

Designer ligands. Part 10.¹ Novel nickel(II)-selective ligands for use in the construction of molecularly imprinted polymers

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Novel, bidentate nickel(II)-selective ligands have been developed for use in the construction of molecularly imprinted polymers (MIPs), preliminary evaluation of which indicates high selectivity for nickel(II) over iron(III).

Keywords: novel nickel(II) -selective ligands, molecularly imprinted polymers

Our research on metal-selective ligands has previously been focused on the development of systems capable of chelating copper,² silver³ and platinum group metals.⁴ In this communication, we discuss the design, synthesis and evaluation of novel bidentate ligands for use in the construction of nickel(II)-selective molecularly imprinted polymers (MIPs).

Various ligands, which contain nitrogen donors (especially pyridyl) and which are capable of forming five-membered chelates, are known to form stable, four-coordinate nickel(II) complexes.⁵ These factors were consequently considered in designing potential nickel(II)-selective ligands, the structural features of which are illustrated in Fig. 1. The bidentate ligands were thus designed to contain: (i) pyridyl and amino-nitrogen donors, located to permit the formation of five-membered metal chelates; (ii) substituents (R^1 , R^2 and R^3) to fine tune donor capacity and steric demand; and (iii) a vinyl group for co-polymerisation to generate MIPs. Retrosynthetic analysis (Fig. 2) suggested use of pyridine-2-carbaldehydes (**4** or **5**) and the phosphorous ylide **6** as initial synthons for the preparation of the type-I target molecules. During the course of the synthesis (outlined in Scheme 1), however, the allyl ethers **13** were identified as alternative (type-II) target molecules.

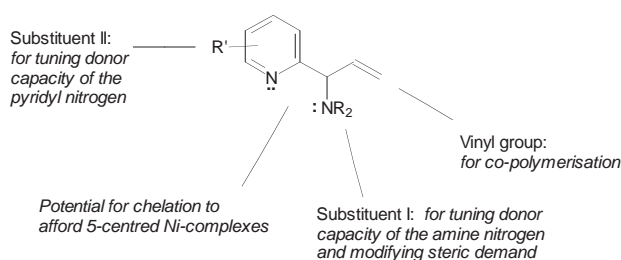


Fig. 1 Design features for the proposed nickel(II)-selective ligands.

The pyridine-2-carbaldehydes **4** and **5** were reacted with the phosphorous ylide **6** in refluxing dichloromethane for 26 hours, following methods reported by Bell and Sondheimer⁶ and Furniss *et al.*,⁷ to afford the esters **7** (93%) and **8** (68%)(Scheme 1).⁸ Evidence for the *trans*-geometry in both products is provided by the large ¹H NMR vinylic coupling constants ($J = 15.0 \pm 1.0$ Hz). The subsequent conjugate addition step was initially explored by treating the α , β -unsaturated ester **7** with piperidine in dry THF at room temperature. When none of the expected addition product **9a** could be iso-

