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Belokon's Ni(II) complex as a chiral masked glycine for the diastereoselective synthesis of 2-substituted 1-aminocyclopropane carboxylic acids†

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Abstract—(1*S*,2*R*)- and (1*R*,2*S*)-Allonorcoronamic acids have been efficiently synthesised from the cyclic sulfate of 1,2-propanediol and Belokon's complex (a complex of Ni(II) with glycine-(*S*)-2-[*N*′-(*N*-benzylprolyl)amino]benzophenone Schiff base ligands). The stereochemical outcome of the reaction was totally controlled by the sulfate partner.

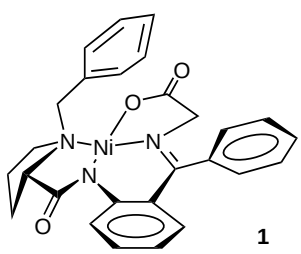
1. Introduction

Asymmetric synthetic methods for 2-substituted 1-aminocyclopropane carboxylic acids are gaining an ever increasing relevance, which is related to their biological activities and their incorporation in conformationally restricted peptides.[1,2] The two-step cycloalkylation of a glycine enolate equivalent with a 1,2-bis-electrophile is probably one of the most straightforward preparative methods for this class of cyclopropanes. These strategies are based on diastereoselective reactions mediated by a chiral auxiliary, for example, Schöllkopf's bis-lactim ether[3] or Seebach's chiral imidazolidinone[4] as well as 1,2-dibromopropane,[5] epichlorhydrine[6] or glycidal triflate.[7] To our knowledge, double asymmetric induction has never been reported in this context. We recently described the synthesis of 2,3-methanoamino acids from optically active sulfates and methyl benzylidene glycinate.[8]

2. Results and discussion

Herein, we report the use of Belokon's Ni(II) complex **1** as an enantiomerically pure masked glycine equivalent and the stereochemical outcome of its reaction with the chiral sulfate **2**. Among the various glycine derivatives, the Ni(II) complex of its Schiff base [(*S*)-BPB] **1** was chosen due to its multigram scale availability, the easy chromatographic separation of the corresponding diastereoisomeric products and the simple recovery of the starting chiral auxiliary, (*S*)- or (*R*)-2-[*N*′-(*N*-benzylprolyl)amino]benzophenone.[9] Cyclic sulfates offer the advantage of being readily available with multiple substituents in both enantiomeric forms (Scheme 1).[10]

The cyclisation conditions were first optimised using **1** and racemic **2**. Experimental and mechanistic aspects of



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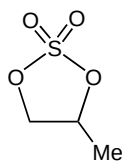

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Scheme 1.

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† Dedicated to the memory of Professor D. Danion deceased on 28th June 2000.

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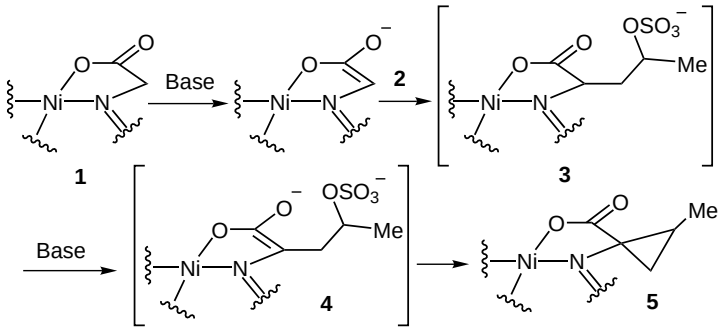


Scheme 2.

Table 1. Cyclopropanation of Ni-BPB-Gly using a 1.1:1:2 mixture of nickel complex **1**, sulfate **2** and base

Entry	Base/solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	K_2CO_3/DMF	25	2	0
2	NaOH/DMF	25	6.5	36
3	NaOH/DMF	60	2	0
4	NEt_3/CH_2Cl_2	45	24	0
5	*tert*-BuOK/DMF	25	4	30
6	*tert*-BuOK/DMF	25	3.5	32
7	NaH/DMF	40	4	0
8	$NaOH/CH_3CN$	40	6	52
9	*tert*-BuOK/THF	40	4.5	70

[a] Yield of product **5** isolated by column chromatography.

the alkylation reactions of Ni(II) complexes of α-amino acids have been extensively studied by Belokon et al.[9] Steric hindrance exerted by the bulky phenyl group at the α-carbon atom is usually invoked to explain the formation of only mono-alkylated products in the case of the glycine derivative. The corresponding alanine carbanion is less reactive and the formation of α,α-disubstituted amino acids is only efficient with activated or sterically unhindered alkyl halides. This limitation should not be encountered in our case where the second alkylation step is an intramolecular process (Scheme 2).

