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Low-valent zirconocene-mediated cyclization of γ,δ-unsaturated oximes

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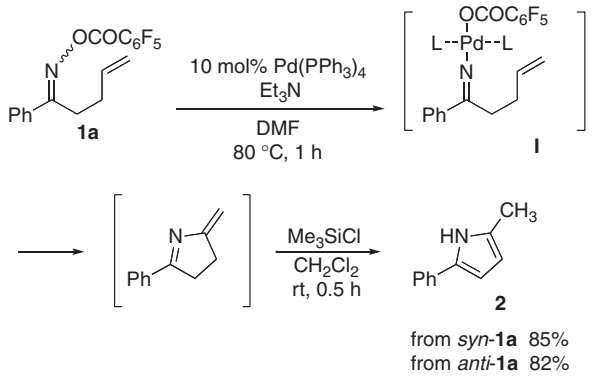
ABSTRACT

γ,δ-Unsaturated *O*-methyl oximes were cyclized to dihydropyrrole by the treatment of (1-butene)$ZrCp_2$ **3** prepared by Negishi's procedure (reaction with Cp_2ZrCl_2 and two equivalents of *n*-BuLi). In this cyclization, the geometry of oximes was affected and *syn*-oximes were cyclized efficiently. However, it was found that the *anti*-oxime is not suitable for the cyclization.

Previously, we reported that N–O bonds of oxime derivatives are cleaved by the oxidative addition to Pd(0) complexes to generate alkylideneaminopalladium(II) species.[1,2] When olefinic *O*-pentafluorobenzoyloximes are treated with a catalytic amount of $Pd(PPh_3)_4$ in the presence of Et_3N, Mizoroki–Heck-type cyclization (amino-Heck reaction) proceeds via the amino-palladium intermediates, affording various aza-heterocycles.[3,4] In Scheme 1, the synthesis of pyrrole is shown as a typical example.[3a,b] In this reaction, the selection of the pentafluorobenzoyloxy group as a leaving group on the oxime nitrogen is important. When the leaving group has higher leaving ability, such as sulfonate, Beckmann rearrangement also proceeds in the reaction conditions. In the case of lower leaving ability, the oxidative addition of the oxime to Pd(0) is difficult. This amino-Heck reaction is not affected by the geometry of oximes, probably due to the linear-like structures of the alkylideneaminometal species **I**.[2,5] Both *syn* and *anti* γ,δ-unsaturated ketone oximes **1a** cyclized to pyrrole **2** in good yields.[6]



Scheme 1. Amino Heck-reaction of γ,δ-unsaturated *O*-pentafluorobenzoyl oxime **1a**.

In our continuation study on the metal-catalyzed cyclization of γ,δ-unsaturated ketone oximes, we were interested in the reaction with low-valent zirconocene species, such as (1-butene)$ZrCp_2$ **3**, which is reported by Negishi et al. to be easily prepared by the reaction of Cp_2ZrCl_2 with two equivalents of *n*-BuLi.[7] If the olefin exchange of (1-butene)$ZrCp_2$ **3** with *anti*-γ,δ-unsaturated ketone oximes **4** occurred to give **5a**, internal S_N2-type substitution is expected to proceed to give a cyclized product since **5a** has a nucleophilic moiety which could place at the backside of the leaving group (R^2O in **5a**) on the oxime sp^2 nitrogen[1b,8] (Scheme 2). If the oxidative addition of oxime to zirconocene **3** similar to low-valent titanocene occurred,[2b] alkylideneaminozirconium species **5b** thus formed may cyclize to **6** similar to a Pd(0)-catalyzed amino-Heck reaction. Therefore, we examined the reaction of (1-butene)$ZrCp_2$ **3** with γ,δ-unsaturated ketone oximes. In this Letter, we describe the outcome of this investigation.

