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A Novel and Efficient Method for the Preparation of Unstable Tetramethylzirconium and Its Application Using a Microflow System

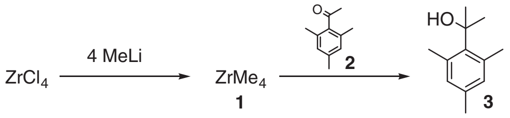
Koji Uehata,[1,2] Mayumi Nishida,[2] and Atsushi Nishida*[1]
[1]*Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675*
[2]*Koei Chemical Company, Ltd., 25 Kitasode, Sodegaura, Chiba 299-0266*

(Received October 13, 2011; CL-111007; E-mail: nishida@p.chiba-u.ac.jp)

We have developed a novel and efficient method for the preparation of unstable tetramethylzirconium and its application to the synthesis of tetrakis(*N*-methylethylamido)zirconium and dimethylbis(indenyl)zirconium using a microflow system.

Over the past decade, flow reactions with microflow systems have been used for chemical reactions because of numerous advantages over conventional macrobatch reactions.[1–3] The features of the flow reaction are as follows; 1) extremely fast mixing due to the short diffusion path, 2) ability to control the reaction residence time, which is the length of time that the solution remains inside the reactor, and 3) efficient heat transfer due to a high surface-to-volume ratio.[1] In addition, 4) an increase in the number of microflow systems makes it possible to increase the production capacity, which may be beneficial from the viewpoint of industrial production. Especially, the features of 1), 2), and 3) are quite advantageous for the precise control of reactive intermediates and thereby facilitate highly selective reactions that are difficult to achieve in conventional reactors.[3] We report here a novel method for the synthesis of tetrakis(*N*-methylethylamido)zirconium and dimethylbis(indenyl)zirconium via thermally unstable tetramethylzirconium (**1**)[4] with the use of a microflow system.

The preparation of **1** can be checked by the reaction with 2,4,6-trimethylacetophenone (**2**) to afford 2-mesityl-2-propanol (**3**). Reetz et al. reported that MeLi and MeMgI induce 100% enolization of **2**. However, **1** methylated **2** to give the corresponding alcohol **3** in 45% yield under batch conditions (Scheme 1).[5] In this study, we examined the same methylation. The reaction of **2** with MeLi failed to give **3**, and instead induced the enolization of **2**, which was detected by 91% incorporation of deuterium at an acetyl group when the reaction was quenched with MeOD. Next, we also studied the methylation of **2** with tetramethylzirconium (**1**) under batch conditions. A suspension of $ZrCl_4$ in ether was treated with 4 equiv of MeLi in ether for 10 min at −78 °C. The suspension was warmed to −30 °C and stirred for 2 h at the same temperature to complete the preparation of **1**. An ether solution of **2** was added to the resulting suspension of LiCl and **1**, and the mixture was stirred for 2 h at −20 °C. After the reaction was quenched, **3** was obtained in 74% yield (Table 1, Run 1).[6,14] Prolongation of the reaction time and an increase in the reaction temperature improved the yield of **3** to 90% (Run 2). However, these conditions are not suitable for a flow system because $ZrCl_4$ and LiCl are insoluble in ether. Therefore, we attempted this methylation in THF, in which both $ZrCl_4$ and LiCl are soluble. When $ZrCl_4$ was dissolved in THF–toluene (11/1) and reacted with MeLi in ether at −78 °C and then warmed to −30 °C, **3** was not obtained at all (Run 3). However, when the temperature of the reaction of $ZrCl_4$ with MeLi was raised to 0 °C followed by addition of a solution of **2**, desired **3** was obtained in 52% yield (Run 4). These results showed that the reaction of zirconium species was much slower in THF than in ether and required higher temperature to proceed with reasonable reaction rate. Although the yield of **3** was lower than that of the reaction in ether, the reaction in a THF/toluene solvent system was applicable in the microflow system. We then began study of the preparation of **1** in a microflow system.



Scheme 1. Reaction of $ZrCl_4$ with MeLi followed by a reaction with 2,4,6-trimethylacetophenone (**2**).

