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Camphor-annelated imidazolines with various N1 and C2 pendants as tunable ligands for nitroaldol reactions

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ABSTRACT

Starting from (1*R*,2*S*,3*R*)-camphordiamine and (hetero)aromatic imidates and orthoformate, nine new camphor-annelated NH-imidazolines were synthesized. Subsequent N-modification was carried out via methylation, acylation, benzoylation, and sulfonylation. Two regioisomers were usually isolated with the ratios reflecting the structure of the starting NH-imidazoline and the electrophile used. All of the successfully prepared N1- and C2-substituted camphor-annelated imidazolines were applied to the asymmetric version of a Cu(II)-catalyzed Henry reaction. The electronic effects of both N1- and C2-pendants on the chemical and asymmetric outcomes of the nitroaldol reaction have been studied and discussed.

1. Introduction

Naturally occurring monoterpenes constitute a readily available and attractive subclass of the chiral pool. Synthetic attempts to incorporate these chiral moieties into the backbone of a heterocyclic compound such as (bi)pyridines, terpyridines, phenathrolines, and pyrazines, have steadily attracted considerable attention from organic chemists due to the resulting unique properties of such derivatives.[1] This class of optically active compounds has found broad application in asymmetric homogeneous catalysis.[2] Whereas the synthesis and applications of the aforementioned six-membered terpene-annelated heterocycles are numerous, reports on five-membered analogues remain scarce.[3] Conversely, oxazolines[4] or imidazolines[5] and their use as efficient transition metal N-coordinating ligands are well known and have recently been reviewed extensively.[6] Nowadays, chiral imidazolines are very often used as ligands that upon coordination of a suitable transition metal, catalyze a wide range of asymmetric reactions such as allylation, epoxidation, copolymerization, hydrogenation, Diels–Alder reactions, Heck reactions, Baylis–Hillman reactions, and Friedel–Crafts alkylations.[7] Hence, the combination of a terpene moiety as a source of chirality and a chelating imidazoline ring could give an interesting N-coordinating ligand. In contrast to very popular oxazolines, imidazoline ligands are capable of further modification at the N1 position, which opens the possibility of further ligand design and the tuning of electronic properties.[7b]

We have recently synthesized (*R*)-(+)-camphor-, (1*S*)-(−)-β-pinene-, and (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheone-derived series of imidazoles as well as cyclohexane- and camphor-annelated imidazolines (Fig. 1).[8–10] All derivatives bear a terpene moiety fused to the imidazole/imidazoline through the C4 and C5 positions and additional pendants at the C2 position. This arrangement assures the generation of a bidentate N=C–C=N coordination pocket. Whereas the imidazoles were synthesized from terpene-derived diketones and monooximes,[8] imidazolines, as dihydroanalogues of imidazoles, were prepared from commercially available (1*R*,2*R*)-cyclohexane-1,2-diamine or (1*R*,2*S*,3*R*)-camphordiamine, reported by Busacca et al.,[11] and (hetero)aromatic imidates.[9,10] Herein we report an extension of the series of camphor-annelated imidazolines by the replacement of the (hetero)aromatic moiety attached to the imidazoline C2, their N-modification, and a subsequent study of such tunable ligands in the asymmetric version of a Cu(II)-catalyzed Henry reaction.[12]

2. Results and discussion

2.1. Synthesis

The synthesis of target camphor-annelated imidazolines is outlined in Scheme 1. In the first step, the starting (hetero)aromatic nitriles were converted into appropriate imidates via a sodium methoxide-catalyzed reaction with methanol or the Pinner synthesis. Whereas the nitriles bearing electron-deficient heteroaromates (pyridine, pyrazine, pyrimidine, isoquinoline) underwent a direct reaction with methanol in the presence of a catalytic amount of sodium methoxide, benzonitrile, pyrrole-2-carbonitrile, and

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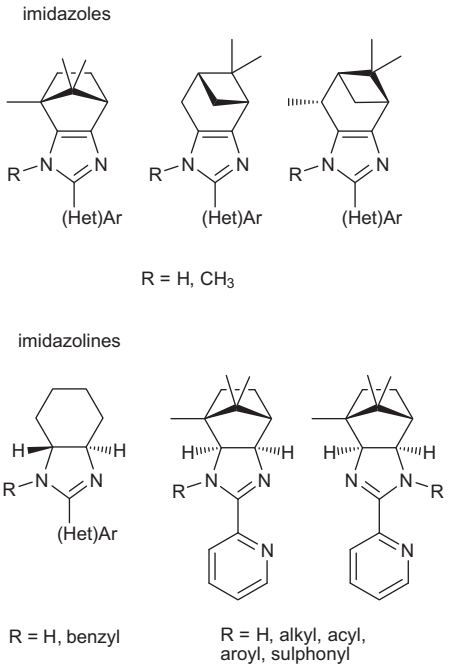
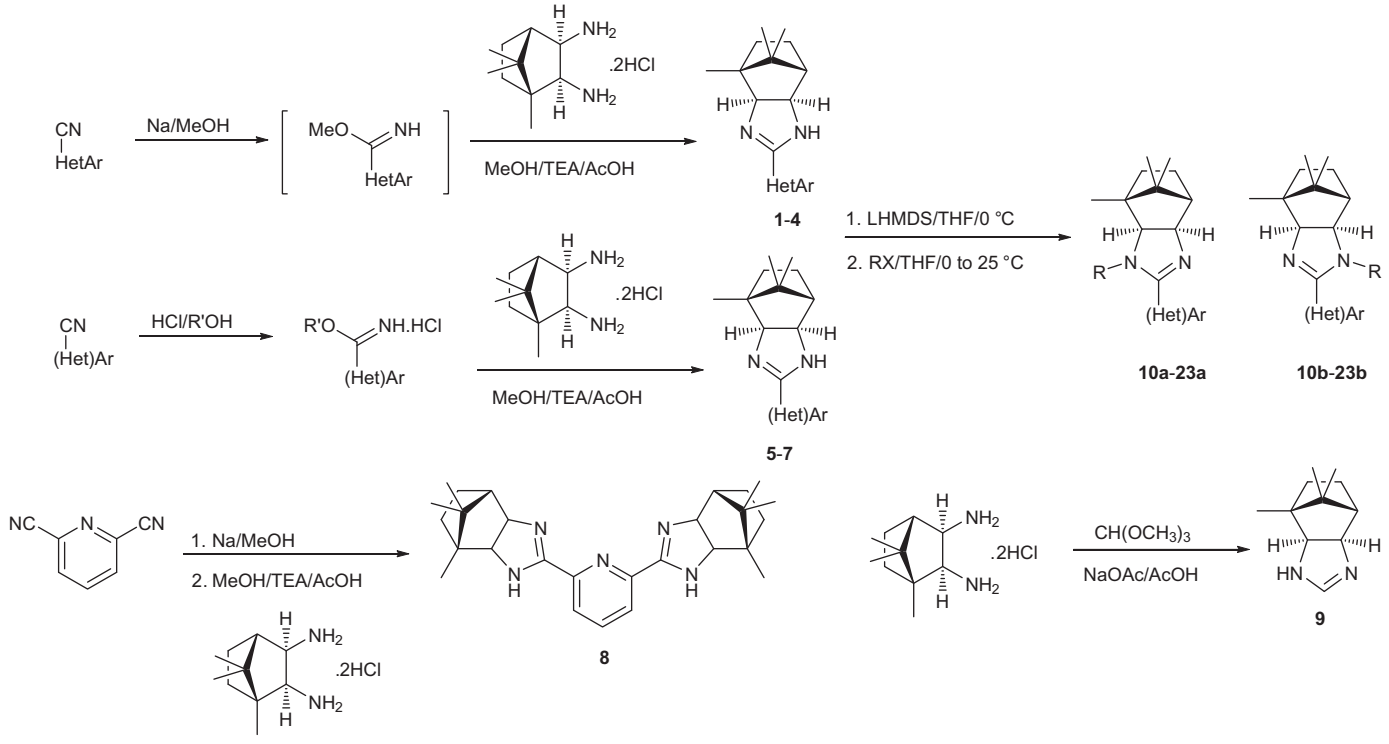


