The Asymmetric [3+2] Cycloaddition Reaction of Chiral Alkenyl Fischer Carbene Complexes with Imines: Synthesis of Optically Pure 2,5-Disubstituted-3-pyrrolidinones

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Alkenyl Fischer carbene complexes have been widely utilized as versatile synthons in various kinds of synthetic reactions such as cycloaddition reactions and Michael addition reactions.[1] Asymmetric versions of these reactions using chiral alkenyl Fischer carbene complexes have been proved to be powerful tools for the synthesis of a wide variety of optically active compounds.[2−4] We have recently reported a novel [3+2] cycloaddition reaction of alkenyl Fischer carbene complexes with imines leading to 3-alkoxy-2,5-disubstituted-3-pyrroline derivatives, which were readily converted into the corresponding 2,5-disubstituted-3-pyrrolidinone derivatives.[5] We anticipated that asymmetric [3+2] cycloaddition reactions would provide a successful method for the synthesis of optically active 2,5-disubstituted-3-pyrrolidinone derivatives. A literature survey reveals that no straightforward procedures to obtain these compounds in optically active forms have been reported. Their potential applications in organic synthesis and their biological activity thus have to be elucidated. We now report the asymmetric [3+2] cycloaddition reaction of chiral alkenyl Fischer carbene complexes with imines, demonstrating its successful application to the syntheses of optically pure 2,5-disubstituted-3-pyrrolidinone derivatives.

First we examined the asymmetric [3+2] cycloaddition reaction of chiral alkenyl Fischer carbene complexes **2a**−**d** prepared from (−)-menthol,[4c] (−)-8-phenylmenthol,[4c] (−)-1-phenylethanol, and (−)-borneol, respectively, with imine **1a** utilizing our standard protocol (Scheme 1, 1.2 equiv of **1a**, 1.0 equiv of **2a**−**d**, and 20 mol % of $GaCl_3$).[5] The results are summarized in Table 1, entries 1−4. The reaction of **2a** with **1a** proceeded smoothly to afford the corresponding adducts in 60% yield as a mixture of four diastereomers (entry 1, trans:cis = 76(75:25):24(76:24)). The absolute configuration of the major trans diastereomer was determined to be 2*S*,5*R* by an X-ray analysis.[6] Although the reaction with **2b** lowered trans/cis selectivity, diastereofacial selectivity of the trans diastereomers was dramatically improved to 95:5 (entry 2). The reaction of **2c** with **1a** led to acceptable results with regard to both trans/cis- and diastereofacial selectivities (entry 3), while the reaction of **2d** proceeded in a nonselective manner (entry 4). Reexamination of the additive in the reaction of **2b** with **1a** showed that both trans/cis- and diastereofacial selectivities highly depend on the additives used (Table 1, entries 5−8). Gratifyingly, $Sn(OTf)_2$ exhibited the highest trans/cis selectivity (84:16) while maintaining excellent diastereofacial selectivity (95:5) (entry 8). The use of other additives gave inferior results. On the basis of these results, the complexes derived from (−)-8-phenylmenthol and $Sn(OTf)_2$ as an additive were used for subsequent reactions.

The asymmetric [3+2] cycloaddition reaction of complexes **2b**,**e**−**g** with a variety of imines **1a**−**f** was carried out under the conditions described above (Scheme 2), and the results are shown in Table 2.[6,7] Various kinds of aromatic imines were used as substrates (entries 1−6). The corresponding adducts were obtained in good yields with good diastereoselectivity. Dramatic changes in selectivity are noted when substituents on the β-carbon in the complex were replaced with *p*-methoxyphenyl or 2-furyl groups. When **2e** was allowed to react with **1a**, trans/cis selectivity was diminished to 45:55, although diastereofacial selectivity was still high (entry 7). Furthermore, the reaction of **2g** with **1a** took place with good cis selectivity (entry 9).

