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[14] Crystal data: $C_{81}H_{30}Br_3F_{15}O_{12}\cdot C_7H_8$, $M_r = 1811.9$, monoclinic, $P2_1/n$ (No. 14), $a = 19.6797(5)$, $b = 15.2198(5)$, $c = 22.5705(6)$ Å, $\beta = 96.231(2)^\circ$, $V = 6720.4(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.79$ Mg m^{-3}, $\mu(Mo_{K\alpha}) = 1.92$ mm^{-1}, $T = 173$ K, crystal (green block) $0.3 \times 0.2 \times 0.1$ mm^3. Nonius Kappa CCD diffractometer, 41040 reflections measured, 9305 unique ($R_{int} = 0.090$). Refinement on F^2 using SHELXL-97, $R1 = 0.049$ for 7096 reflections with $I > 2\sigma(I)$, $wR2 = 0.121$ for all data. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-161000. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Catalytic Enantioselective Addition of Nitro Compounds to Imines—A Simple Approach for the Synthesis of Optically Active β-Nitro-α-Amino Esters**

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

The development of C–C bond-forming reactions that create two new stereogenic centers with high diastereo- and enantioselectivity in a single step can open new routes to highly valuable optically active compounds. The catalytic enantioselective addition to imines[1] belongs to this class of important reactions, and recently new catalytic asymmetric processes, for example, for Mannich-type,[2] ene,[3] allylation and alkylation,[4] aza-Diels–Alder,[5] Strecker,[6] and aromatic electrophilic substitution reactions[7] have appeared. Another important reaction of imines is the nitro-Mannich (aza-Henry) reaction, which is a powerful C–C bond-forming method that leads to 2-nitroamines.[8] To the best of our knowledge there is only one other paper that describes the catalytic enantioselective version of the nitro-Mannich reaction.[9] Although this reaction was catalyzed by a heterobimetallic complex, it has been described for nitromethane only and requires 60 mol% of the chiral ligand. In a very recent paper, we described the first catalytic asymmetric reaction of silyl nitronates with imines.[10] The reaction proceeds at −100 °C in the presence of bisoxazoline–copper catalysts to give 2-nitroamines with high enantioselectivities.

Herein we present a new and significantly simplified approach to the catalytic diastereo- and enantioselective nitro-Mannich reaction of an N-protected α-imino ester **1** with nitro compounds **2**. The reactions can be performed under ambient conditions to give β-nitro-α-amino esters **3** in good yields, and with high diastereo- and enantioselectivies [Eq. (1); Pg = protecting group].

1 **2** **3** (1)

In the screening process, the reaction of *N*-(*p*-methoxyphenyl)-α-imino ester **1**[11] with nitropropane **2a** in the presence of NEt_3 as the base has been studied at room temperature by using different combinations of chiral ligands and Lewis acids (Scheme 1). The use of chiral bisoxazoline

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[*] K. A. Jørgensen, N. Nishiwaki, K. Rahbek Knudsen, K. V. Gothelf
Center for Metal-Catalyzed Reactions
Department of Chemistry, Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 8619-6199
E-mail: kaj@chem.au.dk

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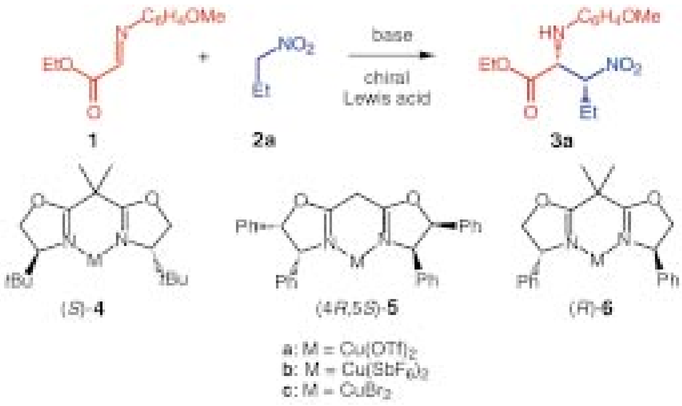


Scheme 1. Reaction of imino ester **1** and nitropropane **2a** in the presence of NEt_3 with different combinations of chiral ligands and Lewis acids (see Table 1).