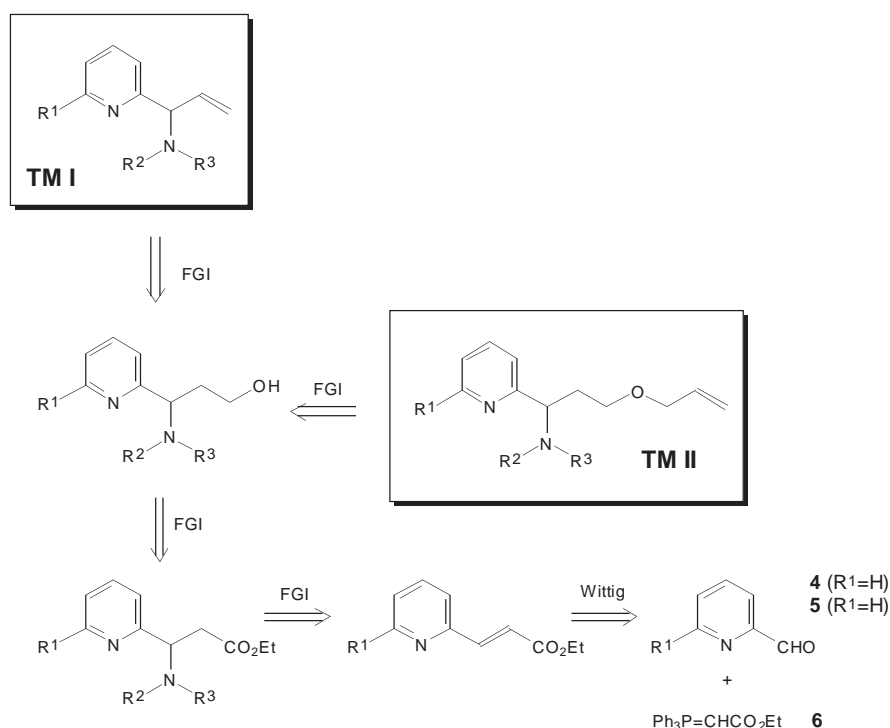
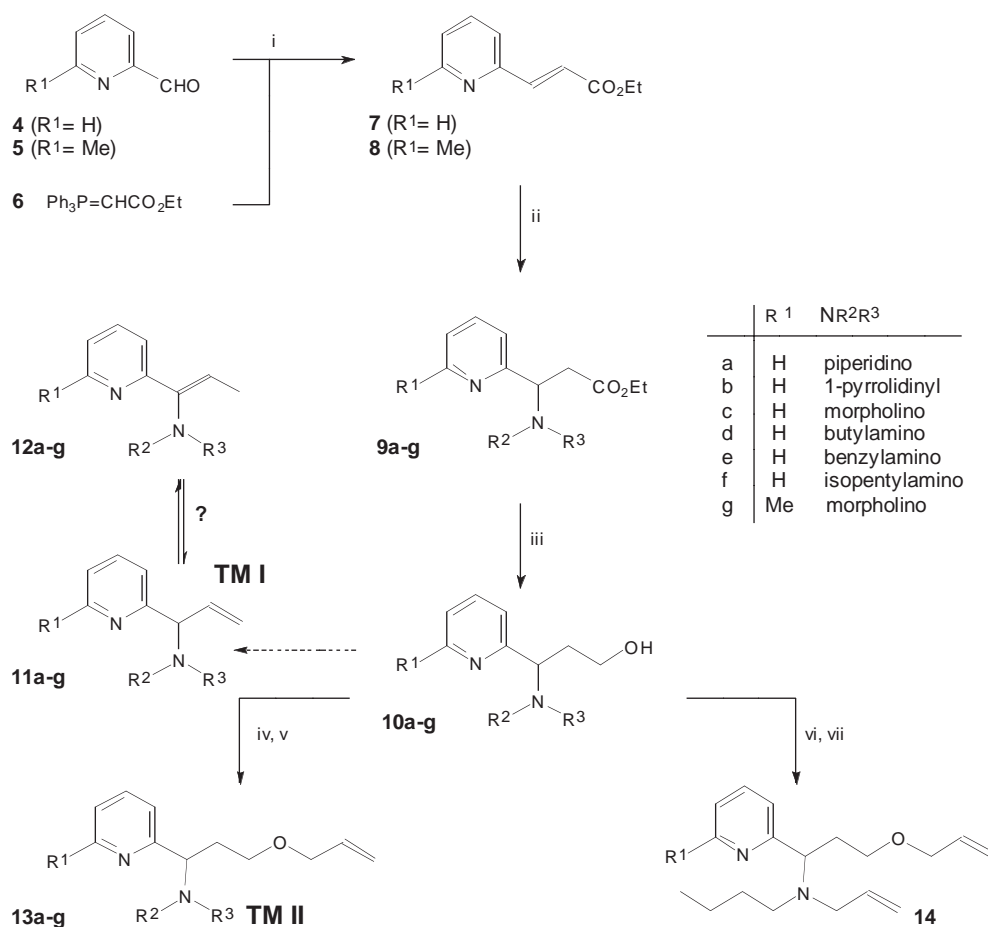


Fig. 2 Retrosynthetic analysis of the target molecules I and II.

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Scheme 1 Reagents and conditions: i, CH_2Cl_2 , reflux; ii, $\text{R}^1\text{R}^2\text{NH}$, reflux; iii, LiAlH_4 , Et_2O , N_2 ; iv, NaH (1 equiv.), THF, N_2 ; v, $\text{CH}_2=\text{CHCH}_2\text{Br}$ (1 equiv.); vi, NaH (4 equiv.), THF, N_2 ; vii, $\text{CH}_2=\text{CHCH}_2\text{Br}$ (4 equiv.).

lated after 9 days, piperidine was used both as nucleophile and solvent to afford compound **9a** in 19% yield after stirring for 4 days. Further improvements in the yield were achieved by heating the neat reactants at reflux temperature for 12 h (34%) and 16 h (99%)! The optimised reaction conditions were then used to generate the analogous products **9b–9g** in yields ranging from 32 to 96%. However, attempts to effect conjugate addition using the secondary amine, 3-pentylamine, and the aromatic amine, aniline, proved unsuccessful.

