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Tetrahedron Letters 48 (2007) 6471–6474
Tetrahedron Letters

Rh(I)-catalyzed conjugate addition of alkenylzirconocene chloride: stereoselective formation of carbocycles through cascade reaction

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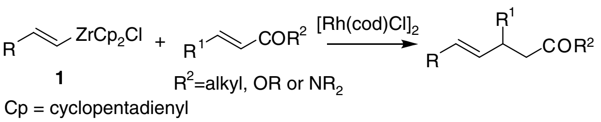
Received 21 June 2007; revised 9 July 2007; accepted 10 July 2007
Available online 13 July 2007

Abstract—Stereoselective formation of carbocycles was carried out through $[RhCl(cod)]_2$-catalyzed reactions of alkenylzirconocene chloride to ω-carbonyl-α,β-ene carbonyls (ketone, ester, and amide) or to bis-enone derivatives. The Rh(I)-catalyzed reaction of alkenylzirconocene chloride with ω-carbonyl-α,β-enoyl amide, which is derived from Oppolzer's sultam, showed high diastereoselectivity to yield an carbocycle (95% yield, >95% de).

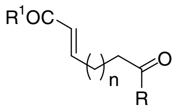
1. Introduction

Additions of carbon nucleophiles to unsaturated bonds are important tactics in organic synthesis. Particularly, the importance of the 1,4-conjugate addition of organometallic reagents to α,β-unsaturated carbonyls has been well recognized, and thus, various organometallic reagents for the purpose of the 1,4-conjugate additions have been devised.[1] Recently, we reported Rh(I)-catalyzed 1,4-additions of alkenylzirconocene chloride complex **1** to activated alkenes such as α,β-ene carbonyls (-ketone, -ester or amide) (Scheme 1).[2]



Scheme 1. Rh(I)-catalyzed 1,4-addition of **1**.

In the course of our study on organozirconocene chloride complexes, we envisioned the formation of carbocycles through the Rh(I)-catalyzed reaction of **1** with ω-carbonyl-α,β-ene carbonyls **2** or bis-α,β-enone **3** compounds.[3] We report herein the stereoselective formation of carbocycles by a cascade process: (i) the 1,4-conjugate addition of **1** and (ii) the subsequent intramolecular aldol or 1,4-conjugate addition reaction.



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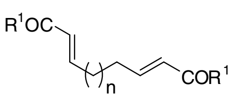

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2. Results and discussion

In the beginning, the reaction of ω-keto α,β-enone **2** was examined, and the results are listed in Table 1. Thus, the $[RhCl(cod)]_2$ (2 mol %)-catalyzed reaction of (*E*)-3,3-dimethyl-1-butenyl zirconocene chloride complex (**1a**)[4] with ω-keto α,β-enone **2a** in toluene at 0 °C for 0.5 h afforded a cyclization product **4a** stereoselectively (93%de) in a good yield (79%) (entry 1). Changing the solvent to THF showed a slight decrease of the stereoselectivity to 73%de in 77% chemical yield (entry 2), and the use of dioxane or CH_2Cl_2 as a solvent at 0 °C gave poor results (entry 3). As expected, the carbonyl group of the α,β-ene carbonyl in **2** is not restricted to ketone,[2] and thus, ester and amide carbonyls gave cyclization products **4c** and **4d**, respectively, in excellent yields

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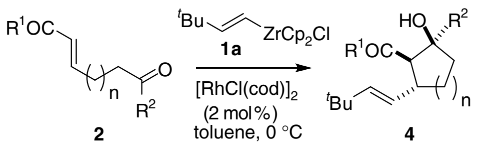
doi:10.1016/j.tetlet.2007.07.056