(BOX) ligands[12] and copper salts gave the most promising results and some of them are presented in Table 1.

The BOX–Cu^{II} catalyst (*S*)-**4a** (20 mol%) affords only a small amount of the nitro-Mannich adduct **3a** in a high diastereomeric ratio and with 89% *ee* of the major *erythro*-diastereomer (Table 1, entry 1). The use of the phenyl-substituted BOX ligands revealed a significant improvement in the catalytic activity to give **3a** in good to high yields. Excellent enantioselectivity of the β-nitro-α-amino ester **3a**, isolated in 80% yield, was achieved by using catalyst (*R*)-**6a**, whereas (4*R*,5*S*)-**5a** afforded a racemic mixture of diastereomers (Table 1, entries 2,3). The reaction is highly solvent dependent and in CH_2Cl_2 adduct **3a** was formed in higher yield than in THF and Et_2O (Table 1, entries 3–5). The diastereo- and enantioselectivities are also dependent on the counterion, as observed by the application of triflate versus hexafluoroantimonate (Table 1, entries 3,6). A good conversion and high diastereo- and enantioselectivity was also obtained when using the $CuBr_2$–BOX catalyst **6c** (Table 1, entry 7), which is a poorer Lewis acid than **6a**,**b**.

The influence of amines on the reaction was also screened. For example, in the presence of cyclohexyldimethylamine, the reaction proceeded in good yield and with high diastereo- and enantioselectivity (Table 1, entry 8). Secondary amines can also be used and give almost the same stereoselectivity (Table 1, entry 9), whereas *N*,*N*-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,2-bis(dimethylamino)ethane, and (−)-sparteine did not afford adduct **3a**. Among the amines tested, NEt_3 gave the best results.

The reaction is affected by the amount of amine and the order in which the reagents are added. An increase in the amount of NEt_3 to 40 mol% led to a nondiastereoselective reaction (Table 1, entry 10), whereas no reaction took place when the amount of amine was reduced to 10 mol%. When NEt_3 was added before the imine to a solution of the catalyst, a complicated product mixture was formed, and a low yield of **3a** with excellent selectivity was obtained (Table 1, entry 11).

The catalyst loading can be reduced to 10 mol%, while still maintaining the catalytic activity and the excellent diastereo- and enantioselectivity, although longer reaction times are required (Table 1, entry 12). The reaction can be performed under very user-friendly conditions by just mixing the reagents under ambient conditions in CH_2Cl_2 (not dried or distilled). Under these conditions, no decrease in catalytic activity was observed, and adduct **3a** was formed in high yield and excellent diastereo- and enantioselectivity (Table 1, entry 13). Furthermore, at 0 °C the reaction takes place with an improvement in both diastereo- and enantioselectivity (Table 1, entry 14). These results are important for the practical application of this reaction.

The scope of the catalytic enantioselective nitro-Mannich reaction of **1** is presented in Table 2. Nitropropane **2a** reacted with **1** to give **3a** in 81% yield and with excellent diastereo- and enantioselectivity (Table 2, entry 1). The reaction with nitromethane **2b** proceeded with high enantioselectivity; however, the yield of the isolated nitro-Mannich adduct **3b** was moderate (Table 2, entry 2). The reactions of nitroethane and nitrohexane, **2c** and **2d**, respectively, gave the nitro-Mannich adducts **3c** and **3d**, in good yields, with very high diastereoselectivities and excellent enantioselectivities (97% *ee* for both reactions; Table 2, entries 3,5). The stereoselec-

Table 1. Catalytic enantioselective nitro-Mannich reactions of *N*-(*p*-methoxyphenyl)-α-imino ester **1** with nitropropane **2a** under various reaction conditions at room temperature.[a]

