The First Catalytic Asymmetric Aza-Henry Reaction of Nitronates with Imines: A Novel Approach to Optically Active β-Nitro-α-Amino Acid- and α,β-Diamino Acid Derivatives

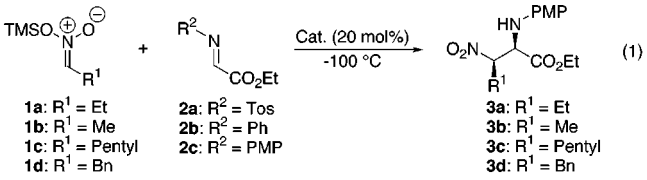
Kristian Rahbek Knudsen, Tine Risgaard, Nagatoshi Nishiwaki, Kurt V. Gothelf, and Karl Anker Jørgensen*

Center for Metal Catalyzed Reactions Department of Chemistry, Aarhus University DK-8000 Aarhus C, Denmark

Received March 5, 2001

The Henry (nitro aldol) reaction,[1] and its aza analogue,[2] are fundamental C−C bond-forming reactions in organic chemistry. Compared with the development of catalytic enantioselective aldol reactions, there are astonishingly few examples on asymmetric catalytic nitro aldol reactions. Only the chiral heterobimetallic catalysts reported by Shibasaki et al. have proven to be effective for asymmetric Henry reactions.[3] In extension of this work, they have developed a catalytic asymmetric aza-Henry reaction (nitro-Mannich reaction).[3c] When nitromethane was used as the substrate, high enantioselectivities were obtained for this reaction using *N*-phosphinoylimines. However, 60 mol % of the chiral ligand in the chiral ytterbium catalyst was required, and successful reactions were reported for only nitromethane.

This communication presents the first catalytic highly diastereo- and enantioselective aza-Henry reaction that proceeds in the absence of a base and with lower catalyst loading. In this reaction, the presence of a base is avoided by the application of silyl nitronates **1a**−**d** instead of nitro compounds for the reaction with α-imino esters **2a**−**c** in the presence of a chiral Lewis acid. It should be noted that a racemic fluoride-induced reaction of silyl nitronates with aldehydes has been described by Seebach et al.,[4] and very recently another racemic version of this reaction using $Sc(OTf)_3$ was reported.[5]



(1)

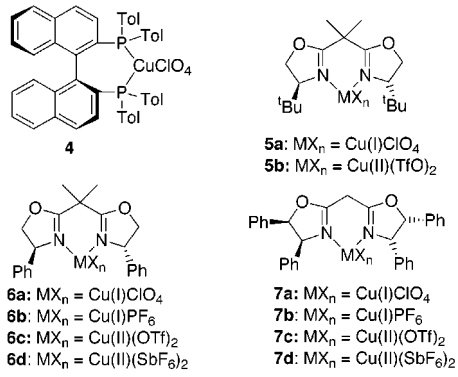
The reaction of the trimethylsilyl nitronate **1a**[6] with *N*-protected α-imino esters **2a**−**c** in the presence of various Lewis acids was investigated first (eq 1). Application of *N*-(*p*-tosyl)-α-imino ester **2a** gave unstable products that underwent retro aza-Henry reaction, or elimination of the nitro group, in the reaction with **1a** catalyzed by a Lewis acid. However, when the more electron-rich *N*-phenyl-α-imino-ester **2b** and *N*-(*p*-methoxyphenyl)-α-imino ester **2c** were applied in the reaction catalyzed by various copper Lewis acids, the aza-Henry products were obtained as stable compounds in satisfactory yields. Application of the *N*-(*p*-methoxyphenyl) (PMP) group for protection of the imine functionality also has the important advantage that it can be easily removed from the product,[2,7] and we have therefore used **2c** for the present development.