Reduction of the 1,4-addition products **9a–g** to the corresponding primary alcohols **10a–g** was achieved in variable yield (30–94%) using lithium aluminium hydride in diethyl ether. Attention was then given to what was expected to be the final, dehydration step. However, the dehydration of primary alcohols to alkenes is typically effected at elevated temperatures,⁹ and it was realised that, under such conditions, the expected type-I target molecules **11a–g** might well isomerise to the conjugated, non-terminal alkenes **12a–g**. Consequently, it was decided to use the alcohols **10a–g** to access the allyl ethers **13a–g** as alternative (type-II) target molecules.¹⁰ It was anticipated that the etherification could be effected under mild conditions to afford the bidentate ligands **13a–g**, which contain the requisite, polymerisable vinyl group. Treatment of the respective sodium alkoxides of the alcohols **10a–g** with one equivalent of allyl bromide at room temperature afforded the targeted allyl ethers **13a–g**. [Reaction of the butylamino analogue **10d** with excess (4 equivalents) of each of the reagents, sodium hydride and allyl bromide, afforded the bis-allylated derivative **14** in low yield (20%).] The bidentate ligands **13a–g** and **14** were fully characterised by elemental (HRMS) and spectroscopic (IR and

¹H and ¹³C NMR) analysis. High-resolution electron-impact (EI) mass spectrometric analysis of the ligands **13a–g** revealed several common fragmentation pathways.

Molecular imprinting technology has been applied *inter alia* in separation methodology,¹¹ drug–receptor-binding¹² and antibody-binding¹³ mimics, and metal-selective ion-exchange resins.¹⁴ The construction of MIPs containing nickel(II)-selective cavities involved the following five phases.

(i) *Pre-arrangement*.¹² Solutions of the nickel(II) salt (the “print species”)¹⁵ with two equivalents of each of the bidentate ligands **13a–g** (the “functional monomers”) in methanol (the “porogenic solvent”) were stirred overnight – a process typically accompanied by a change in colour from light-yellow to light-green.¹⁶

(ii) *Polymerisation*. Ethylene glycol dimethacrylate (EGDMA) was added as the “cross-linker”¹¹ to give an EGDMA:monomer ratio of 95:5, the large excess of cross-linker being used to ensure that the nickel(II) cavities retain their shape after removal of the metal template. Polymerisation was initiated by adding azobis(isobutyronitrile) (AIBN)¹⁷ and heating the mixtures at 60°C for 3 h.

(iii) *Grinding*. After standing overnight, the reaction tubes containing the glassy polymers were shattered and the retrieved polymer pulverised into different “mesh sizes” (fine, medium and coarse) to increase the active surface area.

(iv) *Leaching*. The pulverised MIPs were left to stand overnight in conc. HCl to extract the coordinated metal ions.

(v) *Drying*. The leached MIPs were washed thoroughly with methanol and dried under high vacuum to afford shiny, white particles, which were then used for metal extraction studies.

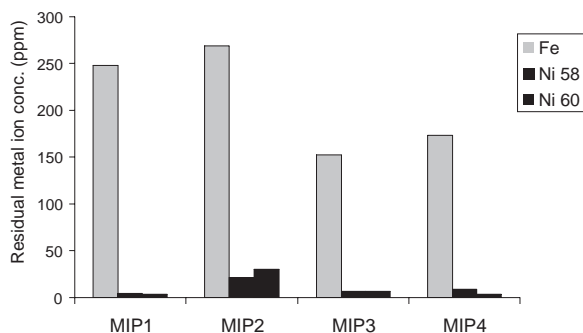


Fig. 3 ICP-MS data for analysis of residual metal ion concentrations following MIP extraction (using "fine" particles") of standard 300ppm solutions containing Ni(II) and Fe(III) ions. [MIP1: Ni(II)tetrafluoroborate-**13c**; MIP2: Ni(II)acetate-**13a**; MIP3: Ni(II)acetate-**13g**; and MIP4: Ni(II)chloride-**13c**.]

The various MIPs were subjected to preliminary evaluation to determine:- relative extraction efficiencies; equilibration times; mesh-size and counter-ion effects.¹⁶ Flame atomic absorption spectroscopy was used to analyse residual metal concentrations in the supernatant solutions after extraction. Following these preliminary studies, four MIP's were selected for final evaluation, using ICP-MS analysis to determine the residual metal concentrations. The results, illustrated graphically in Fig. 3, clearly demonstrate the capacity of these MIPs to facilitate the preferential extraction of nickel(II) in the presence of iron(III).

In summary, a series of novel bidentate ligands has been successfully prepared and used as functional monomers in the construction of MIPs, some of which have been shown to exhibit excellent selectivity for nickel(II) over iron(III).

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Techniques used: NMR spectroscopy, EI mass spectrometry, AA and ICP-MS analysis.

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