J|A|C|S
COMMUNICATIONS

Published on Web 01/06/2005

Brønsted Acid Catalysis of Achiral Enamine for Regio- and Enantioselective Nitroso Aldol Synthesis

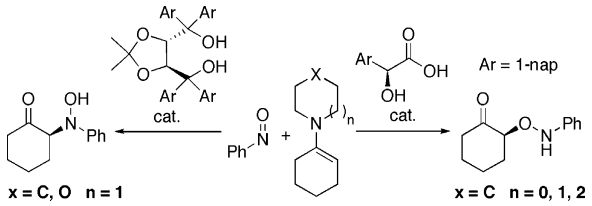
Norie Momiyama and Hisashi Yamamoto*

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

Received September 13, 2004; E-mail: yamamoto@uchicago.edu

There has been considerable interest in the development of catalytic enantioselective enolate−electrophile bond constructions, which typically have employed metal enolates.[1] While enamines have been well-known as useful enol synthons since the pioneering work by Stork,[2] success in such endeavors for asymmetric induction has proven elusive. The diastereoselective reaction using chiral enamine[3] and asymmetric reaction via a chiral proline enamine and its analogues[4] are recent strategies in this context. However, the corresponding enantioselective process has not been fully realized with achiral enamines as nucleophiles.[5] We report herein the first enantioselective Brønsted acid catalysis[6] of achiral enamine in nitroso aldol synthesis, which proceeds in a completely regio- and highly enantioselective manner (Scheme 1).[7]

Scheme 1. Brønsted Acid Catalysis of Achiral Enamine



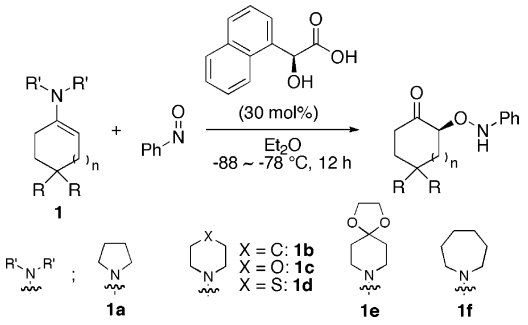
The first nitroso aldol synthesis using enamine was reported in 1972 by Lewis et al.[8] They described that the reaction of morpholine enamine of cyclohexanone provided the *N*-nitroso aldol product in 30% yield. Surprisingly, we found that a similar reaction using the pyrrolidine enamine of cyclohexanone gave rise to the *O*-nitroso aldol product exclusively in benzene at 0 °C.[9] Furthermore, these reactions could be accelerated significantly by the addition of Brønsted acids. Although the reaction of morpholine enamine was very slow in toluene at −78 °C, rapid access to *N*-nitroso aldol synthesis was realized in the presence of methanol.[10] Meanwhile, the pyrrolidine enamine gave no nitroso aldol product at −78 °C in toluene but significant acceleration for the *O*-nitroso aldol pathway took place in the presence of acetic acid.[10]

With these observations in hand, a variety of chiral carboxylic acids were examined using the pyrrolidine enamine **1a** to produce the *O*-nitroso aldol product.[11] 1-Aryl glycolic acids were identified as the most successful promoters. It was also quite interesting to find a significant effect of solvent on this transformation. The best result was obtained using (*S*)-1-naphthyl glycolic acid and piperidine enamine **1b** in diethyl ether, giving 92% ee and 77% isolated yield.

For *N*-nitroso aldol synthesis, we also screened various alcohols and phenols.[11] We immediately found TADDOL to be a promising Brønsted acid catalyst for our purpose. The best result was obtained when the reaction was conducted with 30 mol % of 1-naphthyl TADDOL in toluene using piperidine cyclohexene enamine (**1b**); only the N-adduct was produced in 83% ee and 81% isolated yield.

