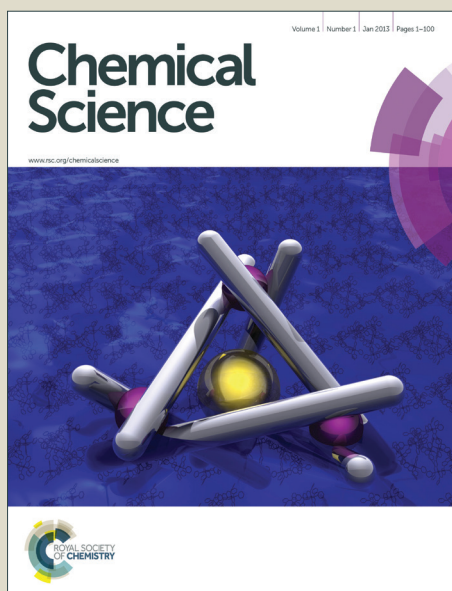


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EDGE ARTICLE

Ether Solvent-induced Chirality Inversion of Helical Poly(quinoxaline-2,3-diyl)s Containing L-Lactic Acid Derived Side Chains

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th June 2014,

Accepted 00th June 2014

DOI: 10.1039/x0xx00000x

www.rsc.org/

Poly(quinoxaline-2,3-diyl)s containing (*S*)-1-(alkoxycarbonyl)ethoxymethyl side chains derived from natural L-lactic acid were synthesized to investigate the induction of single-handed helical chirality of the main chain. In ether solvents, the handedness of the helical chirality of the polymer main chain crucially depends on the length of the alkyl chain in the lactate alkoxy groups. A polymer bearing pentyl ester groups showed an effective solvent-dependent helix inversion between 1,2-dimethoxyethane (1,2-DME, *M*-Helix) and *tert*-butyl methyl ether (MTBE, *P*-Helix). A single-handed copolymer bearing both the pentyl lactate moieties and diphenylphosphino groups was prepared to use as a chiral ligand in asymmetric Suzuki-Miyaura coupling reaction. The chirality of the ligand could be inverted by the choice of solvents (1,2-DME or MTBE) resulting in the production either *R*- or *S*-enantiomers with high enantiomeric excesses.

Helical macromolecules¹ have attracted much attention in chiral applications, mostly due to the development of promising unprecedented functions arising from their potentially single-handed helical structures. One of the most reliable strategies to induce non-racemic helical polymer backbones is the use of chiral substituents as side chains.² Since this strategy usually requires large amounts of chiral precursors, it is strategically beneficial to rely on naturally occurring chiral compounds such as amino acids, saccharides, and their metabolites, all of which are cost-effective and readily available in bulk. As most of the naturally occurring chiral compounds are available in only one of the two enantiomeric forms, it is - from a practical perspective - very important to be able to induce both helical senses (*P*- and *M*-helix) by the introduced single enantiomeric chiral side chains. The bidirectional induction of helical sense can be accomplished by a variety of external stimuli, e.g. by changing temperature,³ light,⁴ metal ions,⁵ pH,⁶ or solvent.⁷

Recently, we reported the solvent-dependent helix inversion of the single-handed screw sense of a poly(quinoxaline-2,3-diyl) with chiral side chains between closely related halogenated solvents such as CHCl₃ and 1,1,2-trichloroethane.⁸ We also reported that a single-handed helically chiral poly(quinoxaline-2,3-diyl) with diarylphosphino pendants⁹ could be used as a highly effective chiral ligand.¹⁰ This polymer-based helically chiral ligands exhibited a solvent-dependent switch of helical chirality, which enabled the highly enantioselective production of both enantiomers from a single

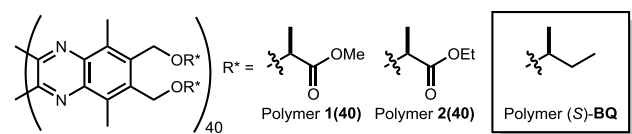
chiral catalyst.¹¹ On the other hand, the need for halogenated solvents is somewhat impedimental for the general applicability of these chiral ligands. To extend the scope of asymmetric reactions, in which these solvent-dependent chirality-switching ligands could be employed, it is desirable to develop poly(quinoxaline-2,3-diyl)s that exhibit these solvent-dependent chirality inversions in other organic solvents, which are typically used in transition metal-catalyzed reactions.

