The First Enantioselective and Diastereoselective Catalytic Nitro-Mannich Reaction: A New Entry to Chiral Vicinal Diamines

Ken-ichi Yamada, Guido Moll, Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Fax +81 (3) 56845206; E-mail: mshibasa@mol.f.u-tokyo.ac.jp

Received 30 January 2001

Dedicated to Professor R. Noyori for his outstanding contributions to the art of practical asymmetric catalysis

Abstract: The first example of an enantioselective and diastereoselective catalytic nitro-Mannich reaction using a second-generation heterobimetallic complex has been developed. The corresponding nitro-Mannich products were obtained in up to 83% *ee* with a *dr* up to 7:1.

Key words: 1,2-diamines, asymmetric catalysis, imines, nitro compounds, nucleophilic additions

The nitro-Mannich reaction, the nucleophilic addition of nitroalkanes to imines, gives rise to β -nitroamines and the nitro group can be converted easily into the amino function providing the useful vicinal diamines.¹ Although the first example of this class of reaction appeared in 1896,² until recent reports by Anderson et al.³ no stereoselective version of the nitro-Mannich reaction had been known. A general enantioselective catalytic version of this reaction should be a powerful tool for the preparation of chiral vicinal diamines. In 1999 we reported about the enantioselective catalytic nitro-Mannich reaction,⁴ and although this was the first example of an enantioselective nitro-Mannich reaction, the reaction suffered from the limitation that only nitromethane could be used as nucleophile. In the case of a nitroalkane with a longer carbon chain than nitromethane, the reaction forms two stereocenters and diastereoselectivity as well as enantioselectivity becomes a matter of concern. If this addition could be achieved both in an enantioselective and diastereoselective manner, this reaction would be much more powerful and useful. Herein, we wish to report the first example of an enantioselective and diastereoselective catalytic nitro-Mannich reaction.

Although our former catalyst $\text{YbKH}_2[(R)\text{-binaphthoxide}]_3$ (**1**) gave the product in 79% yield and 91% *ee* in the case of benzaldehyde imine **2a** and nitromethane,⁴ catalyst **1** did not promote the reaction of **2a** and nitroethane (**3a**) at all. We thought that the binding pocket of catalyst **1** might be too small both for the *N*-phosphinoyl imine and nitroethane, and that a catalyst having a larger binding pocket for substrates might be more suitable for this reaction. $\text{Al-Li}[(R)\text{-binaphthoxide}]_2$ complex, (*R*)-ALB⁵ is a heterobimetallic asymmetric complex containing both Brønsted basic and Lewis acidic functionalities.⁶ Having two binaphthoxide moieties as chiral ligands (*R*)-ALB might have a larger binding pocket for the substrates compared to catalyst **1** with three binaphthoxide units. Although (*R*)-

ALB itself did not promote the reaction of **2a** and **3a** at lower temperature,⁷ we were pleased to find that the complex of ALB (20 mol %) and KO-*t*-Bu (18 mol %), so-called second-generation ALB,⁸ catalyzed the reaction at -40°C in THF giving rise to **4a** after 48 h in 71% yield, a *dr* (*anti:syn*) of 3:1 and an *ee* of 35% for the major diastereomer. Changing the solvent from THF to toluene **4a** was obtained in 83% yield and 51% *ee*, but, unfortunately, the *dr* decreased to 2:1. The best result was achieved when dichloromethane was used as a solvent. Thus, the nitro-Mannich reaction of **2a** and **3a** gave **4a** after 48 h in 77% yield and a *dr* of 6:1 with 83% *ee* for the major diastereomer (Table, entry 1). When the reaction was quenched after 3 h, **4a** was obtained in 58% yield and a *dr* of 6:1 with 80% *ee*, showing that neither epimerization nor racemization took place during the reaction.