Under these optimized conditions, the scope of the reaction was explored (Tables 1 and 2).[12] In general, high enantiomeric excesses are observed for cyclohexene enamines bearing a piperidine-based amine moiety (**1b**). The most gratifying aspect of this study was the exclusive formation of a single regioisomer (O vs N) with proper choice of Brønsted acid and enamine combinations. Thus, enamines derived from pyrrolidine (**1a**) and homopiperidine (**1f**) are generally

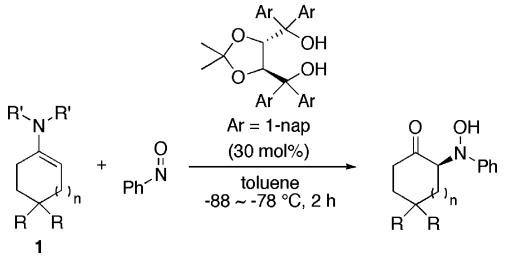
Table 1. *O*-Nitroso Aldol Synthesis Catalyzed by Glycolic Acid[a]



entry	enamine	*n*	R, R	yield, %[b]	ee, %[c]
1[d]	**1a**	1	H, H	69	70
2	**1b**	0	H, H	63	70
3	**1b**	1	H, H	77	92
4	**1b**	1	Me, Me	91	90
5	**1b**	1	−(OCH_2CH_2O)−	83	93
6	**1b**	2	H, H	<1	
7	**1e**	1	H, H	89	91
8	**1f**	1	H, H	64	83

[a] Reactions were conducted with 30 mol % of 1-nap glycolic acid, 1.0 equiv of nitrosobenzene, and 1.0 equiv of enamine in diethyl ether at −88 to −78 °C for 12 h. [b] Isolated yield. [c] Determined by HPLC (see the Supporting Information). [d] Reactions were conducted in THF for 2 h.

Table 2. *N*-Nitroso Aldol Synthesis Catalyzed by TADDOL[a]



entry	enamine	*n*	R, R	yield, %[b]	ee, %[c]
1	**1b**	0	H, H	<1	
2	**1b**	1	H, H	81	83
3	**1b**	1	Me, Me	78	82
4	**1b**	1	−(OCH_2CH_2O)−	63	91
5	**1b**	2	H, H	67	65
6	**1c**	1	H, H	91	79
7	**1d**	1	H, H	88	77
8	**1e**	1	H, H	81	80

[a] Reactions were conducted with 30 mol % of 1-nap TADDOL, 1.0 equiv of nitrosobenzene, and 1.0 equiv of enamine in toluene at −88 to −78 °C for 2 h. [b] Isolated yield. [c] Determined by HPLC (see the Supporting Information).

10.1021/ja0444637 CCC: $30.25

acceptable for *O*-nitroso aldol synthesis, affording the O-adduct in good yields and with high enantioselectivities. Morpholino (**1c**) and thiomorpholino (**1d**) enamine are competent substrates in *N*-nitroso aldol synthesis.

^{1}H and ^{13}C NMR confirmed that neither the cis nor the trans azodioxy dimer was observed in the presence of Brønsted acid.[13] Thus, initial formation of the azodioxy dimer may be excluded. The proposed reaction pathway is outlined as follows. The Brønsted acid coordinates with the nitrogen atom of the N═O bond, followed by nucleophilic attack at the oxygen atom to give the O-adduct,[14] while the oxygen-activated nitrosobenzene is attacked by the β-carbon to provide a hydroxyamino iminium compound. The sense of each Brønsted acid catalysis of achiral enamine can be understood by the fact that the nucleophilicity of enamine is known to be heavily dependent on the structure of the amine moiety.[15] Under acidic conditions, the rate of the hydrolysis[16] of the pyrrolidine enamine was much slower than that of morpholine enamine. On the other hand, the hydrolysis of the morpholine enamine proceeds in highly acidic media. Thus, it is presumed that the less acidic TADDOL facilitates the reaction of morpholine enamine, while the more acidic glycolic acid is required for the reaction of pyrrolidine enamine. Since the hydrolyses of piperidine enamine are not dramatically different over the whole pH range and maintains a value between those of pyrrolidine and morpholine, the piperidine enamines can be used for both N- and O-adduct syntheses.

It should be noted that both catalysts have a possible intramolecular hydrogen bond between two alcoholic and/or carboxylic acid oxygen lone pairs. We attribute this feature to generating reactive and stereochemically rigid Brønsted acid assisted Brønsted acid (BBA) systems which may result in the good selectivities found for the present reactions.[17]

In summary, although the scope of the present regio- and enantioselective nitroso aldol synthesis described herein is still under investigation, the general pattern of results obtained thus far encourages optimism. We believe that the process has advanced to a new level of applicability and generality in nitroso aldol synthesis on the basis of our findings. Further extension of these concepts into a general catalytic enantioselective approach to other enolate−electrophile bond construction is also the subject of ongoing studies.

