yield. [c] Determined by HPLC (see Supporting Information).

***Table 3.*** Reaction of Various Aromatic Nitroso Compounds[a]



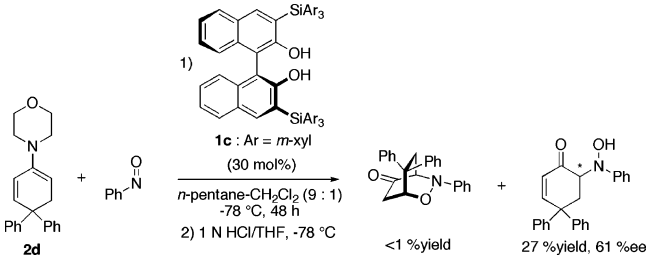

| entry | Ar | yield, %[b] | ee, %[c] |
|---|---|---|---|
| 1 | Ph | 90 | 90 |
| 2 | 4-Br($C_6H_4$) | 65 | 87 |
| 3 | 4-Ph($C_6H_4$) | 78 | 90 |
| 4 | 4-PhO($C_6H_4$) | 63 | 92 |
| 5 | 3,5-$Me_2$($C_6H_3$) | 52 | 80 |

[a] Reactions were conducted with 30 mol % of catalyst, 1.0 equiv of aromatic nitroso compounds, and 1.5 equiv of dienamine in *n*-pentane-$CH_2Cl_2$ (9:1) at −78 °C. [b] Isolated yield. [c] Determined by HPLC (see Supporting Information).

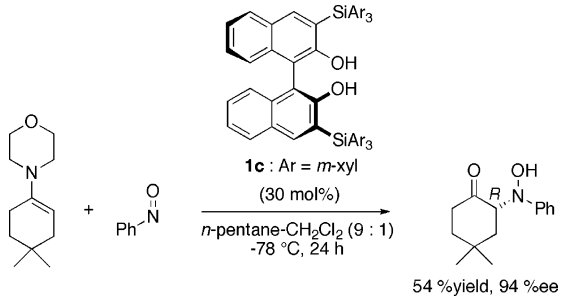
reaction was conducted with piperidine dienamine under the same reaction condition, the enantioselectivity decreased to 64%. A survey of reaction solvents revealed that the mixed solvent of hydrocarbon and $CH_2Cl_2$ was quite effective to achieve both good yield and high enantioselectivity (Table 2). While the **1c**-catalyzed reaction gave only 22 % ee in $CH_2Cl_2$, **1c** exhibited the best performance in *n*-hexane-$CH_2Cl_2$ or *n*-propane-$CH_2Cl_2$ among the solvents tested.

With the optimized reaction conditions in hand, the substrate scope in this system was further explored. Reactions of other aromatic nitroso compounds were examined with 30 mol % of tris(*m*-xylyl)silyl binaphthol **1c** in *n*-propane-$CH_2Cl_2$ as solvent using 2-morpholino-4,4-dimethylcyclohexadiene **2a**. *para*-Substituted aromatic nitroso compounds possessing electron-withdrawing and -donating groups reacted to afford cycloadducts in high enantioselectivities and moderate yields (Table 3). Otherwise, when the reaction was conducted with 2-morpholino-4,4-diphenylcyclohexadiene **2d**, *N*-NA adduct was obtained exclusively in 27% yield with 61 % ee (Scheme 1). It is noteworthy to point out that no cycloadduct has been observed during reaction of diene **2d**.