Scheme 1

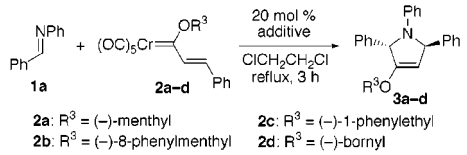

Table 1. Effect of Chiral Auxiliaries and Additives in the Asymmetric [3+2] Cycloaddition Reaction of Chiral Alkenyl Fischer Carbene Complexes **2a**−**d** with Imine **1a**[a]

entry	2	additive	3	yield (%)	trans:cis[b]
1	**2a**	$GaCl_3$	**3a**	60	76(75:25):24(76:24)
2	**2b**	$GaCl_3$	**3b**	51	48(95:5):52(94:6)
3[c]	**2c**	$GaCl_3$	**3c**	69	85(70:30):15(72:28)
4	**2d**	$GaCl_3$	**3d**	60	46(57:43):54(50:50)[d]
5	**2b**	$TiCl_4$	**3b**	47	86(85:15):14(82:18)
6	**2b**	$BF_3{\cdot}OEt_2$	**3b**	47	62(92:8):38(78:28)
7	**2b**	TMSOTf	**3b**	47	80(74:26):20(63:37)
8	**2b**	$Sn(OTf)_2$	**3b**	51	84(95:5):16(94:6)

[a] Molar ratio: **1a**:**2**:additive = 1.2:1.0:0.2. [b] Determined by ^1H NMR. The values in parentheses represent the diastereofacial selectivities of each diastereomer. [c] Reaction time: 1 h. [d] The absolute configuration of the major trans diastereomer was not determined.

Scheme 2

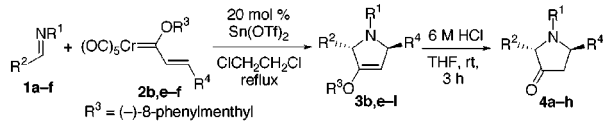

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Table 2. Asymmetric [3+2] Cycloaddition Reaction of Chiral Alkenyl Fischer Carbene Complexes **2b**,**e**−**g** with Imines **1a**−**f**[a] and Hydrolysis of the Products **3b,e**−**i,k,l** into 3-Pyrrolidinones **4a**−**h**

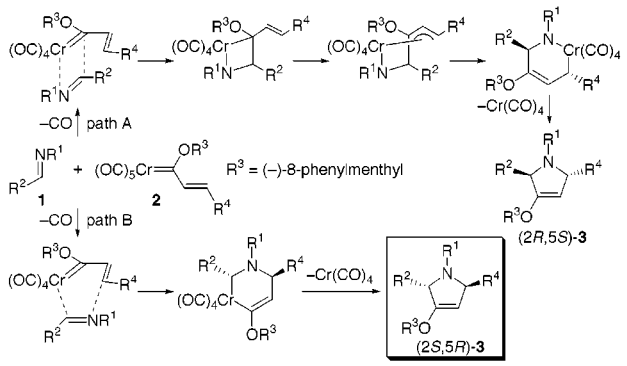
entry	**1**	R^1	R^2	**2**	R^4	time (h)	**3**	yield (%)[b]	trans:cis[c]	**4**	yield (%)[d]	ee (%)[e,f]
1	**1a**	Ph	Ph	**2b**	Ph	3	**3b**	51(34)	84(95:5):16(94:6)	**4a**	96	>99
2	**1b**	*p*-MeC_6H_4	Ph	**2b**	Ph	4	**3e**	50(31)	79(92:8):21(85:15)	**4b**	91	>99
3	**1c**	*p*-$MeOC_6H_4$	Ph	**2b**	Ph	4	**3f**	48(30)	76(88:12):24(73:27)	**4c**	93	>99
4	**1d**	Ph	*p*-MeC_6H_4	**2b**	Ph	4	**3g**	46(35)	84(92:8):16(85:15)	**4d**	92	>99
5	**1e**	Ph	*p*-$MeOC_6H_4$	**2b**	Ph	4	**3h**	50(30)	83(91:9):17(72:28)	**4e**	90	>99
6	**1f**	Ph	*p*-ClC_6H_4	**2b**	Ph	4	**3i**	45(27)	80(91:9):20(84:16)	**4f**	95	>99
7	**1a**	Ph	Ph	**2e**	*p*-$MeOC_{60}H_4$	6	**3j**	30	45(94:6):55(90:10)			
8	**1a**	Ph	Ph	**2f**	*p*-ClC_6H_4	4	**3k**	46(27)	85(84:16):15(76:24)	**4g**	98	>99
9	**1a**	Ph	Ph	**2g**	2-furyl	4	**3l**	40(21)	25(91:9):75(91:9)	**4h**	85	96[g]

[a] Molar ratio: **1**:**2**:$Sn(OTf)_2$ = 1.2:1.0:0.2. [b] Yield of cycloaddition reaction. The values in parentheses represent yield of the diastereomerically pure products (>97%) after chromatography. [c] Determined by ^1H NMR. The values in parentheses represent the diastereofacial selectivities of each diastereomer. [d] Yield of hydrolysis. [e] Ee is measured on **4** that was obtained by hydrolysis of the purified major diastereomer of **3**. [f] Determined by HPLC (Chiralcel OD). [g] Determined by HPLC (Chiralcel OJ).

