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COMMUNICATIONS

Published on Web 03/12/2004

Catalytic, Highly Enantio, and Diastereoselective Nitroso Diels−Alder Reaction

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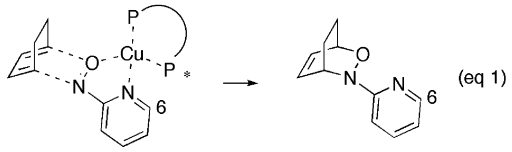
The nitroso Diels−Alder reaction is remarkable especially because of its unique diastereoselectivity when 1,4-amino-oxo stereocenters are produced in a single operation. Reported here is the catalytic enantioselective version of this process with achiral dienes and aryl nitroso derivatives, which depends on a readily available copper catalyst. A number of other approaches to enantioselective nitroso Diels−Alder reactions, mainly using chiral substrates, have been described recently.[1] The development of the new method was guided by the following considerations. Nitroso compounds exist in organic solvents as a monomer-azetoxy dimer equilibrium.[2] Whiting has reported the ability of Lewis acids to form stable complexes with the azetoxy dimer of aryl nitroso compounds.[3] This causes difficulty for the successful asymmetric nitroso Diels−Alder reaction for organic synthesis. We are interested in generating chelated monomeric nitroso derivatives with suitable Lewis acid catalysis. This idea is illustrated for the specific case of a 2-nitrosopyridine derivative in eq 1, the system of which is quite flexible: for example, substituents at the 6-position would increase steric demand to form a fixed chiral environment around the nitroso functional group.



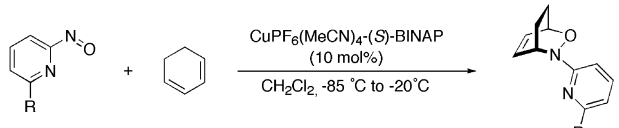
(eq 1)

2-Nitrosopyridine was prepared in two steps from 2-aminopyridine simply following the reported procedure.[2c,4] We chose for initial investigations the hetero Diels−Alder reaction of cyclohexadiene with (*S*)-BINAP−Cu(I)$PF_6(MeCN)_4$ catalyst[5] since copper coordination to nitroso derivative is well-known.[6] The reaction was conducted at −85 °C and gradually warmed to −20 °C to produce the adduct **3a** in quantitative yield with 59% ee. Encouraged by this result, we next introduced alkyl groups at the 6-position of 2-nitrosopyridine, which gave much higher enantioselecvities, as shown in Table 1. Among them, the 6-methyl derivatives gave us the most satisfactory results. Fortunately, this reagent is easy to obtain from the commercially available 6-methyl-2-aminopyridine.

Next, various chiral phosphine ligands were surveyed (Chart 1). Although *p*-Tol-BINAP showed almost no change in enantioselectivity, significant and uniformly increased selectivity was observed by using a chiral biphosphine ligand with a narrow dihedral angle.[7] The best enantioselectivity was observed with SEGPHOS, giving >90% ee. These observations clearly indicated that the copper catalyst is very effective and that these reactions proceed via a highly organized transition state.

Table 2 summarizes the excellent results obtained for six different dienes of widely varying structure using 10 mol % of copper catalyst at −85 °C under standard conditions. All reactions proceeded to completion, and the desired cyclic adduct was the only detectable

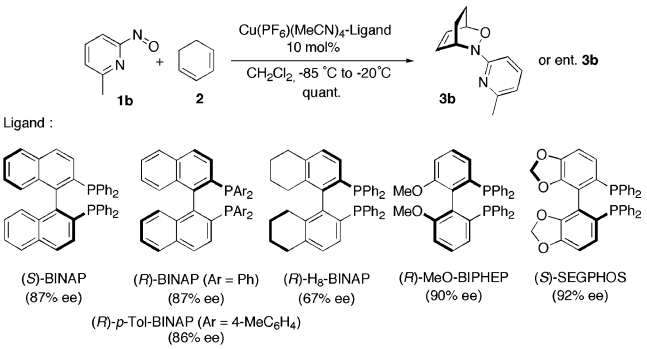
Table 1. Reaction with Various 2-Nitrosopyridines[a,b]



entry	nitroso	yield, %	ee, %
1	**1a**	>99	59
2	**1b**	>99	87
3	**1c**	>99	86
4	**1d**	>99	77

[a] Reaction was conducted with 10 mol % of catalysis, 1 equiv of nitrosopyridine, and 1.5 equiv of cyclohexadinene under N_2 atomsphere at −85 °C and gradually warmed to −20 °C in 5 h. [b] ee value was determined by HPLC (Supporting Information).