***Scheme 1.*** Reaction of 2-Morpholino-4,4-diphenylcyclohexadiene **2d**




***Scheme 2.*** Reaction of Morpholino-4,4-dimethylcyclohexane Enamine Catalyzed by **1c**




**Mechanistic Consideration for *N*-NA/Michael Reaction.** To rationalize the reaction mechanism, the reaction of 4,4-diphenyl diene **2d** was investigated in detail. When the reaction of diene **2d** and nitrosobenzene was conducted in the absence of binaphthol **1c**, nitroso Diels−Alder cyclized product was cleanly obtained in 57% yield; no NA adduct was detectable. In contrast, in the presence of 1 equiv of binaphthol catalyst **1c**, the reaction provided *N*-NA adduct exclusively in 70% yield while the cycloadduct was yielded in less than 5%. Furthermore, reaction of diene **2d** without binaphthol **1c** was carried out for 4 h, followed by addition of 1 equiv of binaphthol **1c**, which afforded cycloadduct in 60% yield: there was thus no change at all from cycloadduct to *N*-NA by addition of the binaphthol **1c**. These data lead to the following insight in this catalysis. (i) In the presence of binaphthol **1c**, the retro Diels−Alder pathway to *N*-NA adduct might be excluded. (ii) The binaphthol has the capability of governing the *N*-NA pathway but is unable to facilitate the [4+2] concerted reaction pathway. In addition, reaction of morpholino 4,4-dimethylcyclohexyl enamine catalyzed by binaphthol **1c** revealed that the absolute configuration of the *N*-NA product was *R*, which was the same as that of cycloadduct at the 4 position (Scheme 2). This result may also support a sequential mechanism *N*-NA/Michael reaction for selective nitroso Diels−Alder synthesis in the present catalysis.

The transition states in Figures 1 and 2 provide an attempt to rationalize the observed sense of stereoinduction and transformation. The overall hydrogen-bond network between the two hydroxyls of **1c** via the Brønsted acid assisted Brønsted acid system and the nitroso oxygen could be the dominant factor accounting for the observed diastereo- and enantioselectivities. The bulky arylsilyl group in **1c** would not allow it to attack diene from the *si* face due to the steric inhibition with

