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COMMUNICATIONS

Published on Web 04/22/2004

Enantioselective Tandem *O*-Nitroso Aldol/Michael Reaction

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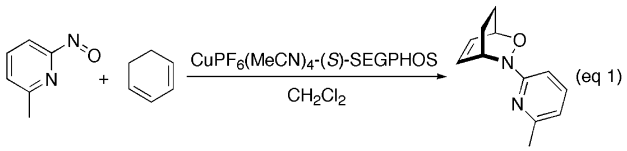
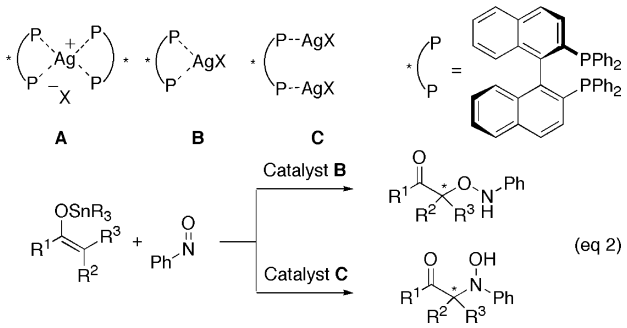
Received January 15, 2004; E-mail: yamamoto@uchicago.edu

One of the most intensely studied areas in chemical synthesis at present is the development of new catalytic and highly enantioselective processes.[1] Hetero Diels−Alder reactions have especially been one of the most powerful synthetic constructions to date.[2] We recently succeeded in developing a catalytic enantioselective nitroso Diels−Alder reaction using a copper catalyst (eq 1).[3] We describe herein a sharply contrasting transformation: a tandem *O*-nitroso aldol/Michael reaction that is synthetically an even more useful process to produce nitroso Diels−Alder adducts and that can completely control both regio- and stereochemistry.



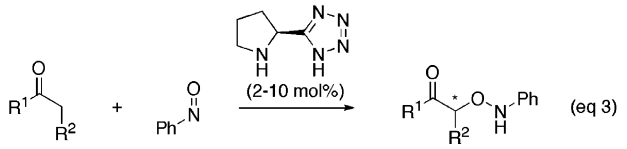
(eq 1)

The present study sprang from our earlier finding involving the nitroso aldol reaction, which produces either an O-adduct or an N-adduct with the choice of catalyst and/or nucleophile.[4] The enantioselective version of each reaction was then first realized by using a silver−BINAP catalyst (eq 2).[5]



(eq 2)

Furthermore, amine catalysts such as proline or pyrrolidine based tetrazoles also gave remarkably excellent enantioselectivity for the *O*-nitroso aldol process (eq 3).[6]



(eq 3)

Assuming that the same mode of *O*-nitroso aldol synthesis would proceed in the reaction of α,β-unsaturated carbonyls, it appears possible to synthesize a nitroso Diels−Alder adduct via an *O*-nitroso aldol reaction, followed by a Michael reaction (Scheme 1).[7] In this case, it is noteworthy to point out that the regiochemistry of the product should be the opposite of that of the normal nitroso Diels−Alder reaction.

Scheme 1

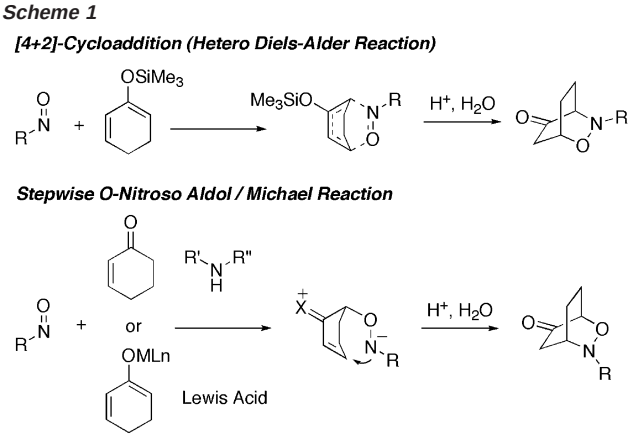
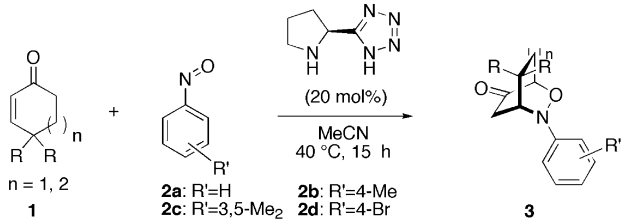


Table 1. Reaction Scope in Amine-Catalyzed Reaction[a]



entry	enone	R,R	ArN=O	yield, %[b]	ee, %[c]
1		**1a**: Me,Me	**2a**	64	99
2		**1b**: H,H	**2a**	34	99
3		**1c**: Ph, Ph	**2a**	56	99
4		**1d**:-(OCH_2CH_2O)-	**2a**	61	98
5		**1a**	**2b**	47	98
6		**1a**	**2c**	52	98
7		**1a**	**2d**	50	99
8		**1e**: H,H	**2a**	14	99
9[d]		**1e**: H,H	**2a**	51	99

[a] Reaction was conducted with 20 mol % of catalysis, 1 equiv of enone and 2 equiv of nitrosobenzene under N_2 atomsphere at 40 °C for 15 h. [b] Isolated yield. [c] ee value was determined by HPLC (Supporting Information). [d] L-Proline was used as catalyst.

