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# Probing electronic and regioisomeric control in an asymmetric Henry reaction catalyzed by camphor-imidazoline ligands

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### ABSTRACT

Starting from (R)-camphordiamine, 13 new camphor-annulated imidazoline ligands are synthesized in good yields as two regioisomeric series. Yields of up to 94% and good enantioselectivities up to 67% are achieved for the copper(II)-catalyzed Henry reaction giving the product stereoselectively according to the regioisomer used.

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Optically active compounds incorporating five-membered heterocycles such as oxazolines<sup>1</sup> or related imidazolines<sup>2</sup> and their use as biomaterials<sup>3</sup> or efficient transition metal N-coordinating ligands, and their ability to catalyze various reactions have been investigated. Whereas the application of chiral oxazoline ligands in asymmetric reactions has been thoroughly examined and extensively reviewed,<sup>4</sup> chiral imidazolines are currently perhaps the most often employed ligands in a wide range of asymmetric reactions including allylation,<sup>5</sup> epoxidation,<sup>6</sup> copolymerization,<sup>7</sup> hydrogenation,<sup>8</sup> addition of diethylzinc to aldehydes,<sup>9</sup> Diels-Alder reactions,<sup>10</sup> Heck reactions,<sup>11</sup> Baylis-Hillman reactions,<sup>12</sup> Friedel-Crafts alkylations,<sup>13</sup> and Henry reactions.<sup>14</sup> Despite recent progress in the preparation of imidazolines,<sup>15</sup> the most common synthesis involves condensation of readily available chiral 1,2-diamines such as 1,2-diphenylethanediamine (DPEDA) or trans-1,2-diaminocyclohexane.<sup>16</sup> However, in 2000, Busacca et al. reported the stereoselective synthesis of (1R,2S,3R)-camphordiamine<sup>17</sup> and, more recently, its application as a chiral building block for the construction of a camphor-annulated imidazoline ligand (BIPI) with utility in the intramolecular asymmetric Heck reaction.<sup>18</sup> We have recently prepared several families of chiral imidazole ligands derived from either  $\alpha$ -amino acids or terpenes such as (R)-(+)-camphor, (1S)-(-)- $\beta$ -pinene, and (1S,2S,3S,5R)-(+)-isopinocampheone and have described their application in the asymmetric Henry reaction.<sup>19</sup> Inspired by Busacca's camphordiamine **1** and moving from terpene-annulated imidazoles to the closely related dihydro analogs, imidazolines, we report herein a modular synthesis of two camphor-imidazoline ligand series **a** and **b** bearing an additional N-chelating pyridyl auxiliary and their catalytic behavior in the copper(II)-catalyzed enantioselective Henry reaction.

The synthesis of the proposed ligands started with the preparation of camphordiamine **1** by condensation of (R)-camphorquinone with (*rac*)-DPEDA yielding two camphorbisimine diastereoisomers that were subsequently reduced with NaBH<sub>4</sub>/MeOH to the diamines. It has been confirmed on the basis of NOESY experiments that this stereoselective reduction takes place exclusively from the  $\alpha$ -face.<sup>17</sup> In addition, we were able to grow a single crystal of the diamine hydrochloride suitable for X-ray analysis which confirmed unambiguously the stereochemical outcome of the above reduction (see Supplementary data). Final removal of the chiral DPEDA auxiliary afforded camphordiamine dihydrochloride **1** in 61% overall yield.

With the optically pure *exo*-camphordiamine dihydrochloride **1** in hand, we examined its reaction with the picolinimidate generated in situ from pyridine-2-carbonitrile and sodium methoxide. The condensation was accomplished in methanol and triethylamine to liberate the free camphordiamine base giving rise to imidazoline **2** in 92% yield. Slow evaporation of **2** from methanol furnished single crystals suitable for X-ray analysis which confirmed the molecular structure of **2** (Fig. 1, see also the Supplementary data).

In contrast to oxazolines, imidazolines offer the possibility for N-functionalization to fine tune their electronic properties in order to achieve good enantioselectivities.<sup>20</sup> Hence, we further examined the N-modification of **2** by alkylation, acylation, benzoylation, and sulfonylation with RX substrates possessing either electron-donating or electron-withdrawing substituents (Scheme 1, Table 1). Whereas routine N-deprotonation of **2** with DMAP proved to be sluggish and reaction with nBuLi caused decomposition of the imidazoline even at -78 °C, treatment of **2** with LHMDS at 0 °C followed by addition of the electrophile RX afforded N-substituted imidazolines **3–11** in good yields (Scheme 1, Table 1). As the starting camphor-imidazoline **2** underwent imidazoline tautomerism, N-substitution yielded two regioisomers **a** and **b**. To our



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**Figure 1.** ORTEP representation of **2**. Vibrational ellipsoids obtained at 150 K are shown at the 50% probability level (solvent omitted). CCDC 717407.

