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Catalytic Enantioselective Hetero-Diels−Alder Reactions of an Azo Compound

Masanori Kawasaki and Hisashi Yamamoto*

Department of Chemistry, University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

Received September 22, 2006; E-mail: yamamoto@uchicago.edu

The hetero-Diels−Alder reaction is one of the most useful reactions in organic chemistry because multifunctionalized compounds can be constructed in a single step.[1] The catalytic enantioselective version of this process has attracted much attention in modern organic chemistry. We recently reported the catalytic highly enantioselective nitroso hetero-Diels−Alder reaction using nitroso pyridine as a dienophile in the presence of a chiral copper catalyst.[2] Encouraged by this success, we focused on hetero-Diels−Alder reaction using a 2-azopyridine derivative since this reaction with azo compounds (azo hetero-Diels−Alder reaction) produces 1,4-diamines.[3] These structural motifs are important building blocks as well as 1,4-amino alcohols. For example, these structures are found in pharmaceutically important compounds such as HIV protease inhibitors.[4] Diastereoselective azo hetero-Diels−Alder reactions using a chiral auxiliary have been developed;[5] however, despite several efforts toward an enantioselective version of this process,[6] there are no reports of a catalytic highly enantioselective azo hetero-Diels−Alder reaction. We herein report the catalytic highly regio- and enantioselective azo hetero-Diels−Alder reaction (Scheme 1).

Scheme 1. Azo Hetero-Diels−Alder Reaction

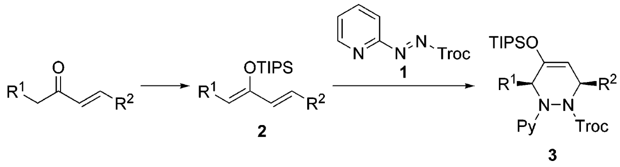
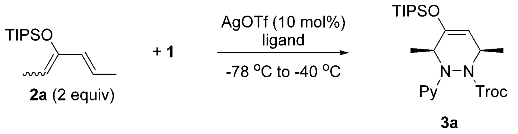


Table 1. Optimization of Reaction Conditions



entry	ligand	solvent	yield (%)	ee (%)[b]
1	(*R*)-BINAP (10 mol %)	THF	73	55
2	(*R*)-BINAP (10 mol %)	Et_2O	74	56
3	(*R*)-BINAP (10 mol %)	toluene	63	67
4	(*R*)-BINAP (10 mol %)	CH_2Cl_2	72	80
5[a]	(*R*)-BINAP (10 mol %)	CH_3CN	61	94
6	(*R*)-BINAP (10 mol %)	EtCN	62	94
7	(*R*)-Difluorophos (10 mol %)	EtCN	76	30
8	(*R*)-Segphos (10 mol %)	EtCN	71	20
9	(*R*)-BINAP (5 mol %)	EtCN	87	>99
10	(*R*)-BINAP (20 mol %)	EtCN	26	0

[a] Reaction was conducted at −40 °C. [b] Enantiomeric excess value was determined by HPLC (Supporting Information).

2-Azopyridine (**1**) was prepared in two steps from commercially available 2-hydrazinopyridine.[7] On the basis of our previous results, we chose for initial investigations the hetero-Diels−Alder reaction of acyclic silyloxydiene **2a** with (*R*)-BINAP and $CuPF_6(CH_3CN)_4$ catalyst.[2,8] Unfortunately, we were unable to observe any chiral induction. Thus, several metal catalysts were surveyed,[9] and we found that the combination of AgOTf and (*R*)-BINAP in THF produced adduct **3a** with 55% ee. Encouraged by this result, various ligands and solvents were tested (Table 1). The use of (*R*)-BINAP as a ligand and CH_3CN or EtCN as a solvent gave **3a** with 94% ee (Table 1, entries 5 and 6). EtCN was selected as a solvent to obtain high reproducibility. Next, the ratio of (*R*)-BINAP to AgOTf was checked since we previously had observed that three types of the Ag−BINAP complex were formed in THF.[10] The 2:1 ratio of AgOTf to (*R*)-BINAP was found to be optimal, producing an adduct **3a** with >99% ee. It should be noted that decreased enantioselectivity was observed by chiral biphosphine ligands with narrow dihedral angles (entries 7 and 8) which are expected to generate a 1:1 complex of Ag ligand preferentially.

Having an optimized condition in hand, the applicability of this reaction was studied for the functionalized silyloxydienes **2b**−**2j**.[11] All of the reactions proceeded in high yields and enantioselectivities, with complete regio- and diastereoselectivities.

The dialkyl-substituted dienes generally gave high enantioselectivities (Table 2, entries 1, 2, and 5). Silyloxydiene **2c** with a sterically hindered substituent afforded **3c** with slightly decreased enantioselectivity. Lewis basic substituents such as ester, ether, protected alcohols, and protected amine (Table 2, entries 4 and 6−8) were also used in the reaction and produced highly functionalized products enantioselectively. Silyloxydiene **2j** having a 2-furyl group gave an adduct **3j** with high regio- and enantioselectivity (Table 2, entry 10). Meanwhile, the enantioselectivity of the reaction using silyloxydiene **2k** with a phenyl group was decreased dramatically (Table 2, entry 11).

