Chiral Polymer Catalysts

Deutsche Ausgabe: DOI: 10.1002/ange.201502209
Internationale Ausgabe: DOI: 10.1002/anie.201502209

Majority-Rules-Type Helical Poly(quinoxaline-2,3-diyl)s as Highly Efficient Chirality-Amplification Systems for Asymmetric Catalysis**

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Abstract: *A highly efficient majority-rules effect of poly(quinoxaline-2,3-diyl)s (PQXs) bearing 2-butoxymethyl chiral side chains at the 6- and 7-positions was established and attributed to large ΔG_h values (0.22–0.41 kJ mol^{-1}), which are defined as the energy difference between P- and M-helical conformations per chiral unit. A PQX copolymer prepared from a monomer derived from (R)-2-octanol (23 % ee) and a monomer bearing a PPh_2 group adopted a single-handed helical structure (> 99 %) and could be used as a highly enantioselective chiral ligand in palladium-catalyzed asymmetric reactions (products formed with up to 94 % ee), in which the enantioselectivity could be switched by solvent-dependent inversion of the helical PQX backbone.*

Helical majority-rules-type polymers,[1,2] which are derived from chiral monomers with low *ee* values and adopt nonlinearly enhanced single-handed helical conformations, are among the most promising platforms for the development of new asymmetric-amplification systems.[3] The concept of the enantioselective synthesis of chiral compounds through asymmetric amplification[4] has attracted considerable interest, as it may afford useful model systems for the elucidation of the origin of natural homochirality[5] as well as practical methods for the generation of optically active molecules.[6] Although a number of helical polymers[7] with efficient asymmetric amplification in terms of helix-sense induction have been developed, the highly enantioselective production of chiral compounds on the basis of asymmetric amplification by majority-rules-type helical polymers has not been reported. According to the theory developed by Green and co-workers for polymers containing helix-sense-reversal conformations (Green theory, case 3),[8] the maximum value of the screw-sense excess (*se*) of a helical polymer, whose degree of polymerization (DP) is sufficiently large, is limited by ΔG_h (the energy difference between *P*- and *M*-helical conformations) and ΔG_r (the energy difference of the helix-sense-reversal conformation relative to the helical conformation). For most helical polymers, the ΔG_h and/or ΔG_r values are too small to induce a purely single handed screw sense. A cis–transoidal poly(aryl acetylene) bearing (*R*)-(1-phenylethyl)-carbamate side chains ($\Delta G_\mathrm{h} = 0.0048$ kJ mol^{-1}, $\Delta G_\mathrm{r} = 15.5$ kJ mol^{-1}), for example, exhibits even at very high degrees of polymerization merely 49.5 % *se* at room temperature.[9] For the enantioselective generation of chiral compounds from a majority-rules-type helical polymer, the use of a polymer backbone exhibiting large ΔG_h and ΔG_r values is therefore of critical importance.

Recently, we reported sergeants-and-soldiers-type[10] poly(quinoxaline-2,3-diyl)s (PQXs) containing (*R*)-2-butoxymethyl and propoxymethyl groups in a random manner.[11] A ΔG_h value of 0.59 kJ mol^{-1} was estimated for the chiral unit of this polymer system, thus indicating that 22 chiral units are required for a screw-sense induction of 99.0 % *se*. We have also reported that single-handed helically chiral PQXs with pendent diarylphosphanyl groups[12] can serve as effective chiral ligands for various asymmetric reactions.[13] However, the controlled screw-sense induction of majority-rules-type PQXs, prepared from monomers with low *ee* values, still remains to be fully explored.

We herein demonstrate efficient asymmetric screw-sense amplification in majority-rules-type PQXs prepared from starting materials with low *ee* values. In contrast to reported majority-rules-type polymers, which bear only one chiral group, the chiral units of the PQXs discussed herein contain two chiral side chains. Accordingly, two different types of majority-rules-type PQXs are discussed separately: 1) PQXs consisting of two enantiomeric monomer units in various ratios, and 2) PQXs that also contain *meso* units. Quantification of the ΔG_h and ΔG_r values by circular dichroism (CD) measurements suggested that they should be sufficient to induce a purely single-handed helical structure. Finally, we carried out asymmetric reactions in the presence of majority-rules-type PQXs with PPh_2 pendant groups as chiral ligands to prove the concept of asymmetric amplification based on majority-rules-type helical polymers.

