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To be cited as: *ChemCatChem* 10.1002/cctc.201601220

Link to VoR: http://dx.doi.org/10.1002/cctc.201601220

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Synthesis of chiral polyamides containing a (*R*,*R*)-1,2-diphenylethylenediamine monosulfonamide structure and their application to asymmetric transfer hydrogenation catalysis

Shinichi Itsuno,*[a] and Shotaro Takahashi[a]

Abstract: A chiral main-chain polyamide containing a (*R*,*R*)-1,2-diphenylethylenediamine monotoluenesulfonamide (TsDPEN) repeat unit was prepared. Polycondensation of dicarboxylic acid dichloride with the chiral bisaniline of *N*-Boc-protected TsDPEN was successful, affording a chiral polyamide with TsDPEN repeat unit as the chiral ligand structure. Treatment of the main-chain polymer chiral ligand with transition metal complexes, such as $[IrCl_2Cp^*]_2$, $[RhCl_2Cp^*]_2$, and $[RuCl_2(p\text{-cymene})]_2$, afforded polymer chiral metal complexes. Asymmetric transfer hydrogenation of a cyclic sulfonamide was efficiently catalyzed by the chiral TsDPEN polymer–metal complex, giving an optically active cyclic sulfonylamine in quantitative conversion with high enantioselectivities. The polymer catalyst was easily recovered from the reaction mixture and reused several times without any loss in catalytic activity and enantioselectivity.

Chiral synthetic polymers have attracted much attention due to their unique properties, such as chiroptical properties, and their applications, including asymmetric catalysis[1] and chiral separation chemistry.[2,3] In asymmetric catalysis, the immobilization of chiral catalysts onto solids, such as crosslinked polystyrene[4,5] and silica,[6] has been frequently used to prepare recoverable heterogeneous catalysts for asymmetric synthesis. In addition to their easy recoverability and reusability, polymer chains can provide specific chiral catalyst conformations in their microenvironment, which sometimes increase the reactivity and stereoselectivity in asymmetric reactions.[7] More precise control of the microenvironment might be possible with chiral polymers containing chiral catalyst sites in their main chain structure, instead of side chain immobilization. Recently, some main-chain chiral polymers have been synthesized and used as polymeric chiral ligands or catalysts.[8,9]

Asymmetric transfer hydrogenation is a promising method for the generation of chiral alcohols and amines. TsDPEN–transition metal complexes as asymmetric transfer hydrogenation catalysts, first discovered by Ikariya and Noyori in 1995, are some of the most powerful catalysts for the asymmetric reduction of C=O[10] and C=N.[11] Polymer-supported[12] and silica-supported variants[13] of TsDPEN have been developed, some of which showed high levels of catalytic activity and enantioselectivity. We have also developed crosslinked polymer-immobilized TsDPENs, which were complexed with $[IrCl_2Cp^*]$ to give polymeric chiral catalysts.[14] Polymeric chiral ligands prepared from TsDPEN monomer and amphiphilic achiral monomers, followed by complexation with transition metals, showed high catalytic activity in asymmetric transfer hydrogenation.[12d,15] Interestingly, chiral main-chain polymers containing TsDPEN ligands as repeat units have not been synthesized. The introduction of a functional group onto TsDPEN phenyl group is necessary for this purpose. We previously synthesized (*R*,*R*)-*N*,*N*'-di(*tert*-butoxycarbonyl)-1,2-bis(*p*-hydroxyphenyl)-1,2-diaminoethane (dihydroxy DPEN), followed by the introduction of 4-vinylbenzyl ether, which was then polymerized under radical polymerization conditions to obtain polymeric chiral (*R*,*R*)-1,2-diphenylethylenediamine (DPEN) ligands.[16] This chiral polymer was successfully used as a chiral ligand in ketone-hydrogenation catalysts. However, the synthesis of dihydroxy DPEN is tedious and low yielding, requiring optical resolution of racemic dihydroxy DPEN after separation of the meso compound. We also attempted the direct introduction of functionality onto the phenyl ring of chiral DPEN, which is commercially available, but all attempts at phenyl ring halogenation failed.[17] We then decided to introduce amino groups on both phenyl groups in TsDPEN. Nitration followed by reduction successfully yielded a bisamino-DPEN derivative. Using these aromatic amino functionalities, polycondensation with diacid dichloride has been investigated. This is the first example of the synthesis of main-chain TsDPEN polymers. The chiral polyamides containing a TsDPEN repeat unit in their main chain were subsequently investigated as polymer ligands for catalysts of the asymmetric transfer hydrogenation of cyclic sulfonimines.

