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Modular iminopyridine ligands. Application to the enantioselective copper(II)-catalyzed Henry reaction

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Abstract—Chiral iminopyridines prepared in a modular fashion from monoterpenic (camphor-derived) ketones and pyridinylalkylamines catalyze the enantioselective Henry (nitro aldol) reaction between nitromethane and *o*-anisol in the presence of copper(II) acetate, with high yields and good ee (up to 86%) under straightforward experimental conditions without the need for air or moisture exclusion.

1. Introduction

Ligands bearing two *N* (sp^2) coordinating atoms have found wide application in enantioselective metal-catalyzed reactions.[1] Great attention has been dedicated to C_2-symmetric *N*,*N*-ligands such as bis-imines,[2] bis-pyridines,[3] and, especially, bis-oxazolines.[4] Furthermore, C_1-symmetric[5] ligands with two sterically and electronically differentiated *N* (sp^2) have also been developed. Thus, oxazolinylpyridines, introduced by Brunner,[6] have received some attention,[7] as well as iminopyridines derived from 2-pyridine carboxaldehyde and chiral amines.[8] However, to the best of our knowledge, iminopyridines derived from chiral ketones have never been used as ligands in asymmetric catalysis.[9] According to this last strategy, we have developed new iminopyridine type ligands based on the design of Figure 1, which allow high modularity by changing the ketone, the spacer and the substitution on the pyridine ring.

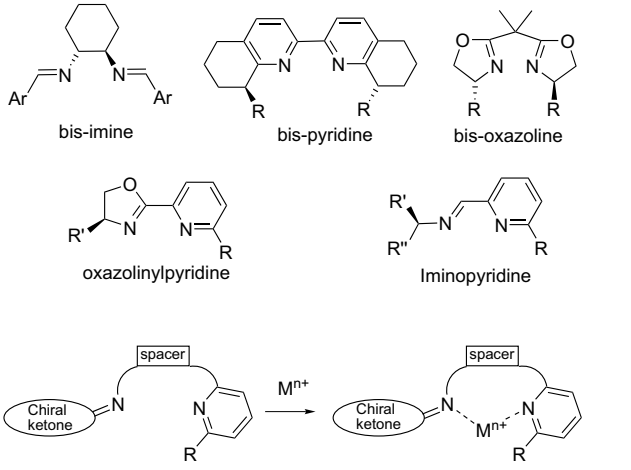

Figure 1. C_2 and C_1 *N*,*N*-ligands and design of modular iminopyridine chiral ligands.

The Henry (or nitroaldol) reaction is one of the most convenient reactions for direct carbon–carbon bond formation to give β-hydroxynitroalkanes.[10] Due to the versatile chemistry of the nitro group,[11] the reaction provides access to valuable structural motifs such as 1,2-amino alcohols and α-hydroxy acids by reduction to amines or by the Nef reaction, respectively. Therefore, considerable effort has been directed over recent years towards the development of the catalytic asymmetric version of this reaction. Examples include the use of metal-based bifunctional chiral catalysts, which rely on concurrent activation of the aldehyde and the nitroalkanes.[12] Independent activation of the aldehyde and nitroalkane has also been achieved by the combined use of metal complexes and a Bronsted base[13] or by the use of silyl nitronates.[14] Some of these systems are

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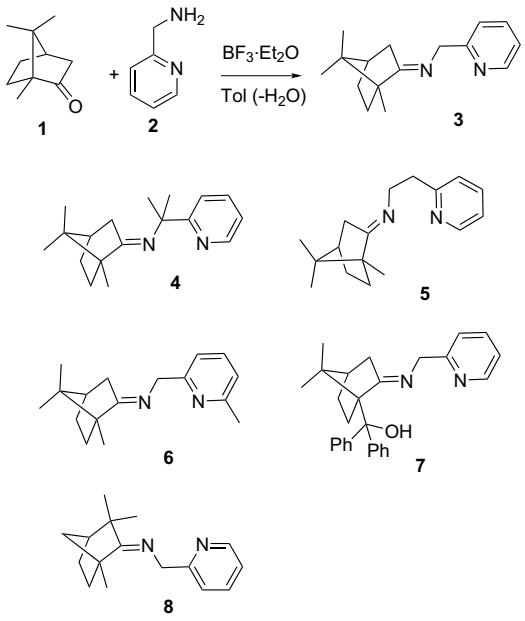
moisture or air sensitive and require the use of an inert atmosphere.