Figure 1. Known terpene- and cyclohexane-annelated imidazole and imidazoline ligands.

thiophene-2-carbonitrile had to be converted into imidate hydrochlorides by the HCl-catalyzed Pinner reaction. Both imidates and imidate hydrochlorides were subsequently treated with (1*R*,2*S*,3*R*)-camphordiamine, prepared in a three step synthesis from (*R*)-camphorquinone and *rac*-DPEDA,[10,11] to afford NH-imidazolines **1**–**4** and **5**–**7** in yields of 43–92% and 57–91%, respectively (Table 1). Pyridine-2,6-dicarbonitrile was also smoothly transformed into tridentate PyBim ligand **8** in a similar way (88% yield). A treatment of *exo*-camphordiamine with trimethyl orthoformate afforded C2-unsubstituted camphor-annelated imidazole **9** (82%), which proved to be very unstable and decomposed within a week.

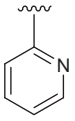
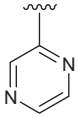
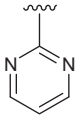
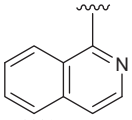
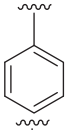
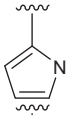
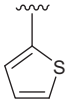
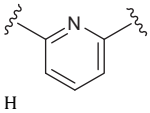
In order to prevent imidazoline tautomerism and to further tune the ligand's electronic properties and complexation ability,[13] NH-imidazolines **1**–**8** were N-functionalized. Starting with imidazoline **1** as the model substrate, we attempted its alkylation, acylation, benzoylation, and sulfonylation. Deprotonation of **1** with LHMDS followed by the reaction with RX electrophiles possessing either electron-donating or electron-withdrawing substituents afforded the target ligands **10**–**18** in good overall yields (Scheme 1, Table 2). Since the starting imidazoline **1** bearing an unsymmetrical camphor moiety underwent tautomerism, N-substitution yielded two regioisomers **a** and **b**. In general, the pronounced formation of the less sterically demanding regioisomers **10b**–**15b** with an *anti*-arrangement of the camphor 1-methyl and R groups was observed. More importantly, both regioisomers were separable by simple column chromatography, but the N-sulfonylated regioisomers **16b**–**18b**, that were detected in the crude reaction mixture by GC/MS, decomposed during column chromatography, to yield N,N-disubstituted camphordiamines/diamides **24**–**26** (Scheme 2). We have recently reported on similar ring-openings of N-functionalized cyclohexane-annelated imidazolines.[9]

According to the preliminary results of the ligand screening in the asymmetric version of a Cu(II)-catalyzed Henry reaction (see below),[10] all of the remaining NH-imidazolines **2**–**8** were anisoylated. Whereas the anisoylation of pyrazine- and isoquinoline-substituted NH-imidazoline **2** and **4** afforded separable regioisomers for compounds **19a**/**b** and **21a**/**b**, the separation of regioisomers **20a**/**b** derived from pyrimidine-substituted imidazoline **3** was unsuccessful. In contrast to the N-functionalization of all NH-imidazolines **1**–**4**, anisoylation of the phenyl- and thienyl-substituted imidazolines **5** and **7** mainly afforded regiosiomers **22a** (77%) and



Scheme 1. Synthetic approach to terpene-annelated imidazolines and their subsequent N-functionalization.

Table 1
Structure, yields, and specific rotations of NH-imidazolines **1–9**

Compd.	(Het)Ar	Yield (%)	$[\alpha]_D^{20}$ (*c* 0.5, MeOH)
1		92	−43.2
2		82	−34.5
3		67	−36.0
4		43	−74.9
5		91	−30.0
6		57	−13.8
7		63	−27.2
8		88	−24.4
9	H	82	−26.6

23a (61%) and only trace amounts of regioisomers **22b** (7%) and **23b** (6%). Functionalization of pyrrole-substituted imidazoline **6** and PyBim ligand **8** yielded an inseparable mixture of products, although compound **6** was also N-protected by methylation. All of the isolated target compounds **20–23** showed a higher stability during the purification by column chromatography than **16–18** but regioisomers **19a** and **23a** decomposed slowly to diamides **27** and **28** after one month of storing (Scheme 2). However, this ring-opening could be significantly suppressed by storing the ligands with a few drops of triethylamine.

2.2. Crystallography

Crystals suitable for X-ray analysis were prepared by slow diffusion of hexane into EtOAc, CH_2Cl_2, or MeOH solutions of imidazolines **5**, **7**, **8**, **19b**, and **23b**. The ORTEP plots in Figure 2 confirm the proposed molecular structure and absolute configurations on the particular stereogenic centers and show the spatial arrangement in the solid state. Front and side views are provided. While the thiophene ring in **7** is almost coplanar with the imidazoline (torsion angle of about 2°), the phenyl ring in **5** is substantially twisted out of the imidazoline plane by 36°. This twist is, however, usual for 2-(hetero)aryl imidazoles and imidazolines.[14] The PyBim ligand **8** showed two camphor moieties oppositely oriented. This compound showed very strong hydrogen bonding to water or other protic solvents (the molecule of H_2O bonded to N3 and N3A was omitted for clarity). The two anisoylated regioisomers **19b** and **23b** differ considerably. While the anisoyl moiety in pyrazine-derived imidazoline **19b** is bent coplanar to the pyrazine ring to allow π–π stacking, the anisoyl moiety in thiophene-substituted ligand **23b** adopted the opposite arrangement with the benzene ring almost perpendicular to the imidazoline central plane (torsion angle of about 79°).

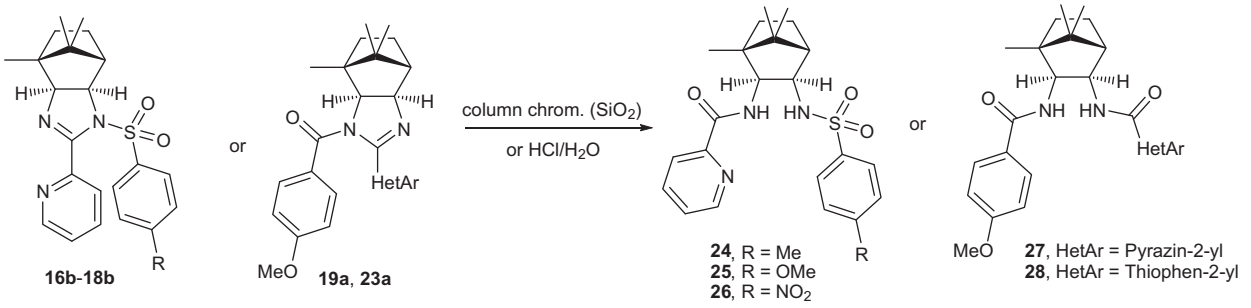
2.3. Asymmetric Henry reaction

The enantioselectivities of the successfully synthesized ligands **10–23** were preliminarily tested in a copper(II)-catalyzed asymmetric nitroaldol reaction (Henry reaction).[15] 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 3).[8,10,16] No additional base was used in order to study the ligand's electronic behavior. While the NH-imidazolines, which undergo imidazoline tautomerism, afforded the desired nitroaldol almost as racemates (e.g., **1**, Table 3, entry 1), N-substituted imidazolines yielded nitroaldol in enantiomeric excesses of up to 67%. The nitroaldol reaction catalyzed by the *N*-methyl and *N*-benzyl imidazolines **10a**/**b** and **11a**/**b** afforded nitroaldol products in chemical yields of 92–94% and enantioselectivities of up to 51% (Table 3, entries 2 and 3). More importantly, the use of either regioisomer **a** or **b** enabled the formation of either the (*R*)- or (*S*)-nitroaldol. Thus, the reaction catalyzed by regioisomers **a** afforded (*R*)-nitroaldols and the reaction with regioisomers **b** yielded (*S*)-nitroaldols. *N*-Isobutyryl and *N*-benzoyl