The first step of chiral TsDPEN monomer synthesis was the introduction of nitro groups onto the phenyl rings of DPEN. Conventional nitration of the phenyl rings of DPEN proceeded smoothly to afford bis(*m*-nitrophenyl)-1,2-diaminoethane **1**, as shown in Scheme 1.[18] Sulfonamide formation was then conducted at one of the amino groups in **1**, giving **2** (Scheme 2). Another amino group in **2** was then Boc-protected to afford **3**. The nitro groups in **3** were then hydrogenated to amines, giving chiral bisaniline **4**, which was the monomer for polymerization.

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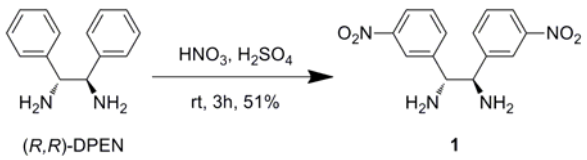
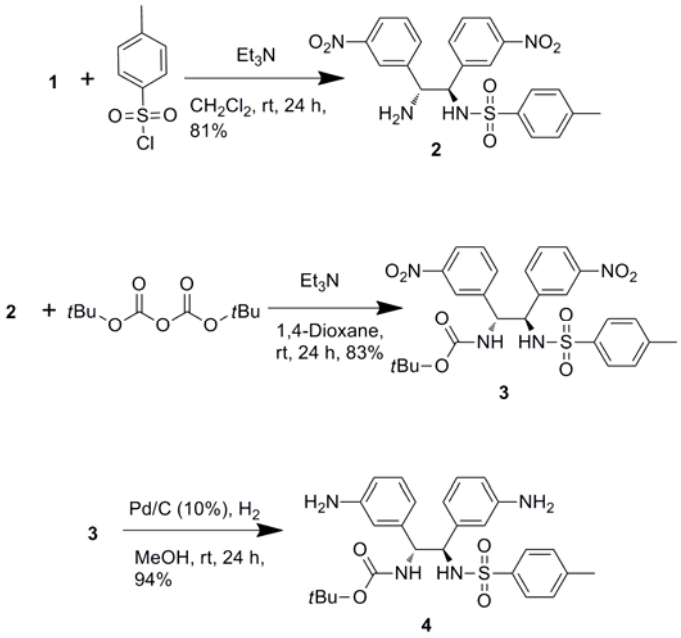
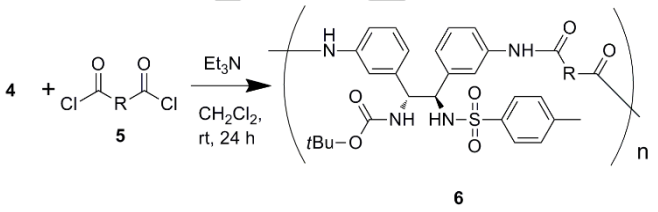


Scheme 1. Synthesis of bis(*m*-nitrophenyl)-1,2-diaminoethane **1**.

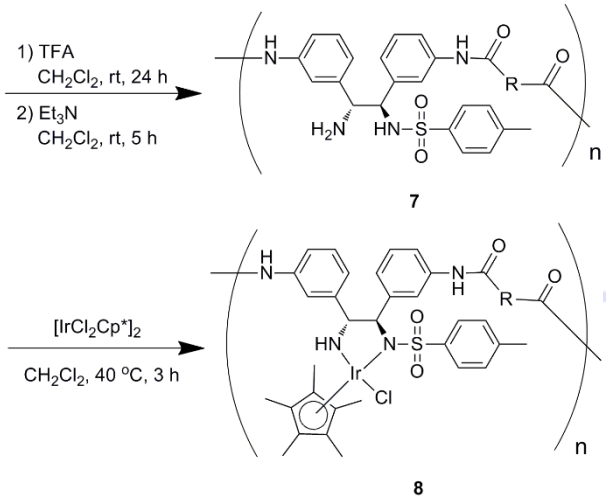


Scheme 2. Synthesis of chiral bisaniline monomer **4**.