delight, both regioisomers were separable by simple column chromatography. Their molecular structures were assigned on the basis of <sup>1</sup>H-<sup>1</sup>H COSY, HMQC, and HMBC NMR spectroscopy (see Supplementary data). More importantly, the ratio of both regioisomers differed considerably according to the nature of RX (Table 1). Whereas alkylation of 2 with methyl iodide or benzyl bromide afforded regioisomers **a** and **b** in approximate ratios of 1:1 (Table 1, entries 1 and 2), acylation with isobutyrylchloride or benzoylation gave exclusively the less sterically demanding regioisomers **5b** and **6b** with anti-arrangement of the camphor 1-methyl and R groups (Table 1, entries 3 and 4). Benzoylation with 4-methoxy- and 4-nitrobenzoyl chloride also resulted in the pronounced formation of regioisomers 7b and 8b (Table 1, entries 5 and 6). In contrast, sulfonylation of 2 gave both regioisomers in a 1:1 ratio. However, slow decomposition of regioisomers 9b-11b occurred during purification by column chromatography to yield N,N'-disubstituted camphordiamines 12-14 (Scheme 1, Table 1, entries 7-12). The easy formation of such products was confirmed by adding 0.5 M HCl (0.5 mL) to the crude reaction mixture of 9-11 resulting in immediate precipitation of insoluble 14 and the gradual formation of 12 and 13 within 2 h.

The camphor-imidazolines synthesized were tested as ligands in the copper(II)-catalyzed enantioselective Henry reaction.<sup>21,22</sup> The reactions were carried out on 4-nitrobenzaldehyde with  $CH_3NO_2/Cu(OAc)_2/ligand$  in ethanol on a 0.5 mmol scale (Table 2).<sup>19a</sup> The N-unsubstituted imidazoline **2** afforded the nitroaldol

| Table 1                               |   |
|---------------------------------------|---|
| N-Modification of camphor-imidazoline | 2 |

| Entry          | Product        | RX/R <sup>1</sup>                         | Vield (%)  | Ratio <b>a</b> /b |
|----------------|----------------|---|--|-------------------|
| 1              | 3a/3b          | CH3I                                      | 95 <sup>a</sup>  | 1:1ª              |
| 2              | 4a/4b          | Br  | 91 <sup>a</sup>  | 1:1 <sup>a</sup>  |
| 3              | 5a/5b          | )—o<br>⊂I                                 | 89 <sup>a</sup>  | 0:1 <sup>a</sup>  |
| 4              | 6a/6b          | CI  | 78 <sup>a</sup>  | 0:1 <sup>ª</sup>  |
| 5              | 7a/7b          | MeO                                       | 90 <sup>a</sup>  | 1:3ª              |
| 6              | 8a/8b          | O <sub>2</sub> N CI                       | 98 <sup>a</sup>  | 1:4 <sup>a</sup>  |
| 7              | 9a/9b          | 0<br>S-O<br>Cl                            | 53 <sup>b</sup>  | 1:1 <sup>c</sup>  |
| 8              | 10a/10b        | MeO CI                                    | 51 <sup>b</sup>  | 1:1 <sup>c</sup>  |
| 9              | 11a/11b        | 0.0<br>02N CI                             | 41 <sup>b</sup>  | 1:1 <sup>c</sup>  |
| 10<br>11<br>12 | 12<br>13<br>14 | $R^1 = Me$<br>$R^1 = OMe$<br>$R^1 = NO_2$ | $\begin{array}{c} 43^{\mathrm{d}} \\ 46^{\mathrm{d}} \\ 39^{\mathrm{d}} \end{array}$ |                   |

<sup>a</sup> Overall isolated yield.

<sup>b</sup> Isolated yield of regioisomer **a**.

<sup>c</sup> Estimated by comparing the isolated yields of regioisomers **9a-11a** and **12-14**, respectively.

<sup>d</sup> Isolated yields of N,N'-disubstituted camphordiamines after acidification.

product in 90% yield but with a very low 8% ee (Table 2, entry 1). This was most probably due to imidazoline tautomerism that allows complexation of the copper on both imidazoline coordination sites resulting in the formation of almost a racemate. This explanation is also applied to the reactions with N-methyl and *N*-benzyl imidazoline regioisomers **3a**/**3b** and **4a**/**4b** which afforded the nitroaldol products in 92–94% yields and enantioselectivities up to 51% (Table 2, entries 2 and 3). More importantly, the use of either regioisomer **a** or **b** enabled the formation of either the (*R*)-or (*S*)-nitroaldol. With reaction times and yields similar to those observed for N-alkylated ligands **3** and **4**, the N-acylated or N-benzoylated ligands **5b** and **6b** gave the (*S*)-nitroaldols in higher enantioselectivities up to 60% (Table 2, entries 4 and 5). Moreover,



Scheme 1. Synthesis of camphor-imidazoline ligands.