We obtained chiral monomers with varying *ee* values by preparing the enantiomeric diisocyanobenzenes (*R*,*R*)-**1** and (*S*,*S*)-**1** separately and then mixing them in various ratios (Scheme 1). To investigate the influence of the DP on the screw-sense induction, we first polymerized a 55:45 mixture of (*R*,*R*)-**1** and (*S*,*S*)-**1** (10 % *ee*), which resulted in the formation of oligo- and polymeric PQXs (DP: 40–1000; Figure 1). These polymers exhibited a nonlinear relationship between their DPs and their Kuhn dissymmetry factors (g_abs), that is, they

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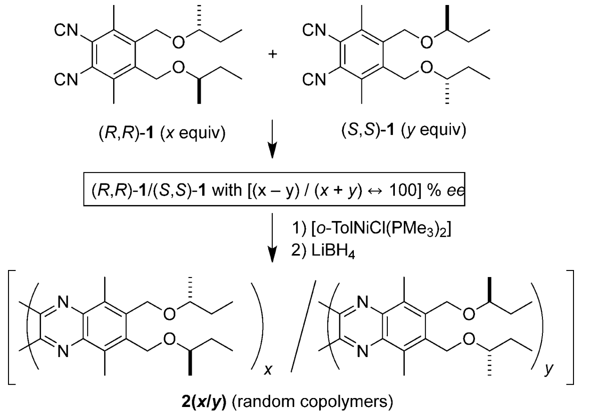
[**] Financial support for this research was provided by the Japan Science and Technology Corporation (CREST, “Development of High-Performance Nanostructures for Process Integration” and “Establishment of Molecular Technology towards the Creation of New Function”).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201502209.



Scheme 1. Synthesis of random copolymers **2(*x*/*y*)** from chiral monomers (*R*,*R*)-**1** and (*S*,*S*)-**1** with varying *ee* values.

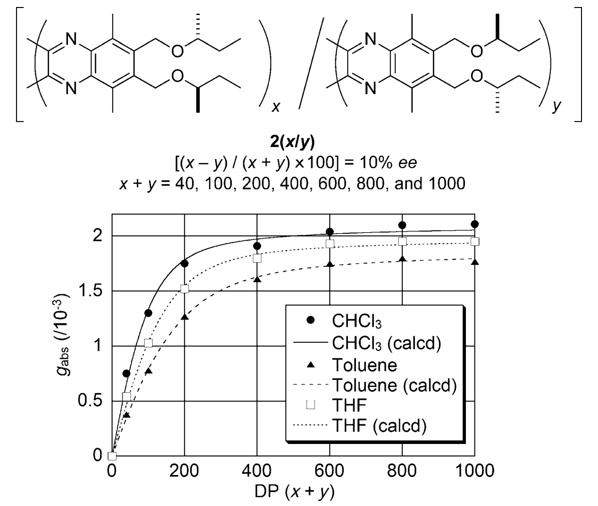


Figure 1. Correlation between the DP and g_{abs} values ($\Delta\varepsilon/\varepsilon$ at 362.5 nm) of **2(*x*/*y*)** prepared from monomers with 10% *ee* in $CHCl_3$, toluene, or THF.

Table 1: Calculated ΔG_h, ΔG_r, and g_{max} values for **2(*x*/*y*)** (DP: 40–1000).

Solvent	ΔG_h [kJ mol^{-1}]	ΔG_r [kJ mol^{-1}]	g_{max} [$\times 10^{-3}$]
$CHCl_3$	−0.41	13.4	+2.37
toluene	−0.22	14.9	+2.14
THF	−0.30	14.4	+2.24

did not obey the Green theory for polymers without helix-reversal conformations (Green theory, case 1).[8] Although we previously reported that the helix-sense-reversal conformation in the polymer chain of PQXs is negligible for low molecular weights (DP < 200; see also the Supporting Information),[11b] these results nevertheless suggested that it is necessary to take the helix reversal into account for a quantitative understanding of high-molecular-weight PQXs containing chiral units with low *ee* values. Therefore, the observed g_{abs} values were fitted by using the general theory proposed by Green and co-workers for polymers containing helix-reversal conformations (Green theory, case 3).[8] Accordingly, nonlinear least-square fittings of g_{abs} versus DP were carried out, and the square sums of the deviations were minimized by variation of the three parameters ΔG_h, g_{max}, and ΔG_r.