Table 1. Reaction of $ZrCl_4$ with MeLi followed by a reaction with **2** under batch reactions

Run	Reaction of $ZrCl_4$ with MeLi		**2**/solvent (0.2 M)	Reaction of **1** with **2**		Yield/%[a]		
	$ZrCl_4$/solvent	Conditions		Temp/°C	Time/h	**2**	**3**	**4**
1	ether	−30 °C, 2 h	ether	−20	2	18	74	1
2	ether	−30 °C, 2 h	ether	−20 → 25	12 + 2	4	90	2
3	THF/Tol. (11/1)	−30 °C, 2 h	THF	−20 → 25	12 + 2	91	0	0
4	THF/Tol. (11/1)	0 °C, 30 min	THF	−20 → 25	12 + 2	30	52	8

[a]Determined by GC with phenanthrene as an internal standard.

A microflow system consisted of T-shaped micromixers (M-0 and M-1) and microtube reactor (R-1). The mixers and tube reactor were immersed in a water bath (Figure 1).[14] A solution of 1.0 M MeLi in ether (flow rate: 0.8 mL min^{-1}, 0.8 mmol min^{-1}) was diluted with THF (flow rate: 2.4 mL min^{-1}) to prevent clogging of the flow system by introduction to M-0 ($\phi = 1000\,\mu m$) at 20 °C using syringe pumps. The resulting solution of 0.25 M MeLi in ether–THF and a solution of 0.1 M $ZrCl_4$ in THF–toluene (11:1, flow rate: 2.0 mL min^{-1}, 0.2 mmol min^{-1}) were introduced to M-1 ($\phi = 500\,\mu m$) at 20 °C using syringe pumps. After the resulting solution was passed through R-1 ($\phi = 1000\,\mu m$, length = 200 cm, residence time = 18.1 s), the reaction mixture was added to 0.2 M of **2** in THF solution (1.0 mL, 0.2 mmol) at −20 °C over 1 min (5.2 mL, which contains 0.2 mmol of **1**) and stirred for 12 h at −20 °C and then for 2 h at 25 °C. After workup, compound **3** was obtained in 49% yield with

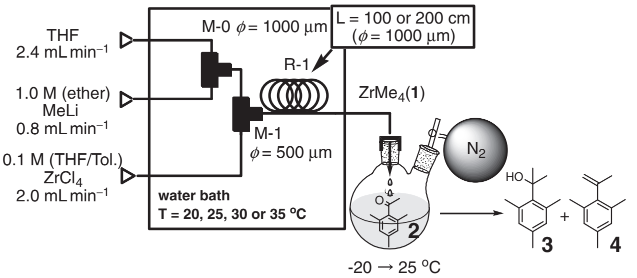


Figure 1. Microflow system for the preparation of **1** followed by a reaction with **2**.

Table 2. Reaction of $ZrCl_4$ with MeLi followed by a reaction with **2** using a microflow system

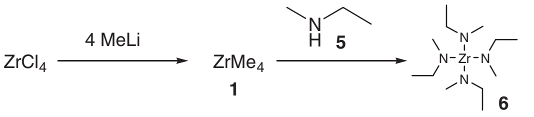
Run	R-1		Yield/%[a]		
	Temp /°C	Residence time /s	**2**	**3**	**4**
1	20	18.1	37	49	6
2	25	18.1	32	56	6
3	35	18.1	41	44	7
4	25	9.1	49	40	6
5	30	9.1	36	53	7
6	35	9.1	36	55	6

[a] Determined by GC with phenanthrene as an internal standard.

recovered **2**, 37% and dehydrated **4**, 6% (Table 2, Run 1).[14] As shown in Table 2, various temperatures and residence times in R-1, which was controlled by changing the length of R-1 with a fixed flow rate, were tested.