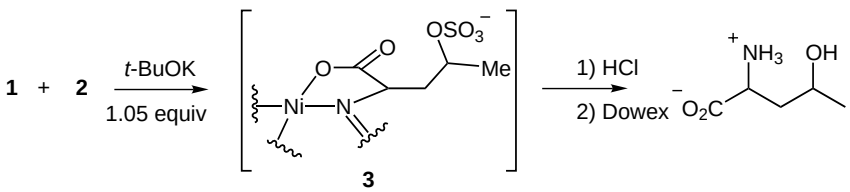
The influence of the base/solvent system was first investigated using a nearly stoichiometric ratio of reagents. After the first alkylation, the resulting complex **3** was converted to the corresponding enolate **4**, which afforded the cyclopropane **5** by intramolecular cyclisation. After purification by column chromatography **5** was fully characterised by mass spectroscopy and ^1H and ^{13}C NMR. Results for the cyclopropanation of **1** are summarised in Table 1. The best yields were obtained in THF using *tert*-BuOK as base (entry 9).

It merits mention that the reaction can be stopped after the first alkylation step. An equimolar mixture of **1** and **2** in the presence of only 1.05 equivalents of *tert*-BuOK afforded, after hydrolysis of the intermediate **3**, 2-amino-4-hydroxypentanoic acid[11] in a modest 27% yield as a 1:1 mixture of diastereoisomers (Scheme 3).

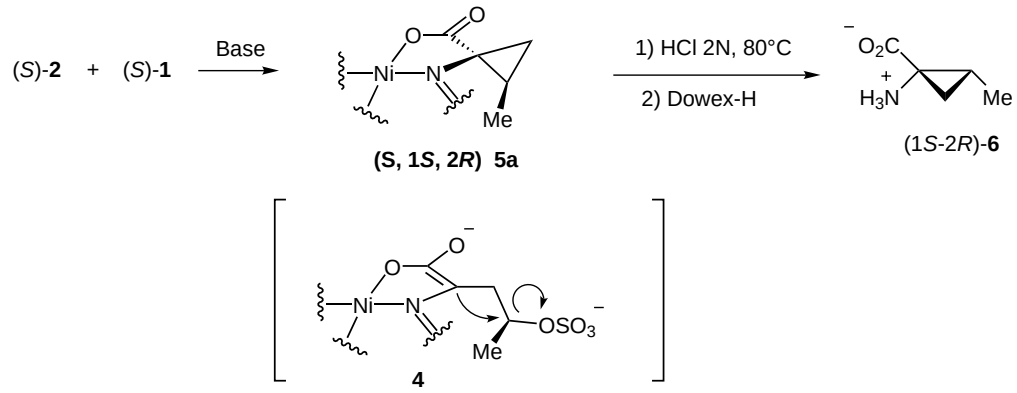
Having established the optimum conditions for the cyclisation we then examined the stereochemical outcome of these reactions. A single diastereoisomer **5a** was obtained from the reaction of (*S*)-Ni(II) complex **1** and (*S*)-sulfate **2** (Scheme 4). The relative and absolute configurations of the cyclopropane moiety were assigned after cleavage of the chiral auxiliary by hydrolysis and comparison with data reported in the literature for the known amino acid (1*S*,2*R*)-**6**.[7] Attempts to isolate other diastereoisomers among the minor side products were unsuccessful.

This high degree of asymmetric induction is attributed to an efficient control of the configuration of the newly created stereogenic centre in the intramolecular cyclisation step. The stereochemistry of the first alkylation has no effect on the stereochemistry overall, owing to subsequent formation of the enolate **4**. The configuration of C-(2) is the result of a clean inversion while the configuration of C-(1) can be explained by a kinetically controlled S_i facial selectivity.[9]

Using the same procedure, (*S*)-Ni(II) complex **1** and (*R*)-sulfate **2** led to (1*R*,2*S*)-allonorcoronamic acid via Ni(II) complex **5b**. These results are indicative of complete stereochemical control by the sulfate partner and



Scheme 3.



Scheme 4.

that it is able to override the intrinsic diastereofacial selectivity of the Ni complex.