Table 2
N-Functionalization of NH-imidazolines **1–7**

HetAr (starting NH-imidazoline)	RX	Products	Yield (%)/ratio[a]
Pyridin-2-yl **1**	MeI	**10a**/**10b**	95/1:1
Pyridin-2-yl **1**	BnBr	**11a**/**11b**	91/1:1
Pyridin-2-yl **1**	$(CH_3)_2CHCOCl$	**12a**/**12b**	89/0:1
Pyridin-2-yl **1**	PhCOCl	**13a**/**13b**	78/0:1
Pyridin-2-yl **1**	4-(MeO)PhCOCl	**14a**/**14b**	90/1:3
Pyridin-2-yl **1**	4-(NO_2)PhCOCl	**15a**/**15b**	98/1:4
Pyridin-2-yl **1**	4-(Me)PhSO_2Cl	**16a**/**16b** (**24**)	53/43[b]
Pyridin-2-yl **1**	4-(MeO)PhSO_2Cl	**17a**/**17b** (**25**)	51/46[b]
Pyridin-2-yl **1**	4-(NO_2)PhSO_2Cl	**18a**/**18b** (**26**)	41/39[b]
Pyrazin-2-yl **2**	4-(MeO)PhCOCl	**19a** (**27**)/**19b**	84/2:3
Pyrimidin-2-yl **3**	4-(MeO)PhCOCl	**20a**/**20b**	49/7:10[c]
Isoquinolin-1-yl **4**	4-(MeO)PhCOCl	**21a**/**21b**	96/1:1
Phenyl **5**	4-(MeO)PhCOCl	**22a**/**22b**	84/11:1
Thiophen-2-yl **7**	4-(MeO)PhCOCl	**23a** (**28**)/**23b**	67/10:1

[a] Overall isolated yields and ratios of regioisomers **a**:**b**.
[b] Isolated yields of regioisomer **a**/diamides **24–26**.
[c] Overall isolated yield of the mixture of regioisomers **a** and **b**, the ratio was estimated according to ^{1}H NMR spectra.



Scheme 2. Observed ring-opening of N-functionalized imidazolines.

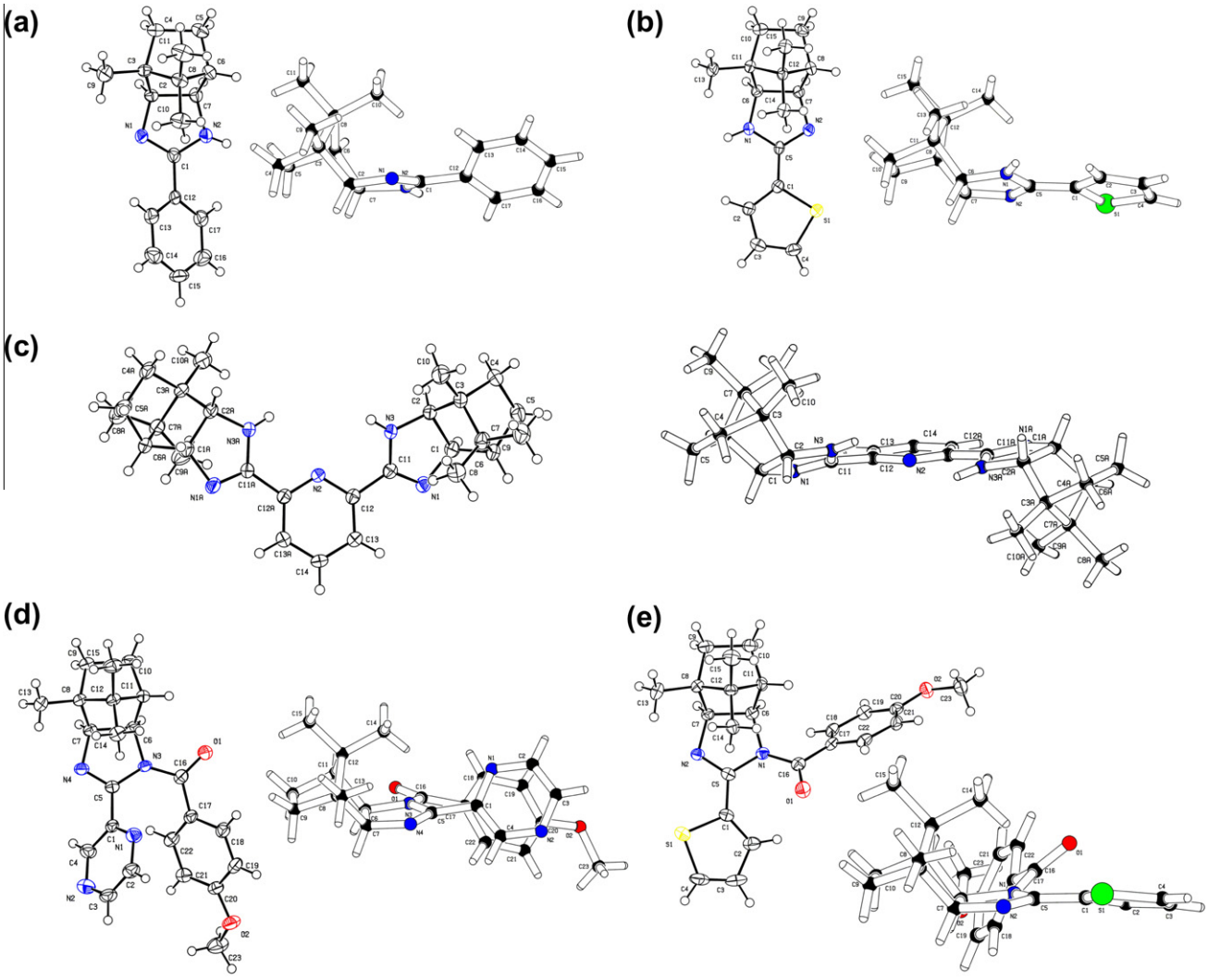
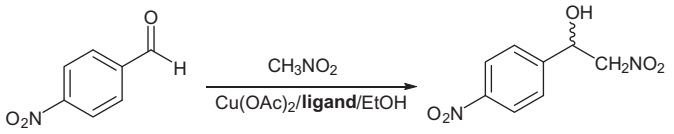


Figure 2. ORTEP representations and spatial arrangement of the NH-imidazolines (a) **5**, (b) **7**, and (c) **8** and regioisomers (d) **19b** and (e) **23b** measured at 150 K. The thermal ellipsoids are shown at the 50% probability with arbitrary spheres for H atoms. Molecules of the solvents were omitted for clarity.

regioisomers **12b** and **13b** gave the (*S*)-nitroaldol in the yields of 87% and 90% and with enantiomeric excesses of 45% and 60%, respectively (Table 3, entries 4 and 5). In addition to *N*-benzoyl ligand **13b**, the reaction times and stereochemical outcomes can be affected by attaching electron-donating (methoxy) and electron-withdrawing (nitro) substituents to the benzoyl moiety. While the reaction with the anisoyl-substituted regioisomer **14b** gave the (*S*)-nitroaldol in a yield of 89% and with ee 67% within 24 h, the 4-nitrobenzoyl-substituted analogue **15b** afforded the same product in 76% yield and with 46% ee after 54 h (Table 3, entries 6 and 7). According to the proposed mechanism of the Cu(II)-catalyzed nitroaldol reaction,[15a] and the fact that both ligands possess the same N=C–C=N binding pocket and absolute configurations, the observed variation in the yields and enantioselectivities must be due to the electronic density on the copper(II) ion. Higher imidazoline basicity and subsequent higher electron saturation of the active Cu(II)-coordination site in the anisoyl-substituted imidazolines **14a**/**14b** resulted in higher complex stability. Hence, the