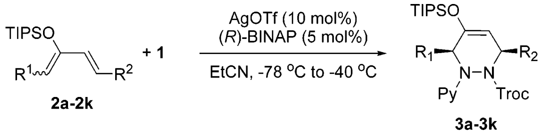
The products can be cleanly converted into the corresponding diamino alcohols. For example, deprotection of the TIPS group of **3a** with TBAF/AcOH[12] followed by reduction and protection of the resulting alcohol gave **4a** as a single diastereomer. Removal of the pyridine ring was cleanly achieved by the known procedure,[2c] accompanied by the conversion of a 2,2,2-trichloroethoxycarbonyl group to a methoxycarbonyl group. The resulting amine was protected with a trifluoroacetyl group to afford **5a**. To cleave the N−N bond of **5a**, **5a** was treated with SmI_2 to give **6a** in 71% yield (Scheme 2).[13] Thus, two amino groups are differentiated for further transformation.

The absolute and relative configurations of azo hetero-Diels−Alder adducts were assigned by X-ray crystallographic analysis. Deprotection of Troc and TIPS groups followed by reduction afforded **7a** as a single diastereomer. Subsequently, **7a** was converted into 4-bromobenzoate derivative **8a** which was crystallized from Et_2O (Scheme 3 and Supporting Information).

In summary, we have developed a highly regio-, diastereo-, and enantioselective azo hetero-Diels−Alder reaction using 2-azopy-

10.1021/ja066726y CCC: $33.50 © 2006 American Chemical Society

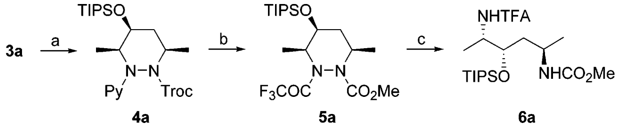
Table 2. Reaction with Various Dienes[a]



entry	diene	R^1	R^2	yield (%)	ee (%)[b]
1	**2a**	Me	Me	87	>99
2	**2b**	Me	n-C_5H_{11}	84	95
3	**2c**	Me	i-Pr	65	84
4	**2d**	Me	$CH_2CH_2CH_2CO_2Me$	74	98
5	**2e**	Bn	Me	74	92
6	**2f**	4-MOMO-Bn	Me	85	90
7	**2g**	$CH_2CH_2CH_2OTBS$	i-Bu	82	95
8	**2h**	$CH_2CH_2CH_2OTBS$	CH_2OBn	84	98
9	**2i**	$CH_2CH_2CH_2NNsBoc$	i-Bu	77	98
10	**2j**	Me	2-Furyl	78	92
11[c]	**2k**	Me	Ph	70	55

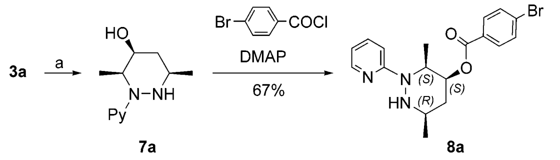
[a] Reaction was conducted with AgOTf (10 mol %), (*R*)-BINAP (5 mol %), azopyridine (1 equiv), and silyloxydiene (2 equiv) under Ar at −78 °C and gradually warmed to −40 °C over 3 h. [b] Enantiomeric excess value was determined by HPLC (Supporting Information). [c] 20 mol % of AgOTf and 10 mol % of (*R*)-BINAP were used.

Scheme 2. Conversion to Protected Diamino Alcohol[a]



[a] Conditions: (a) (i) TBAF, AcOH, (ii) $NaBH_4$, (iii) TIPSOTf, NEt_3, 65% (3 steps); (b) (i) MeOTf, (ii) NaOH, (iii) TFAA, NEt_3, 71% (3 steps); (c) SmI_2, MeOH, 71%.

Scheme 3. Determination of Absolute Stereochemistry[a]



[a] Conditions: (a) (i) Zn, AcOH, (ii) TBAF, AcOH, (iii) $NaBH_4$, 53% (3 steps).

ridine (**1**) and silver(I)−BINAP 2:1 catalyst. This catalytic process could be one of the effective synthetic routes to a number of chiral 1,4-diamines which are pharmaceutically important compounds. Further studies of the detailed mechanism of the reaction and synthetic applications are currently underway in our laboratory.

Acknowledgment. Support of this research was provided by National Institutes of Health (NIH) Grant No. GM068433-01, and Merck Research Laboratories. We thank Dr. Ian M. Steel for X-ray crystallographic analysis.