#### Table 2

The asymmetric Henry reaction<sup>a</sup>



| Entry | Ligand | Time <sup>b</sup> (h) | Yield <sup>c</sup> (%) | ee (%) configuration <sup>d</sup> |
|-------|--------|-----------------------|------------------------|-----------------------------------|
| 1     | 2      | 24                    | 90                     | 8 ( <i>R</i> )                    |
| 2     | 3a/3b  | 36/36                 | 92/94                  | 21 (R)/46 (S)                     |
| 3     | 4a/4b  | 36/36                 | 94/92                  | 43 (R)/51 (S)                     |
| 4     | 5b     | 36                    | 87                     | 45 (S)                            |
| 5     | 6b     | 36                    | 90                     | 60 ( <i>S</i> )                   |
| 6     | 7a/7b  | 24/24                 | 92/89                  | 41 (R)/67 (S)                     |
| 7     | 8a/8b  | 54/54                 | 81/76                  | 29 (R)/46 (S)                     |
| 8     | 9a     | 36                    | 92                     | 17 (R)                            |
| 9     | 10a    | 24                    | 89                     | 18 (R)                            |
| 10    | 11a    | 48                    | 87                     | 17 ( <i>R</i> )                   |

 $^a$  Reactions were performed on a 0.5 mmol scale with Cu(OAc)\_2 (10%) and ligands (10.5%) with nitromethane (10 equiv) in ethanol (5 mL) under  $N_2$  at room temperature.

<sup>b</sup> Monitored by TLC (SiO<sub>2</sub>; hexane/EtOAc 2:1).

<sup>c</sup> Isolated yields after column chromatography.

 $^d$  Determined by chiral HPLC analysis on a Daicel Chiracel OB column and confirmed from  $[\alpha]$  values,  $^{22a}$ 

the enantioselectivities of such ligands could be varied easily by attaching electron-donating (methoxy) or electron-withdrawing (nitro) groups on the benzoyl moiety (Table 1, entries 6 and 7, series **b**).With respect to the proposed mechanism of the copper(II)-catalyzed asymmetric Henry reaction as described by Evans,<sup>22a</sup> and to the identical bidentate N=C-C=N coordination pocket and stereochemistry of 6b-8b, the observed variation in the enantioselectivities can be explained as a result of the electronic density on the copper(II) ion. Thus, the methoxy group in ligand 7b resulted in higher basicity of the imidazoline nitrogens and, subsequently, higher electron saturation of the active Cu(II)-complex. The generated complex possessed higher stability and, therefore, the Henry reaction may take place exclusively on the active chiral catalyst with good asymmetric induction (ee of 67%). Since no additional base was used, such an electron-rich catalyst also facilitated the deprotonation of nitromethane which was accomplished by acetate in the rate-limiting step<sup>21c</sup> which resulted in the shortest reaction time (24 h). This finding is in agreement with that observed for other Cu(II) carboxylates applied in the Henry reaction while carboxylates with higher basicity (e.g., 4-methoxybenzoate<sup>19a</sup> or 2,4-dimethoxybenzoate<sup>22a</sup>) gave short reaction times and high ees. The nitro group in **8b** had the opposite effect and, therefore, the enantiomeric excess was lower (46%) while the reaction time was longer (54 h). N-Sulfonyl imidazolines 9a-11a were able to catalyze the Henry reaction affording the expected nitroaldol product in good chemical yields of 87-92%, but the enantioselectivities were modest (Table 2, entries 8-10). Thus, the electronegative N-sulfonyl linker seemed to be unsuitable for electronic fine-tuning. Application of the N,N'-disubstituted camphordiamines 12-14 as ligands in the Henry reaction did not afford any nitroaldol product even after a prolonged reaction time of up to 72 h.

In summary, starting from the optically pure camphordiamine, 13 new camphor-annulated imidazolines were synthesized involving modular synthetic steps. Whereas regioisomers **a** as ligands in the asymmetric Henry reaction afforded (R)-nitroaldols, regioisomers **b** gave the (*S*)-products. The latter also gave higher ees of up to 67%. The enantioselectivity of the N-benzoylated ligands was strongly affected by the electronic nature of the benzoyl moiety. Thus, either (*R*)- or (*S*)-nitroaldol products could be obtained with one set of ligands, while N-modification of the ligand allowed tailoring of the degree of enantioselectivity.

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## Supplementary data

Supplementary data (experimental procedures, <sup>1</sup>H, <sup>13</sup>C, <sup>1</sup>H-<sup>1</sup>H COSY, HMQC, and HMBC NMR spectra and representative GC/MS or MALDI data for all new compounds as well as the X-ray structures of the diamine hydrochloride and imidazoline **2**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.010.

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