Polyamides are widely recognized for their excellent thermal, mechanical, and chemical properties.[19] One typical polyamide synthesis is the reaction of a diamine and dicarboxylic acid dihalide.[20] For example, aramid (aromatic polyamide) fibers have been prepared using this method.[21] Therefore, chiral bisaniline monomer **4** was allowed to react with adipoyl chloride (R = $(CH_2)_4$) to afford chiral polyamide **6a** in high yield with a molecular weight (M_n) of 12,200 (Scheme 3, Table 1, entry 1). Several other dicarboxylic acid dichlorides (**5**) were also used as comonomers in the chiral polymerization with TsDPEN monomer **4**, as summarized in Table 1. Both aliphatic and aromatic dicarboxylic acid dichlorides easily reacted with **4** to afford corresponding chiral polymers **6** with high molecular weights. After polymerization, Boc groups in the chiral polymers (**6**) were removed using trifluoroacetic acid (TFA) in CH_2Cl_2 (Scheme 4). In some cases, due to chemical modification of the high-molecular-weight polymer, some Boc groups remained intact in the polymer main chain after TFA treatment. For example, chiral polymer **6a** showed poor solubility in common organic solvents, such as CH_2Cl_2, ethyl acetate, diethyl ether, and hexane; therefore, the deprotection of **6a** was achieved under heterogeneous suspension conditions. The degree of deprotection was confirmed by the ^{1}H-NMR spectrum of polymer **7a** in DMSO-d_6. At least 88% of the Boc groups were removed by TFA treatment. However, **6a** is soluble in high-polarity solvents, such as DMSO and DMF. The molecular weights of **6** were determined by size-exclusion chromatography (SEC) measurements of DMF solutions. In most cases, the deprotection of **6** proceeded well in CH_2Cl_2, giving the corresponding TsDPEN polymers in high yields (Table 1). The molecular weights of the TsDPEN polymers synthesized using this polymerization method were higher than 10,000.

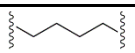
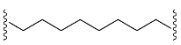


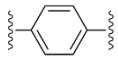
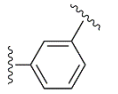
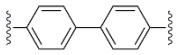
Scheme 3. Polymerization of **4** and dicarboxylic acid dichloride **5**.



Scheme 4. Preparation of chiral polymer Ir complex **8**.

Table 1. Yield and gel permeation chromatography (GPC) characterization of chiral polymers **6**.

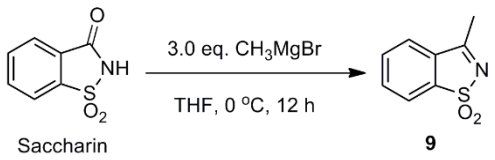
Polymeric ligand [a]	-R-	Yield %[b]	M_n[c]	M_w	M_w/M_n
6a		82	12,200	21,900	1.79
6b		88	13,300	33,800	2.54
6c		97	10,200	15,400	1.50

6d		94	6,800	13,600	1.99
6e		76	12,700	25,200	1.99
6f		91	14,700	45,000	3.07

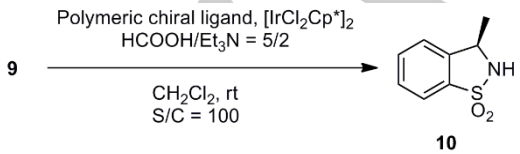
[a] Polymerized in DMF at 100 °C for 24 h. [b] Isolated yield. [c] Determined by SEC (polystyrene standards) using DMF as an eluent at a flow rate of 1.0 mLmin^{-1} at 40 °C.

