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Enantioselective Addition of Nitromethane to 2-Acylpyridine *N*-Oxides. Expanding the Generation of Quaternary Stereocenters with the Henry Reaction

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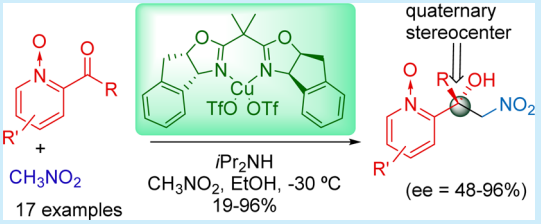
Supporting Information

ABSTRACT: The direct asymmetric Henry reaction with prochiral ketones, leading to tertiary nitroaldols, is an elusive reaction so far limited to a reduced number of reactive substrates such as trifluoromethyl ketones or α-keto carbonyl compounds. Expanding the scope of this important reaction, the direct asymmetric addition of nitromethane to 2-acylpyridine *N*-oxides catalyzed by a BOX-Cu(II) complex to give the corresponding pyridine-derived tertiary nitroaldols having a quaternary stereogenic center with variable yields and good enantioselectivity, is described.



Asymmetric nucleophilic additions to prochiral carbonyl compounds provide an attractive approach toward chiral building blocks containing a stereocenter bearing a hydroxyl group. In particular, the enantioselective addition of nitroalkanes to carbonyl compounds (Henry or nitroaldol reaction) allows the preparation of enantiomerically enriched nitroalkanols,[1] which have a high scientific and commercial value as building blocks for the synthesis of pharmaceuticals and agrochemicals.[2] In recent years, a considerable advance in the development of asymmetric procedures for the addition of nitroalkanes to aldehydes[3] and aldimines[4] leading to products with tertiary stereocenters has been achieved. In contrast, the asymmetric addition of nitroalkanes to ketones that would give rise to the challenging formation of a quaternary stereogenic center has experienced little progress.[5] In fact, even for the nonenantioselective version only a few methods are available with a limited substrate scope.[6] Regarding asymmetric methodologies for the synthesis of tertiary nitroaldols, Shibasaki[7] has reported a kinetic resolution of racemic mixtures, while the direct nucleophilic addition of nitromethane has been carried out only with very reactive substrates such as trifluoromethyl ketones,[8] α-keto esters, and α-keto amides.[9] Very recently, our group has described the asymmetric addition of nitromethane to the ketone group of substituted glyoxal hydrates bearing a latent aldehyde carbonyl in the α-position.[10]

On the other hand, pyridine derivatives are of great importance for the pharmaceutical industry, as demonstrated by the existence of more than 7000 drugs featuring this heterocyclic ring, as well as for the agrochemical industry due to their applications as herbicides, fungicides, or bactericides.[11] Furthermore, the pyridine moiety is present in a good number of chiral ligands for asymmetric catalysis.[12]

Here, we describe the catalytic enantioselective addition of nitromethane to 2-acyl pyridine *N*-oxides to give the corresponding tertiary nitroaldols bearing a quaternary stereocenter bonded to a 2-pyridyl moiety.

We[13] and others[14] have shown the excellent chelating properties of the 2-acyl pyridine *N*-oxide moiety in several asymmetric metal-catalyzed reactions. Following this strategy, our investigation was started by studying the addition of nitromethane to ketone **1a** in the presence of different metal complexes with nitrogenated ligands as catalysts (Scheme 1).