In Table 1, the results of the reaction of *syn*-1-phenyl-4-penten-1-one oxime **1** with (1-butene)$ZrCp_2$ **3** are listed.[6] First we examined the effect of the substituents on the oxime nitrogen atom in THF (runs 1–7). *O*-Pentafluorobenzoyl oxime **1a** cyclized to cyclic imine **7** in 43% yield accompanied with the formation of oxime **10**, which was predominantly formed in the reaction of *O*-acetyl oxime **1b** (runs 1 and 2). Oxime **10** would be formed by the reaction of zirconocene **3** and ester part in **1**.[9] Although the formation

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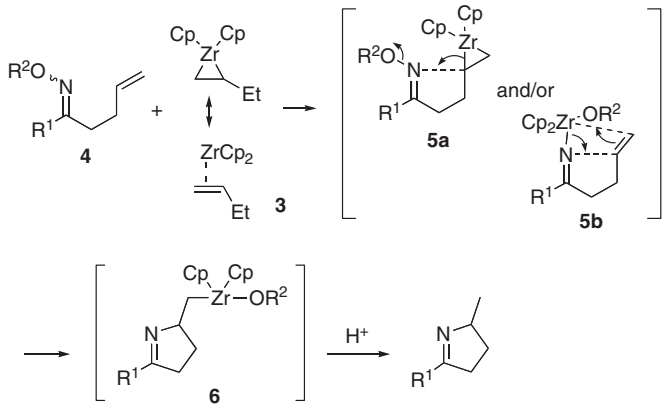
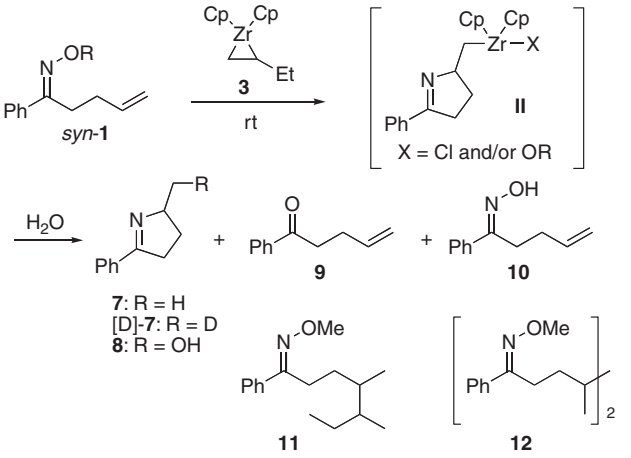


Scheme 2. Expected cyclization reaction of γ,δ-unsaturated oxime **4** with (1-butene)$ZrCp_2$ **3**.

of oxime **10** was suppressed by using the bulky pivaloyl group (Piv) as a substituent R, the yield of cyclized product **7** was 6% (run 3). In the Pd(0)-catalyzed amino-Heck reaction, *O*-alkyl oxime cannot be

Table 1
Reaction of γ,δ-unsaturated oxime **1** with (1-butene)$ZrCp_2$ **3**[a]



Run	R	1	Solvent	Time	Yield[b] (%)			
					7	9	10	1
1	C_6F_5CO	**1a**	THF	1 d	43	5	22	15
2	Ac	**1b**	THF	1 d	0	0	88	7
3	Piv	**1c**	THF	1 d	6	25	6	9
4	Me	**1d**	THF	6 h	53	6	0	—
5[c]	Me	**1d**	THF	5 h	9	36	0	—
6	MOM	**1e**	THF	2 d	30	24	0	18
7[d]	Bn	**1f**	THF	2 d	35	32	0	6
8	Me	**1d**	Et_2O	3 h	47	10	0	10
9[e]	Me	**1d**	Benzene	2 h	49	10	0	—
10	Me	**1d**	Toluene	2 h	36[f]	10	0	
11	Me	**1d**	Hexane	1 d	21	25	0	25
12	Me	**1d**	CH_2Cl_2	1 d	0	0	0	64
13[g]	Me	**1d**	THF	3 h	37	4	0	—
14[g]	Me	**1d**	Et_2O	3 h	48	3	0	—

[a] Each reaction is carried out by treating Cp_2ZrCl_2 (0.5 mmol) with *n*-BuLi in hexane (1.0 mmol) for 30 min at −78 °C in given solvent followed by addition of a oxime (0.47 mmol) at −78 °C, warming the mixture to room temperature for 1 h, and further stirring for given time.
[b] Isolated yield.
[c] *anti*-*O*-Methyl oxime **1d** was used for the reaction.
[d] BnOH was obtained in 66% yield.
[e] Compound **1d** was added at 0 °C.
[f] Compound **8** was obtained in 14% yield.
[g] To a solution of **1d** and Cp_2ZrCl_2, *n*-BuLi was added at 0 °C, and the mixture was warmed to room temperature.

employed, while *O*-methyl oxime **1d** was cyclized to **7** in 53% yield (run 4). However, from *anti*-oxime **1d**, the yield of cyclic imine **7** was only 9% (run 5). *O*-Methoxymethyl (MOM) and *O*-benzyl (Bn) oximes were ineffective for the cyclization (runs 6 and 7).

