博士論文 (要約)

Study on Organic Synthesis by Olefin Oligomerization Reactions

(オレフィンのオリゴマー化を用いた有機合成の研究)

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1. General Introduction

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Since the discovery of Ziegler-Natta catalysts in 1950s,[1,2] coordination-insertion polymerization of olefins has been intensively explored academically and industrially. Of the numerous reports in this field, the Kaminsky catalyst, discovered in 1970s,[3] deserves special mention. Utilizing metallocene frameworks, more precise control of the polymer structure in molecular weight and stereo regularity was achieved. For Ziegler-Natta and Kaminsky catalysts, the polymerization proceeds via linear chain growth mechanism. Another milestone in this field is the chromium-catalyzed trimerization of ethylene, first observed in 1967[4] and later mechanistically addressed in 1977.[5] It has been proposed that this reaction proceeded via metallacycle intermediates, which led to unique selectivity on the chain length due to the ring strain of the intermediates.

On the other hand, the field of total synthesis has been mainly driven by the development of new carbon-carbon bond forming reactions. Outstanding discoveries including cross-coupling and olefin metathesis have made a great contribution to the field, leading to the widespread application to the field of pharmaceuticals and agrochemicals.

These seemingly unrelated research fields, polymer chemistry and total synthesis, have previously had little exchange, although they share the same principle of carbon-carbon bond formation. Strategies in polymer chemistry have the potential to boost the field of total synthesis if the reactivity is controlled to selectively afford oligomers.

This dissertation consists of two major parts: Firstly, stereospecific propylene oligomerization catalyzed by zirconocenes was explored to synthesize deoxypropionate motif, which is the fully reduced variant of polyketide.

2. Asymmetric isospecific oligomerization of propylene for the synthesis of *syn*-deoxypropionate motif

2.1. Introduction

The deoxypropionate motif, which is the fully reduced polyketide structures with methyl side chains, is common substructure found in natural products (Figure 1a).[6] There have been a great amount of attention to the synthesis of the deoxypropionate motif due to its abundance in natural products.[7,8]

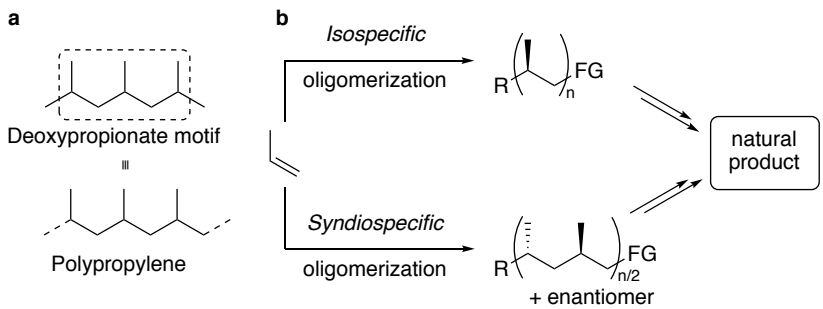


Figure 1. Synthesis of deoxypropionate motifs.

Most of the conventional syntheses of the deoxypropionate motif employ iterative stereoselective reactions including functional-group interconversions to construct the structures consisting of multiple stereocenters but no functionalities. Multiple reaction steps per repeating unit are typically necessary, which results in long reaction routes, and consequently low yields towards the natural products.

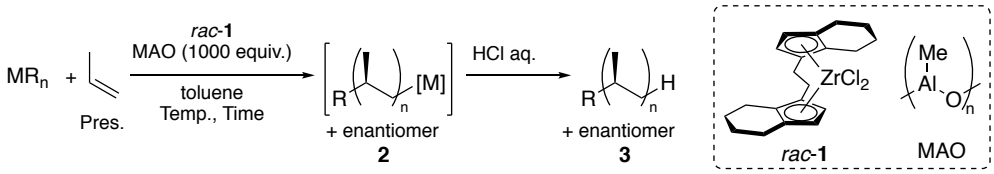
To construct the deoxypropionate motif in a facile manner, the author envisioned using propylene as a building block. Since the deoxypropionate motif is identical to the partial structure of polypropylene, stereospecific oligomerization of propylene would afford the structure in a single step (Figure 1b).

2.2. Optimization of reaction conditions

In order to control both the chain length and the stereospecificity, the author focused on the polymerization mode called "coordination chain-transfer polymerization", where excess amount of alkylmetal reagent is added to the reaction system as a chain transfer agent (CTA).[9]

The reaction conditions were first optimized using highly isospecific propylene polymerization catalyst *rac*-**1** because *syn*-deoxypropionate motif is a partial structure of isotactic polypropylene (Table 1). While use of $AlMe_3$ as a CTA afforded the product as a mixture of isomers after protonation

Table 1. Oligomerization of propylene.