Based on the degree of deprotection in chiral polymers **7**, a transition metal complex was added to suspensions of **7** in CH_2Cl_2 to form chiral polymeric transition metal complexes. Preparation of the Ir complex of **7** is illustrated in Scheme 4. During the reaction, the orange color of the Ir complex, dichloro-(pentamethylcyclopentadienyl)iridium(III) dimer $[IrCl_2Cp^*]_2$, in CH_2Cl_2 solution completely disappeared and yellow polymer–Ir complex **8** was obtained.

In order to evaluate the catalytic activity of the chiral polymer–Ir complexes, we chose the enantioselective hydrogen transfer reaction of cyclic sulfonimine **9** to chiral cyclic sulfonylamine **10** (Scheme 6). Cyclic sulfonimine **9** was easily prepared from saccharine (Scheme 5).[22] In the presence of polymeric chiral catalyst **8a**, the reaction proceeded smoothly in CH_2Cl_2. Cyclic sulfonimine **9** was completely converted to **10** with quantitative conversion within 1 h at room temperature. As shown in Table 2, the enantioselectivity of 90% (entry 2) obtained with **8a** was almost equal to that obtained using the original DPEN monosulfonamide–Ir complex (89% ee) (entry 1). Other polymer–Ir catalysts prepared from polymer ligands (**7a**–**7f**) showed similar performance in the asymmetric transfer hydrogenation of **9** (entries 3–7).



Scheme 5. Preparation of cyclic sulfonamide.



Scheme 6. Asymmetric transfer hydrogenation of cyclic sulfonamide.

Table 2. Asymmetric transfer hydrogenation using Iridium complex.[a]

entry	Ligand	Time h	Yield %[b]	Ee %[c]
1	TsDPEN	10 min	91	89
2	**7a**	1	92	90
3	**7b**	1	76	87
4	**7c**	1	96	89
5	**7d**	1	80	89
6	**7e**	1	92	89
7	**7f**	1	81	87

[a] All reactions were carried out in HCOOH/Et_3N (5:2, *v/v*, 5 equiv. relative to **9**) with a substrate/catalyst mole ratio (S/C) of 100 in 1 mL of CH_2Cl_2 at rt. [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiralcel OD-H column. Major products had *R* configurations in all cases.

Another polymer chiral catalyst was prepared from dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer $[RhCl_2Cp^*]_2$. Polymeric Rh complexes prepared from **7** and $[RhCl_2Cp^*]_2$ were successfully applied to the asymmetric transfer hydrogenation of **9**. Compared with Ir complexes, polymeric Rh complexes required longer reaction times to afford product **10** with lower enantioselectivities (Table 3). Ru complexes were also prepared from chiral polymer ligands **7** and dichloro(*p*-cymene)ruthenium(II) dimer $[RuCl_2(p\text{-cymene})]_2$. As shown in Table 4, the chiral polymer Ru complexes were efficient catalysts in the same asymmetric reaction, giving chiral cyclic sulfonylamine **10** with high enantioselectivities (>90% ee). Compound **7a**, prepared from adipoyl chloride, containing a C4 alkylene chain, always gave higher enantioselectivities than the other polymer catalysts (Table 2, entry 2; Table 3, entry 1; Table 4, entry 1), indicating that appropriate flexible linker structures might be suitable in chiral polymer catalysts. Notably, polymer catalysts prepared from **7f**, containing a rigid biphenyl linker, gave relatively low enantioselectivities (Table 2, entry 7; Table 3, entry 6; Table 4, entry 6).

Table 3. Asymmetric transfer hydrogenation using Rhodium complex.[a]

entry	Ligand	Time h	Yield %[b]	Ee %[c]
1	**7a**	5	71	58
2	**7b**	3	84	51
3	**7c**	3	81	52
4	**7d**	3	73	53
5	**7e**	2	89	53
6	**7f**	3	81	45

[a] All reactions were carried out in HCOOH/Et_3N (5:2, *v/v*, 5 equiv. relative to **9**) with S/C=100 in 1 mL of CH_2Cl_2 at rt. [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiralcel OD-H column. Major products had *R* configurations in all cases.