Next, we examined the solvent using *O*-methyl oxime **1d** (runs 8–12). In Et_2O and benzene, the reaction proceeded more rapidly than in THF, and **7** was obtained in 47% and 49%, respectively (runs 8 and 9). In toluene, cyclic imines **7** and **8** having hydroxymethyl group were formed as cyclized products in combined yields of 50% (run 10). Hexane and dichloromethane were not suitable for the cyclization of oxime **1d** (runs 11 and 12). When the reaction of **1a** in THF was quenched with D_2O, deuterated cyclic imine[D]-**7** (D 78%) was obtained suggesting that alkyl zirconium species like **II** were formed before quenching. Cyclic imine **7** was also obtained by adding *n*-BuLi to the mixture of oxime **1d** and Cp_2ZrCl_2 (runs 13 and 14), while **7** was not obtained only by treating with *n*-BuLi. In addition, we should mention that the formation of many by-products such as **11** and **12** in small amounts was observed in all reactions in Table 1, which is one of the reasons for the mid-level yield of the cyclized product **7** even though the starting oxime **1** was consumed.

To explore the scope and limitation of this cyclization reaction, we examined various *O*-methyl oximes with particular focus on the stereochemistry of the oximes (Table 2). For the oximes having terminal alkenes, the efficiency of the cyclization of *syn*-isomers of oximes was observed regardless of the aryl or alkylketone oximes (runs 1–7). From *anti*-oxime **15**, a trace amount of cyclic imine **19** was obtained and ketone **20** was obtained predominantly (run 7). In contrast, the cyclization of oximes **16** having a di- or tri-substituted alkene did not proceed smoothly, though the oximes were *syn* isomers (runs 11 and 12).

In Figure 1, two plausible reaction mechanisms for the formation of cyclic imine **7** from **1d** are depicted (paths A and B). Path A is as follows: (1-butene)$ZrCp_2$ **3** reacted with the alkene part in **1d** to form zirconium species **23**, which reacted with the oxime part via metathesis to give a cyclic compound. With *syn*-**23** derived from *syn*-oxime **1d**, interaction occurred easily between the methoxy group on the oxime nitrogen and the alkene–zirconium complex because of their proximity, while *anti*-**23** did not interact

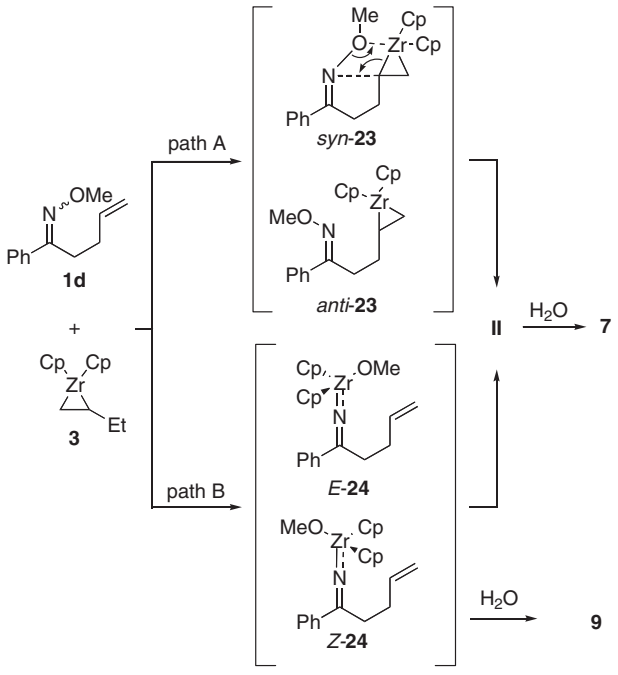
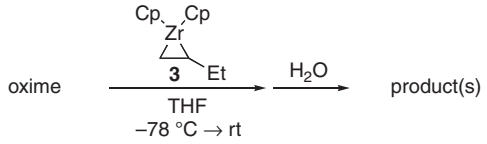
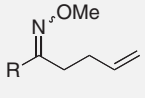
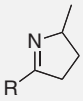
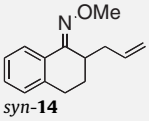
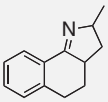
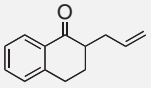
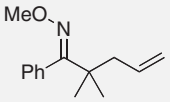
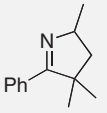
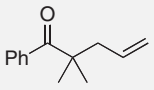
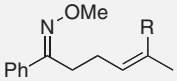
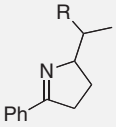
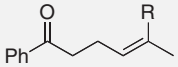