According to the conditions of our previously reported Henry reaction with keto esters,[9h] the reaction was initially carried out in nitromethane as the solvent and in the presence of triethylamine. Several complexes of divalent metal triflates (Cu, Zn, Mg) with ligand **BOX1**, as well as complexes of trivalent metal triflates (La, Yb, Sc, In) with ligand **pyBOX1**, were tested as catalysts. This screening showed the combination of $Cu(OTf)_2$ with **BOX1** to be the most active catalyst in this reaction (see Table S-1 in the Supporting Information (SI)). Other bases were tested in the presence of this complex, showing little effect (see Table S-2 in the SI). When the yield and enantioselectivity of the reaction were considered, diisopropylamine was determined to be the best option which afforded compound **3a** in 50% yield with 44% *ee* when the reaction was performed at −15 °C (Table 1, entry 1).[15] Several BOX ligands were then tested (Table 1, entries 1−7). **BOX4** gave the best enantiomeric excess (72%) for **3a**, although with a low yield (Table 1, entry 4).

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Scheme 1. Enantioselective Henry Reaction with Ketone 1a and Ligands Used in This Research

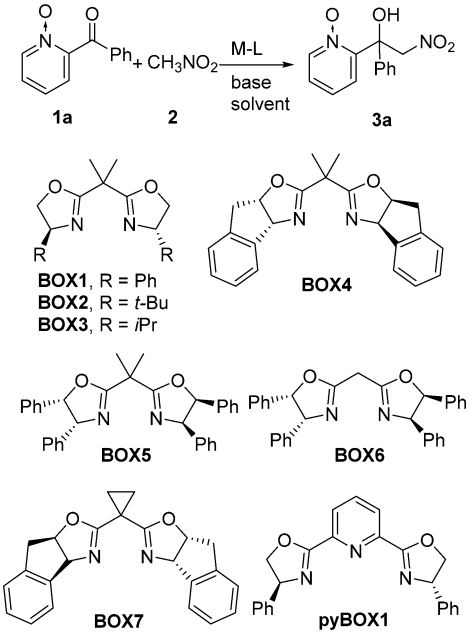


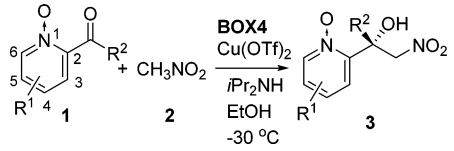
Table 1. Enantioselective Addition of Nitromethane to Ketone 1a Catalyzed by Cu(II)-BOX Complexes; Screening of Ligands and Solvents[a]

entry	L	solvent	temp (°C)	*t* (h)	yield (%)	*ee* (%)[b]
1	**BOX1**	CH_3NO_2	−15	44	50	−44
2	**BOX2**	CH_3NO_2	−15	42	21	−52
3	**BOX3**	CH_3NO_2	−15	45	19	−40
4	**BOX4**	CH_3NO_2	−15	42	24	72
5	**BOX5**	CH_3NO_2	−15	44	32	62
6	**BOX6**	CH_3NO_2	−15	44	9	64
7	**BOX7**	CH_3NO_2	−15	44	35	−51
8	**BOX4**	EtOH/CH_3NO_2 (2:1)	−15	44	34	75
9	**BOX4**	CH_2Cl_2/CH_3NO_2 (2:1)	−15	44	24	77
10	**BOX4**	Et_2O/CH_3NO_2 (2:1)	−15	46	38	62
11	**BOX4**	EtOH/CH_3NO_2 (5:1)	−30	90	40	95
12	**BOX4**	EtOH/CH_3NO_2 (5:1)[c]	−30	90	39	96

[a]**1a** (0.17 M), $Cu(OTf)_2$ (20 mol %), **L** (20 mol %), *i*-Pr_2NH (25 mol %). [b]Ee determined by HPLC. The sign indicates the optical rotation sign of the major enantiomer. [c]**1a** (0.33 M).