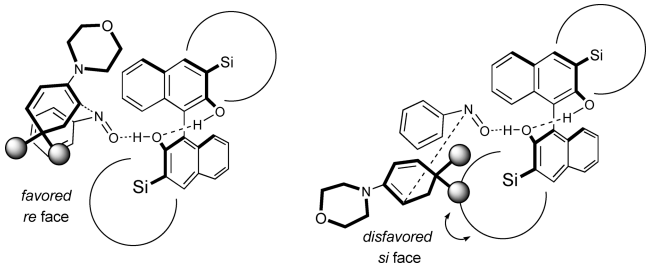



***Figure 1.*** Possible transition state in **1c**-catalyzed reaction.

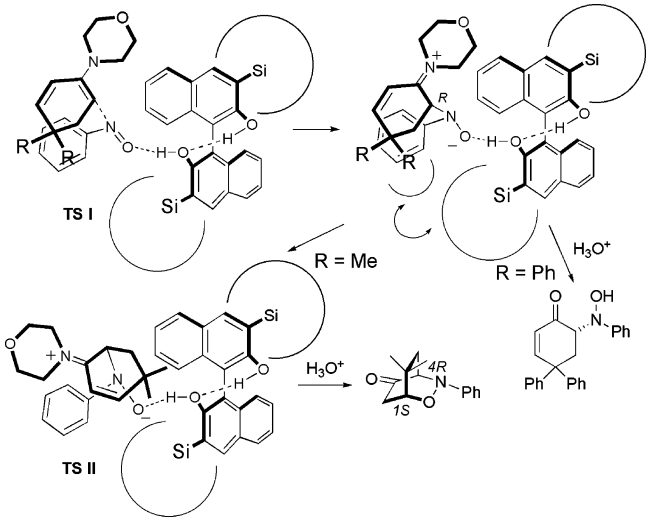


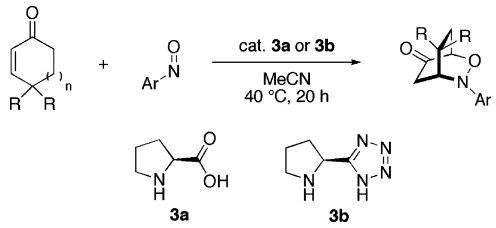

***Figure 2.*** Mechanistic model for the reaction of dienamine.

substituents of dienamine at the 4 position. As a consequence, nucleophilic attack of dienamine is postulated to occur from the *re* face as described in **TS I**, which delivers the *N*-NA adduct. The following Michael addition occurs in the case of dimethyl group via conformational change by 60° counterclockwise rotation as **TS II**. In contrast, the sterically more demanding diphenyl group did not allow the counterclockwise rotation to receive the subsequent Michael attack. Thus, the *N*-NA iminium compound is hydrolyzed during workup to yield the *N*-NA product (Figure 2).

**Diastereo- and Enantioselective Synthesis of 3-Oxa-2-aza Bicycloketone.** According to the results in *O*-NA reaction,[3a,5] investigations of diastereo- and enantioselective synthesis of 3-oxa-2-aza bicycloketone were preliminarily evaluated by two kinds of catalyst systems: Brønsted acid catalysis and chiral enamine catalysis. Reaction between 2-cyclohexen-1-one and nitrosobenzene at 40 °C revealed that proline afforded a completely regio- and enantioselective process; however, no catalyst turnover was observed. When 4,4-dimethyl-2-cyclohexen-1-one was used as the diene precursor, the yield was increased to 27% with complete enantioselectivity. (*R*)-Mandelic acid was also attempted as the catalyst in reactions of either in situ generated or preformed amino diene; however, these were totally unsuccessful.

The completely regio- and enantioselectivity with proline as catalyst prompted us to employ it for the reaction optimization. The pyrrolidinyl tetrazole exhibited higher reactivity than proline, affording the cycloadduct in complete enantioselectivity. Of the examined solvents, employment of those other than MeCN led to a significant decline in reactivity or no reaction.

***Table 4.*** Reaction Scope of α,β-Unsaturated Ketones and Aromatic Nitroso Compounds[a]




| entry | *n* | R, R | Ar | **3a** yield, %[b] (ee[c]) | **3b** yield, %[b] (ee[c]) |
|---|---|---|---|---|---|
| 1 | 1 | H, H | Ph | 8% (99% ee) | 34% (99% ee) |
| 2 | 1 | Me, Me | Ph | 24% (99% ee) | 64% (99% ee) |
| 3 | 1 | Ph, Ph | Ph | <1% | 56% (99% ee) |
| 4 | 1 | −(OCH$_2$CH$_2$O)− | Ph | 57% (99% ee) | 61% (98% ee) |
| 5 | 2 | H, H | Ph | 51% (99% ee) | 14% (99% ee) |
| 6 | 1 | Me, Me | 4-Me(C$_6$H$_4$) | | 47% (99% ee) |
| 7 | 1 | Me, Me | 3,5-Me$_2$(C$_6$H$_3$) | | 52% (98% ee) |
| 8 | 1 | Me, Me | 4-Br(C$_6$H$_4$) | | 50% (99% ee) |

[a] Reactions were conducted with 20 mol % of catalyst, 1.0 equiv of nitrosobenzene, and 0.5 equiv of enone at 40 °C. [b] Isolated yield. [c] Determined by HPLC (see Supporting Information).

As a result, the reaction proceeded smoothly in the presence of pyrrolidinyl tetrazole at 40 °C for 20 h in MeCN as solvent and afforded cycloadduct in moderate yield and 99 % ee.

Reactions with various α,β-unsaturated ketones were surveyed (Table 4, entries 2−5). The substrate tolerance for this reaction was broad, and uniformly high levels of enantiomeric excess were found in the cycloadduct. Alkyl-, aryl-, and alkoxy-substituted α,β-unsaturated cyclic ketone reacted with nitrosobenzene to give cyclized products in over 98 % ee. In 4,4-diphenyl substituents, the pyrrolidinyl tetrazole-catalyzed reaction yielded cycloadduct in 56% yield with 99 % ee; in contrast, it was not possible to facilitate this reaction with proline. When cycloheptenone was used as amino diene precursor, proline provided a better yield than did pyrrolidinyl tetrazole. This catalyst system was further tested for a representative selection of aromatic nitroso compounds (Table 4, entries 6−8). Various aromatic nitroso compounds afforded moderate yields and exceptionally high enantioselectivities.