Entry	Catalyst	Amount [mol%]	Solvent	*t* [days]	Conversion [%][b]	dr[c] *erythro*/*threo*	*ee* [%][c] *erythro*/*threo*
1	**4a**	20	CH_2Cl_2	1	8	95/5	89/70
2	**5a**	20	CH_2Cl_2	1	62	84/16	2/2
3	**6a**	20	CH_2Cl_2	1	85	92/8	94/85
4	**6a**	20	THF	1	14	96/4	97/90
5	**6a**	20	Et_2O	1	26	97/3	97/83
6	**6b**	20	CH_2Cl_2	1	85	60/40	26/21
7	**6c**	20	CH_2Cl_2	1	69	95/5	93/86
8[d]	**6a**	20	CH_2Cl_2	1	83	82/18	95/95
9[e]	**6a**	20	CH_2Cl_2	1	40	95/5	97/91
10[f]	**6a**	20	CH_2Cl_2	1	80	54/46	72/76
11[g]	**6a**	20	CH_2Cl_2	1	43	95/5	96/86
12	**6a**	10	CH_2Cl_2	7	83	92/8	91/85
13[h]	**6a**	20	CH_2Cl_2	1	86	93/7	95/79
14[i]	**6a**	20	CH_2Cl_2	5	87	95/5	97/87

[a] The reactions were performed on a 0.2 mmol scale with 150 mol% of nitropropane. The catalyst and NEt_3 were used in a 1:1 ratio. For further details, see Supporting Information. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] The diastereomeric ratios and enantiomeric excesses were determined by HPLC. [d] *c*-$HexNMe_2$ was used. [e] $HNEt_2$ was used. [f] 40 mol% of NEt_3 was used. [g] NEt_3 was added before imine **1**. [h] Open-air reaction. [i] At 0 °C.

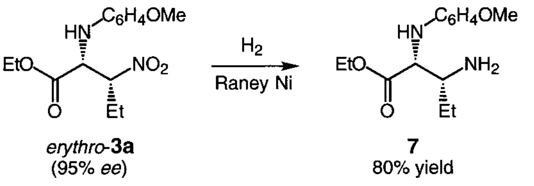
Table 2. Nitro-Mannich reactions of *N*-(*p*-methoxyphenyl)-α-imino ester **1** with different nitro compounds **2a-f** catalyzed by (*R*)-**6a** at room temperature or 0 °C.

Entry	R	Yield [%][a]	dr[b] *erythro*/*threo*	*ee* [%][b] *erythro*[c]/*threo*
1[d]	Et (**2a**)	81 (**3a**)	95/5	97/87
2	H (**2b**)	38 (**3b**)	–	87
3	Me (**2c**)	61 (**3c**)	70/30	97/95
4[d]	Me (**2c**)	50 (**3c**)	73/27	99/98
5	Pentyl (**2d**)	52 (**3d**)	93/7	97/89
6	$PhCH_2$ (**2e**)	80 (**3e**)	95/5	95/88
7	Ph (**2f**)	59 (**3f**)	55/45[e]	74/77

[a] Yield of isolated products. [b] Diastereomeric ratios and enantiomeric excesses were determined by HPLC. [c] *erythro*: (2*R*,3*R*). [d] The reaction was performed at 0 °C. [e] Determined by ^1H NMR spectroscopy.