Bis-oxazoline-based complexes have been successfully used as catalysts for the enantioselective Henry reaction, either with concurrent or independent activation of both reagents.[12e,13a,b,14] In the view of this, we decided to study the activity of the designed iminopyridines as catalysts in the Henry reaction. Herein, we report our preliminary results on this reaction, which is the first example of the application of this kind of ligands in enantioselective metal-catalyzed reactions.

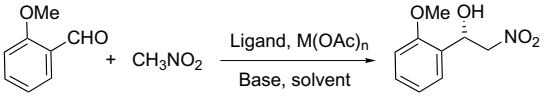
2. Results and discussion

A set of ligands **3**–**8** based on the camphane and fenchane frameworks were synthesized.[15] Ligands **3**, **5** and **6** were prepared in one step by condensation of commercially available (1*R*)-(+)-camphor with the corresponding pyridinylalkylamines according to Scheme 1.[16] Ligand **4** was obtained from ligand **3** via a double alkylation at the benzylic position with BuLi and MeI.[9d] Ligand **7** was synthesized by the condensation between picolylamine and a ketone prepared by a Grignard synthesis from (1*S*)-(+)-ketopinic acid methyl ester.[17] Finally, direct condensation of picolylamine and (1*R*)-fenchone, both of which are commercially available, afforded ligand **8**. These ligands differ on the substitution and length of the spacer, and on the steric hindrance in the proximities of the pyridine and imine nitrogens.



Scheme 1. Synthesis of iminopyridine ligands derived from monoterpenic ketones and pyridinylalkylamines.

The reaction between nitromethane and *o*-anisole was used to test the ability of these ligands to induce enantioselectivity in the metal-catalyzed Henry reaction (Scheme 2).



Scheme 2. Henry (nitro aldol) reaction between nitromethane and *o*-anisol.

According to the reaction conditions described by Evans for the bis-oxazoline-copper catalyzed Henry reaction[12e] the reaction was initially carried out at room temperature in ethanol using 10 mol % acetate as the source for the metal ion. The reactions were performed in test tubes stopped with a septum with no special attention given for air or moisture exclusion. Screening of some late transition metal acetates showed copper acetate to be the best promoter for this reaction (Table 1, entry 5). When copper(II) triflate was used, the reaction gave the corresponding nitroalkene, resulting from elimination. Ethanol was found to be superior to other solvents tested (entries 6–9). Ligands **4**–**9** were also tested under similar reaction conditions. It was observed that the elongation (entry 11) and introduction of substituents (entry 10) on the spacer which alter the bite angle of the ligand had a negative effect. Similarly, the introduction of steric hindrance in the proximities of the pyridine (entry 12) or the imine (entry 13) nitrogen brought about a decrease in enantioselectivity. Ligand **9** derived from (1*R*)-(−)-fenchone gave the expected product with the same configuration and in similar ee as ligand **3** (entry 14). Further improvements of the reaction were carried out with the combination **3**-Cu(II)OAc. Since copper acetate can catalyze the non-enantioselective background reaction, the reaction temperature was lowered in order to increase the enantioselectivity. Thus, at 0 °C, the enantiomeric excess increased up to 67% (entry 15). Unfortunately, lowering the reaction temperature to −20 °C resulted in impractical reaction times. The addition of a Bronsted base (entries 16–21) accelerated the reaction and allowed us to lower the reaction temperature to −65 °C, which brought about a noticeable increase in the ee of the product. Diisopropylethylamine (DIPEA) gave the best results (up to 85% ee) when used in either stoichiometric (entry 18) or catalytic amounts (entry 19). Finally, variations in the catalyst loading (entries 20 and 21) did not give a significant variation in the result of the reaction.

3. Conclusion

In conclusion we have developed a type kind of *N*,*N*-ligand, which can be used in enantioselective metal-catalyzed reactions. These ligands can form complexes with different late transition metals. The copper(II)-complex generated in situ catalyzes the Henry reaction between nitromethane and *o*-anisol with excellent yield and high enantioselectivity under straightforward experimental conditions.[18] The study of the scope of this reaction, the preparation of new ligands from chiral ketones and pyridinylalkylamines and their application in other catalytic enantioselective reactions is currently in progress.