Table 4. Asymmetric transfer hydrogenation using Ruthenium complex.[a]

entry	Ligand	Time h	Yield %[b]	Ee %[c]
1	**7a**	14	82	95
2	**7b**	12	90	93
3	**7c**	12	74	90
4	**7d**	10	79	93
5	**7e**	10	88	93
6	**7f**	10	87	90

[a] All reactions were carried out in HCOOH/Et_3N (5:2, *v/v*, 5 equiv. relative to **9**) with S/C=100 in 1 mL of CH_2Cl_2 at rt. [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiralcel OD-H column. Major products were *R* configurations in all cases.

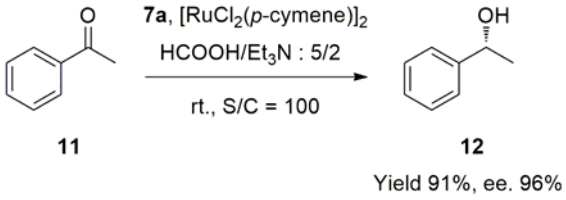
Since the polymeric catalysts formed an insoluble suspension in CH_2Cl_2, they were easily separated from the reaction mixture by simple filtration. We confirmed that the filtrate had no catalytic activity in the reaction.[23] The recovered polymer powder was reused in subsequent reactions, without any loss in catalytic activity or enantioselectivity. Polymeric catalyst **8a** could be reused at least four times (Table 5).

Table 5. Reuse of **8a** in the asymmetric transfer hydrogenation of **9**.[a]

Cycle	Time h	Yield %[b]	Ee %[c]
1	1	92	90
2	1	89	91
3	1	88	91
4	2	94	93
5	2	92	92

[a] All reactions were carried out in HCOOH/Et_3N (5:2, *v/v*, 5 equiv. relative to **9**) with S/C=100 in 1 mL of CH_2Cl_2 at rt. [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiralcel OD-H column.

In addition to the asymmetric transfer hydrogenation of the cyclic sulfonimine **9**, acetophenone **11** was also smoothly reduced to corresponding chiral secondary alcohol **12**. Using catalyst **7a-Ru**, **12** was produced in 91% yield with 96% ee (Scheme 7). The polymeric catalyst **7a-Ru** showed higher enantioselectivity compared with the silica-supported TsDPEN-Ru complex,[24] which gave 91% ee in the same reaction.



Scheme 7. Asymmetric transfer hydrogenation of acetophenone.

In conclusion, a novel chiral polymer ligand was successfully synthesized using a polycondensation method. This was the first synthesis of a chiral main-chain polymer ligand with a TsDPEN structure. The chiral polymer formed transition metal complexes with Ir, Rh, and Ru. These chiral polymer–metal complexes showed catalytic activity in the asymmetric transfer hydrogenation of a cyclic sulfonimine and acetophenone, with high enantioselectivities observed. These polymeric catalysts were easily separated from the reaction mixture and reused several times without any loss in catalytic activity or enantioselectivity. As TsDPEN and its derivatives are known to be excellent chiral ligands in catalysts of various asymmetric reactions, the polymers developed in this study should find further application as ligands in alternative asymmetric catalytic transformations.

Acknowledgements

The authors would like to thank Dr. Naoki Haraguchi at the Toyohashi University of Technology for useful discussions. This work is financially supported by JSPS KAKENHI Grant Number JP15H00732, JP15K05517.

Keywords: 1,2-diphenylethylenediamine • chiral polyamide • asymmetric transfer hydrogenation • transition metal catalyst • polymer catalyst

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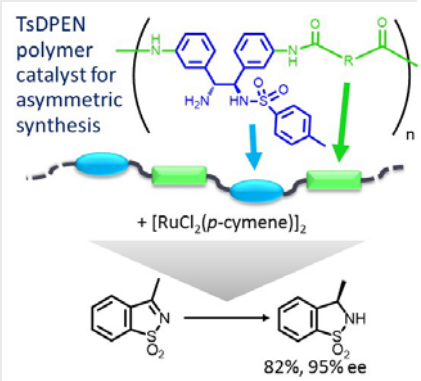

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Synthesis of chiral polyamides having (*R*,*R*)-1,2-diphenylethylenediamine monosulfonamide structure and their application to Asymmetric transfer hydrogenation catalysis

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