The reaction of **1a** with **2c** proceeds to some extent in the absence of a catalyst even at −78 °C. Thus, the catalytic reactions (eq 1) were performed at −100 °C to avoid the racemic reaction. Various chiral Lewis acid complexes such as BINOL-AlMe, TADDOLate-$TiCl_2$, DBFOX-$Ni(ClO_4)_2$,[8] DBFOX-$Mg(ClO_4)_2$, and DBFOX-$Zn(OTf)_2$ were initially tested as catalysts, but very low enantioselectivities were obtained. Much more promising results were obtained when the chiral copper catalysts **4**−**7** were used (Table 1). Application of catalyst (*R*)-Tol-BINAP−$CuClO_4$ **4**[9] for the reaction of **1a** with **2c** led to a high yield of **3a** in a 1:3 ratio of the *erythro*:*threo*-isomers; however, only 16% ee of *erythro*-**3a** (entry 1) (*threo*-**3a**, 55% ee) was obtained. The use of (*S*)-^{t}Bu-BOX−copper complexes[10] **5a**,**b** as the catalyst also gave low to medium enantiomeric excess; however, these catalysts improved and reversed the diastereoselectivity to 11:1 and 7:1,

Table 1. Enantioselective Aza-Henry Reactions of Nitronates **1a**−**d** with *N*-(*p*-Methoxyphenyl)-α-Imino Ester **2c** Catalyzed by a Series of Chiral Copper Complexes **4**−**7**

entry[a]	nitronate	catalyst	product	yield[b] (%)	*erythro*: *threo*	ee *erythro*[d] (%)	config. (C2,C3)
1	**1a**	(*R*)-**4**	**3a**	99	1:3	16	(*R*,*R*)
2	**1a**	(*R*)-**5a**	**3a**	99	11:1	12	(*S*,*S*)
3	**1a**	(*R*)-**5b**	**3a**	58	7:1	56	(*R*,*R*)
4	**1a**	(*S*)-**6a**	**3a**	90	3:1	90	(*S*,*S*)
5	**1a**	(*S*)-**6b**	**3a**	63	5:1	56	(*S*,*S*)
6	**1a**	(*S*)-**6c**	**3a**	67	18:1	89	(*S*,*S*)
7	**1a**	(*S*)-**6d**[e]	**3a**	92	6:1	70	(*S*,*S*)
8	**1a**	(4*R*,5*S*)-**7a**	**3a**	52	6:1	96	(*R*,*R*)
9	**1a**	(4*R*,5*S*)-**7b**	**3a**	68	10:1	97	(*R*,*R*)
10	**1a**	(4*R*,5*S*)-**7c**	**3a**	54	9:1	26	(*R*,*R*)
11	**1a**	(4*R*,5*S*)-**7d**[e]	**3a**	94	25:1	95	(*R*,*R*)
12	**1b**	(*S*)-**6a**	**3b**	67	5:1	>98	(*S*,*S*)[f]
13	**1c**	(4*R*,5*S*)-**7d**[e]	**3c**	87	39:1	83	(*R*,*R*)[f]
14	**1d**	(4*R*,5*S*)-**7a**	**3d**	93	32:1	88	(*R*,*R*)[f]

[a] The reactions were performed in THF by adding 1.5 equiv of **1** during a period of 1 h, to a mixture of the catalyst (20 mol %) and **2c** at −100 °C. [b] Isolated yield of a mixture of the diastereomers of **3**. [c] The diastereomeric ratio was determined using ^{1}H NMR. [d] The enantiomeric excess was determined by chiral HPLC analysis. [e] CH_2Cl_2 was used as the solvent. [f] Proposed absolute configuration obtained by comparing the absolute configuration induced by the respective catalysts for **3a**.



(1) (a) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (b) Torssell, K. B. G.; Gothelf, K. V. Nitroethane. In *Encyclopaediea of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1995; Vol. 6, p 3735. (c) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298. (d) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.

(2) (a) Baer, H. H.; Urbas, L. In *the Chemistry of the Nitro and Nitroso Groups, Part 2*; Patai, S., Ed.; Interscience: New York, 1970; p 117. (b) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.

(3) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368. (c) Yamada, K.; Harwood: S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504.

(4) (a) Colvin, E. W.; Seebach, D. *Chem. Commun.* **1978**, 689. (b) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101.

(5) Anderson, J. C.; Paece, S. *Synlett* **2000**, 850.