At a residence time in R-1 of 18.1 s, the highest 56% yield of **3** was observed at 25 °C (Run 2). On the other hand, when the residence time in R-1 was 9.1 s, **3** was obtained in 55% yield at 35 °C (Run 6). In the scale-up reaction (0.9 mmol) under the conditions Run 2 followed by quenching with MeOD for 5 min at −20 °C, **3** was obtained in 53% isolated yield along with recovered **2** (31%). A ^{1}H NMR study of recovered **2** showed that the incorporation of deuterium at the acetyl group was only 1%. This result suggests that at least 99.9% of MeLi reacted with $ZrCl_4$ under these flow conditions. Therefore, under these conditions, **1** was produced in at least the same level as under batch conditions.

Generation of tetramethylzirconium under a microflow system was further tested by the reaction with *N*-methylethylamine (**5**) to give tetrakis(*N*-methylethylamido)zirconium (**6**), which has been used as a Zr gaseous precursor in ALD (atomic layer deposition) for the deposition of zirconia films (Scheme 2).[9] It has been reported that processes for producing **6** require the transfer of $ZrCl_4$ to a slurry of a lithium alkylamide under conventional batch conditions.[10] It is difficult to introduce hazardous solids ($ZrCl_4$) to a reaction mixture on a commercial scale. A solution of **1** was prepared under microflow conditions as described above and mixed with a solution of **5** at M-2, and then the resulting solution was passed through R-2 (Figure 2: $\phi = 1000\,\mu m$, length = 200 cm, residence time = 12.4 s).[14] Product **6** was isolated by evaporation of the solvents. As shown in Table 3, the results were obtained under varying temperature and residence time in R-1. At a residence time of 18.1 s in R-1, the highest yield was observed at 25 °C (Run 2; 70%). On the other hand, when the residence time in R-1 was shorter (9.1 s), the yield was further increased to 76% at 35 °C (Run 5). In a conventional batch reaction, much lower temperatures were required for the generation and reactions of **1** (Runs 6 and 7).[14] However, with a microflow system, the reaction has been completed with shorter reaction times at higher temperatures with better yield. As a result of Tables 2 and 3, the yield of tetramethylzirconium (**1**) should be more than 76% yield without the contamination of MeLi.



Scheme 2. Reaction of **1** with *N*-methylethylamine (**5**).

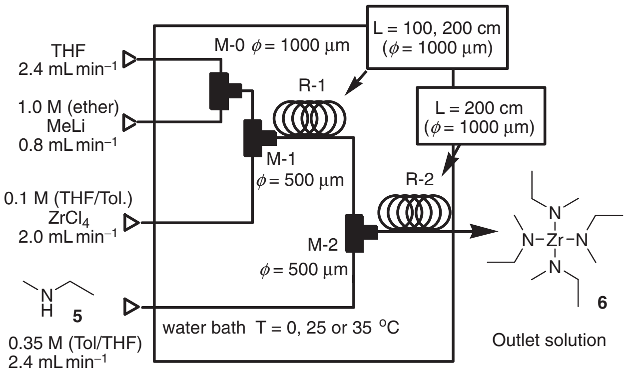


Figure 2. Microflow system for the reaction of **1** with **5**.

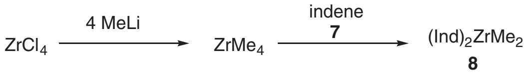
Table 3. Reaction of **1** with **5**

Run	Residence time in R-1/s	Temp /°C	Yield/%[a]
1	18.1	0	58
2	18.1	25	70
3	9.1	35	61
4	9.1	25	53
5	9.1	35	76
6	batch reaction[b]	−78[c]	66
7	batch reaction[b]	25[c]	54

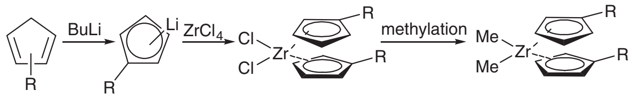
[a] Determined by ^{1}H NMR with mesitylene as an internal standard. [b] **1** was prepared under the same conditions as Table 1, Run 1. [c] Temperature of the reaction of **1** with **5**.