In order to minimize a possible nonenantioselective background reaction that could be detrimental to the enantioselectivity, we carried out the reaction in the presence of a solvent to reduce the concentration of nitromethane. A slight increase of enantioselectivity was observed in ethanol and dichloromethane (Table 1, entries 8 and 9). But more important, the use of other solvents also allowed a decrease in the reaction temperature. In this way, compound **3a** could be obtained with very high ee (95%), although in moderate yield (40%) by using a 5:1 ethanol/CH_3NO_2 mixture at −30 °C (Table 1, entry 11). The amount of solvent and nitromethane could be reduced without any effect on the result (Table1, entry 12). Although the yield of the nitroaldol obtained under these conditions was only moderate, no other byproducts were formed during the reaction and the unreacted starting material **1a** could be recovered after column chromatography. Moreover, it should be taken into account that this yield is close to the maximum yield affordable via kinetic resolution of a racemic mixture according to Shibasaki's procedure,[7] especially if we consider the overall yield of the racemic synthesis−kinetic resolution process. Taking into account this consideration and encouraged by the high ee obtained in the synthesis of compound **3a**, we studied the applicability of the reaction to other related substrates (Table 2).

Table 2. Enantioselective Addition of Nitromethane to 2-Acylpyridine *N*-Oxides 1; Scope of the Reaction[a]



entry	1	R^1	R^2	*t* (h)	yield (%)	*ee* (%)[b]
1	**a**	H	Ph	96	39	96
2[c]	**b**	H	4-$MeOC_6H_4$	96	17	87
3	**c**	H	4-ClC_6H_4	96	19	90
4	**d**	H	3-ClC_6H_4	96	85	61
5	**e**	H	Me	24	80	86
6	**f**	H	Et	24	87	81
7	**g**	H	Bu	48	84	84
8	**h**	H	*i*-Pr	48	65	70
9	**i**	3-Me	Me	96	–	–
10	**j**	4-Me	Me	48	72	84
11[c]	**k**	4-Ph	Me	48	96	76
12	**l**	5-Me	Me	48	84	81
13[c]	**m**	5-Br	Me	66	85	89
14	**n**	6-Me	Me	72	87	55
15	**o**	6-Br	Me	96	90	48
16[c]	**p**	4-Ph	Et	48	73	91
17	**q**	5-Me	Et	48	79	92
18[c]	**r**	5-Br	Et	72	80	91

[a]**1** (0.33 M), $Cu(OTf)_2$ (20 mol %), **BOX4** (20 mol %), *i*-Pr_2NH (25 mol %), EtOH/CH_3NO_2 (5:1), −30 °C. [b]Ee determined by HPLC. [c]Reaction carried out at −20 °C

Compounds **1b** and **1c** bearing a *p*-substituted phenyl group with an electron-donating (MeO) or an electron-withdrawing (Cl) group, respectively, gave similar results providing the expected products with low yields but good *ee* (Table 2, entries 2, 3), while the 3-chlorophenyl derivative **1d** reacted with CH_3NO_2 to give compound **3d** (Table 2, entry 4) with high yield (85%) and fair *ee* (61%). More consistent results were obtained with aliphatic ketones. High yields and enantiomeric excesses above 80% were obtained with methyl, ethyl, or butyl ketones **1e−g** (Table 2, entries 5−7). The branched isopropyl ketone **1h** was less reactive and gave compound **3h** with a 65% yield but still 70% *ee* (Table 2, entry 7). Then we studied the effect of substituents on the pyridine ring. The reaction was sensitive to steric factors. The presence of a substituent (Me or Br) at position 6 of the pyridine ring led to the corresponding products with moderate enantioselectivities although high yields (Table 2, entries 14, 15), while the presence of a methyl group at position 3 of the pyridine ring completely prevented the reaction from taking place. However, compounds substituted at the 4 and 5 positions of the pyridine ring