Table 1. Henry reaction between nitromethane and *o*-anisol according to Scheme 2

Entry	Ligand (11 mol %)	Metal salt (10 mol %)	Solvent	Base (1 equiv)	T (°C)	t (h)	Yield[a] (%)	ee[b] (%)
1	**3**	$Co(OAc)_3{\cdot}2H_2O$	EtOH	—	rt	24	94	rac
2	**3**	$Ni(OAc)_2{\cdot}4H_2O$	EtOH	—	rt	24	94	rac
3	**3**	$Zn(OAc)_2{\cdot}2H_2O$	EtOH	—	rt	93	77	−10[d]
4	**3**	$Pd(OAc)_2{\cdot}H_2O$	EtOH	—	rt	70	40[c]	37
5	**3**	$Cu(OAc)_2{\cdot}H_2O$[e]	EtOH	—	rt	24	93	61
6	**3**	$Cu(OAc)_2{\cdot}H_2O$	MeOH	—	rt	24	95	53
7	**3**	$Cu(OAc)_2{\cdot}H_2O$	$MeNO_2$	—	rt	70	90	48
8	**3**	$Cu(OAc)_2{\cdot}H_2O$	CH_2Cl_2	—	rt	70	62[c]	49
9	**3**	$Cu(OAc)_2{\cdot}H_2O$	DMF	—	rt	24	54[c]	52
10	**4**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	—	rt	64	45[c]	21
11	**5**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	—	rt	26	62	19
12	**6**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	—	rt	64	47[c]	16
13	**7**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	—	rt	70	95	7
14	**8**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	—	rt	24	77	61
15	**3**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	—	0	88	98	67
16	**3**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	Cy_2NH	−65	45	84	80
17	**3**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	Et_3N	−65	88	56	83
18	**3**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	DIPEA	−65	48	90	85
19	**3**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	DIPEA (0.1 equiv)	−55	70	92	83
20	**3** (22 mol %)	$Cu(OAc)_2{\cdot}H_2O$ (20 mol %)	EtOH	DIPEA	−65	70	96	86
21	**3** (6 mol %)	$Cu(OAc)_2{\cdot}H_2O$ (5 mol %)	EtOH	DIPEA	−65	70	94	84

[a] Yields refer to isolated product after column chromatography.
[b] Determined by HPLC analysis using a Chiralcel OD-H column. The (*S*)-enantiomer was obtained unless otherwise stated.
[c] Uncomplete reaction after the indicated time.
[d] The (*R*) enantiomer was obtained.
[e] Under similar reaction conditions, $Cu(OTf)_2$ gave the corresponding nitroalkene.

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18. Typical experimental procedure for the enantioselective Henry reaction catalyzed by **3**: $Cu(OAc)_2{\cdot}H_2O$ (9.9 mg, 0.05 mmol) was added to a solution of compound **3** (15 mg, 0.055 mmol) in absolute EtOH (1.5 mL) and the mixture stirred for 1 h. To the resulting blue solution was added nitromethane (0.27 mL, 5 mmol) and the recipient was introduced in a bath at −65 °C. *o*-Anisol (68 mg, 0.5 mmol) dissolved in absolute ethanol (1.5 mL) was added followed by DIPEA (82 μL, 0.5 mmol) and the reaction mixture was stirred until completion (TLC). The solvent was removed under reduced pressure and the residue chromatographed on silica gel (hexane:diethyl ether, 85:15) to give 89 mg of (*S*)-1-(2-methoxyphenyl)-2-nitroethanol: Enantiomeric excess was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*)$t_r = 13.6$, minor enantiomer (*R*)$t_r = 12.1$, to be 85% ee; $[\alpha]_D^{25} = +39.8$ (*c* 1.05, CH_2Cl_2, ee 85%); ^{1}H NMR ($CDCl_3$) δ 7.44 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.33 (td, $J = 7.5$, 1.5 Hz, 1H), 7.04–6.99 (m, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 5.63 (dd, $J = 9.0$, 3.3 Hz, 1H), 4.65 (dd, $J = 13.2$, 3.3 Hz, 1H), 4.57 (dd, $J = 13.2$, 9.0 Hz, 1H), 3.88 (s, 3H), 2.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 155.9, 129.7, 127.1, 125.9, 121.0, 110.5, 79.8, 67.7, 55.3.