For DP > 200, the g_{abs} values were found to converge (final values for the three different solvents are given in Table 1). The observed ΔG_h values (0.22–0.41 kJ mol^{-1}) were almost identical to those of previously reported PQXs (0.24–0.59 kJ mol^{-1})[11] and significantly larger than those of other helical polymers, such as polyacetylenes, polyisocyanates, and polysilanes (0.005–0.06 kJ mol^{-1}).[2e] The ΔG_r values (13.4–14.9 kJ mol^{-1}) for **2(*x*/*y*)** were found to be comparable with those of previously reported helical polymers (7–17 kJ mol^{-1}).[2e] The large ΔG_h values of PQXs played a central role in the highly efficient control of the screw sense of their helical main chains. Nevertheless, the values in Table 1 and Figure 1 also suggest that the use of monomers with 10% *ee* is insufficient for the induction of absolute screw senses, even for polymers with a DP of 1000.

Subsequently, polymers **2(*x*/*y*)** with a DP of 1000 were prepared from chiral monomers with varying *ee* values (Figure 2a). These polymers also showed a nonlinear relationship between their g_{abs} value and the *ee* value of the monomer. Regression curves were calculated in accordance with the Green general theory (case 3),[8] in which the reversal conformation is considered with the determined values of ΔG_h, ΔG_r, and g_{max}. Good agreement was observed between the experimentally obtained g_{abs} values and the calculated

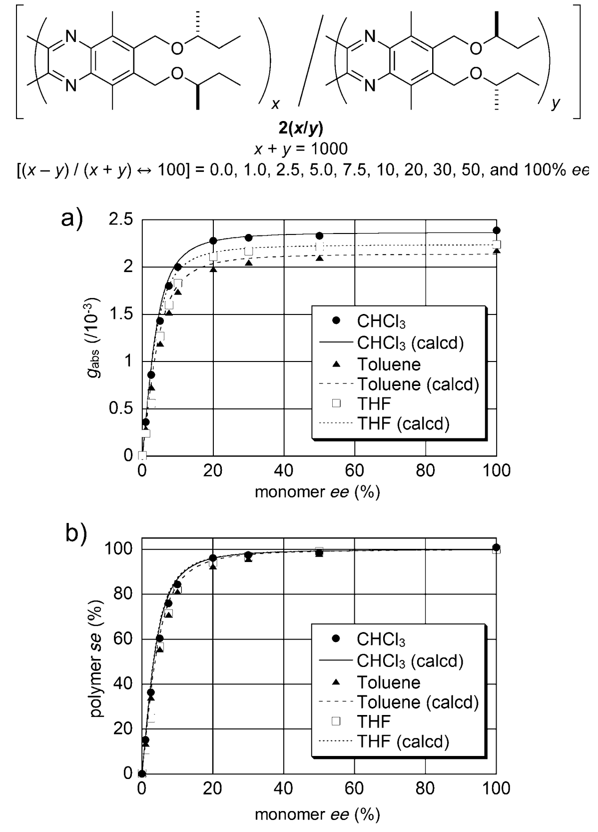
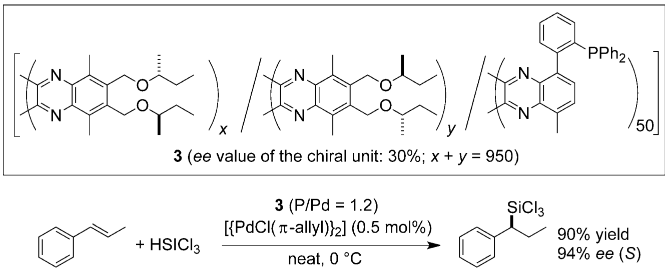


Figure 2. Correlation between the monomer *ee* value and the a) g_{abs} ($\Delta\varepsilon/\varepsilon$ at 362.5 nm) or b) *se* value of **2(*x*/*y*)** (DP: 1000) in $CHCl_3$, THF, or toluene.

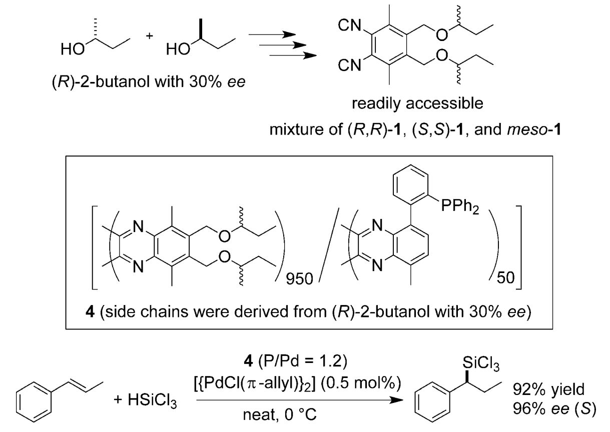
curves, thus suggesting that the obtained values should be representative for these PQX polymers. On the basis of the calculated values, a correlation between the *se* value of the polymer backbone and the *ee* value of the monomer was established (Figure 2b). The majority-rules effect was clearly observable, and in the examined solvents, monomers with 30% *ee* were able to induce >97% *se* in the polymer backbone.