Table 3
Asymmetric Henry reaction[a]



Entry	Ligand	Time (h)[b]	Yield (%)[c]	ee (%) configuration[d]
1	**1**	24	90	9/(*S*)
2	**10a**/**10b**	36/36	92/94	21 (*R*)/46 (*S*)
3	**11a**/**11b**	36/36	94/92	43 (*R*)/51 (*S*)
4	**12b**	36	87	45 (*S*)
5	**13b**	36	90	60 (*S*)
6	**14a**/**14b**	24/24	92/89	41 (*R*)/67 (*S*)
7	**15a**/**15b**	54/54	81/76	29 (*R*)/46 (*S*)
8	**16a**	36	92	17 (*R*)
9	**17a**	24	89	18 (*R*)
10	**18a**	48	87	17 (*R*)
11	**19a**/**19b**	24/24	36/30	28 (*R*)/24 (*S*)
12	**21a**/**21b**	24/24	66/74	22 (*R*)/14 (*S*)
13	**22a**/**22b**	24/24	12/8	10 (*R*)/5 (*R*)
14	**23a**/**23b**	24/24	14/9	9 (*R*)/6 (*R*)

[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.
[b] Monitored by TLC (SiO_2; Hexane/EtOAc 2:1).
[c] Isolated yields after column chromatography.
[d] Determined by HPLC analysis with a Chiralcel OD-H column and simultaneously deduced from [α] values.

Henry reaction may take place exclusively on the active chiral catalyst with asymmetric induction of up to 41/67%. Moreover, the electron rich (basic) imidazoline also facilitated deprotonation of the nitromethane in the rate-limiting step[12c] and the nitroaldol is generated faster (24 h, 92/89% yields). The observed ligand electronic tuning is in accordance with that observed for the nitroaldol reaction catalyzed by electron-rich Cu(II) carboxylates (e.g., methoxybenzoate or 2,4-dimethoxybenzoate).[15a,16] These copper(II) carboxylates afforded the desired nitroaldols in short reaction times and with generally higher ees. The nitro group in ligands **15a**/**15b** had the opposite effect; prolonged reaction time (54 h) and lower ee (29/46%). The application of *N*-sulfonyl imidazolines **16a**–**18a** provided the nitroaldol products within reaction times of 24–48 h, according to the substitution of the benzenesulfonyl moiety, and rather low enantioselectivities (17–18%). Compared to an amide linker as in **12**–**15**, the more electronegative sulfonamidic one in **16**–**18** seemed to be less suitable for electronic fine-tuning.

In an extension of our study on ligand design and tuning, the remaining NH-imidazolines **2**–**7** were *N*-anisoylated to yield target ligands **19**–**21** and **22**–**23**. Whereas the application of pyrazine- and isoquinoline-derived regioisomers **19a**/**b** and **21a**/**b** (Table 3, entries 10 and 11) afforded similar chemical and stereochemical outcomes as those for pyridine-derived ligands **14a**/**b**, both regioisomers of the phenyl- and thiophene-derived imidazolines **22a**/**b** and **23a**/**b** yielded only the (*R*)-nitroaldols with very low chemical yields and ees (Table 3, entries 13 and 14). This observation clearly demonstrates the crucial role of the N=C–C=N binding pocket (similar to bipy and other related ligands)[2,17] for efficient chelation of Cu(II) ions. The aforementioned differences in the spatial arrangement of **19b** and **23b** also play an important role. However, the results obtained with ligands **19** and **21** are generally worse than those observed for pyridine-derived imidazolines **14**, which may be explained as a result of the higher electron-withdrawing character of the pyrazine and isoquinoline rings. Diamides **24**–**28**, when applied as ligands in the nitroaldol reactions, yielded only trace amounts of the desired nitroaldol even after prolonged reaction times of up to 72 h.

3. Conclusion

In conclusion, starting from enantiomerically pure (1*R*,2*S*,3*R*)-camphordiamine, we have synthesized nine new camphor-annelated NH-imidazolines **1**–**9**. Two general methods starting with the in situ generated imidates or imidate hydrochlorides were employed. Molecular structures and absolute configurations of imidazolines **1**,[10] **5**, **7**, and **8** were confirmed by X-ray analysis. The NH-imidazolines **1**–**5** and **7** were further N-functionalized by methylation, acylation, benzoylation, and sulfonylation **10**–**23**. Two regioisomers **a** and **b** were generally obtained. The spatial arrangements and absolute configurations of two regioisomers **19b** and **23b** were also confirmed by crystallography. The ratio of regioisomers **a**/**b** differed according to the structure of the starting NH-imidazoline and the electrophile used. More importantly, both regioisomers were separable by column chromatography. Some regioisomers proved to be unstable, yielding camphor-derived diamides **24**–**28**. All successfully synthesized and isolated regioisomers were applied as nitrogen ligands in the asymmetric version of a Cu(II)-catalyzed nitroaldol reaction. Whereas regioisomers **a** afforded (*R*)-nitroaldols, regioisomers **b** gave the (*S*)-product. Thus, either (*R*)- or (*S*)-nitroaldol products could be obtained as the major products with one set of ligands. In addition, the reaction times/yields and stereochemical outcomes of the nitroaldol reaction can be affected by the electronic nature of the appended auxiliaries. Ligands possessing electron-donating anisoyl pendants afforded the desired nitroaldols after relatively short times, in good chemical yields, and with generally high ees; ligands with an electron-withdrawing nitrobenzoyl moiety required longer reaction times and gave lower chemical yields and ees. Thus, by having the basic camphor-annelated imidazoline scaffold as in **9**, the ligand property-tuning and subsequent chemical and stereochemical outcomes of the Henry reaction can easily be tailored by modification of the N1- and C2-pendants.

4. Experimental

4.1. General

The starting (Het)Ar-nitriles are commercially available. The starting methyl 1*H*-pyrrole-2-carbimidate hydrochloride and methyl thiophene-2-carbimidate hydrochloride were synthesized according to the literature.[9] For full spectroscopic characterization of compounds **1**, **10**–**18**, and **24**–**26** see our preliminary communication.[10] Preliminary enantioselectivity screening of ligands **10**–**23** in the Cu(II)-catalyzed Henry reaction was carried out according to the literature.[8,10,16] The enantiomeric excesses were determined by HPLC analysis with a Chiralcel OD-H column (85/15 hexanes/*i*-PrOH, 0.8 mL/min, 230 nm): (*R*)-enantiomer t_R = 23.19 min, (*S*)-enantiomer 28.59 min. THF was freshly distilled from Na/benzophenone under Ar. Evaporation and concentration in vacuo were performed at water aspirator pressure. Column chromatography (CC) was carried out with SiO_2 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminum sheets coated with SiO_2 60 F_{254} obtained from Merck, with visualization by a UV lamp (254 or 360 nm). Melting points (mp) were measured on a Büchi B-540 melting-point apparatus in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz or 100 MHz, respectively, with Bruker AVANCE 400 instruments at 25 °C. Chemical shifts are reported in ppm relative to the signal of Me_4Si. Residual solvent signals in the ^1H and ^{13}C NMR spectra were used as the internal reference ($CDCl_3$—7.25 and 77.23 ppm for ^1H and ^{13}C NMR, respectively). Coupling constants (J) are given in Hz. The apparent resonance

multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), and m (multiplet). Additional NMR techniques such as ^{1}H–^{1}H COSY, HMBC, and HMQC were used for regular signal assignment. Optical rotation values were measured on a Perkin Elmer 341 instrument, concentration *c* is given in g/100 mL MeOH. The mass spectra were measured on GC/MS configuration comprised of an Agilent Technologies—6890N gas chromatograph (HP-5MS column, length 30 m, I.D. 0.25 mm, film 0.25 μm) equipped with a 5973 Network MS detector (EI 70 eV, mass range 33–550 Da). Elemental analyses were performed on a Thermo Flash 2000 CHNS experimental organic analyzer.