Finally, (*S*)-Ni(II) complex **1** was treated with racemic sulfate to afford a mixture of diastereoisomers **5a** and **5b** in a 1:1 ratio (estimated by ^{1}H NMR). These products were easily separated by column chromatography on silica gel, providing, after hydrolysis with aqueous HCl, the two chiral non-racemic (1*S*,2*R*)- and (1*R*,2S)-allonorcoronamic acids. All attempts to favour the formation of one diastereoisomeric complex by kinetic resolution were unsuccessful.

3. Conclusion

In conclusion, this work confirms the high tendency of the cyclic sulfate of 1,2-propanediol to afford 1-amino-2-methylcyclopropanecarboxylic acids with a relative *cis*-configuration when treated with glycine derivatives. We have developed a practical method for the preparation of (1*S*,2*R*)- and (1*R*,2*S*)-allonorcoronamic acids by reaction of the Ni(II) complex (*S*)-**1** and racemic 1,2-cyclic sulfate, followed by a chromatographic separation. Numerous racemic 1,2-diols, the precursors of these versatile bis-alkylating agents, are commercially available or readily prepared. This approach should therefore constitute an efficient route for the synthesis of a wide range of enantiomerically pure aminocyclopropane carboxylic acids.

4. Experimental

All melting points were determined on a Köfler apparatus and are uncorrected. NMR spectra were measured on a Bruker AC 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) and a Bruker AC 300 (300 MHz for ^{1}H, 75.5 MHz for ^{13}C). For ^{1}H and ^{13}C NMR, TMS was used as internal standard ($\delta = 0$ ppm) and coupling constants (J) are given in Hz. High-resolution mass spectra were obtained on a Varian MAT 311 (electron impact) or Micromass ZABSpec TOF [LSIMS or electrospray (CH_3CN–H_2O), as stated] spectrometers by the Centre Régional de Mesures Physiques, Université de Rennes 1, France. Silica gel 60F254 (Merck) was used for column chromatography. Specific optical rotations were measured on a Perkin–Elmer 341 polarimeter. The Ni(II) complex **1**, of the Schiff base derived from glycine and (*S*)-2-[*N*′-(*N*-benzylprolyl)amino]benzophenone, was prepared according to the literature.[8]

4.1. General procedure for the reaction of complex 1 with racemic or enantiopure cyclic sulfate 2

To a stirred solution of complex **1** (2 mmol) and sulfate **2** (2.2 mmol) in dry THF (12 mL) at 0°C under nitrogen, *tert*-BuOK (8 mmol) was added in portions over a period of 30 min. The resulting mixture was allowed to stand for 4.5 h at 40°C. The reaction was monitored by TLC (SiO_2). After completion of the reaction, the solvent was evaporated and water (50 mL) was added. The mixture was then acidified by addition of 5% acetic acid aqueous solution (10 mL). The red product was extracted with CH_2Cl_2 (3×50 mL), dried over $MgSO_4$ and the solvent removed in vacuo. The diastereoisomers were separated by chromatography on silica gel to give enantiomerically pure cycloalkylated products **3**. Preparative TLC on silica gel (CH_3CN) could remove eventual traces of the starting glycine complex.

4.1.1. Ni(II) complex of the Schiff base of (*S*)-BPB and (1*S*,2*R*)-allonorcoronamic acid 5a. Chromatography eluent: CH_2Cl_2–Me_2CO, 2/1, 74%. $[\alpha]_D^{25} = -2261$ (*c* 0.044, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.25 (t, $J = 6.6$ Hz, 1H), 1.28 (d, $J = 6.2$ Hz, 3H), 1.44 (dd, $J = 6.9$ and 9.8 Hz, 1H), 1.64–1.75 (m, 1H), 1.95–2.09 (m, 1H), 2.18–2.35 (m, 1H), 2.55–2.95 (m, 2H), 3.35–3.46 (m, 2H), 3.44 and 4.30 (AB, $J = 12.5$ Hz, 2H), 3.81–4.08 (m, 1H), 6.62–6.81 (m, 3H), 7.05–7.18 (m, 2H), 7.20–7.55 (m, 6H), 8.07–8.11 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.0, 23.8, 24.1, 28.3, 31.1, 56.9, 58.1, 62.7, 71.0, 101.3, 120.6, 121.8, 127.6, 128.6, 128.8, 128.9, 129.8, 130.0, 131.3, 132.2, 131.3, 133.6, 135.6, 142.6, 168.0, 176.9, 179.8. HRMS (LSIMS) $[M+H]^+$ calcd for $C_{30}H_{30}N_3NiO_3$ 538.1641. Found 583.1635.