**Transformation of 3-Oxa-2-aza Bicycloketone to Protected 1-Amino-3,4-diol.** We next applied 3-oxa-2-aza bicycloketone to synthesis of protected 1-amino-3,4-diol. It is well known that nitroso Diels−Alder reaction is widely employed in the convenient assembly of 1-amino-4-ol.[6] Thus, the optically pure aza oxa bicycloketones reflect rapid access to either 1-amino-2,4-diol or 1-amino-3,4-diol (Scheme 3).

During the course of our interest in this field, we previously realized catalytic highly diastereo- and enantioselective nitroso Diels−Alder reaction using nitroso pyridine in the presence of chiral phosphine−Cu(PF$_6$)(MeCN)$_4$.[7] The provided nitroso Diels−Alder product can be easily transformed to the protected optically active amino alcohols. Of two prospective chiral amino diols synthesized from regioisomeric aza oxa bicycloketones, while 1-amino-2,4-diol may be readily accessible from chiral phosphine−copper-catalyzed nitroso Diels−Alder reaction of nitroso pyridine, the approach to 1-amino-3,4-diol has not yet been fully established. The challenges to be addressed for 1-amino-3,4-diol synthesis include (A) diastereoselective reduction of 3-oxa-2-aza bicycloketone and (B) cleavage of the N−Ph bond.

***Scheme 3.*** Conversion to Amino Diol

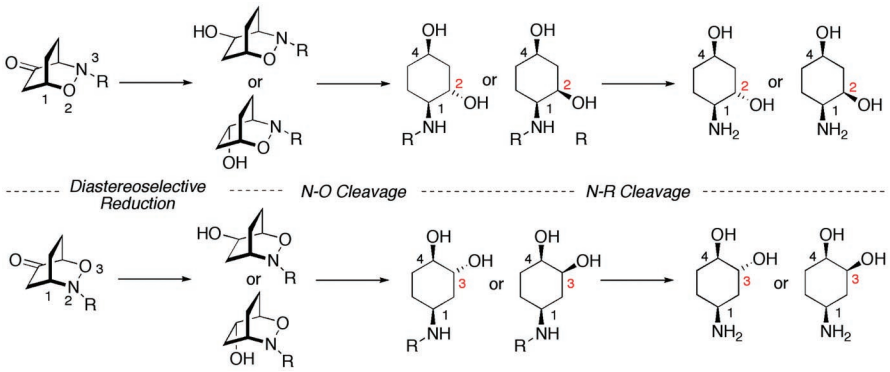
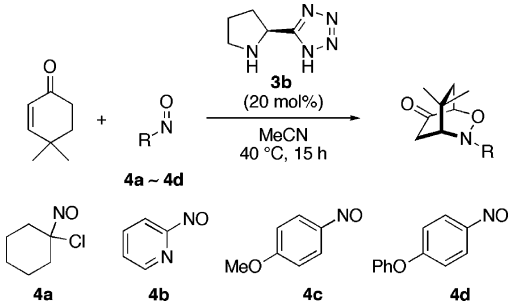



***Table 5.*** Reactions with Various Nitroso Compounds[a]




| entry | RNO | additive | yield, %[b] | ee, %[c] |
|---|---|---|---|---|
| 1 | **4a** | | <1 | |
| 2 | **4b** | | <1 | |
| 3 | **4c** | | 7 | 98 |
| 4 | **4d** | | 62 | 98 |
| 5 | **4d** | AcOH (1 equiv) | 74 | 98 |