Entry	MR_n	/equiv.[a]	Pres. /MPa	Temp. /°C	Time /h	3-mer[b] /%	4-mer[b] /%	%main di-astereomer[c]	%alkene[d]
1	$AlMe_3$	1,800	0.1	40	22	n.d.	n.d.	n.d.	n.d.
2	$ZnEt_2$	1,800	0.1	0	29	1.8	0.89	89	29
3	$ZnEt_2$	1,900	0.1	–20	25	2.6	1.4	89	15
4	$ZnEt_2$	5,200	0.1	–20	25	0.32	0.10	92	9.8
5	$ZnEt_2$	2,000	0.2	–20	16	9.6	7.9	>99	2.6

[a] Against *rac*-**1**. [b] Based on MR_n. [c] Percentage of main diastereomer of tetramer.
[d] Percentage of vinylidene-terminated tetramer. n.d., not determined.

of alkylaluminum species **2** (entry 1), oligopropylenes **3** were obtained with high diastereoselectivity in the presence of $ZnEt_2$ (entry 2). The difference of diastereoselectivity may be explained by the observation that stereospecificity of propylene insertion into a metal–carbon bond is very high for metal–CH_2CH_3, but much lower for metal–CH_3.[10] Lowering the temperature to −20 °C improved the oligomer yields and lowered the ratio of alkene-terminated oligomers which originate from undesired β-hydride elimination from **2** (entry 3). Increased amount of $ZnEt_2$ resulted in a higher ratio of shorter oligomer yields, but with lower oligomer yields (entry 4). Finally, propylene addition was optimized to be the continuous feed at 0.2 MPa, which furnished oligomers with high diastereoselectivity and low alkene formation (entry 5).

2.3. Asymmetric oligomerization and consecutive oxidation

The process was then expanded to asymmetric reaction. Propylene oligomerization was carried out using (*S*,*S*)-**1** instead of *rac*-**1**, and in-situ oxidation of alkylzinc species **2′** by dioxygen was performed to afford alcohols **4** (Figure 2a). Each oligomer alcohols were separated by liquid chromatography, and

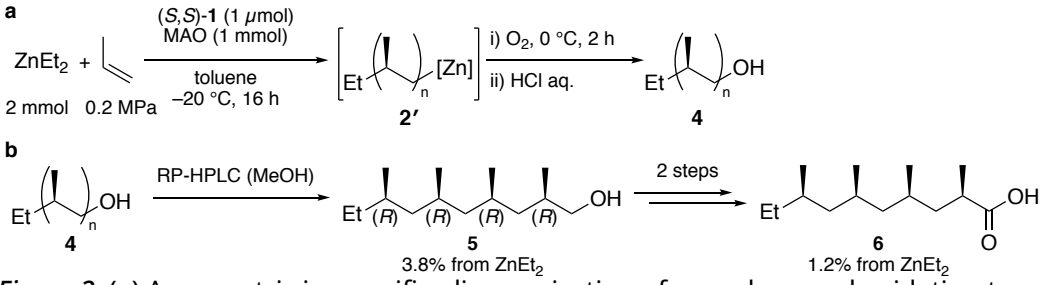


Figure 2. (a) Asymmetric isospecific oligomerization of propylene and oxidation to alcohols. (b) Total synthesis of **6**.

tetramer alcohol **5** was isolated in 3.8% yield (Figure 2b). Enantiomeric excess of **5** was determined to be >99%, and absolute configuration was determined by optical rotation. Finally, **5** was oxidized to (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethyldecanoic acid **6**, which is a major acid component of preen-gland wax secreted by graylag goose,[11] in two steps. Thus, three-step synthesis of **6** from propylene is the shortest known sequence to date.

3. Syndiospecific oligomerization of propylene for the synthesis of *anti*-deoxypropionate motif

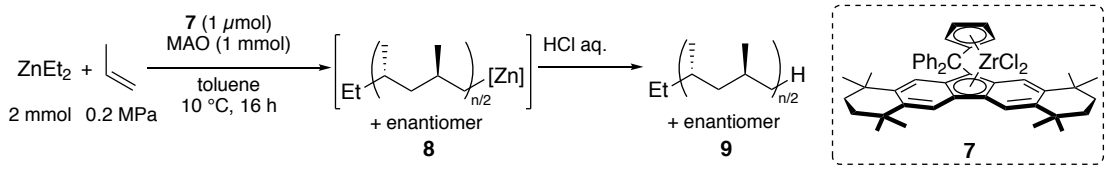
3.1. Introduction

In chapter 2, the author developed the single-step synthesis of deoxypropionate motif from propylene. However, the product was limited to the *syn*-configured deoxypropionate motif owing to the isospecificity provided by C_2-symmetric zirconocene catalyst. Although the significant majority of the deoxypropionate motifs found in natural products have a *syn* configuration, there are several naturally occurring examples featuring the anti-configured deoxypropionate motif. Therefore, the author then explored the construction of *anti*-deoxypropionate motif, utilizing a C_S-symmetric zirconocene catalyst.