Table 1. Formation of **4**



Entry	R1	R2	n	2	Yield[a] (%)	de[b] (%)	4
1	C_6H_5	CH_3	2	**2a**	79	93	**4a**
2				**2a**	77[c]	73	**4a**
3				**2a**	33[d]	—	**4a**
4	CH_3	CH_3	2	**2b**	50	28	**4b**
5	OC_2H_5	CH_3	2	**2c**	91	86	**4c**
6	*N*-Pyperidyl	CH_3	2	**2d**	76	>95	**4d**
7	C_6H_5	H	2	**2e**	71	84	**4e**
8	C_6H_5	CH_3	1	**2f**	88	85	**4f**
9	CH_3	CH_3	1	**2g**	80	86	**4g**
10	OC_2H_5	CH_3	1	**2h**	92	88	**4h**
11	C_6H_5	CH_3	3	**2i**	—[e]		

[a] Isolated yields.

[b] Diastereomeric excess (de) was determined by HPLC and ^{1}H NMR.

[c] Solvent: THF.

[d] Solvent: dioxane. 15% yield in CH_2Cl_2.

[e] Only 1,4-addition product was obtained in 75% yield.

under the identical conditions (entries 5 and 6). It is worth noting that the formation of **4e** indicates the tolerance of ω-aldehyde for the initial attack of the vinyl group (entry 7).[5] Although five- and six-membered ring compounds were obtained in excellent yields and selectivity (entries 1–10), the formation of seven-membered ring is unsuccessful (entry 11). The stereochemistry of the major products **4** was determined as shown in Table 1 by ^{1}H NMR analysis.[6]

The formation of **4** is a result of a series of reactions; (i) the formation of alkenyl Rh(I) species (transmetalation), (ii) the 1,4-addition of the alkenyl Rh(I) to the α,β-enone portion of **2** giving **5**, and (iii) the intramolecular aldol reaction of the enolate **5** with the ω-carbonyl group (Fig. 1). The stereochemical outcome of products **4** suggests that the reaction of (*Z*)-Rh(I)-enolate **5** with the ω-carbonyl group proceeds through six-membered chair-form transition state **A** (Scheme 2) as proposed by Krische et al.[3] It should be mentioned that the reaction of *alkyl*zirconocene chloride complex instead of alkenylzirconocene complex **1** turned out to be inefficient under the present conditions. This is considered to be the result of the inefficiency of the *alkyl*zirconocene complex in the transmetalation step.[2]

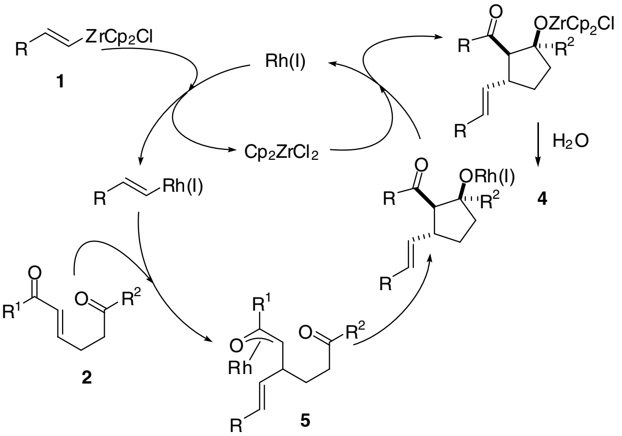
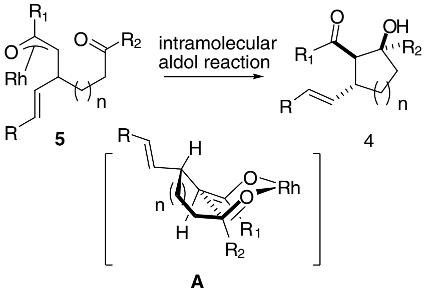


Figure 1. Catalytic cycle for the formation of **4**.



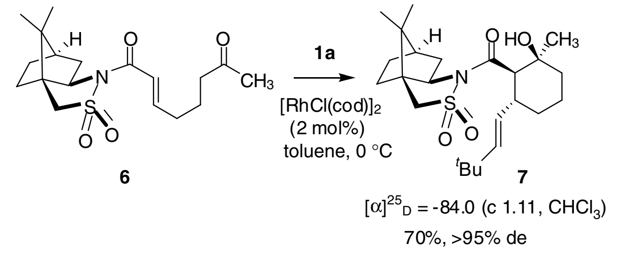
Scheme 2. Intramolecular aldol reaction of Rh(I) (*Z*)-enolate.