(6) (a) Torssell, K. B. G.; Zeuthen, O. *Acta Chem. Scand.* **1978**, *B32*, 118. (b) Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz; J. D. *Helv. Chim. Acta* **1980**, *63*, 697.

(7) Fukuyama, T.; Frank, R. K.; Jewell, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 2, 2122.

(8) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, H.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074.

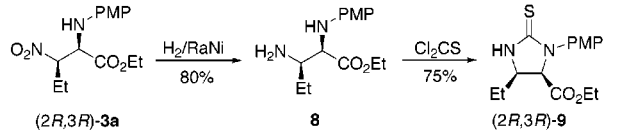
10.1021/ja010588p CCC: $20.00
Published on Web 05/23/2001

respectively (entry 2,3). Much better results were obtained when turning to the (*S*)-Ph-BOX−copper catalysts **6a**-**d**. The reaction between **1a** and **2c** catalyzed by **6a** gave the *N*-protected *β*-nitro-α-amino ester **3a** in an excellent yield and with 90% ee of the *threo*-isomer (entry 4). It is notable that similar high enantioselectivity of the major diastereomer was obtained when using the chiral copper(II) catalyst **6c**, and, additionally the diastereoselectivity was significantly improved (entry 6). For the reaction between **1a** and **2c**, the *cis*-DiPh-BOX−copper catalysts **7a**-**d** turned out to be superior.[11] The chiral copper(I) catalysts **7a**,**b** induced good diastereoselectivities and remarkably high enantioselectivities of up to 97% ee (entry 8,9). Very high yield and diastereoselectivity of 25:1 were also obtained using the chiral copper(II) catalyst **7d**, and furthermore, *erythro*-**3a** was obtained with 95% ee (entry 11).

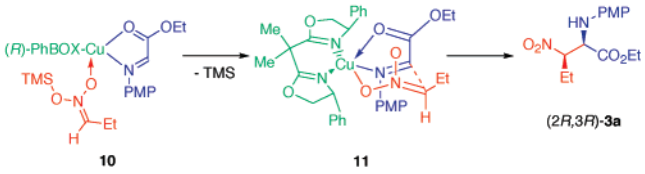
To show the potential of this new reaction, it is demonstrated that the catalytic approach can be applied to other trimethylsilyl nitronates. The choice of catalyst was optimized for the reactions of silyl nitronates **1b**−**d** with imine **2c** to give **3b**−**d**, and the best results of these reactions are presented in Table 1 as entries 12−14. For the reaction of the nitroethane-derived nitronate **1b** with **2c** catalyzed by **6a**, an excellent enantioselectivity >98% ee was obtained (entry 12), and furthermore, this reaction also proceeds with a satisfactory diastereoselectivity. The analogous reactions of nitronates **1c**,**d** catalyzed by **7d** and **7a**, respectively, gave also satisfactory enantioselectivities as 83 and 88% ee of **3c** and **3d**, respectively, were obtained. Furthermore, very high diastereoselectivities of 39:1 and 32:1 were obtained in favor of *erythro*-**3c** and *erythro*-**3d**, respectively (entries 13,14). Thus, the reactions of the silyl nitronates **1a**−**d** with **2c** all proceed in high yield, diastereo- and enantioselectivity giving *β*-nitro-α-amino esters which are a new class of optically active α-amino acid derivatives. Furthermore, it is notable that the reaction is very flexible with respect to both chiral ligands and copper salts.

The high synthetic potential of the aza-Henry reaction (eq 1) is also due to the easy conversion of the *β*-nitro-α-amino acid derivatives into a variety of important functionalities, for example, 1,2-diamines. This has previously been demonstrated for alkyl- and aryl-substituted 2-nitro amines;[2b,5,12] however, the conversion of *β*-nitro-α-amino esters into α,*β*-diamino acid derivatives has not been described previously. As a matter of fact, only few syntheses of optically active α,*β*-diamino acid derivatives have been reported.[13] For compound *erythro*-**3a** (catalyst (*R*)-**6a** used: 90% ee) the reduction of the nitro group was performed using Raney-Ni to give the protected diamino ester **8** in 80% yield (Scheme 1). Compound **8** was converted into the corresponding 2-thioimidazolidine derivative **9** by cyclization with Cl_2CS. Both the reduction and cyclization reactions proceeded without loss of enantioselectivity. Product **9** was obtained as a crystalline compound which was characterized by X-ray crystallography (see Supporting Information). From the knowledge of the absolute configuration of **9**, the absolute configuration of *erythro*-**3a** was assigned to be (2*R*,3*R*).