Acknowledgment. We gratefully acknowledge Prof. Viresh H. Rawal for helpful discussions. We also thank Dr. Ian M. Steele for X-ray crystallographic analysis and acknowledge Yamakawa Chemical Co. for the gift of (*S*)-2-naphthyl glycolic acid. Support for this research has been provided by National Institutes of Health (NIH) Grant No. GM068433-01 and a grant from the University of Chicago.

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

References

(1) For a general review of enantioselective reactions of metal enolates, see: (a) *Comprehensive Asymmetric Catalysis III*; Jacobsen, E. N., Pfalts, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 465−697. (c) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1 and 2.

(2) For a general review of reactions of enamines, see: (a) Cook, A. G. In *Enamines: Synthesis, Structure, and Reactions*; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; pp 1−101. (b) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975−2050.

(3) For representative papers, see: (a) Yamada, S.; Hiroi, K.; Achiwa, K. *Tetrahedron Lett.* **1969**, *10*, 4233−4236. (b) Matsushita, H.; Noguchi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1928−1930. (c) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663−1664. (d) Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715−716.

(4) For general reviews of enamine-based organo catalysis, see: (a) List, B. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, pp 161−200. (b) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975−978. (c) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995−2997.

(5) (a) Matsushita, H.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3715−3717. (b) Duhamel, L.; Plaquevent, J. C. *Tetrahedron Lett.* **1977**, *18*, 2285−2288. (c) Matsushita, H.; Tsujino, Y.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 862−865. (d) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535−2538. (e) Halland, N.; Velgaard, T.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 5067−5074.

(6) For recent representative papers, see: (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965. (b) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (c) MacDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094−12095. (d) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (e) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296. (f) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418−3419. (g) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (h) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357. (i) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846−5850. (j) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. (k) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804−11805.

(7) For the enantioselective nitroso aldol reaction and related papers, see: (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038−6039. **2004**, *126*, 6498. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360−5361. (c) See ref 4c. (d) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374−5378. (e) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962−5963. (f) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317−3321. (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) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizumi, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435−1439. (j) Wang, W.; Wang, J.; Li, H.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 7235−7238. (k) Iwamura, H.; Wells, D. H.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312−16313.

(8) Lewis, J. W.; Myers, P. L.; Ormerod, J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, *20*, 2521−2524.

(9) See ref 7d.

(10) Detailed results are described in the Supporting Information.

(11) The results are summarized in the Supporting Information.

(12) Unfortunately, this system did not afford enough enantioselectivity for enamines of aldehydes and acyclic ketones.

(13) (a) Orrell, K. G.; Sik, V.; Stephenson, D. *Magn. Reson. Chem.* **1987**, *25*, 1007−1011. (b) Orrell, K. G.; Stephenson, D. *Magn. Reson. Chem.* **1989**, *27*, 368−376.

(14) (a) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558−569. (b) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912−13913.

(15) (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222. (b) Stamhuis, E. J.; Maas, W. *J. Org. Chem.* **1965**, *30*, 2156−2160. (c) Kuehne, M. E.; Garbacik, T. *J. Org. Chem.* **1970**, *35*, 1555−1558. (d) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209−2218.

(16) Mass, W.; Janssen, M. J.; Stamhuis, E. J.; Wynberg, H. *J. Org. Chem.* **1967**, *32*, 1111−1115.

(17) (a) Weber, E.; Dorphinhaus, N.; Wimmer, C. *J. Org. Chem.* **1992**, *57*, 6825−6833. (b) Cuenca, A.; Meido-Simon, M.; Aguilar, A.; Weibel, D.; Beck, A. K.; Seebach, D. *Helv. Chim. Acta* **2000**, *83*, 3153−3162. (c) Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Maluszynska, H.; Polonski, T. *J. Org. Chem.* **2001**, *66*, 501−506. (d) Seebach, D.; Albert, K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138. (e) Kaku, H.; Takaoka, S.; Tsunoda, T. *Tetrahedron* **2002**, *58*, 3401−3407. (f) See ref 6i. (g) Du, H.; Zhao, D.; Ding, K. *Chem. Eur. J.* **2004**, *10*, 5964−5970.

JA0444637