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Synthesis and evaluation of novel pseudopeptide chiral stationary phases for enantioselective resolution

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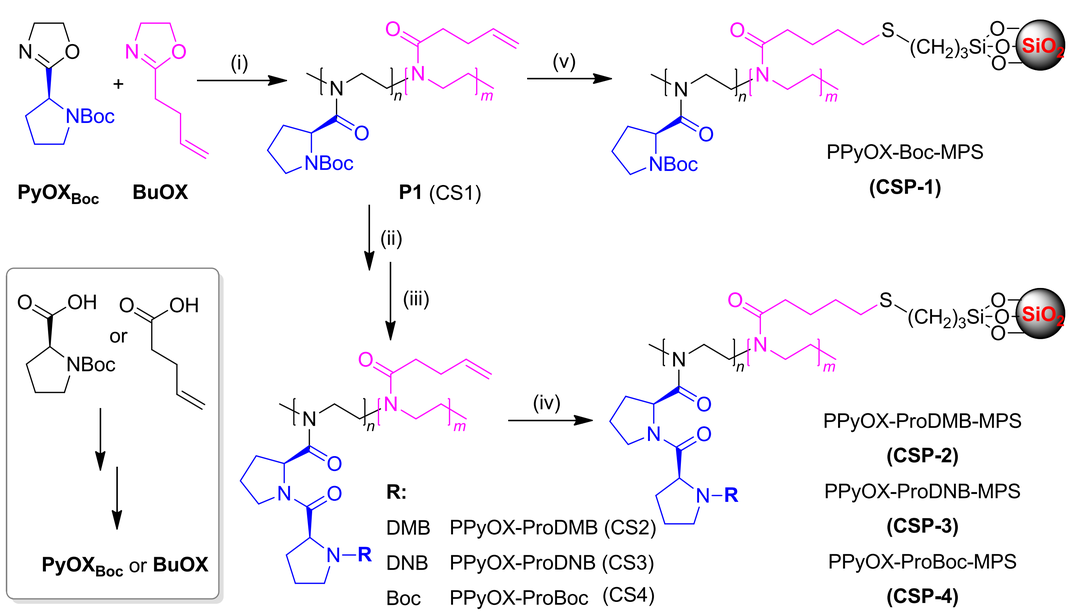
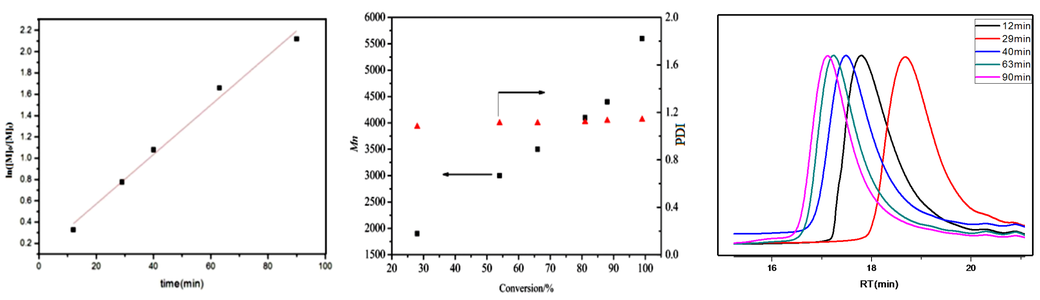
Abstract: A new kind of poly(2-oxazoline) derivatives containing dipeptide segments in the side chain was synthesized, which involves ring-opening copolymerization of $PyOX_{Boc}$ with BuOX followed by deprotection and amide coupling with *N*-protected L-proline. The resulting vinyl-functionalized polymers were subsequently immobilized onto mercaptopropylated silica bead matrices by means of thio-click chemistry and their optical resolution ability was evaluated as the chiral stationary phase (CSP) for high-performance liquid chromatography with a series of structurally different racemic compounds. These CSPs proved to be particularly adapted the separation of acyloin compounds such as benzoin as well as 1,1'-bi-2-naphthol under normal-phase conditions. Moreover, it was found that the increase in molecular weight of the polymeric selector has a beneficial to the enhancement of chromatographic performance. In some cases, analysis time could be shorten by elevating column temperature without significant loss of stereodiscriminating effects.