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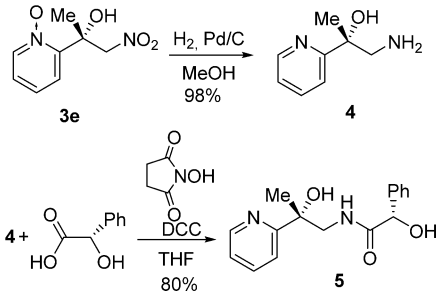
provided the nitroaldol products in good yields and remarkable enantioselectivities, with enantiomeric excesses above 90% for ethyl ketones **1p−r** (Table 2, entries 16−18). The nitroalkanols obtained in this reaction can be transformed into pyridyl aminoalcohols bearing a quaternary stereocenter. For instance, compound **3e** was quantitatively transformed into **4** upon hydrogenation over 5% Pd/C in methanol (Scheme 2). To

Scheme 2. Hydrogenation of 3e and Synthesis of Amide 5



determine the absolute stereochemistry of the nitroaldol products, compound **4** was transformed into amide **5** by treatment with (+)-(*S*)-mandelic acid using dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide as a coupling reagent in THF.

X-ray analysis of amide **5** crystals, obtained by successive crystallizations from chloroform and toluene, allowed determining that the quaternary stereogenic center in compound **5**, and hence in compounds **4** and **3e**, was of an *R* configuration (Figure 1). For the remainder of nitroaldol products **3**, the

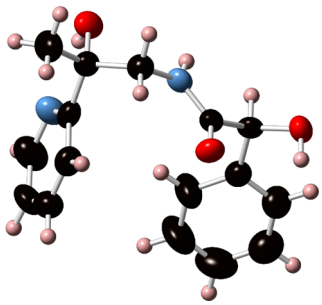


Figure 1. Ortep plot for the X-ray structure of compound **5**. The thermal ellipsoids are drawn at the 50% probability level.

absolute stereochemistry was assigned upon the assumption of a uniform stereochemical mechanism. The observed stereochemistry is in agreement with the model outlined in Figure 2.[16] In this model, the acylpyridine *N*-oxide coordinates the catalyst Cu(II) center in a bidentate fashion giving a distorted

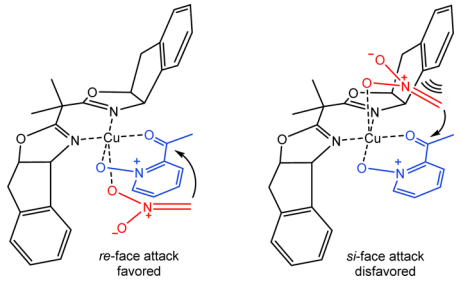


Figure 2. Stereochemical model.

square planar complex[13,14a,b] with both the oxygen atom of the *N*-oxide and that of the carbonyl group occupying the most acidic equatorial positions for the maximum electrophilic activation.[17] The nitronate is positioned in one of the apical positions for nucleophilic activation.[17] Attack of the nitronate from the *si*-face of the carbonyl group is hampered by one of the Indane moieties of the ligand, and therefore it takes place preferentially from the *re*-face to give the nitroaldol with the *R* configuration.

In summary, a novel direct asymmetric Henry reaction with ketones was reported. A Cu(II)-BOX complex catalyzed the addition of nitromethane[18] to 2-acylpyridine *N*-oxides to give the corresponding tertiary nitroaldols bearing a quaternary stereocenter bonded to a pyridine ring with good yields and moderate to high enantiomeric excesses. The reaction expands the scope of the elusive enantioselective Henry reaction with ketones.

■ ASSOCIATED CONTENT

Supporting Information

Additional optimization data. Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for compounds **1**, **3−5**, and chiral analysis for compounds **3**. CIF file for compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Under identical conditions, the nonoxidized 2-benzoylpyridine gave the corresponding nitroaldol with 30% yield and 4% ee, indicating the importance of the *N*-oxide moiety in this reaction.

(16) For a discussion on intermediates in BOX-Lewis acid catalyzed reactions, see: Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2002**, *8*, 1888−1898.

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(18) The reaction of compound **3e** with nitroethane showed little advance and gave a mixture of diastereomers which reverted to the starting materials during attempts of purification by column chromatography on silica gel.