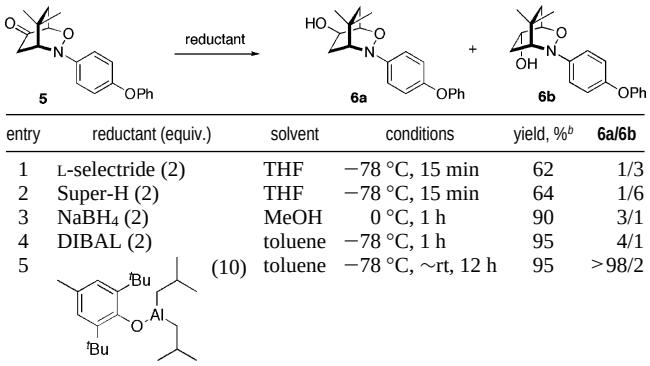
[a] Reactions were conducted with 20 mol % of catalyst, 1.0 equiv of aromatic nitroso compounds, and 0.5 equiv of enone at 40 °C. [b] Isolated yield. [c] Determined by HPLC (see Supporting Information).

The reported cleavable nitroso compounds, 1-chloro nitrosocyclohexane[9] and 2-nitrosopyridine,[7] were first evaluated for reaction of 4,4-dimethyl cyclohexenone in the presence of 20 mol % tetrazole catalyst under the optimized conditions. Disappointingly, these nitroso compounds did not deliver any of the objective products (Table 5, entries 1 and 2).

The need for a more reactive nitroso compound became apparent during attempts to develop amino diol synthesis via N−Ph bond cleavage. For example, *p*-methoxynitrosobenzene was added to 4,4-dimethylcyclohexenone in the presence of pyrrolidinyl tetrazole to afford only 7% of desired product (Table 5, entry 3). This observation led us to examine the use of *p*-phenoxynitrosobenzene as a more electrophilic reactant. Gratifyingly, the reaction of *p*-phenoxynitrosobenzene provided the objective cyclized product in 98 % ee and 62 %yield (Table 5, entry 4). Also, the reaction of *p*-phenoxynitrosobenzene in the presence of 1 equiv of acetic acid as additive produced the desired product in 74% yield without loss of enantioselectivity (Table 5, entry 5).

3-Oxa-2-aza bicycloketone **5** derived from *p*-phenoxynitrosobenzene provided the opportunity to study diastereoselective reduction (Table 6). Reduction with $NaBH_4$ gave alcohol

***Table 6.*** Diastereoselective Reduction of **5**[a]




| entry | reductant (equiv.) | solvent | conditions | yield, %[b] | **6a/6b** |
|---|---|---|---|---|---|
| 1 | L-selectride (2) | THF | −78 °C, 15 min | 62 | 1/3 |
| 2 | Super-H (2) | THF | −78 °C, 15 min | 64 | 1/6 |
| 3 | $NaBH_4$ (2) | MeOH | 0 °C, 1 h | 90 | 3/1 |
| 4 | DIBAL (2) | toluene | −78 °C, 1 h | 95 | 4/1 |
| 5 |  (10) | toluene | −78 °C, ∼rt, 12 h | 95 | >98/2 |

[a] Reactions were conducted with corresponding reductant and **5**. [b] Isolated yield (see Supporting Information).

in a 3:1 ratio (**6a**:**6b**). The reaction in the presence of bulky borane reductants (entries 1 and 2) exhibited a high level of diastereoselection for **6b**. In contrast, when the reductant was sterically hindered aluminum, the reaction proceeded to give the opposite diastereomer **6a** with complete selectivity. It is interesting to note that a completely different diastereoselectivity took place by switching reductant from bulky borane to bulky aluminum.

In studying the synthesis of amino diol, the pathway to protected diols is illustrated in Scheme 4. The obtained diastereoselective 3-oxa-2-aza bicyclo monol **6a** was successfully protected by benzoyl chloride, which was further transformed to protected diol through cleavage of the N−O bond by hydrogenation followed by protection of the generated hydroxyl group in excellent yield.