Synthesis and characterization



Scheme. 1 Synthesis route of the chiral stationary phases.



(a) (b) (c)

Fig. 1 (a) Kinetic plot of $PyOx_{Boc}$ polymerization initiated by $Sc(OTf)_3$ ($[M]_0/[I]_0$= 60/1) in acetonitrile ($[M]_0$= 2M) at 90℃; (b) Evolution of M_n and PDI value with monomer conversion (GPC, PMMA as the calibration, DMF as the eluent.); (c) Evolution of GPC traces with polymerization time.

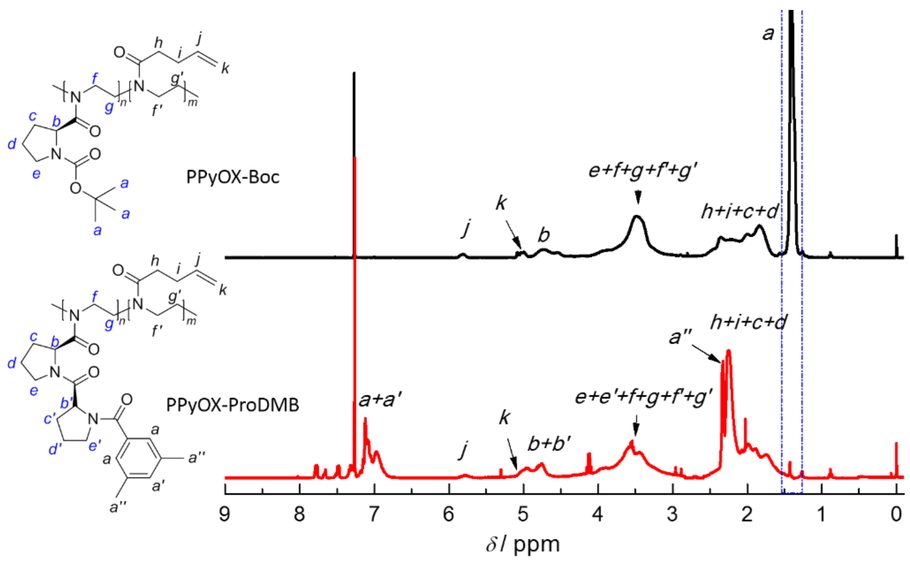


Fig. 2 ^1H NMR spectra ($CDCl_3$, 400 MHz) of PPyOX-Boc (P1; top) and its prolinamide derivative PPyOX-ProDMB (CS2).

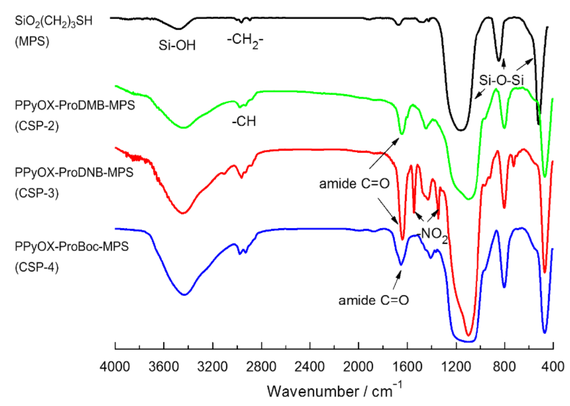


Fig.3. FT-IR spectra of 3-mercaptopropyl-silica gel (MPS), CSP-2, CSP-3, and CSP-4.

Table 1 Characterization of the prepared chiral stationary phases.