4.2. General method for the synthesis of NH-imidazolines 1–4 and 8

Sodium (5 mg) was added to dry methanol (10 mL) followed by the appropriate heteroaromatic nitrile (1.24/0.62 mmol) and the resulting solution was stirred at 25 °C until TLC (SiO_2; EtOAc) or GC/MS showed total conversion of the nitrile into the corresponding imidate (usually 1–4 h). (1*R*,2*S*,3*R*)-Camphordiamine dihydrochloride (299 mg, 1.24 mmol), triethylamine (0.5 mL) and acetic acid (3 drops) were then added and the resulting solution was stirred at 40 °C for 12 h. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (SiO_2; EtOAc/MeOH 2:1) to afford pure product.

4.2.1. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-4-(pyrazin-2-yl)-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-3-ene 2

The title compound was synthesized from pyrazine-2-carbonitrile (130.3 mg) following the general method. Off-white solid, yield 260 mg (82%), mp 120–121 °C, $[\alpha]_D^{20} = -34.5$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.66 (s, 3H), 0.78 (s, 3H), 0.86 (s, 3H), 0.80–0.95 (m, 2H), 1.28–1.36 (m, 1H), 1.52–1.61 (m, 1H), 1.92 (d, *J* = 4.8 Hz, 1H), 3.73 (d, *J* = 10.0 Hz, 1H), 4.04 (d, *J* = 10.0 Hz, 1H), 6.85 (br s, 1H), 8.32–8.33 (m, 1H), 8.43 (d, *J* = 2.8 Hz, 1H), 9.22 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.77, 18.27, 23.40, 25.73, 33.86, 47.64, 48.27, 49.46, 73.36, 74.34, 143.00, 143.44, 144.35, 145.55, 161.44; EI-MS (70 eV) *m*/*z* (rel. int.): 256 (M+, 26), 186 (40), 173 (100), 147 (76), 95 (35); Elemental analysis calcd for $C_{15}H_{20}N_4$ (256.34): C 70.28, H 7.86, N 21.86; found: C, 69.99, H 7.72, N 21.83.

4.2.2. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-4-(pyrimidin-2-yl)-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-3-ene 3

The title compound was synthesized from pyrimidine-2-carbonitrile (130.3 mg) following the general method. Off-white solid, yield 213 mg (67%), mp 138–140 °C, $[\alpha]_D^{20} = -36.0$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.81 (s, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 1.04–1.07 (m, 2H), 1.45–1.51 (m, 1H), 1.66–1.73 (m, 1H), 2.12 (d, *J* = 4.8 Hz, 1H), 3.94 (d, *J* = 10.4 Hz, 1H), 4.23 (d, *J* = 10.4 Hz, 1H), 7.25 (br s, 1H), 7.30 (t, *J* = 4.8 Hz, 1H), 8.75 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.15, 18.73, 23.69, 26.05, 34.24, 48.12, 48.70, 49.72, 73.61, 75.05, 121.83, 156.67, 157.39, 162.43; EI-MS (70 eV) *m*/*z* (rel. int.): 256 (M+, 17), 186 (19), 173 (84), 147 (100), 95 (16); Elemental analysis calcd for $C_{15}H_{20}N_4$ (256.34): C 70.28, H 7.86, N 21.86; found: C 70.02, H 7.70, N 21.70.

4.2.3. (1*R*,2*S*,6*R*,7*S*)-4-(Isoquinolin-1-yl)-1,10,10-trimethyl-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-3-ene 4

The title compound was synthesized from isoquinolin-1-carbonitrile (192.2 mg) following the general method. Off-white solid, yield 163 mg (43%), mp 105–107 °C, $[\alpha]_D^{20} = -74.9$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (s, 1H), 0.97–1.16 (m, 8H), 1.51–1.56 (m, 1H), 1.73–1.79 (m, 1H), 2.15 (d, *J* = 3.6 Hz, 1H), 3.92 (br s, 1H), 4.29 (br s, 1H), 6.52 (br s, 1H), 7.62–7.68 (m, 3H), 7.77–7.79 (m, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 9.63 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.37, 19.04, 23.88, 26.22, 34.41, 48.05, 48.62, 50.15, 122.94, 126.81, 127.15, 128.56, 128.56, 130.37, 136.91, 141.13, 148.20, 163.96; EI-MS (70 eV) *m*/*z* (rel. int.): 305 (M+, 29), 222 (100), 196 (74), 128 (14); Elemental analysis calcd for $C_{20}H_{23}N_3$ (305.42): C 78.65, H 7.59, N 13.76; found: C 78.37, H 7.53, N 13.61.

4.2.4. 4,4′-Pyridin-2,6-diylbis[(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-3-ene] 8

The title compound was synthesized from pyridine-2,6-dicarbonitrile (80.1 mg) following the general method. Off-white solid, yield 236 mg (88%), mp 104–106 °C, $[\alpha]_D^{20} = -24.4$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.86 (s, 6H), 0.96 (s, 6H), 1.05–1.08 (m, 2H), 1.11 (s, 6H), 1.26–1.32 (m, 2H), 1.51–1.57 (m, 2H), 1.73–1.79 (m, 2H), 2.19 (d, *J* = 4.0 Hz, 2H), 4.01 (d, *J* = 10.4 Hz, 2H), 4.22 (d, *J* = 10.4 Hz, 2H), 6.08 (br s, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 8.34 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.96, 18.71, 23.67, 25.75, 34.0, 48.00, 48.87, 49.60, 66.33, 71.72, 125.86, 138.30, 163.47, 178.52; EI-MS (70 eV) *m*/*z* (rel. int.): 431 (M+, 23), 348 (100), 322 (54), 238 (17), 207 (21), 95 (21); Elemental analysis calcd for $C_{27}H_{37}N_5$ (431.62): C 75.13, H 8.64, N 16.23; found: C 75.46; H 8.79; N 16.65.

4.3. General method for the synthesis of NH-imidazolines 5–7

To a suspension of imidate hydrochloride (1.24 mmol) in dichloromethane (10 mL), (1*R*,2*S*,3*R*)-camphordiamine dihydrochloride (299 mg, 1.24 mmol), triethylamine (0.5 mL), and acetic acid (3 drops) were added and the resulting solution was stirred at 25 °C for 24 h. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (SiO_2; EtOAc/MeOH 2:1) to afford pure product.

4.3.1. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-4-phenyl-3,5-diazatricyclo-[5.2.1.0^{2,6}]dec-3-ene 5

The title compound was synthesized from ethyl benzimidate hydrochloride (230.2 mg) following the general method. Off-white solid, yield 287 mg (91%), mp 150–152 °C, $[\alpha]_D^{20} = -30.0$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.81 (s, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.00–1.06 (m, 2H), 1.42–1.49 (m, 1H), 1.66–1.74 (m, 1H), 2.02 (d, *J* = 4.4 Hz, 1H), 3.75 (d, *J* = 10.0 Hz, 1H), 4.09 (d, *J* = 10.0 Hz, 1H), 5.46 (br s, 1H), 7.29–7.39 (m, 3H), 7.70 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.18, 18.59, 23.73, 26.13, 34.28, 47.61, 48.32, 49.73, 127.37, 128.48, 130.65, 131.03, 164.40; EI-MS (70 eV) *m*/*z* (rel. int.): 254 (M+, 26), 184 (38), 171 (100), 145 (67), 95 (18); Elemental analysis calcd for $C_{17}H_{22}N_2$ (254.37): C 80.27, H 8.72, N 11.01; found: C 80.01, H 8.50, N 10.60.