Supporting Information Available: Experimental details, spectroscopic data, including determination of absolute configuration, and complete ref 4h. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a general review of hetero-Diels−Alder reactions, see: (a) *The Diels−Alder Reaction: Selected Practical Methods*; Fringuelli, F., Taticchi, A., Eds.; John Wiley & Sons: New York, 2002. (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 151−209. (c) *Comprehensive Asymmetric Catalysis III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 1237−1254. (d) Gouverneur, V.; Reiter, M. *Chem.—Eur. J.* **2005**, *11*, 5806. (e) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (f) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.

(2) (a) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031. (b) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082; *Angew. Chem.* **2005**, *117*, 7244. (c) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128.

(3) (a) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (c) Patel, M.; Kaltenbach, R. F., III; Nugiel, D. A.; McHugh, R. J., Jr.; Jadhav, P. K.; Bacheler, L. T.; Cordova, B. C.; Klabe, R. M.; Erickson, V. S.; Garber, S.; Reid, C.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1077. (d) Reedijk, J. *Chem. Commun.* **1996**, 801. (e) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28. (f) Cummins, C. C.; Beachy, M. D.; Schrock, R. R.; Vale, M. G.; Sankaran, V.; Cohen, R. E. *Chem. Mater.* **1991**, *3*, 1153.

(4) (a) Izawa, K.; Onishi, T. *Chem. Rev.* **2006**, *106*, 2811. (b) Specker, E.; Böttcher, J.; Brass, S.; Heine, A.; Lilie, H.; Schoop, A.; Müller, G.; Griebenow, N.; Klebe, G. *Chem. Med. Chem.* **2006**, *1*, 106. (c) Engstrom, K.; Henry, R.; Hollis, L. S.; Kotecki, B.; Marsden, I.; Pu, Y.-M.; Wagaw, S.; Wang, W. *J. Org. Chem.* **2006**, *71*, 5369. (d) Yeung, C. M.; Klein, L. L.; Flentge, C. A.; Randolph, J. T.; Zhao, C.; Sun, M.; Dekhtyar, T.; Stoll, V. S.; Kempf, D. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2275. (e) Ikunaka, M. *Chem.—Eur. J.* **2003**, *9*, 378. (f) Abdel-Rahman, H. M.; Al-Karamany, G. S.; El-Koussi, N. A.; Youssef, A. F.; Kiso, Y. *Curr. Med. Chem.* **2002**, *9*, 1905. (g) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (h) Kempf, D. J.; et al. *J. Med. Chem.* **1998**, *41*, 602. (i) Ettmayer, P.; Hübner, M.; Gstach, H. *Tetrahedron Lett.* **1994**, *35*, 3901. (j) Kempf, D. J.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Marsh, K. C.; Bryant, P.; Sham, H. L.; Green, B. E.; Betebenner, D. A.; Erickson, J.; Norbeck, D. W. *J. Med. Chem.* **1993**, *36*, 320.

(5) (a) Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand, B. J. *J. Org. Chem.* **2003**, *68*, 9809. (b) Adam, W.; Bosio, S. G.; Degen, H.-G.; Krebs, O.; Stalke, D.; Schumacher, D. *Eur. J. Org. Chem.* **2002**, 3944. (c) Urabe, H.; Kusaka, K.; Suzuki, D.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 285. (d) Zhang, A.; Kan, Y.; Jiang, B. *Tetrahedron* **2001**, *57*, 2305. (e) Kaname, M.; Arakawa, Y.; Yoshifuji, S. *Tetrahedron Lett.* **2001**, *42*, 2713. (f) Dussault, P. H.; Han, Q.; Sloss, D. G.; Symonsbergen, D. J. *Tetrahedron* **1999**, *55*, 11437. (g) Wyatt, P. B.; Villalonga-Barber, C.; Motevalli, M. *Tetrahedron Lett.* **1999**, *40*, 149. (h) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Raynor, C. M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2591. (i) Virgili, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron* **1999**, *55*, 3959. (j) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179.

(6) Aburel, P. S.; Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2344.

(7) For synthesis of similar compounds, see: Srinivasan, V.; Jebaratnam, D. J.; Budil, D. E. *J. Org. Chem.* **1999**, *64*, 5644.

(8) The reaction of 2-triisopropylsilyloxy-1,3-cyclohexadiene with $CuPF_6(CH_3CN)_4$ and (*R*)-BINAP gave the corresponding adduct with >99% ee. The origin of this result is being investigated in our laboratory.

(9) Reactions using the following metal catalysts were checked on TLC: Al, B, Mg, Zn, Ti, Sc, Hf, Yb, Zr, In, La. None of them accelerated the reaction.

(10) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360.

(11) For synthesis of silyloxydienes, see: (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082.

(12) Excess amount of AcOH was necessary to avoid epimerization of the methyl group via retro-Michael reaction.

(13) For SmI_2-mediated cleavage of the N−N bond with trifluoroacetyl group, see: (a) Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867. (b) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

JA066726Y