Code	CSs /M_n / mol-% of $PyOX_{Boc}$[a]	Elemental analysis			CS loading
		C (%)	H (%)	N (%)	(mmol/g)[b]
CSP-1	PPyOX-Boc (P1)/8500/98	10.57	2.330	2.05	0.73
CSP-2a	PPyOX-ProDMB/8500/98	13.63	2.279	1.91	0.45
CSP-2b	PPyOX-ProDMB/13000/95	16.63	2.793	1.90	0.46
CSP-3	PPyOX-ProDNB/8500/98	17.24	2.439	4.36	0.62
CSP-4	PPyOX-ProBoc/8500/98	10.69	1.816	1.66	0.39

[a] M_n and molar percentage of $PyOX_{Boc}$ in CSs were characterized in their precursor polymer **P1**. [b] The CS loading was expressed in the $PyOX_{Boc}$ monomeric units in the main chain.

Chromatographic performance

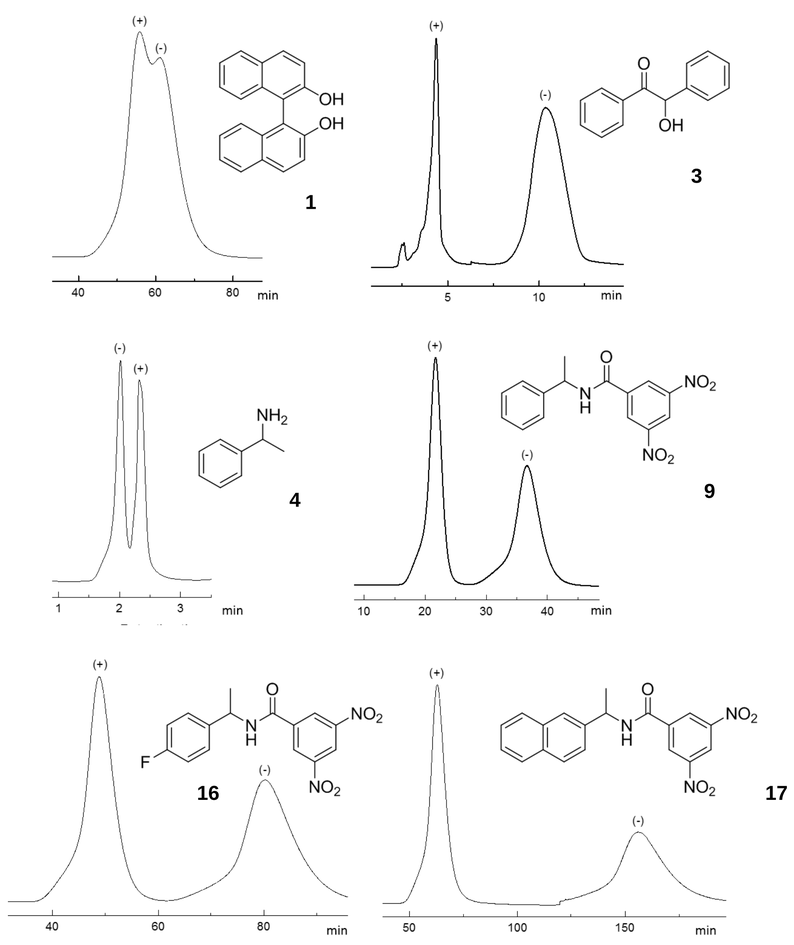


Fig. 4 Typical chromatograms on CSP-2a. Flow rate 1.0 mL/min, column temp. 23°C, UV detection at 254 nm. Analytes **1**, **3**, and **4**, *n*-hexane/2-PrOH (90:10, v/v); analyte **9**, *n*-hexane/2-PrOH (70:30, v/v); analytes **16** and **17**, *n*-hexane/2-PrOH (80:20, v/v).

Conclusions: In summary, we have prepared a class of novel poly(2-oxazoline)-linked diproline CSPs covalently bonded to silica gel and investigated their enantioseparation abilities for HPLC. The pseudopeptide CSPs proved to be particularly adapted the separation of 1,1'-bi-2-naphthol and acyloin compounds such as benzoin under normal-phase conditions, in which the chiral recognition could be achieved by a proper combination of hydrogen bond, steric hindrances, and π–π interactions. In addition, the polymer scaffold appear to play an active and synergistic role in the chiral recognition process. Although the prepared CSPs present some limitations and more work remains to be done to expand the analyte scope, this study introduces a new platform for the design of chiral separation materials.

Acknowledgement

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