3.2. Optimization of Reaction Conditions

Highly syndiospecific propylene polymerization catalyst **7** was chosen after brief screening. Under a similar reaction conditions to the isospecific propylene oligomerization, after protonation of alkylzinc species **8,** syndiotactic oligopropylenes **9** were obtained with high stereoregularity (Table 2, entry 1). Increase in propylene pressure to 0.4 MPa led to a steep decrease in oligomer yields (entry 2) and increase in the ratio of diethylzinc to **5** to either 5000 or 10000 improved oligomer yields and the

Table 2. Syndiospecific oligomerization of propylene.



Entry	Variation	3-mer[a] /%	4-mer[a] /%	%main di-astereomer[b]
1	n.a.	9.9	8.4	92
2	0.4 MPa	4.4	3.7	88
3	0.4 MPa, 5 mmol Zn	13.1	11.1	94
4	0.4 MPa, 10 mmol Zn	12.2	9.1	95
5	−20 °C	4.3	3.8	90

[a] Based on $ZnEt_2$. [b] Percentage of main diastereomer of hexamer. n.a. = not applicable.

diastereoselectivity (entries 3 and 4). Lower reaction temperature of −20 °C only decreased oligomer yields (entry 5).

3.3. Oligomerization and consecutive oxidation

The CTA was then switched to di(*n*-propyl)zinc, and oligomerization proceeded with the diastereoselectivity comparable to diethylzinc system (Figure 3a). Then oxidation of alkylzinc species

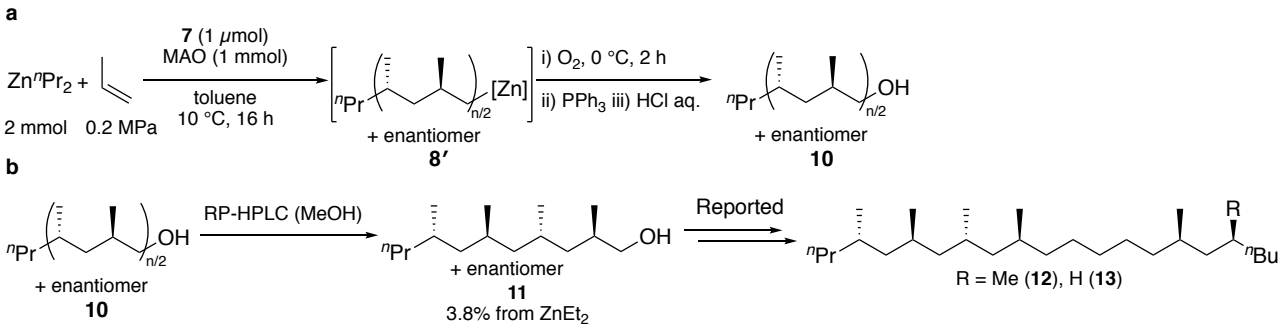


Figure 3. (a) ^{n}Pr-initiated syndiospecific oligomerization of propylene and oxidation to alcohols. (b) Formal total syntheses of 2 and 3.

8′ to alcohols **10** were carried out, and tetramer alcohol **11** was isolated in 3.8% yield (Figure 3b). Alcohol **11** is the racemic mixture of the common synthetic intermediate for (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-4,6,8,10,16,18-hexamethyldocosane **12** and (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **13**, major cuticular hydrocarbons isolated from the cane beetle *Antitrogus parvulus*.[12,13] Thus, the facile formal total syntheses of **12** and **13** were completed.

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5. Conclusions and Perspectives

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In chapters 2 and 3, the author developed the single-step construction of *syn*- and *anti*-deoxypropionate motif by stereospecific propylene oligomerization and demonstrated the facile (formal) total syntheses of natural products. Although isospecific propylene oligomerization was successfully expanded to asymmetric reaction, syndiospecific oligomerization was not. Further modification in either zirconocene framework or initiating alkyl group would enable the asymmetric syndiospecific oligomerization of propylene.

6. References

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7. Publications related to this dissertation

[1] Y. Ota[†], T. Murayama[†], K. Nozaki, *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 2857–2861. ([†]Co-first authors)

[2] T. Murayama, K. Nozaki, *Angew. Chem. Int. Ed.* **2018**, *57*, 11394–11398.