The major isomer of the trans product can be separated from the crude reaction mixture by chromatography to give material of high purity (>97% purity judged by ^1H NMR, 76−52% recovery). Furthermore, these purified products were successfully converted into the corresponding optically pure 3-pyrrolidinone derivatives **4a**−**h** in excellent yields by hydrolysis with 6 M HCl in THF, and (−)-8-phenylmenthol was recovered in high yield (>90%) (Table 2).

It should be noted that the diastereofacial selectivity of the present asymmetric [3+2] cycloaddition reaction is opposite to those of previously reported cycloaddition reactions[3d−h] and Michael addition reactions[4b,c,e] using (−)-8-phenylmenthyloxy-substituted alkenyl Fischer carbene complexes. Thus, the observed diastereofacial selection of the present reaction cannot be interpreted in terms of the well-known model, in which the chiral auxiliary phenyl group in the complex shields selectively the *Re*,*Re* face of the alkenyl moiety, allowing the nucleophiles to attack from the *Si*,*Si* face. This observation strongly indicates that the present reaction does not occur by a simple Michael addition. On the other hand, it was found that applying the mechanism which we have proposed in a previous paper[5] into the asymmetric reaction leads to an incorrect stereochemistry of the major product (2*R*,5*S*) if it is assumed a [2+2] cycloaddition reaction occurs between the Cr−C double bond and the C−N double bond, in which the imine approaches from the less hindered *Si* face of the Cr−C double bond (Scheme 3, path A). On the basis of these facts, we propose an alternative mechanism, which is outlined in Scheme 3. The observed stereochemistry can be explained by assuming a [4+2] cycloaddition reaction between the tetracarbonyl chromadiene system[8] and the C−N double bond in the imine via an s-cis conformation of the complex, where the imine approaches from the less hindered *Si* face of the complex (path B). Formation of six-membered chromacycles via a [4+2] cycloaddition reaction

Scheme 3



of chromadienes with C−C unsaturated compounds has been proposed in some reactions.[9] The resultant chromacycle would then lead to the 2*S*,5*R* isomer by reductive elimination of the chromium moiety.

In summary, the asymmetric [3+2] cycloaddition reaction of chiral alkenyl Fischer carbene complexes derived from (−)-8-phenylmenthol with imines has been achieved in the presence of a catalytic amount of $Sn(OTf)_2$. In addition, we have demonstrated that the present asymmetric [3+2] cycloaddition reaction provides a new methodology for the synthesis of optically pure 2,5-disubstituted-3-pyrrolidinone derivatives.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and X-ray structural information on **4f** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The diastereomer ratio was determined by a ^1H NMR analysis, and assignment of trans and cis configurations was based on the ^1H NMR coupling constants as we reported.[5] In addition, the absolute configuration of the major trans diastereomers was determined to be 2*S*,5*R*, except for **3j** and **3l**, as follows: An X-ray crystallographic analysis of **4f** using the anomalous scattering contribution of chlorine atom established its absolute configuration to be 2*S*,5*R*. Thus, the absolute configuration of the original major product **3i** must be 2*S*,5*R*. Comparison of optical rotation of both **3i** and **4f** to that of **3a**−**c**,**e**−**i**,**k**, and **4a**−**f**,**g** allows the determination of the absolute configuration as shown above. For **3j** and **3l**, the relative configuration was assigned to be cis on the basis of the ^1H NMR coupling constants, and the absolute configuration was not determined.

(7) In most experiments compounds $R^4CH{=}CHC(OR^3){=}CHR^2$ were isolated in 9−2% yields as byproducts along with a considerable amount of polar, unidentified products.

(8) When the reaction of isopropoxy-substituted complex **2** (R^3 = *i*Pr, R^4 = Ph) with imine **1a** was carried out in a CO atmosphere (5 MPa CO, 20 mol % $GaCl_3$, $ClCH_2CH_2Cl$, 85 °C), the complex was recovered in 92% yield and only a trace amount of the corresponding product was detected. This result strongly suggests the formation of a coordinatively unsaturated, tetracarbonyl species is critical for the subsequent cycloaddition reaction.

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