4.1.2. Ni(II) complex of the Schiff base of (*S*)-BPB and (1*R*,2*S*)-allonorcoronamic acid. Chromatography eluent: CH_2Cl_2–Me_2CO, 5/1, 69%. $[\alpha]_D^{25} = -3056$ (*c* 0.063, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ −0.27 (t, $J = 6.6$ Hz, 1H), 1.11 (d, $J = 6.2$ Hz, 3H), 1.43 (dd, $J = 6.8$ Hz and $J = 9.5$ Hz, 1H), 1.60–1.74 (m, 1H), 1.81–2.32 (m, 4H), 2.83–2.95 (m, 1H), 3.02 and 4.20 (AB, $J = 12.8$ Hz, 2H), 3.71–3.86 (m, 1H), 4.32–4.42 (m, 1H), 6.67–6.89 (m, 3H), 7.19–7.61 (m, 8H), 8.17–8.21 (m, 2H), 8.60–8.64 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.8, 22.7, 24.1, 28.4, 29.5, 58.4, 59.5, 60.1, 68.7, 120.5, 122.3, 126.8, 128.9, 129.2, 129.9, 131.1, 132.8, 134.2, 134.5, 136.1, 143.4, 168.7, 177.1, 181.1. HRMS (LSIMS) $[M+H]^+$ calcd for $C_{30}H_{30}N_3NiO_3$ 538.1641. Found 583.16347.

4.2. Hydrolysis of Ni(II) complexes

To a solution of a complex **5** (4 mmol) in MeOH (25 mL) at 50°C was added aqueous HCl (2 M, 25 mL) dropwise. The solution was then heated at 80°C until disappearance of the red colour of the starting complex. After cooling to room temperature, conc. NH_3 was added until pH 9. The chiral auxiliary (BPB) was extracted with CH_2Cl_2 (2×50 mL). The aqueous solution was then evaporated and purified on Dowex 50× 8H to afford the corresponding amino acid.

4.2.1. Hydrolysis of (*S*)-(1*S*,2*R*) complex 5a: (1*S*,2*R*)-allonorcoronamic acid. White powder; mp 225°C dec.; yield = 96%; $[\alpha]_D^{20} = -72.7$ (*c* 0.3, H_2O) (lit.[12] mp 215°C dec.; $[\alpha]_D^{25} = -69.7$ (*c* 0.3, H_2O)); ^1H NMR (300 MHz, D_2O): δ 0.76 (dd, $J = 6.2$ Hz and 6.7 Hz, 1H), 1.13 (d, $J = 6.5$ Hz, 3H), 1.37 (dd, $J = 6.2$ Hz and 9.6 Hz, 1H), 1.54–1.62 (m, 1H). ^{13}C NMR (75 MHz, D_2O): δ 14.1, 20.9, 21.7, 42.3, 178.9. HRMS (EI) $[M]^+$ calcd for $C_5H_9NO_2$ 115.0633. Found 115.0637.

4.2.2. Hydrolysis of (*S*)-(1*R*,2*S*) complex: (1*R*,2*S*)-allonorcoronamic acid. White powder; yield = 93%. Same mp and NMR spectra. $[\alpha]_D^{20} = +69.0$ (*c* 0.3, H_2O).

4.3. Synthesis of 2-amino-4-hydroxypentanoic acid

The alkylation of complex **1** with racemic cyclic sulfate **2** was performed as previously described, except that only 1.05 equivalents of *tert*-BuOK in THF were used. Hydrolysis was completed as previously described to give 2-amino-4-hydroxypentanoic acid as a 1:1 mixture of diastereoisomers.

Diastereoisomer A (27%): ^1H NMR (200 MHz, D_2O): δ 1.14 (d, $J = 6.3$ Hz, 3H), 1.70 (ddd, $J = 14.9$, 9.1 and 9.1 Hz, 1H), 2.00 (ddd, $J = 15.1$, 4.0 and 3.8 Hz, 1H), 3.70 (dd, $J = 9.1$ and 4.5 Hz, 1H), 3.9–4.1 (m, 1H). ^{13}C NMR (50 MHz, D_2O): δ 23.0, 38.9, 54.6, 67.1, 175.0. Diastereoisomer B: ^1H NMR (200 MHz, D_2O): δ 1.13 (d, $J = 6.3$ Hz, 3H), 1.84–1.94 (m, $J = 14.9$, 2H), 3.77–3.85 (m, 1H), 3.9–4.1 (m, 1H). ^{13}C NMR (50 MHz, D_2O): δ 23.1, 38.0, 53.4, 65.4, 174.8. MS-FAB$^+$ [M+H] calcd for $C_5H_{10}O_3N$ 134.0817. Found 134.0812.

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