4.3.2. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-4-(1*H*-pyrrol-2-yl)-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-3-ene 6

The title compound was synthesized from methyl 1H-pyrrole-2-carbimidate hydrochloride (160.7 mg) following the general method. Off-white solid, yield 172 mg (57%), mp 203–205 °C, $[\alpha]_D^{20} = -13.8$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.82 (s, 1H), 0.90 (s, 1H), 0.96–1.03 (m, 2H), 1.08 (s, 3H), 1.48–1.55 (m, 1H), 1.68–1.74 (m, 1H), 2.11 (d, *J* = 4.4 Hz, 1H), 3.96 (d, *J* = 10.4 Hz, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 6.17 (s, 1H), 7.00 (s, 1H), 7.56 (s, 1H), 10.23 (s, 1H), 12.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.72, 18.53, 23.51, 25.05, 33.33, 47.63, 49.05, 49.06, 65.84, 70.97, 111.53, 114.93, 119.67, 127.13, 157.48; EI-MS (70 eV) *m*/*z* (rel. int.): 243 (M+, 42), 173 (32), 160 (100), 134 (62), 95 (28); Elemental analysis calcd for $C_{15}H_{21}N_3$ (243.35): C 74.03, H 8.70, N 17.27; found: C 74.33; H 8.88; N 17.54.

4.3.3. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-4-(thiophen-2-yl)-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-3-ene 7

The title compound was synthesized from methyl thiophene-2-carbimidate hydrochloride (181.9 mg) following the general method. Off-white solid, yield 203 mg (63%), mp 124–126 °C, $[\alpha]_D^{20} = -27.2$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.83 (s, 3H), 0.96 (s, 3H), 1.05 (s, 3H), 1.22–1.27 (m, 2H), 1.45–1.53 (m, 1H), 1.68–1.75 (m, 1H) 2.12 (d, *J* = 4.4 Hz, 1H) 3.88 (d, *J* = 10.0 Hz, 1H), 4.12 (d, *J* = 10.0 Hz, 1H), 7.02–7.04 (m, 1H), 7.46 (m, 1H), 7.92 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.09, 18.61, 23.65, 25.72, 33.89, 47.75, 48.90, 49.37, 70.76, 73.16, 128.27, 129.43, 131.60, 132.13, 159.82; EI-MS (70 eV) *m*/*z* (rel. int.): 260 (M+, 34), 190 (51), 177 (100), 151 (71), 95(29); Elemental analysis calcd for $C_{15}H_{20}N_2S$ (260.40): C 69.19, H 7.74, N 10.76, S 12.31; found: C 69.39; H 7.81; N 10.56; S 12.49.

4.4. (1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-3,5-diazatricyclo[5.2.1.0^{2,6}]-dec-3-ene 9

(1*R*,2*S*,3*R*)-Camphordiamine dihydrochloride (80 mg, 0.33 mmol), trimethyl orthoformate (0.1 mL; 0.91 mmol), and NaOAc (4.1 mg, 0.05 mmol) were dissolved in AcOH (1 mL). The reaction mixture was then stirred at 25 °C for 24 h, diluted with EtOAc, and washed with aq NaOH (1 M). The layers were separated, the water layer was extracted with EtOAc (2 × 50 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The crude product was triturated with petroleum ether to afford **9** as a white solid. White solid, yield 48 mg (82%), mp 122–124 °C, $[\alpha]_D^{20} = -26.6$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.78 (s, 3H), 0.96 (s, 3H), 1.01 (s, 3H), 0.98–1.05 (m, 2H), 1.44–1.49 (m, 1H), 1.66–1.70 (m, 1H) 1.96 (d, *J* = 4.6 Hz, 1H) 3.63 (d, *J* = 10.2 Hz, 1H), 3.88 (d, *J* = 10.2 Hz, 1H), 4.68 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.11, 18.75, 23.85, 26.12, 34.46, 48.12, 48.20, 49.63, 71.52, 74.10, 155.16; EI-MS (70 eV) *m*/*z* (rel. int.): 178 (M+, 8), 108 (29), 95 (100), 69 (46); Elemental analysis calcd for $C_{11}H_{18}N_2$ (178.27): C 74.11, H 10.18, N 15.71; found: C 73.58; H 10.01; N 15.46.

4.5. General method for the synthesis of imidazolines 19–23

Lithium bis(trimethylsilyl)amide (0.78 mL, 0.78 mmol, 1 M solution in THF, LHMDS) was added to a solution of imidazoline **2–7** (0.39 mmol) in dry THF (10 mL) under Ar at 0 °C. The resulting yellow solution was stirred for 30 min whereupon a solution of 4-anisoylchloride (80.2 mg, 0.47 mmol) in THF (1 mL) was added dropwise and the reaction was stirred at 25 °C for an additional 3 h (monitored by TLC). The reaction was quenched with aq NH_4Cl (5 drops), the solvents were evaporated in vacuo, and the crude mixture of regioisomers was purified by column chromatography (SiO_2; indicated solvent system). Triethylamine (5 drops) was added to the combined fractions from the column chromatography before the solvent was evaporated.

4.5.1. Imidazoline 19a

The title compound was synthesized from NH-imidazoline **2** (100 mg) following the general method. Viscous oil, yield 52 mg (34%), R_f = 0.23 (EtOAc/CH_2Cl_2/NH_4OH(aq) 1:1:0.01), $[\alpha]_D^{20} = +26.0$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (s, 3H), 1.03 (s, 3H), 1.09 (s, 3H), 1.17–1.24 (m, 1H), 1.28–1.35 (m, 1H), 1.51–1.59 (m, 1H), 1.81–1.89 (m, 1H), 2.29 (d, *J* = 4.4 Hz, 1H), 3.66 (s, 3H), 4.36 (d, *J* = 9.2 Hz, 1H), 4.65 (d, *J* = 9.2 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 8.03 (dd, *J* = 2.4 Hz, *J* = 1.2 Hz, 1H), 8.22 (d, *J* = 2.4 Hz, 1H), 8.62 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.93, 19.68, 23.55, 26.45, 34.22, 47.78, 48.87, 51.26, 55.46, 73.00, 76.81, 113.31, 128.51, 130.28, 143.06, 144.16, 144.59, 147.28, 157.73, 161.66, 169.59; EI-MS (70 eV) *m*/*z* (rel. int.): 390 (M+, 7), 255 (37), 172 (12), 135 (100), 77 (10); Elemental analysis calcd for $C_{23}H_{26}N_4O_2$ (390.48): C 70.75, H 6.71, N 14.35; found: C 70.47, H 6.67, N 14.11.