We herein demonstrate an induced switch of chirality in the polymer main chain by introducing chiral side chains based on L-lactic acid. The screw sense of these polymers was found to be crucially dependent on the alkoxy groups of the L-lactate moieties and we eventually developed a single-handed poly(quinoxaline-2,3-diyl) that performed a perfect switch of helical chirality between two ether solvents. In order to prove the effectiveness of this type of polymeric ligands with switchable chirality, a representative asymmetric reaction was carried out.

Firstly, polymers **1(40)** and **2(40)** with a degree of polymerization (*DP*) of 40, containing L-lactic acid-based methyl and ethyl esters in the side chains were synthesized by living polymerization of 1,2-diisocyanobenzenes,¹² and their circular dichroism (CD) and UV-vis absorption spectra were measured in various solvents (Table 1). The CD intensity was evaluated via Kuhn's dissymmetry factor g_{abs} , which is defined as the CD intensity normalized by the UV-vis absorbance ($\Delta\epsilon/\epsilon$). According to previous reports,^{12c} *P*- and *M*-helical

poly(quinoxaline-2,3-diyl)s show around 360 nm positive or negative g_{abs} values, respectively.^{12c} Polymer **1(40)** with methyl ester groups in side chains adopted an *M*-helical structure in CHCl_3 , CH_2Cl_2 , 1,1,2-TCE, toluene, and most ether solvents such as tetrahydrofuran (THF), 1,2-dioxane, and 1,2-dimethoxyethane (1,2-DME). However, a solvent-dependent helix inversion to a *P*-helical structure was observed for **1(40)** in diethylether (Et_2O) and *tert*-butyl methyl ether (MTBE). Polymer **2(40)** with ethyl ester groups also showed a helix inversion in these ether solvents, although its solvent dependency was significantly different from **1(40)**. Polymer **2(40)** adopts an *M*-helical backbone in THF and inverted the screw sense to a *P*-helix in the other ether solvents (1,4-dioxane, 1,2-DME, Et_2O , and MTBE). This result is even more interesting considering that previously reported polymer (*S*)-**BQ**,⁸ which adopts an *M*-helical backbone in CHCl_3 and a *P*-helical backbone in 1,1,2-TCE, did not exhibit any solvent-dependent helix inversion in these ether solvent (see SI).

Table 1 Structures and screw-sense induction properties of **1(40)** and **2(40)** in various solvents. The structure of (*S*)-**BQ** is shown for comparison.



Solvent	$g_{\text{abs}} / 10^{-3} \text{ }^a$	
	1(40)	2(40)
CHCl_3	-2.28 (<i>M</i>)	-2.38 (<i>M</i>)
CH_2Cl_2	-2.01 (<i>M</i>)	-2.04 (<i>M</i>)
1,1,2-TCE	-2.64 (<i>M</i>)	-2.70 (<i>M</i>)
Toluene	-1.73 (<i>M</i>)	-0.58 (<i>M</i>)
THF	-1.49 (<i>M</i>)	-0.18 (<i>M</i>)
1,4-Dioxane	-1.64 (<i>M</i>)	+0.48 (<i>P</i>)
1,2-DME	-0.17 (<i>M</i>)	+1.29 (<i>P</i>)
Et_2O	+1.38 (<i>P</i>)	+1.96 (<i>P</i>)
MTBE	+1.54 (<i>P</i>)	+1.98 (<i>P</i>)

^a Kuhn's dissymmetry factor g_{abs} at 363.5 nm.

We subsequently examined the effect of the length of the alkyl chains in the ester moieties of the side chains in various solvents. For that purpose, a series of polymers **1(40)**–**10(40)** ($DP = 40$), containing a variety of alkyl esters ($-(\text{CH}_2)_{x-1}\text{CH}_3$, $x = 1$ – 10) were prepared and their CD spectra measured (Figure 1). All polymers adopted *M*-helical structures in both CHCl_3 and 1,1,2-TCE, and a helical inversion could not be observed. However, in ether solvents, the g_{abs} values crucially depended on the length of alkyl chains and showed a clear odd-even effect in the region of $x = 1$ – 5 , i.e. methyl to pentyl esters. For higher alkyl groups ($x \geq 6$), no such odd-even effect was observed anymore, but in THF, 1,4-dioxane, 2-methyltetrahydrofuran (2-MeTHF) and 1,2-DME, the *M*-helical structure was generally preferred, regardless of the length of alkyl chains ($x \geq 6$). On the other hand, the use of Et_2O and cyclopentyl methyl ether (CPME) induced a switch of the screw-sense from *M* to *P* following the elongation of the alkyl chain. Furthermore, the use of MTBE generally induced a

P-helical structure. This solvent-dependent helical induction was most clearly observed with a pentyl ester ($x = 5$) in the side chain of **5(40)**: the use of either MTBE or 1,2-DME highly selectively induced *P*- or *M*-helical structures, respectively.