Recently, Oi[7] and Nicolaou[8] groups reported highly enantioselective additions of **1** to α,β-enones by the use of $[Rh(cod)(MeCN)_2]BF_4$-(*R*)-BINAP catalyst system. The application of the enantioselective protocol to **2a**–**d**, however, gave mostly racemic products albeit excellent chemical yields (>90%), and other examined ligands such as Chiraphos, Pyraphos, Duphos etc., provided us with a disappointingly poor induction of enantiomeric excess (ee) in less than 20% ee.[9]

Thus, we turned our attention to the use of a chiral amide auxiliary based on the excellent reactivity of amide compound **2d** in the present ring formation (see, Table 1, entry 6). As the chiral amide auxiliary, Oppolzer's chiral sultam[10] was used since the highly diastereoselective 1,4-addition of **1** to α,β-enoyl chiral sultam under the Rh(I)-catalyzed conditions has been established by us.[2]

The reaction of **1a** with chiral sultam **6** under the established conditions for the formation of **4** gave cyclization product **7** in 70% chemical yield with excellent diastereoselectivity (>95% de), and the relative and absolute stereochemistry of **7** was confirmed by a single crystal X-ray analysis as shown in Scheme 3.[11] It should be mentioned that the Rh(I)-catalyzed reaction of alkenylzirconocene chloride complex **1** has been suggested proceeding through a nonchelating mechanism.[2] Thus, the absolute stereochemistry of **7** indicates that the π-facial differentiation of the alkenyl group of **6** for the initial attack of vinyl group could be explained by taking into consideration either of the reactive conformer **B** or **C** (Fig. 2); (i) *s*-cis C=O/S=O and *s*-cis C=O/C=C in conformer **B** as proposed for the reaction of OsO_4 oxidation[10] or (ii) *s*-trans C=O/S=O and *s*-cis C=O/C=C in conformer **C** as proposed for the reaction of the 1,3-dipolar cycloaddition of nitrile oxide.[12] No matter which reactive conformer is, the attack of the vinyl group to the less crowded C_β *si*-face would explain the observed chirality.

The Rh(I)-catalyzed reactions of ω-carbonyl-α,β-enones **2** with **1** prompted us to examine bis-enone compounds **3** which would be expected to yield carbocycles **8** through the initial 1,4-conjugate addition of the vinyl



$[\alpha]^{25}_D = -84.0$ (c 1.11, $CHCl_3$)
70%, >95% de

Scheme 3. Reaction of chiral sultam **6**.

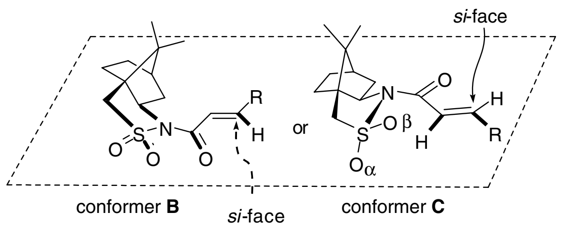
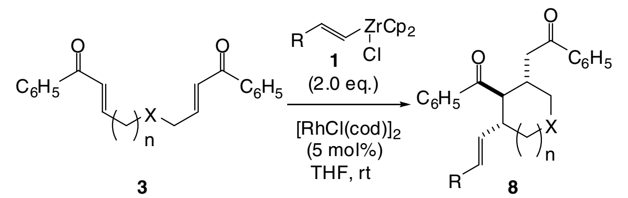


Figure 2. Transition state models for **6**.

group and the subsequent intramolecular 1,4-conjugate addition. The reactions of bis-enone compounds **3** with various organometallic reagents have been reported to show a peculiar reactivity of **3** giving the reductive cyclization product depending on the organometallic reagent and catalyst employed.[13,14]