Then, we studied the reaction of **1** with indene (**7**) to afford dimethylbis(indenyl)zirconium (**8**) (Scheme 3). Metallocene-based catalysts have been used for the production of novel polyolefins with tailor-made properties, since these catalysts can easily control the molecular weight, the narrow molecular weight distribution and polymer stereochemistry.[11] Dimethylzirconocenes are usually produced by the three-step procedure shown in Scheme 4. However, the use of three steps with the isolation of dichlorozirconocene intermediates gives unsatisfactory total yields.[12]

Resconi and co-workers reported a simpler method for the preparation of **8** by reacting **7** with a twofold excess of MeLi, followed by the addition of slurries of $ZrCl_4$ in pentane.[13] In this method, **8** was produced in 87% yield. However, the complete transfer of slurries of $ZrCl_4$ in pentane to the mixture of MeLi



Scheme 3. Reaction of **1** with indene (**7**).



Scheme 4. Conventional method for dimethylzirconocenes.

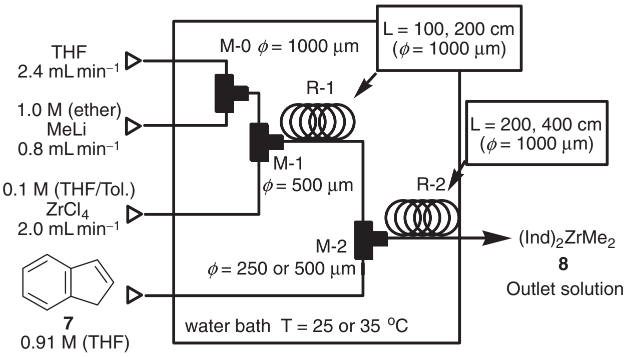


Figure 3. Microflow system for the reaction of **1** with **7**.

Table 4. Reaction of **1** with **7**

Run	Residence time/s		**7** /equiv	Temp /°C	Inner diameter of M-2 /μm	Yield /%[a]
	R-1	R-2				
1	9.1	16.7	2	35	500	22
2	9.1	15.0	5	35	500	55
3	18.1	29.9	5	25	250	61
4	batch reaction[b]		5	25[b]	—	1

[a] Determined by ^{1}H NMR with mesitylene as an internal standard.
[b] **1** was prepared under the same conditions as Table 1, Run 1 and then an ether solution of **7** was added to **1**. The reaction was continued for 1 h at 25 °C.

and π-ligand is difficult at low temperature in the industrial production.

We examined the reaction of **1** with **7** (0.91 M THF solution) using a microflow system to provide **8**, as shown in Figure 3. The results are summarized in Table 4. We successfully obtained **8** in 22% yield with this microflow system at 35 °C (Run 1; flow rate of 0.91 M indene: 0.44 mL min^{-1}, 0.40 mmol min^{-1}). The ^{1}H and ^{13}C NMR data of **8** were identical to those reported in the literature.[13] The yield of **8** increased with an increase in the molar equivalent of **7**/$ZrCl_4$ (Run 2; 55% yield, flow rate of 0.91 M of **7**: 1.1 mL min^{-1}, 1.0 mmol min^{-1}). Under further optimization, a decrease in the diameter of M-2 and increase in the length of R-1 and R-2 at 25 °C gave **8** in the highest yield (Run 3; 61% yield). On the other hand, a trace amount of **8** was observed under batch conditions using **1** prepared under the same conditions as Table 1, Run 1 (Run 4).[14] This result indicated a microflow system is more effective than a batch system in the reaction of **1** with **7**.

In this work we synthesized tetrakis(*N*-methylethylamido)-zirconium (**6**) and dimethylbis(indenyl)zirconium (**8**) via thermally unstable tetramethylzirconium using a microflow system. We expect to produce dimethylzirconocenes with functional groups which might be difficult to prepare by conventional methods.

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6 ^{1}H NMR data for 2-mesityl-2-propanol (**3**), but not the ^{13}C NMR results, were identical to those reported in the literature.[7] While the second carbon position was observed at 75.83 ppm in our case, the corresponding carbon was reported to be at 56.09 ppm in ref. 7. Further NMR experiments that included DEPT, HMQC, and HMBC methods clearly showed that our product had the structure shown as compound **3**. In addition, in the ^{13}C NMR spectrum of 2-phenyl-2-propanol, the second position has been reported to be at 72.46 ppm.[8]

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14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.