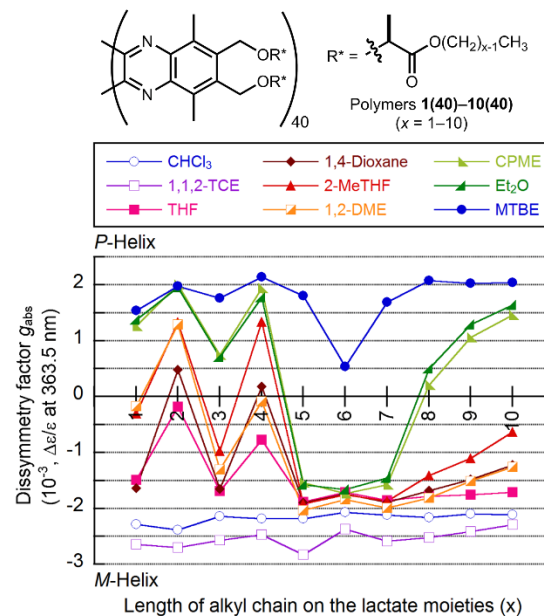


Fig. 1 (a) Correlation between the length of alkyl side chains x and the g_{abs} values of polymers **1(40)**–**10(40)** ($x = 1$ – 10) in different solvents.

We synthesized a series of polymers **5(20)**–**5(300)** ($DP = 20$ – 300) containing pentyl lactate side chains in order to measure their CD spectra in MTBE and 1,2-DME. In accordance with Green's theory,¹³ these polymers exhibited a non-linear relationship between g_{abs} values and DP . The gained energy differences between the *P*- and *M*-helices per chiral repeat unit (ΔG_{h}) were determined to be 0.12 kJ/mol (MTBE) and 0.13 kJ/mol (1,2-DME). On the basis of the calculated values, the correlation between screw-sense excess (se) and DP are plotted (Figure 2). Increased levels of se were observed for polymers with higher molecular weight: the se for polymers with $DP = 40$, 100, and 200 were found to be 72, 94, and >99% (MTBE) or 82, 97, and >99% (1,2-DME) as estimated from their g_{abs} values.

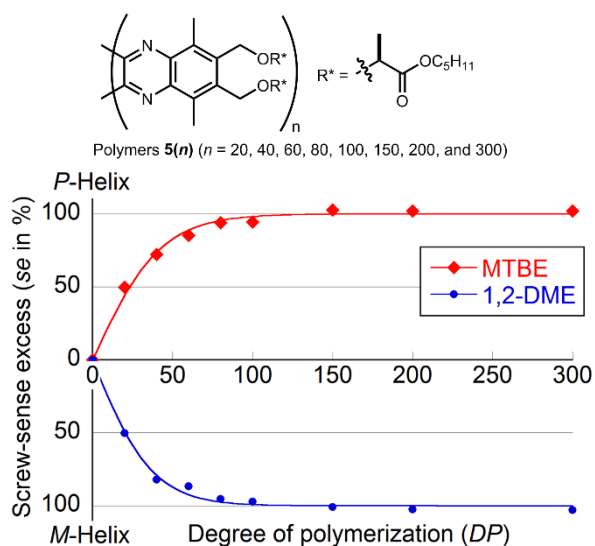
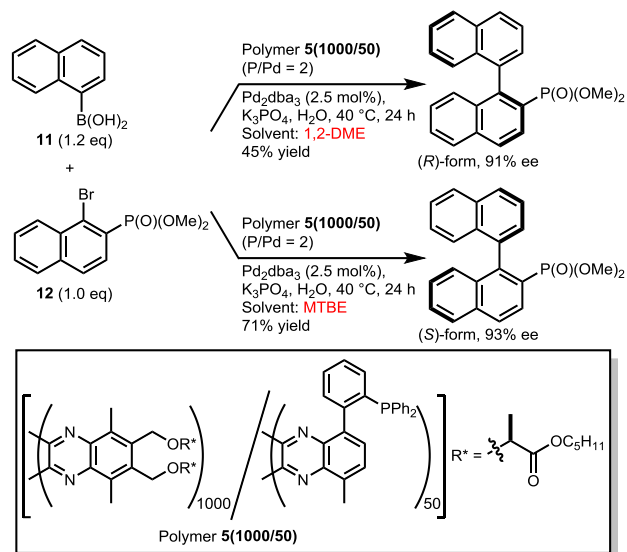


Fig. 2 Correlations between the degree of polymerization (DP), i.e. the number of chiral repeat units and the screw-sense excess (se) of **5**(*n*) (*n* = 20–300) in MTBE and 1,2-DME.