Using these optimized conditions,⁹ we examined the scope and limitations of the system: the reaction of **2a** and nitropropane (**3b**) proceeded smoothly to give the product **4b** in 98% yield with a *dr* of 6:1 and 74% *ee* for the major diastereomer (entry 2). Reactions of nitroalkanes having an ether functionality also proceeded nicely: 1-benzyloxy-3-nitropropane (**3c**) and **2a** gave the product **4c** in 95% yield and a *dr* of 7:1. The *ee* of the major diastereomer was found to be 82% (entry 3). In the case of 1-benzyloxy-4-nitrobutane (**3d**) the product **4d** was obtained in 75% yield and a *dr* of 6:1 with 77% *ee* for the major diastereomer (entry 4). Next, we investigated the reaction of other aromatic imines and **3b**: using *p*-anisaldehyde imine **2b** the product **4e** was obtained in 77% yield, a *dr* of 6:1 and 78% *ee* for the major diastereomer (entry 5). Reaction of *p*-tolualdehyde imine **2c** yielded **4f** in 68%, a *dr* of 6:1 with 77% *ee* for the major diastereomer (entry 6). Using imine **2d**, having an electron-withdrawing group, the nitro-Mannich product **4g** was obtained in 89% yield, a *dr* of 3:1 and 71% *ee* for the major diastereomer (entry 7). The reactions also proceeded smoothly with a reduced amount of the catalyst. Thus, in the presence of 10 mol % catalyst, the desired products were given in good yields, though in slightly lower diastereoselectivity and/or enantioselectivity (Table, entries 8–14). In some cases the *ee* of the minor diastereomers could also be determined, but only *ee*'s up to 43% were obtained.¹⁰ So far, aliphatic imines such as pivalaldehyde imine gave less satisfactory results. Preliminary results showed that it was also possible to perform the reaction using 2 g of **2a**. Under diluted conditions and without further optimization the reaction of **2a**

Table Diastereoselective Catalytic Asymmetric Nitro-Mannich Reaction of Various Substrates

entry	imine		nitroalkane		catalyst (mol %)	product			
	no.	Ar	no.	R		no.	yield (%)	<i>dr</i> (anti : syn) ^b	% <i>ee</i> (anti) ^c
1	2a	Ph	3a	Me	20	4a	77	6 : 1	83
2	2a	Ph	3b	Et	20	4b	98	6 : 1	74
3	2a	Ph	3c	(CH ₂) ₂ OBn	20	4c	95	7 : 1	82
4	2a	Ph	3d	(CH ₂) ₃ OBn	20	4d^d	75	6 : 1	77
5	2b	4-MeOC ₆ H ₄	3b	Et	20	4e^d	77	6 : 1	78
6	2c	4-CH ₃ C ₆ H ₄	3b	Et	20	4f	68	6 : 1	77
7	2d	4-ClC ₆ H ₄	3b	Et	20	4g	89	3 : 1	71
8	2a	Ph	3a	Me	10	4a	97	5 : 1	75
9	2a	Ph	3b	Et	10	4b	87	5 : 1	71
10	2a	Ph	3c	(CH ₂) ₂ OBn	10	4c	87	5 : 1	60
11	2a	Ph	3d	(CH ₂) ₃ OBn	10	4d^d	93	5 : 1	63
12	2b	4-MeOC ₆ H ₄	3b	Et	10	4e^d	96	5 : 1	63
13	2c	4-CH ₃ C ₆ H ₄	3b	Et	10	4f	98	5 : 1	81
14	2d	4-ClC ₆ H ₄	3b	Et	10	4g	97	3 : 1	74
15 ^e	2a	Ph	3a	Me	10	4a	78	6 : 1	76

(a) Catalyst = (*R*)-ALB-KO-*t*-Bu (1:0.9). (b) The *dr* was determined by ¹H NMR of the crude reaction mixture. (c) For **4a** and **4f**, the *ee*'s were determined by chiral HPLC analysis. For other products, the *ee*'s were determined by chiral HPLC analysis after reduction of the nitro group and acylation of the resulting amino group. (d) The absolute configuration was tentatively assigned. (e) The reaction was performed using 2 g of **2a** under diluted conditions (0.5 M).

and **3a** afforded the desired product **4a** in 78% yield with a *dr* of 6:1 and 76% *ee* using 10 mol % of the catalyst (entry 15).

To demonstrate the usefulness of this reaction, nitroamine **4a** was converted to versatile diamine **5a** as shown in the Scheme. The nitro group of **4a** could be reduced easily to the amino group using Sm^{II} chemistry.^{11,12} By treatment of the obtained mono-protected diamine with methanolic HCl at room temperature the diphenylphosphinoyl group was removed,¹³ providing the free optically active diamine **5a** (Scheme). Comparison of the optical rotation sign with that reported in literature¹⁴ showed that the absolute configuration of the major diastereomer obtained by the (*R*)-ALB-catalyst was (1*R*,2*S*).¹⁵

Scheme Conversion of nitroamine **4a** to diamine **5a**

In conclusion, we have developed the first diastereoselective catalytic asymmetric nitro-Mannich reaction.¹⁶ The products, β -nitroamines can be converted easily into chiral vicinal diamines in two steps. We believe that this contribution will provide a new, more general access to chiral vicinal diamines. Further studies concerning a larger substrate variety and the possible mechanism are currently under investigation.