Subsequently, we attempted to apply this substantial majority-rules effect in asymmetric catalysis. For that purpose, polymer **3**, bearing pendent PPh_2 groups, was synthesized from the corresponding chiral monomer **1** with 30% *ee*. According to its CD spectrum, polymer ligand **3** exhibited an almost absolute *P*-helical conformation (see the Supporting Information). When **3** was used as a ligand in the palladium-catalyzed asymmetric hydrosilylation of β-methylstyrene with trichlorosilane, the corresponding product was obtained with 94% *ee*, thus reflecting the almost exclusive single-handedness of the helical main chain as induced by the chiral monomers with 30% *ee*. (Scheme 2).[14]



Scheme 2. Asymmetric hydrosilylation of β-methylstyrene in the presence of polymer ligand **3** prepared from a chiral monomer (30% *ee*) and a monomer bearing a PPh_2 group.

To prevent the formation of *meso*-**1** during the preparation of **3**, we synthesized optically pure (*R*,*R*)-**1** and (*S*,*S*)-**1** separately and then mixed them. To increase the practicality of this system, we prepared monomers with 30% *ee* from (*R*)-2-butanol. Monomers consisted of (*R*,*R*)-**1**, (*S*,*S*)-**1**, and *meso*-**1** in a 43.3 : 13.3 : 43.4 ratio (see the Supporting Information). According to the Green theory,[8] the *se* value of a helical polymer is determined from the difference between the numbers of repeating units derived from *d* and *l* monomers in the polymer chain. Although enantiomeric enrichment of *d*,*l* monomers ((*R*,*R*)-**1** and (*S*,*S*)-**1**; 53% *ee*) occurs, the difference between the numbers of repeating units derived from *d* and *l* monomers in a polymer prepared from (*R*,*R*)-**1**, (*S*,*S*)-**1**, and *meso*-**1** is equal to that of a polymer prepared from (*R*,*R*)-**1** and (*S*,*S*)-**1** (30% *ee*) as long as their DPs are identical, owing to the inclusion of *meso* isomers. Therefore, the screw-sense induction in polymers obtained from a ternary monomer mixture including the *meso* isomer is expected to be identical to that in polymers obtained from a corresponding binary monomer mixture consisting of (*R*,*R*)-**1** and (*S*,*S*)-**1** (30% *ee*). Indeed, polymer **4**, obtained from such a ternary monomer mixture, exhibited an absolute *P*-helical single-handed screw sense (Scheme 3). Polymer **4** can be regarded both as a majority-rules-type polymer, as well as a sergeants-and-soldiers-type polymer, whereby the *meso*-**1** units act as the soldiers. In the asymmetric hydrosilylation, **4** generated the corresponding product with high enantioselectivity (96% *ee*), which indicates that the *meso* units behaved as normal soldier units in the sergeants-and-soldiers-type screw-sense induction and did not affect the enantioselectivity of the catalysis.

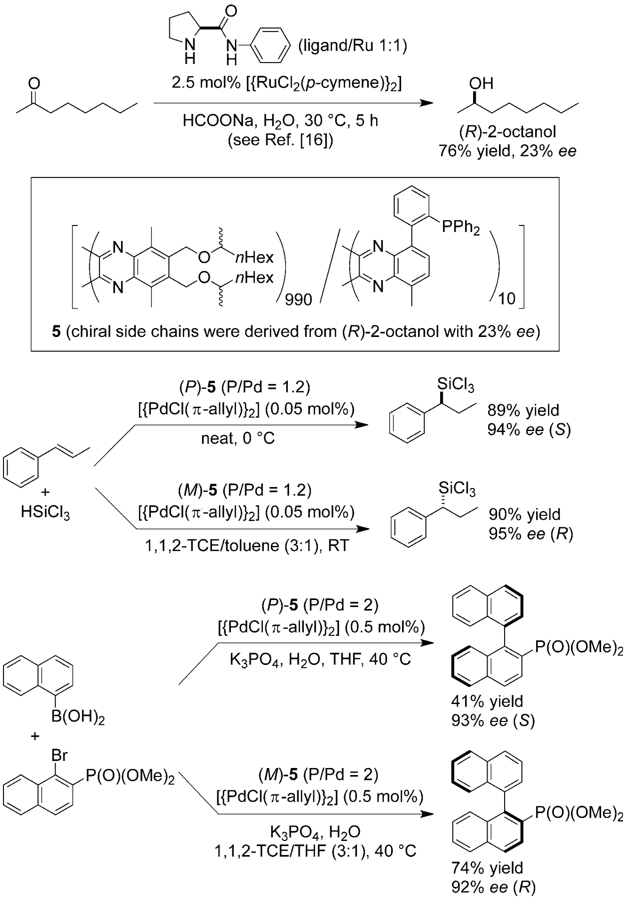


Scheme 3. Asymmetric hydrosilylation of β-methylstyrene in the presence of polymer ligand **3** derived from (*R*)-2-butanol with 30% *ee*.