Chart 1. Effects of Ligand on Enantioselectivity[a,b]



[a] Reaction was conducted with 10 mol % of catalysis, 1 equiv of nitrosopyridine, and 1.2 equiv of cyclohexadinene under N_2 atomsphere at −85 °C and gradually warmed to −20 °C in 5 h. [b] ee value was determined by HPLC (Supporting Information).

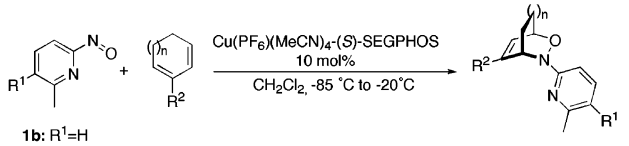
product. Even more noteworthy is the fact that reactions with 2-substituted 1,3-cyclohexadienes proceeded in a completely regioselective manner.[8] Thus, the reaction with 2-methyl, 2-phenyl, or 2-*tert*-butyldimethylsiloxy-1,3-cyclohexadienes provided the single nitroso Diels−Alder adduct, where the R^2 substituents are close to nitrogen, with excellent enantioselectivities.

The Diels−Alder adduct can easily be transformed to protected amino alcohols. Cleavage of the N−O bond was performed by $Mo(CO)_6$ and $NaBH_4$.[9] The resulting alcohol and amine were protected by TBS and Tosyl group, respectively. Quaternization of pyridine followed by treatment of NaOH afforded protected amino alcohol **6** in good yield without loss of enantioselectivity (Scheme 1).[10]

The absolute stereochemical course of the reaction was found to be in accord with the mechanistic model.[11] It is well-known that the first and third quadrants are more crowded than the second and fourth quadrants for (*S*)-BINAP transition-metal complexes (Figure 1).[12]

10.1021/ja049849w CCC: $27.50

Table 2. Reaction with Various Dienes[a,b]

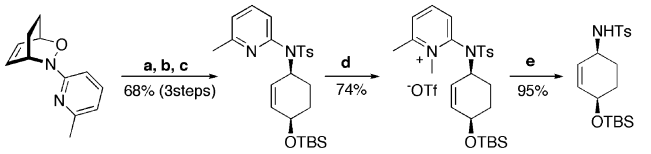


1b: R^1=H
1e: R^1=Br

entry	nitroso	diene	R	yield, %	ee, %
1	**1b**			> 99	90
2	**1b**		H	> 99	92
3	**1e**		H	> 99	94
4[c]	**1b**		Me	> 99	94
5[c]	**1b**		Ph	> 99	97
6[d]	**1e**		Ph	> 99	94
7	**1b**		OTBS	95	92
8	**1b**			> 99	72 (99)[e]

[a] Reaction was conducted with 10 mol % of catalysis, 1 equiv of nitrosopyridine, and 1.2 equiv of diene under N_2 atomsphere at −85 °C and gradually warmed to −20 °C in 5 h. [b] ee value was determined by HPLC (Supporting Information). [c] Structure was determined by X-ray analysis (Supporting Information). [d] (*S*)-BINAP was used instead of (*S*)-SEGPHOS. [e] After single recrystallization (hexanes/Et_2O).

Scheme 1. Conversion to Protected Amino Alcohol[a]



3b 92% ee **4** **5** **6** 92% ee

[a] Reaction conditions: (a) $Mo(CO)_6$, $NaBH_4$, MeCN/H_2O. (b) TBSCl, TEA, DMAP, MeCN. (c) Ts_2O, TEA, CH_2Cl_2. (d) MeOTf, CH_2Cl_2. (e) NaOH, MeOH/H_2O.

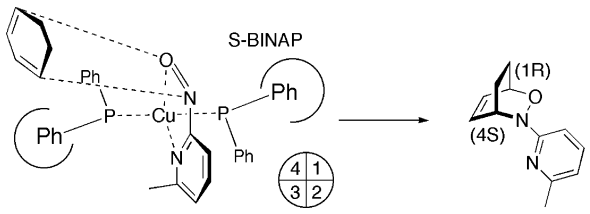


Figure 1. Plausible chelate intermediate.

We believe that the reactions expressed herein provide a useful new paradigm for enantioselective synthesis. Further, the present concepts should present clear guidance for the design of still more effective catalysts for nitroso Diels−Alder reaction.

Acknowledgment. Support of this research was provided by SORST project of Japan Science and Technology Agency (JST), National Institutes of Health (NIH) GM068433-01, and a starter grant from the University of Chicago. We acknowledge Dr. Ian Steele for X-ray measurements. We thank Takasago International Corporation for its generous gift of (*S*)-SEGPHOS and (*R*)-H_8-BINAP. Y.Y. thanks Dr. K. Suzuki, BANYU Pharmaceutical Co. Ltd. for generous support.

Supporting Information Available: Experimental details and spectroscopic data, including determination of absolute configuration (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA049849W