Acknowledgement

G. M. thanks the Japanese Science and Technology Corporation (JST) for a postdoctoral grant. K. Y. thanks the Japanese Society for Promotion of Science (JSPS) for a Research Fellowship for Young Scientists.

References and Notes

- (1) For a review about the application and preparation of vicinal diamines, see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2580.
- (2) Henry, L. *Bull. Acad. Roy. Belg.* **1896**, [3] 32, 33.

- (3) (a) Anderson, J. C.; Peace, S.; Pih, S.; *Synlett* **2000**, 850. (b) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, 63, 9932.
- (4) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, 38, 3504.
- (5) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 104.
- (6) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1236 and references cited therein.
- (7) The reaction of **2a** and **3a** was promoted by (*R*)-ALB at room temperature to give the racemic product **4a** in 75% yield and a diastereomeric ratio of 9:1 after 36 h.
- (8) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem.-Eur. J.* **1996**, 2, 1368.
- (9) General procedure for the enantioselective and diastereoselective catalytic nitro-Mannich reaction. Preparation of the catalyst solution: To a flame-dried round-bottom flask was added the THF solution of the $\text{AlLi}[(R)\text{-binaphthoxide}]_2$ complex (0.1 M, 1.0 mL) prepared according to our procedure reported in *J. Org. Chem.* **1998**, 63, 7547. The solvent was removed in vacuo, and the resulting solid was dried for 1 h. The dried solid was dissolved in CH_2Cl_2 (1.0 mL), and after being stirred for 1 h the solution was directly used as 0.1 M CH_2Cl_2 solution of the catalyst. (1*R*,2*S*)-*N*-(2-Nitro-1-phenylpropyl)-*P,P*-diphenylphosphinic amide (**4a**): To imine **2a** (61 mg, 0.20 mmol) in a flame-dried round-bottom flask was added the 0.1 M CH_2Cl_2 solution of the catalyst (0.40 mL, 0.20 equiv), and the mixture was stirred for 10 min at r.t. The mixture was cooled to -40°C and stirred for 10 min before a 0.97 M solution of KO-*t*-Bu in THF (37 μL , 0.18 equiv) and then nitroethane (72 μL , 1.0 mmol) were added at -40°C . The mixture was stirred for 48 h at the same temperature, diluted with cold CH_2Cl_2 (-78°C , ca. 5 mL) and then quenched by the addition of HOAc (ca. 4 drops). The mixture was transferred to a separatory funnel and diluted with further CH_2Cl_2 (ca. 5 mL). The mixture was washed with H_2O , sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification of the resulting residue by flash column chromatography [silica gel, CH_2Cl_2 /acetone 19/1 to 9/1 (v/v)] gave nitroamine **4a** (59 mg, 77%) as an off-white solid in a *dr* of 6:1 with the title compound as the major isomer (83% *ee*).
- (10) In the cases of entries 2, 5 and 9 in the Table, the *ee*'s of the minor diastereomers were 40%, 43%, and 33%, respectively.
- (11) (a) Sturges, M. A.; Yarberry, D. J. *Tetrahedron Lett.* **1993**, 34, 4743. (b) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, 32, 1699.
- (12) Using freshly prepared SmI_2 (0.25 M in THF) almost no epimerization (< 3%) was observed.
- (13) Ramage, R.; Hopton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357.
- (14) Gust, R.; Gelbcke, M.; Angermaier, B.; Bachmann, H.; Krauser, R.; Schönenberger, H. *Inorg. Chim. Acta* **1997**, 264, 145.
- (15) Determination of the absolute configuration of other products was achieved after conversion to the corresponding diamines by comparison of their specific rotations with those of the same diamines which were derived from known optically active cyanohydrins in 6 steps. (a) For the preparation of the optically active cyanohydrins, see: Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1990**, 1364. (b) For the conversion of the cyanohydrins to amino alcohols, see: Effenberger, F.; Gutterer, B.; Ziegler, T. *Liebigs Ann. Chem.* **1991**, 269. (c) For the conversion of the amino alcohols to the corresponding diamines, see reference 14.
- (16) Added in proof: For another enantioselective and diastereoselective catalytic nitro-Mannich reaction, see: Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* in press.

Article Identifier:

1437-2096,E;2001,0,SI,0980,0982,ftx,en;Y03301ST.pdf