The results of the Rh(I)-catalyzed reactions of **3** with **1** are listed in Table 2. The addition of **1** (2 equiv) to bis-enone **3** in THF (0.033 M) in the presence of $[RhCl(cod)]_2$ (5 mol %) at ambient temperature afforded a cyclization product **8** as a single stereoisomer along with bis vinyl 1,4-addition product **9**. The reaction was effective for five- and six-membered ring formation as in the reactions of **2** (entries 1–9). The stereochemistry of the cyclization product **8** was determined by NMR analysis.[15] Attempted preparation of a seven-membered ring ended with the formation of a mixture of mono vinyl 1,4-addition (46% yield) and bis vinyl 1,4-addition (23% yield, a mixture of diastereomers) products, and no cyclization product was observed in the reaction mixture (entry 10). It should also be mentioned that the reaction of bis α,β-ene-ester did not give even six-membered carbocycles but gave a mixture of mono- and bis 1,4-addition (a mixture of diastereomers) products in 54% and 28% yields, respectively. The stereoselective formation of **8** by a mechanism involving sequential conjugate additions showed the identical stereoselectivity with the reported example.[13a]

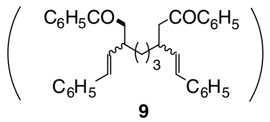
Table 2. Reactions of bis enone **3**



Entry	**1** R	**3** X	n	Time (h)	**8** Yield[a] (%)
1	^{t}Bu **1a**	CH_2 **3a**	1	17	70 **8a**
2	*n*Bu **1b**	**3a**	1	8	71 **8b**
3	C_6H_5 **1c**	**3a**	1	5	73 **8c**[b]
4	**1a**	O **3b**	1	10	70 **8d**
5	**1c**	O **3b**	1	10	62 **8e**
6	**1a**	$C(CO_2C_2H_5)_2$ **3c**	1	1	89 **8f**
7	**1a**	NTs **3d**	1	1	73 **8g**
8	**1a**	CH_2 **3e**	0	5	86 **8h**
9	**1c**	**3e**	0	16	88 **8i**
10	**1a**	CH_2 **3f**	2		—[c]

[a] Isolated yield.

[b] Formation of bis-1,4-addition side-product **9** (16%).



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[c] Formation of a mixture of bis- (23%) and mono-1,4-addition (46%) products.

In summary, the Rh(I)-catalyzed 1,4-conjugate addition reaction of the alkenylzirconocene chloride complex was extended to stereoselective formations of five- and six-membered carbocycles. The procedure was applied to the preparation of an enantiomerically pure carbocycle through the use of Oppoltzer's chiral sultam auxiliary. Although the enantioselective procedure by the use of chiral catalyst for the corresponding ring formation was unsatisfactory, the diastereoselective preparation of the carbocycle using chiral auxiliary would indicate the usefulness of the vinylzirconocene chloride complex as a reagent for the organic synthesis.

3. Typical experimental procedure

Preparation of **4**: Under an Ar atmosphere, to a solution of **1** (1.25 mmol) in toluene (4 mL) was added a solution of **2** (0.5 mmol) and $[RhCl(cod)]_2$ (2 mol %) in toluene (1 mL) at 0 °C, and the solution was stirred at the same temperature for 0.5 h. After being quenched with aqueous $NaHCO_3$, the mixture was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography using hexane–ethyl acetate to give **4**.

Preparation of **8**: Under an Ar atmosphere, to a solution of **1** (1.25 mmol) in THF (14 mL) was added a solution of **3** (0.5 mmol) and $[RhCl(cod)]_2$ (5 mol %) in THF (1 mL) at ambient temperature, and the solution was stirred at the same temperature for 3–8 h. After being quenched with aqueous $NaHCO_3$, the mixture was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography using hexane–ethyl acetate to give **8**.

Acknowledgment

This research was supported by Grant-in-Aid for Scientific Research (C) (16590017), Japan Society for the promotion of Science (JSPS).