Finally, we tried to demonstrate the utility of these solvent-induced helical chirality switches between *P*- and *M*-helices of poly(quinoxaline-2,3-diyl)s with pentyl lactates in asymmetric catalysis using either 1,2-DME or MTBE. In general, ether solvents are widely used in transition metal-catalyzed reactions including the Suzuki-Miyaura coupling (SMC) reaction.¹⁴ In our previous paper,^{11b} a polymer ligand bearing (*R*)-2-butoxy side chains and 2-[bis(2-naphthyl)phosphino]phenyl pendants was used in asymmetric SMC for the enantioselective synthesis of axially chiral biaryls.¹⁵ We were able to successfully demonstrate the synthesis of both enantiomeric products with high enantioselectivities using THF or 1,1,2-TCE as solvents inducing either *P*- or *M*-helical catalysts, respectively. Although switching the catalyst chirality worked effectively, the need for halogenated solvents was hardly desirable in these palladium-catalyzed reactions. Therefore, we prepared random copolymer **5**(**1000/50**) bearing lactic acid groups with pentyl esters and diphenylphosphino pendants as a chiral polymeric ligands for the asymmetric SMC between **11** and **12** (Scheme 1). Initially, the reaction was carried out in 1,2-DME, inducing an *M*-helical polymer backbone and resulting in the formation of the (*R*)-product in high enantiomeric excess (91% ee), which is comparable to previously reported results in THF.^{11b} When the same reaction was carried out in MTBE, the (*S*)-product was obtained in with higher enantioselectivity (93% ee) than that in the previous system. This result demonstrates that almost absolute *P*- or *M*-helical structures of **5**(**1000/50**) were induced in either 1,2-DME or MTBE, corroborating our estimates from the CD measurements.



Scheme 1 Asymmetric Suzuki-Miyaura cross-coupling reaction in 1,2-DME or MTBE using polymer **5**(**1000/50**) as a chiral ligand.

Conclusions

In summary, we have described the induction of single-handed helical chirality of the main chain of poly(quinoxaline-2,3-diyl) containing *L*-lactic acid-derived side chains. In ether solvents, the handedness of the helical chirality of the polymer main chain crucially depends on the length of the alkyl chain in the lactate moieties of the side chains. A polymer with pentyl ester groups exhibited an effective solvent-dependent helix inversion between 1,2-DME (*M*-helix) and MTBE (*P*-helix). We also prepared a copolymer bearing both pentyl ester groups and diphenylphosphino groups as a chiral polymeric ligand for asymmetric SMC reactions. Both enantiomeric product forms could be obtained in high enantiomeric excess using 1,2-DME (91% ee, (*R*)-form) and MTBE (93% ee, (*S*)-form) as solvents. Although each chiral unit gained just a very small energy difference between *P*- and *M*-helix, its accumulation in the rigid helical backbones enabled to cause a macroscopic helix inversion. At this moment the smallness of the energy difference makes it difficult to clarify the origin of the solvent effect for instance by calculation. Further investigations into catalytic applications of these single-handed helical poly(quinoxaline-2,3-diyl)s as a new class of chiral supporting ligands exhibiting highly selective solvent-dependent helix inversions are currently being undertaken in this laboratory.

Acknowledgements

Financial support for this research was provided by the Japan Science and Technology Corporation (CREST, “Development of High-performance Nanostructures for Process Integration” Area).

Notes and references

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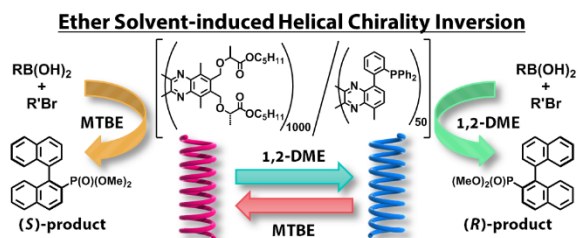
^b CREST, Japan Science and Technology Agency (JST), Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

† Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data for the new compounds. See DOI: 10.1039/c000000x/

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Helical poly(quinoxaline-2,3-diyl) bearing PPh_2 pendants along with chiral side chains derived from L-lactic acid exhibited induction of single-handed M - and P -helical conformations in 1,2-dimethoxyethane and *tert*-butyl methyl ether, respectively, affording enantiomeric coupling products with high enantioselectivities in asymmetric Suzuki-Miyaura reaction.