4.5.2. Imidazoline 19b

The title compound was synthesized from NH-imidazoline **2** (100 mg) following the general method. Off-white solid, yield 76 mg (50%), mp 155–157 °C, R_f = 0.18 (EtOAc/CH_2Cl_2/NH_4OH(aq) 1:1:0.01), $[\alpha]_D^{20} = -114.6$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.82 (s, 3H), 0.99–1.02 (m, 1H), 1.05 (s, 3H), 1.15 (s, 3H), 1.17–1.23 (m, 1H), 1.53–1.60 (m, 1H), 1.64–1.72 (m, 1H), 2.04 (d, *J* = 4.8 Hz, 1H), 3.76 (s, 1H), 4.16 (d, *J* = 9.6 Hz, 1H), 4.41 (d, *J* = 9.2 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 8.27 (s, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.00, 19.20, 23.50, 25.65, 34.88, 47.43, 49.25, 49.76, 55.53, 69.40, 81.96, 113.65, 127.71, 130.50, 143.27, 144.26, 144.58, 147.43, 159.00, 162.25, 169.44; EI-MS (70 eV) *m*/*z* (rel. int.): 390 (M+, 5), 255 (21), 186 (20), 135 (100), 77 (8); Elemental analysis calcd for $C_{23}H_{26}N_4O_2$ (390.48): C 70.75, H 6.71, N 14.35; found: C 70.35, H 6.76, N 14.02.

4.5.3. Imidazolines 20a/b

The mixture of regioisomers was synthesized from NH-imidazoline **3** (100 mg) following the general method. Both regioisomers **a** and **b** (ratio 7:10) were not separable by column chromatography. Viscous oil, yield 75 mg (49%), R_f = 0.41 (EtOAc/CH_2Cl_2/NH_4OH(aq) 1:1:0.01). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.84 (s, 3H), 0.89 (s, 2.1H), 1.05 (s, 2.1H), 1.05–1.12 (m, 0.7H), 1.13 (s, 3H), 1.17 (s, 3H), 1.18 (s, 2.1H), 1.21–1.25 (m, 2H), 1.31–1.37 (m, 0.7H), 1.54–1.61 (m, 1.7H), 1.68–1.73 (m, 1H), 1.82–1.86 (m, 0.7H), 2.13 (d, *J* = 4.7 Hz, 1H), 2.33 (d, *J* = 4.6 Hz, 1H), 3.67 (s, 2.1H), 3.75 (s, 3H), 4.19 (d, *J* = 9.2 Hz, 1H), 4.37 (d, *J* = 9.2 Hz, 0.7H), 4.45 (d, *J* = 9.2 Hz, 1H), 4.69 (d, *J* = 9.2 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 1.4H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.92 (t, *J* = 4.9 Hz, 0.7H), 7.07 (d, *J* = 4.8 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1.4H), 7.43 (d, *J* = 8.8 Hz, 2H), 8.40 (d, *J* = 4.8 Hz, 1.4H), 8.56 (d, *J* = 5.2 Hz, 2H). EI-MS (70 eV) *m*/*z* (rel. int.): 390 (M+, 1), 255 (48), 186 (30), 135 (100), 77 (6).

4.5.4. Imidazoline 21a

The title compound was synthesized from NH-imidazoline **4** (119.1 mg) following the general method. Viscous oil, yield 82 mg (48%), R_f = 0.38 (EtOAc/CH_2Cl_2/NH_4OH(aq) 1:1:0.01), $[\alpha]_D^{20} = +102.4$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (s, 3H), 1.06 (s, 3H), 1.22–1.30 (m, 2H), 1.43 (s, 3H), 1.58–1.65 (m, 1H), 1.86–1.94 (m, 1H), 2.39 (d, *J* = 4.8 Hz, 1H), 3.51 (s, 3H), 4.46 (d, *J* = 9.2 Hz, 1H), 4.87 (d, *J* = 9.2 Hz, 1H), 6.12 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 6.0 Hz, 1H), 7.51–7.59 (m, 3H), 8.00 (d, *J* = 7.6 Hz, 1H), 8.21 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.97, 20.22, 23.62, 26.74, 34.27, 47.97, 48.73, 51.20, 55.29, 71.27, 76.97, 112.31, 121.21, 125.35, 126.92, 126.98, 128.02, 128.09, 129.44, 130.31, 135.79, 141.79, 151.60, 157.79, 160.99, 169.94; EI-MS (70 eV) *m*/*z* (rel. int.): 439 (M+, 5), 304 (54), 135 (100), 77 (11); Elemental analysis calcd for $C_{28}H_{29}N_3O_2$ (439.55): C 76.51, H 6.65, N 9.56; found: C 76.29, H 6.70, N 9.49.

4.5.5. Imidazoline 21b

The title compound was synthesized from NH-imidazoline **4** (119.1 mg) following the general method. Off-white solid, yield 82 mg (48%), R_f = 0.31 (EtOAc/CH_2Cl_2/NH_4OH(aq) 1:1:0.01), $[\alpha]_D^{20} = -116.6$ (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.90 (s, 3H), 1.14–1.21 (m, 1H), 1.24 (s, 3H), 1.26–1.29 (m, 1H), 1.35 (s, 3H), 1.60–1.67 (m, 1H), 1.75–1.83 (m, 1H), 2.25 (d, *J* = 4.8 Hz, 1H), 3.60 (s, 3H), 4.26 (d, *J* = 9.6 Hz, 1H), 4.62 (d,

J = 9.6 Hz, 1H), 6.35 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 5.6 Hz, 1H), 7.54–7.61 (m, 2H), 7.65–7.67 (m, 1H), 8.23–8.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.20, 20.01, 23.50, 25.79, 35.12, 47.65, 48.60, 49.86, 55.37, 68.28, 81.65, 112.80, 121.34, 125.66, 126.90, 127.02, 128.06, 128.09, 129.55, 130.29, 136.23, 141.72, 151.37, 158.50, 161.28, 168.82; EI-MS (70 eV) m/z (rel. int.): 439 (M+, 5), 304 (45), 235 (12), 207 (15), 135 (100), 77 (11); Elemental analysis calcd for $C_{28}H_{29}N_3O_2$ (439.55): C 76.51, H 6.65, N 9.56; found: C 76.35, H 6.72, N 9.51.

4.5.6. Imidazoline 22a

The title compound was synthesized from NH-imidazoline **5** (99.2 mg) following the general method. Viscous oil, yield 116 mg (77%), R_f = 0.21 (EtOAc/hexane 1:2), $[\alpha]_D^{20} = +1.4$ (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (s, 3H), 1.07 (s, 6H), 1.30–1.35 (m, 2H), 1.53–1.60 (m, 1H), 1.81–1.89 (m, 1H), 2.28 (d, J = 4.8 Hz, 1H), 3.66 (s, 3H), 4.30 (d, J = 9.2 Hz, 1H), 4.62 (d, J = 9.2 Hz, 1H), 6.48 (d, J = 8.8 Hz, 2H), 7.05–7.13 (m, 3H), 7.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.01, 19.77, 23.64, 26.48, 34.40, 47.52, 48.81, 51.22, 55.46, 73.49, 75.94, 113.07, 127.88, 128.14, 128.32, 129.40, 130.65, 132.58, 160.75, 161.63, 170.37; EI-MS (70 eV) m/z (rel. int.): 388 (M+, 5), 253 (18), 170 (25), 135 (100), 77 (11); Elemental analysis calcd for $C_{25}H_{28}N_2O_2$ (388.50): C 77.29, H 7.26, N 7.21; found: C 77.15, H 7.52, N 7.18.

4.5.7. Imidazoline 22b

The title compound was synthesized from NH-imidazoline **5** (99.2 mg) following the general method. Off-white solid, yield 11 mg (7%), mp 151–153 °C, R_f = 0.16 (EtOAc/hexane 1:2), $[\alpha]_D^{20} = -62.8$ (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.80 (s, 3H), 0.98–1.02 (m, 1H), 1.03 (s, 3H), 1.13 (s, 3H), 1.15–1.24 (m, 1H), 1.49–1.56 (m, 1H), 1.62–1.70 (m, 1H), 2.06 (d, J = 4.8 Hz, 1H), 3.71 (s, 3H), 4.05 (d, J = 9.2 Hz, 1H), 4.37 (d, J = 9.2 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 7.09–7.17 (m, 3H), 7.26 (d, J = 8.4 Hz, 3H), 7.37 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.03, 19.23, 23.47, 25.72, 34.89, 47.13, 49.24, 49.47, 55.44, 69.55, 80.69, 113.37, 127.81, 127.87, 128.02, 129.48, 130.50, 132.53, 161.42, 161.98, 169.68; EI-MS (70 eV) m/z (rel. int.): 388 (M+, 10), 253 (10), 184 (45), 135 (100), 77 (6); Elemental analysis calcd for $C_{25}H_{28}N_2O_2$ (388.50): C 77.29; H 7.26, N 7.21; found: C 76.92, H 7.28, N 6.96.