Subsequently, we demonstrated the synthesis of single-handed polymer ligands by using an optically active secondary alcohol with a low *ee* value. This alcohol was obtained by ruthenium-catalyzed asymmetric hydrogenation in the presence of an inexpensive chiral ligand based on L-proline.[15] Thus, 2-octanol was obtained with 23% *ee* from the hydrogenation of 2-octanone (Scheme 4). This optically active alcohol enabled the synthesis of the corresponding optically active monomer in a ratio of 38.8 : 15.8 : 45.4 with respect to *d*, *l*, and *meso* isomers (see the Supporting Information). Polymerization of this mixture of stereoisomers with the corresponding phosphorous-containing monomer provided copolymer **5**. CD measurements revealed a purely right handed helical structure for this polymer ligand, (*P*)-**5**, which afforded the *S* product with 94% *ee* when used in the palladium-catalyzed asymmetric hydrosilylation.

Most importantly, the helical sense of the PQXs bearing optically active 2-butoxymethyl side chains was found to be chirality-switchable:[13a–d] The corresponding exclusively left handed helical polymer ligand (*M*)-**5** was obtained when a solution of (*P*)-**5** in 1,1,2-TCE/toluene (3:1 v/v) was heated at 60 °C for 24 h. The left-handed-helical polymer (*M*)-**5** was then used as a ligand in the asymmetric hydrosilylation, and under similar conditions, the *R* product was obtained with high enantioselectivity (95% *ee*). This result demonstrates that the treatment of (*P*)-**5** in 1,1,2-TCE/toluene induced an almost absolute *M*-helical conformation in **5**.

To prove the general viability of this asymmetric-amplification system, we also carried out an asymmetric Suzuki–Miyaura coupling reaction[16] in the presence of (*P*)-**5**. The reaction afforded the axially chiral *S* product with high enantioselectivity (93% *ee*). When (*M*)-**5** with inverted helical chirality was used, the corresponding *R* product was obtained with high enantioselectivity (92% *ee*; Scheme 4).



Scheme 4. Asymmetric hydrosilylation of β-methylstyrene and asymmetric Suzuki–Miyaura cross-coupling in the presence of polymeric ligand **5** prepared from (*R*)-2-octanol with 23% *ee*. 1,1,2-TCE = 1,1,2-trichloroethane.

These results again demonstrate that the low enantiomeric purity of 2-octanol was amplified by the formation of a single-handed screw sense and multiplied through the generation of enantiomerically pure products in the asymmetric reactions. Furthermore, the highly enantioselective generation of both enantiomers from a single chiral source with low *ee* values was possible by taking advantage of the solvent-dependent helix inversion of PQXs.

In summary, we have described screw-sense induction in the helical main chain of majority-rules-type poly(quinoxaline-2,3-diyl)s derived from starting materials with low *ee* values. A copolymer bearing pendent PPh_2 groups and chiral side chains derived from (*R*)-2-octanol with a low *ee* value adopted a purely single handed helical structure, thus affording high enantioselectivities in asymmetric palladium-catalyzed hydrosilylation and Suzuki–Miyaura cross-coupling reactions. From these reactions, both enantiomeric products were obtained with high enantioselectivity through solvent-dependent inversion of the helical sense in the same polymer catalyst. To the best of our knowledge, the highly enantioselective generation of both enantiomers of a catalyst from a single chiral source with a low *ee* value has not been reported previously. It was made possible by the asymmetric amplification of majority-rules-type helical polymers. This outstanding molecular function of PQXs relies on their extremely large intrinsic ΔG_h values. We are currently carrying out further investigations into catalytic applications of these single-handed-helical PQXs as a new class of chiral supporting ligands characterized by highly efficient asymmetric amplification and multiplication.

Keywords: asymmetric amplification · asymmetric synthesis · helical structures · ligand design · polymer catalysts

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9333–9337
Angew. Chem. **2015**, *127*, 9465–9469

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Received: March 9, 2015
Revised: April 25, 2015