To cleave the *N*-phenoxyphenyl group of **8a**, representative single-electron-transfer oxidants such as CAN[10] or $Ag(NO)_3$−$(NH_4)S_2O_8$[11] were employed; however, these systems did not lead to the desired free amine. To our delight, use of $PhI(OAc)_2$ as an oxidant was found to be an efficient method to remove the phenoxyphenyl group. Accordingly, oxidation of **8a** was readily accomplished with $PhI(OAc)_2$ to yield phenol and **9a**. Hydrolysis of **9a** proceeded at imine, yielding the primary amine, which was further protected by acetic anhydride (Scheme 5).

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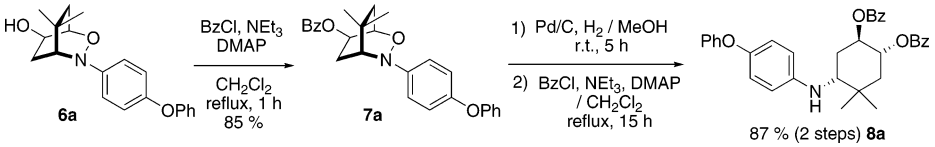
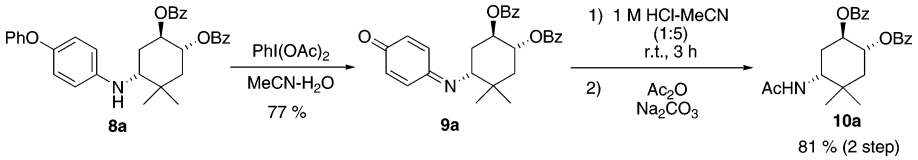
(10) (a) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765−2768. (b) Ha, D. C.; Hart, D. J. *Tetrahedron Lett.* **1987**, *28*, 4489−4492.

(11) Bhattarai, K; Cainelli, G.; Panunzio, M. *Synlett* **1990**, 229−230.

***Scheme 4.*** Cleavage of N−O Bond and Protection of Hydroxyl Group




***Scheme 5.*** Transformation to Protected Amino Diol




## Conclusions

Completely regioselective and efficient enantioselective nitroso Diels−Alder-type bicycloketone synthesis has been documented utilizing preformed- or in situ-generated dienamine. We find that silyl binaphthol possessing a tris-*m*-xylylsilyl group at the 3,3′ position provides single regioisomer 2-oxa-3-aza-bicycloketone with high enantioselectivities. The reaction proceeds through sequential *N*-NA reaction followed by Michael reaction. For 3-oxa-2-aza-bicycloketone synthesis, use of pyrrolidine-derived tetrazole has been established as an effective catalyst. The α,*β*-unsaturated ketone can be employed as diene precursor to provide the cycloadducts in moderate yields with complete enantioselectivities. In addition, we disclose the synthesis of optically pure 1-amino-3,4-diol from chiral 3-oxa-2-aza-bicycloketone. We find that use of *p*-phenoxynitrosobenzene allows access to protected amino diol via cleavage of the N−Ph bond. The study presented here would open a new avenue of nitroso Diels−Alder-type bicycloketone synthesis as well as provide a valuable contribution to optically pure amino alcohol synthesis.

**Acknowledgment.** We thank Dr. Ian M. Steele for X-ray crystallographic analysis. Support for this research has been provided by the National Institutes of Health (NIH) GM068433-01 and a grant from the University of Chicago. N.M. acknowledges a graduate fellowship from Abbott Laboratories. Y.Y. thanks Dr. K. Suzuki, BANYU Pharmaceutical Co., Ltd., for general support.

**Note Added after ASAP Publication:** After ASAP publication of this article on January 12, 2007, Schemes 4 and 5 were updated to show the correct absolute configuration of **8a**, **9a**, and **10a**. The Supporting Information was also updated. The corrected version was published ASAP on January 23, 2007.

**Supporting Information Available:** Experimental details, optimization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA066037M