4.5.8. Imidazoline 23a

The title compound was synthesized from NH-imidazoline **7** (101.6 mg) following the general method. Viscous oil, yield 94 mg (61%), R_f = 0.29 (EtOAc/hexane 1:2), $[\alpha]_D^{20} = +9.4$ (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.85 (s, 3H), 0.96 (s, 3H), 1.06 (s, 3H), 1.14–1.30 (m, 2H), 1.49–1.57 (m, 1H), 1.77–1.85 (m, 1H), 2.26 (d, J = 4.4 Hz, 1H), 3.69 (s, 3H), 4.27 (d, J = 8.8 Hz, 1H), 4.50 (d, J = 8.8 Hz, 1H), 6.57–6.60 (m, 4H), 7.10 (dd, J = 4.8 Hz, J = 1.2 Hz, 1H), 7.29 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.90, 19.53, 23.58, 26.33, 34.34, 47.27, 48.92, 51.06, 55.44, 74.53, 75.83, 113.18, 126.83, 127.95, 128.59, 129.60, 130.36, 134.00, 155.50, 161.82, 170.46; EI-MS (70 eV) m/z (rel. int.): 394 (M+, 5), 259 (20), 176 (27), 135 (100), 77 (12); Elemental analysis calcd for $C_{23}H_{26}N_2O_2S$ (394.53): C 70.02, H 6.64, N 7.10, S 8.13; found: C 69.91, H 6.54, N 7.03, S 8.02.

4.5.9. Imidazoline 23b

The title compound was synthesized from NH-imidazoline **7** (101.6 mg) following the general method. Off-white solid, yield 9 mg (6%), R_f = 0.42 (EtOAc/hexane 1:2), $[\alpha]_D^{20} = -78.1$ (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.82 (s, 3H), 0.95–0.99 (m, 1H), 1.01 (s, 3H), 1.14 (s, 3H), 1.17–1.20 (m, 1H), 1.50–1.58 (m, 1H), 1.62–1.68 (m, 1H), 2.04 (d, J = 4.8 Hz, 1H), 3.81 (s, 3H), 4.08 (d, J = 9.0 Hz, 1H), 4.32 (d, J = 9.0 Hz, 1H), 6.78–6.81 (m, 3H), 6.95–6.97 (m, 1H), 7.24–7.25 (m, 1H), 7.53 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.13, 19.22, 23.59, 25.80, 34.92, 47.15, 49.67, 49.74, 55.62, 70.30, 80.71, 113.65, 127.01, 128.15, 128.35, 129.66, 130.68, 133.98, 156.18, 162.42, 170.32; EI-MS (70 eV) m/z (rel. int.): 394 (M+, 5), 259 (13), 190 (26), 135 (100), 77 (4); Elemental analysis calcd for $C_{23}H_{26}N_2O_2S$ (394.53): C 70.02, H 6.64, N 7.10, S 8.13; found: C 69.53, H 6.76, N 6.62, S 8.15.

4.6. Ring-opening of imidazolines 19a and 23a

Pure regioisomers **19a** and **23a** underwent spontaneous slow hydrolysis to diamides **27** and **28** within 1 month. These products were purified by column chromatography.

4.6.1. *N*-[(1*R*,2*S*,3*R*,4*S*)-3-(4-Methoxybenzoylamino)-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]pyrazine-2-carboxamide 27

The title compound was obtained from regioisomer **19a**. Off-white solid, mp 249–251 °C, R_f = 0.37 ($EtOAc/CH_2Cl_2/NH_4OH$(aq) 1:1:0.01), $[\alpha]_D^{20} = -78.6$ (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.90 (s, 3H), 0.97 (s, 3H), 1.15 (s, 3H), 1.42–1.53 (m, 2H), 1.65–1.71 (m, 1H), 1.82–1.86 (m, 1H), 2.12 (d, J = 4.4 Hz, 1H), 3.83 (s, 3H), 4.27 (t, J = 8.4 Hz, 1H), 4.46 (t, J = 8.4 Hz, 1H), 6.06 (br d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 8.11 (br d, J = 6.4 Hz, 1H), 8.33 (dd, J = 2.4 Hz, J = 1.6 Hz, 1H), 8.67 (d, J = 2.4 Hz, 1H), 9.32 (d, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.16, 2 × 21.51, 26.39, 35.71, 47.95, 48.87, 50.54, 55.65, 56.72, 60.31, 114.04, 127.10, 128.77, 142.62, 144.55, 144.66, 147.42, 162.47, 162.49, 167.29. EI-MS (70 eV) m/z (rel. int.): 408 (M+, 1), 285 (6), 257 (42), 229 (5), 150 (4), 135 (100), 107 (4), 77 (4).

4.6.2. *N*-[(1*R*,2*S*,3*R*,4*S*)-3-(4-Methoxybenzoylamino)-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]thiophene-2-carboxamide 28

The title compound was obtained from regioisomer **23a**. Off-white solid, mp 161–163 °C, R_f = 0.18 (EtOAc/hexane 1:2), $[\alpha]_D^{20} = -30.0$ (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (s, 3H), 0.96 (s, 3H), 1.12 (s, 3H), 1.38–1.50 (m, 2H), 1.62–1.69 (m, 1H), 1.80–1.84 (m, 1H), 2.12 (d, J = 4.4 Hz, 1H), 3.83 (s, 3H), 4.18 (dd, J = 8.8 Hz, J = 5.6 Hz, 1H), 4.46 (t, J = 8.8 Hz, 1H), 6.07–6.10 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.99 (dd, J = 4.8 Hz, J = 4.0 Hz, 1H), 7.34 (d, J = 4.0 Hz, 1H), 7.38 (d, J = 4.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.12, 21.48, 21.49, 26.30, 35.58, 47.82, 49.03, 50.42, 55.64, 57.33, 60.27, 114.17, 126.73, 127.89, 128.37, 128.73, 129.77, 139.09, 150.79, 162.56, 167.18. EI-MS (70 eV) m/z (rel. int.): 285 (9), 261 (50), 233 (8), 135 (100), 111 (41), 77 (5).

4.7. Crystallography

The X-ray data for colorless crystals of **5** (CCDC 874023), **7** (CCDC 874024), **8** (CCDC 717409), **19b** (CCDC 874026), and **23b** (CCDC 874025) were obtained at 150 K using Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with MoK_α radiation (λ = 0.71073 Å), a graphite monochromator, and the φ and χ scan mode. Data reductions were performed with DENZO-SMN.[18] The absorption was corrected by integration methods.[19] Structures were solved by direct methods (Sir92)[20] and refined by full matrix least-square based on F^2 (SHELXL97).[21] Hydrogen atoms were mostly localized on a difference Fourier map, however to ensure uniformity of the treatment of the crystal, all hydrogen atoms were recalculated into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$ (pivot atom) or of 1.5 U_{eq} for the methyl moiety with C–H = 0.96, 0.97, 0.98, and 0.93 Å for methyl, methylene, and hydrogen atoms

on sp^2 carbon atoms, respectively. H-atoms in the N–H groups were placed according to Fourier map, in **5**, one half of the H atom was placed to both nitrogen atoms.

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EY, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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