Figure 1. Plausible reaction mechanisms for the formation of cyclic imine **7**.

Table 2
Reaction of various γ,δ-unsaturated *O*-methyl oxime with (1-butene)$ZrCp_2$ **3**[a]



Run	Oxime (*syn*:*anti*)	Time (h)	Product(s) (%)	
				
1	*syn*-**13a**: R = 4-$MeOC_6H_4$	14	**17a**	49
2	**13b**: R = 2,4-$(MeO)C_6H_3$ (5:1)	20	**17b**	42
3	**13c**: R = $Ph(CH_2)_2$ (1:1)	5	**17c**	32
4	**13d**: R = $(PhCH_2)_2CH$ (2:1)	16	**17d**	33
5	*syn*-**13e**: R = $PhCH_2C(Me)_2$	24	**17e**	51
				
6	*syn*-**14**	2	**17f** 52%	**18** 11%
				
7	*anti*-**15**	18	**19** Trace	**20** 95%
				
8[b]	*syn*-**16a**[c]: R = H	21	**21a** 6%	**22a** 20%
9[d]	*syn*-**16b**: R = Me	68	**21b** 2%	**22b** 11%

[a] Each reaction is carried out by treating Cp_2ZrCl_2 (0.5 mmol) with *n*-BuLi in hexane (1.0 mmol) for 30 min at −78 °C in given solvent followed by addition of an oxime (0.47 mmol) at −78 °C, warming the mixture to room temperature for 1 h, and then further stirring for given time.
[b] Compound **16a** was recovered in 43% yield.
[c] The stereochemistry of olefin moiety was *E*/*Z* = 4:1.
[d] Compound **16b** was recovered in 74% yield.

easily. Path B is similar to the Pd(0)-mediated cyclization. That is oxidative addition of the oxime part to low-valent zirconocene **3** and the successive addition of alkylideneamino zirconium species **24** to the internal olefin. Erker et al. have reported that geometric isomerization of (*E*)- and (*Z*)-$Cp_2ZrCl(N{=}CHPh)$ could be effected neither thermally nor photochemically.[5a,b] Although Erker et al. also reported that linear-to-bent-to-linear isomerization of $Cp_2ZrX(N{=}CR_2)$ occurred rapidly in solution,[5b] the good yield of **7** from the *syn*-oxime may be attributed to the selective formation of *syn*-**24** which did not isomerize to *anti*-**24**, and the internal addition to the alkene. Ketone **9** would be formed by the hydrolysis of **24**. The result that ketone was formed as a main by-product when the yield of cyclic imine was low suggested that the formation of alkylideneamino zirconium species like **24** prevents the cyclization. Therefore, we suppose that path A is the main pathway to form cyclic imine **7**.

In conclusion, we found that γ,δ-unsaturated oximes cyclized to dihydropyrrole by the treatment of low-valent zirconocene prepared by Negishi's procedure. In this reaction the geometry of oxime is strongly affected, *syn*-oximes having terminal olefin cyclized efficiently but *anti*-oxime was not suitable for the cyclization.

Acknowledgment

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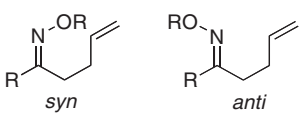
6. In this manuscript, *syn* of γ,δ-unsaturated oxime means the alkoxy or acyloxy group on the oxime nitrogen and an alkenyl moiety are on the same side of the oxime carbon–nitrogen double bond and *anti* means that these groups are on opposite sides.



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