We started our investigation using nitrosobenzene, 4,4-dimethyl-2-cyclohen-1-one as the diene precursor and pyrrolidine-based tetrazole as the catalyst due to the high catalytic turnover for the *O*-nitroso aldol reaction of ketones.[8] The reaction proceeded smoothly at 40 °C in MeCN as the solvent and afforded the Diels−Alder adduct in 99% ee (Table 1, entry 1). Reactions with various enones were surveyed and are summarized in Table 1. All reactions gave the cyclized adducts cleanly. Enantioselectivity was uniformly high, ranging above 98%, and good yields were observed.[9] Furthermore, this system was applicable for various aromatic nitroso compounds, for example, 4-methyl-, 3,5-dimethyl-, and 4-bromonitrosobenzene (Table 1, entries 5−7). In the case of cycloheptenone, the tetrazole catalyst could not furnish good yields, but fortunately, an acceptable yield of this reaction was achieved using

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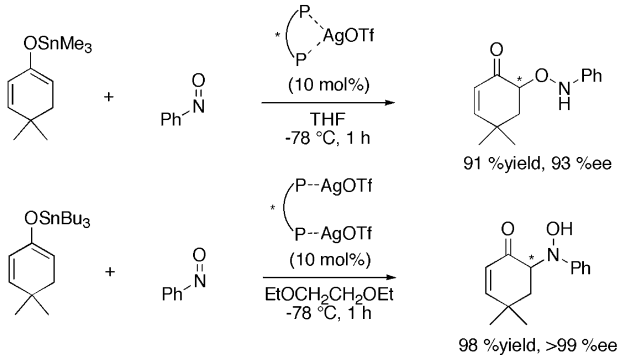
Scheme 2



the proline catalyst (Table 1, entries 8 and 9). The X-ray structure of the product provided by the reaction of *p*-bromonitrosobenzene and 4,4-dimethyl-2-cyclohen-1-one revealed the expected regiochemical structure with the *R* configuration.[10,11] The oxygen atom was close to the carbonyl group, which indicates the reaction proceeds via an O-selective stepwise pathway.

Turning now to the silver−BINAP catalyst system, the O-selective stepwise process was initially evaluated by a AgOTf·(*R*)-BINAP (1:1) complex, which was a promising catalyst for the *O*-nitroso aldol reaction. The reaction of the trimethyl stanyloxy diene of 4,4-dimethyl cyclohexenone with nitrosobenzene produced the *O*-nitroso aldol adduct exclusively (91% yield, 93% ee), without affording any of the cyclized product (Scheme 2). On the other hand, the analogous reaction carried out with AgOTf·(*R*)-BINAP (2:1) complex afforded the *N*-nitroso aldol adduct in 98% yield and >99% ee, again without any trace of Diels−Alder adducts. The attempt to cyclize these *O*- and *N*-nitroso aldol products, however, was conducted with several kinds of base or acid such as potassium *tert*-butoxide, potassium bis(trimethylsilyl)amide, DBU, *p*-TsOH·H_2O, and trifluoroacetic acid without any success.

The above results of these two catalyst systems have provided insight into the mechanism of this transformation. As illustrated in Figure 1, addition of nitrosobenzene from the same side of the tetrazole moiety to *anti*-dienylamine affords the iminium salt existing in boat form, and the aminooxy group should be positioned in the axial site, which is favorable for cyclization. Since iminium salts are known to be significantly more reactive than the corresponding α,β-unsaturated keones,[12] the counterion, aminooxy anion, can cyclize smoothly to generate the bicyclic product. Such a counterion effect and/or favorable contribution of the boat form are not present for the silver-ion-catalyzed nitroso aldol synthesis.

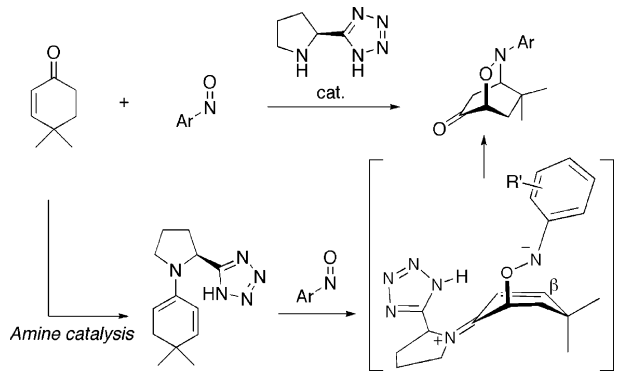


Figure 1. Possible reaction pathway.

In summary, a highly enantioselective approach for the synthesis of the nitroso Diels−Alder adduct was realized using a simple amine catalyst. The results disclosed herein considerably extend the control of regio- and stereochemistry for the synthesis of the nitroso Diels−Alder adduct. Further applications of the nitroso electrophiles to other synthetically useful transformations are underway.

Acknowledgment. We thank Dr. Ian M. Steele for X-ray crystallographic analysis. Support for this research was provided by the SORST project of the Japan Science and Technology Agency (JST), National Institutes of Health (NIH) GM068433-01, and a starter grant from the University of Chicago. Y.Y. acknowledges Dr. K. Suzuki, BANYU Pharmaceutical Co., Ltd. for generous support.

Supporting Information Available: Experimental procedures, spectral data for all new compounds, and crystallographic data. X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See ref 6f.
(9) The same reaction catalyzed by L-proline was also examined. Although the reaction provided 98−99% ee, the yields were <1−40%. The detailed results are described in Supporting Information.
(10) The structure by X-ray analysis is shown in Supporting Information.
(11) The product **3a**, of opposite absolute configuration, was provided in 61%yield and 99% ee by using 20 mol % of D-tetrazole catalyst.
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JA049741G