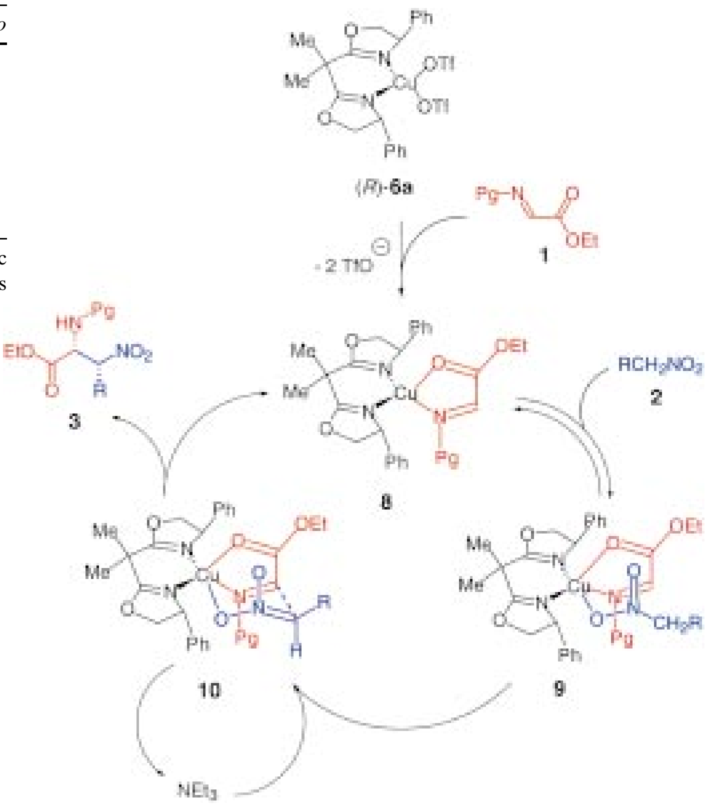
tivity can be improved by lowering the reaction temperature. The reaction of **2c** gave a diastereomeric ratio of 73/27 and 99% *ee* of *erythro*-**3c** when the reaction was performed at 0 °C (Table 2, entry 4). The present reaction is not only restricted to simple 1-nitroalkanes, as shown by the fact that 2-phenyl-1-nitroethane **2e** reacted with **1** to give the nitro-Mannich adduct **3e** in 80% yield and with excellent diastereo- and enantioselectivity (Table 2, entry 6). α-Nitrotoluene **2f** reacted with **1** under the present catalytic conditions to give **3f** in moderate yield and diastereoselectivity, but with good enantioselectivities of both diastereomers (Table 2, entry 7). The reactions of methyl nitroacetate and 2-nitroethanol with **1** catalyzed by (*R*)-**6a** gave the corresponding nitro-Mannich adducts for both compounds in good yields; however, moderate diastereo- and enantioselectivities were observed, which might be a result of a competitive binding of the acetate and hydroxy functionality to the Cu^{II} center (see below). For the reaction of 2-nitroethanol, the diastereomeric ratio is temperature dependent and at room temperature the ratio was 67:37, whereas at −15 °C the ratio was 14:86 with >70% *ee* of the major diastereomer of the adduct.

The present new catalytic enantioselective nitro-Mannich reaction leads to a simple procedure for the formation of optically active N-protected β-nitro-α-amino esters, a new class of α-amino acid derivatives. The optically active N-protected β-nitro-α-amino esters such as *erythro*-**3a** can easily be reduced to the corresponding N-protected α,β-diamino ester **7** in high yield [Eq. (2)].[10] For example, further reaction of the N-protected α,β-diamino ester has been used for the determination of the absolute configuration of the products.[10]



(2)

In Scheme 2 a proposal for the catalytic cycle of the new nitro-Mannich reaction is suggested to account for the catalytic activity, and for the diastereo- and enantioselectivity. It is important for the outcome of the reaction that catalyst **6a** is mixed with the α-imino ester **1** first to give intermediate **8**. Nitro compounds coordinate relatively weakly to the copper center, as it has been reported that some BOX–Cu^{II}-catalyzed reactions can be performed in nitromethane as the solvent.[13] Thus, it is proposed that intermediate **9** is in a fast equilibrium with **8**. In intermediate **9**, the acidity of the nitro compound is increased by the coordination of the nitro group to Cu^{II}. This facilitates the catalytic deprotonation of the nitro compound with Et_3N to give intermediate **10**, which is proposed to be the key intermediate in the reaction. This intermediate would lead to a cyclohexane-like cyclic transition state with additional coordination of the carbonyl group of **1** to the metal center in a pentacoordinated fashion. In this structure the nitro substituent occupies the less sterically crowded and more stable equatorial position, which accounts for the diastereoselectivity of the reaction. The chiral (*R*)-Ph-BOX ligand in **10** favors the formation of the (2*R*,3*R*)-enantiomer of the product, since the intermediate that leads to the opposite enantiomer would lead to steric repulsion between the bulky *N*-(*p*-methoxyphenyl) substituent of the α-imino ester and the chiral phenyl substituent of the ligand.