Scheme 1



Scheme 2



The absolute configuration of *erythro*-**3a**, led us to propose the mechanism outlined in Scheme 2 to account for the stereochemical induction of the reaction. It is proposed that both the α-imino ester **2c**, in a bidentate fashion, and the silyl nitronate coordinate to the copper center. It is well-known that silyl nitronates decompose in the presence of acids, and therefore, it is assumed that when the silyl nitronate interacts with the Lewis acid, as described for **10**, the TMS-group dissociates from the nitronate to give **11**. As it has been described for silyl nitronates,[6b] it should also be expected that there is a rapid equilibrium between the *E*- and *Z*-forms of the copper nitronate **11**. This enables a six-membered cyclic transition state for **11**, with a pentacoordinated copper center. This model can account for both the catalytic activity, diastereo- and enantioselectivity of the reaction. By coordination to the copper center, the α-imino ester is activated for addition of the nucleophilic nitronate. In the chair-conformation of the cyclohexane-like transition state the nitronate substituent obtains the less sterically crowded and more stable equatorial position. This explains the predominant formation of the *erythro*-product. The chiral (*R*)-Ph-BOX ligand shown in **11** favors the formation of the (2*R*,3*R*) enantiomer of the product, since the intermediate leading to the opposite enantiomer of the product would have unfavorable steric interaction between the bulky PMP-substituent of the α-imino ester and of the phenyl substituent of the ligand.

In summary, the development of a new highly enantio- and diastereoselective copper−bisoxazoline-catalyzed aza-Henry reaction between silyl nitronates and an α-imino ester giving highly valuable optically active *β*-nitro-α-amino esters has been described. It was demonstrated that high selectivities could be obtained for various trimethylsilyl nitronates in the presence of various copper−bisoxazoline catalysts. Furthermore, it was shown that the optically active *β*-nitro-α-amino esters can be converted to a synthetically valuable α,*β*-diamino acid derivatives. The absolute configuration of one of the products was determined, and a model for the catalytic intermediate was proposed.

Acknowledgment. We are grateful to Dr. Rita G. Hazell for performing the X-ray crystallographic analysis of compound **9**. This work was made possible by a grant from the Danish National Research Foundation.

Note Added in Proof: See also Shibasaki et al., *Synlett*, **2001**, June 1 issue for nitro-Mannich reactions of nitro compounds with imines.

Supporting Information Available: Complete experimental procedure, characterization and ^1H and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010588P

(9) For the use of Tol-BINAP−Cu(I) as catalyst for addition reaction to related imines, see e.g.: (a) Drury, W. J., III; Ferraris, D.; Cox, C..; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006; (b) Yao, S.; Fang, X.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (d) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168. (e) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. (f) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114; see also: Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450; Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474.

(10) For recent reviews dealing with the use of chiral bisoxazoline-Lewis acids as catalysts see: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(11) (a) Lowental, R. E.; Masamune, S. *Tetrahedron* **1991**, *32*, 7373. (b) Reichel, F.; Fang, X.; Yao, S.; Ricci, M.; Jørgensen, K. A. *Chem. Commun.* **1999**, 1505.

(12) (a) Barrett, A.; G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733. (b) Sturgess, M. A.; Yarberry, D. J. *Tetrahedron Lett.* **1993**, *34*, 4743.

(13) (a) Nakamura, Y.; Hirai, M.; Tamotsu, K.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1369. (b) Burke, S. G.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1996**, 621. (c) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett.* **1997**, *38*, 1813. (d) Baumgartner, H.; O'Sullivan, A. C. *Tetrahedron* **1997**, *53*, 2775.