References and notes

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3. By the use of organoboronic acid as an organometallic reagent, tandem conjugate addition-aldol cyclization reactions of **2** under Rh(I)-catalyzed conditions have been reported. See, Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110, and references cited therein.
4. A solution of **1a** in the indicated solvent was prepared by (i) the hydrozirconation of ^{t}Bu-acetylene (1.2 equiv) with $Cp_2Zr(H)Cl$ in CH_2Cl_2 (4 mL/mmol) at ambient temperature, (ii) concentration of the solution to dryness in vacuo, and addition of the required solvent. We used **1a** for most of the examined cases because of its NMR simplicity.
5. As a side product, 1,2-addition product to ω-aldehyde was obtained in 12% yield.
6. *Representative characterization data*; Compound **4a**: colorless crystals, mp 83–85 °C. IR (KBr) ν 3435, 1648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 9H), 1.11 (s, 3H), 1.19–1.92 (m, 6H), 2.60–2.69 (m, 1H), 3.28 (d, $J = 11.2$ Hz, 1H), 4.50 (s, 1H), 4.87 (dd, $J = 8.9$, 15.6 Hz, 1H), 5.26 (d, $J = 15.5$ Hz, 1H), 7.45–7.89 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6, 29.1, 30.1, 32.3, 32.6, 38.5, 41.7, 55.9, 70.6, 126.6, 128.5, 128.6, 133.4, 138.9, 141.9, 208.5. ESIMS m/z 323 $(M+Na)^+$; HRMS Calcd for $C_{20}H_{28}O_2Na$: 323.1987. Found: 323.2003.
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9. It should be mentioned that the reaction of organoboronic acid with **2** under $[Rh(cod)(MeCN)_2]BF_4$-(*R*)-BINAP-catalyzed conditions has been reported to give **4** in a high enentioselectivity. See, Ref. 3. In the reaction of **1a** with **2a**, (*S*,*S*)-Chiraphos showed a slight enantioselectivity (20% ee). Other enoyl compounds such as, ester **2c** and amide **2d**, afforded unsatisfactory results (<20% ee) by the use of other chiral ligands.
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11. Deposited Data-CCDC 651166 contains the supplementary crystallographic data for **7**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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14. Recently, we reported Pd(0)-catalyzed reactions of *acylzirconocene chloride* with compounds **2** and **3**. In these reactions, we indicated that the reaction of **3** afforded bicyclo[3.3.0] compounds without the incorporation of acyl group of *acylzirconocene chloride*. Available online; Hanzawa, Y.; Oka, Y.; Yabe, M. *J. Organomet. Chem.* **2007**, 10.1016/j.jorganchem.2007.04.033. Similar observations have been made in Ni(0)-catalyzed reaction of **3** with nBu$_2$Zn or in the reaction of **3** with cuprate. See, 13a and 13e.
15. *Representative characterization data*; Compound **8a**: colorless crystals, mp 95–97 °C. IR (KBr) ν 1681, 1664 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.59 (s, 9H), 1.12–1.46 (m, 3H), 1.74–1.85 (m, 3H), 2.21–2.32 (m, 1H), 2.43–2.61 (m, 2H), 2.97 (dd, $J = 2.0$, 13.3 Hz, 1H), 3.29 (t, $J = 10.4$ Hz, 1H), 4.93 (dd, $J = 6.8$, 15.6 Hz, 1H), 5.23 (d, $J = 15.6$ Hz, 1H), 7.40–7.96 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 29.1, 31.0, 32.3, 33.0, 37.4, 44.2, 46.2, 55.0, 127.0, 128.3, 128.4, 128.5, 128.5, 132.9, 132.9, 136.7, 139.3, 141.6, 199.4, 205.4. FAB-HM Calcd for $C_{27}H_{33}O_2$: 389.2495. Found: 389.2472. Anal. Calcd for $C_{27}H_{32}O_2$: C, 83.46; H, 8.30. Found: C, 83.16; H, 8.24.