Scheme 2. Proposed catalytic cycle of the new nitro-Mannich reaction, which accounts for the catalytic activity, and for the diastereo- and enantioselectivity

In summary, a new enantioselective catalytic addition reaction of nitro compounds to an α-imino ester in the presence of chiral bisoxazoline–Cu^{II} complexes has been presented. Even under ambient conditions, the reaction gives optically active β-nitro-α-amino esters with excellent diastereo- and enantioselectivity.

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[11] A series of different N-protected α-imino esters were tested for the reaction and it was found that the *N*-(*p*-methoxyphenyl)-α-imino ester **1** led to a stable product as α-imino esters that have electron-withdrawing substituents at the nitrogen atom gave products which tended to decompose during workup.

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Catalytic Asymmetric Direct Mannich Reactions of Carbonyl Compounds with α-Imino Esters**

Karsten Juhl, Nicholas Gathergood, and
Karl Anker Jørgensen*

The Mannich reaction is an important class of C–C bond-forming reactions in organic chemistry.[1] A number of methods for the diastereoselective reaction of imines with enolates has been reported,[1a, 2] and recently the first examples of catalytic enantioselective addition of enolates to imines were reported.[1c, 3] One disadvantage of these stereoselective Mannich reactions is the preparation and stability of the enolate, and a major step forward for this important class of reactions would be a catalytic enantioselective version that uses carbonyl compounds rather than the enolates.[4]

Recently, we demonstrated that simple chiral Lewis acids such as the bisoxazoline (BOX)–Cu^{II} complexes[5] can mimic aldolase enzymes, and a highly enantioselective homo-aldol reaction of pyruvate which gave diethyl-2-hydroxy-2-methyl-4-oxo-gluterate in up to 96% *ee* was developed.[6] In this homo-aldol reaction, the chiral Lewis acid acts both as a catalyst for the in situ generation/stabilization of the enol-pyruvate from pyruvate, and as a catalyst for the enantioselective addition step. This new aspect of Lewis-acid catalysis led us to try to develop other reactions based on this concept.

Herein we present the first catalytic diastereo- and enantioselective Mannich reaction of activated carbonyl compounds **1** with the α-imino ester **2** catalyzed by chiral Lewis acids (Scheme 1). This new development leads to a simple synthetic procedure for the formation of optically active highly functionalized α-amino acid derivatives **3** by using readily available carbonyl compounds rather than the often troublesome silyl enol ethers or silyl ketene acetals.

The reaction between ethyl pyruvate **1a** (R = H) and *N*-tosyl-α-imino ester **2** has been used for screening the reaction conditions for the chiral Lewis-acid catalyzed direct Mannich reaction. The metal ion is crucial for the success of this reaction. It has been found that copper(II) possesses the properties necessary for both the in situ generation of the enol species from **1a** and, in combination with chiral C_2-symmetric ligands, the stereoselectivity of the reaction. Table 1 presents some results for the reaction of **1a** with **2** in the presence of bisoxazolines and BINAP (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) as chiral ligands. The use of the *t*Bu-BOX-Cu(OTf)$_2$ catalyst (*S*)-**4** in CH_2Cl_2 led to the formation of the Mannich adduct **3a** (R = H) in reasonable yield and 33% *ee* (Table 1, entry 1), whereas the di-Ph-BOX-Cu(OTf)$_2$ catalyst

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[*] K. A. Jørgensen, K. Juhl, N. Gathergood
Center for Metal-Catalyzed Reactions
Department of Chemistry, Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 8619-6199
E-mail: kaj@chem.au.dk

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