

### Novel [3 + 2] Cycloaddition Reaction of Alkenyl Fischer Carbene Complexes with Imines Leading to 3-Pyrroline Derivatives

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Received June 22, 2000

Fischer carbene complexes have attracted much attention of synthetic chemists because of their diverse reactivity toward unsaturated bonds.<sup>1</sup> Indeed, they have been widely used for cycloaddition reactions with olefins, giving cyclopropanes.<sup>1b,2</sup> On the other hand, alkenyl Fischer carbene complexes, which are attractive substrates as three-carbon synthons, reacted with both alkenes and dienes to afford cyclopentenes<sup>3</sup> and cycloheptadienes,<sup>1a,4</sup> respectively. Fischer carbene complexes also participated in the synthesis of aza heterocycles,<sup>5–7</sup> wherein imines have been often used as nitrogen sources.<sup>5,6d,e,g–j,7</sup> As part of our continued interest in the reaction of imines,<sup>8</sup> we have developed a novel [3 + 2] cycloaddition reaction of alkenyl Fischer carbene complexes with simple imines. In this communication, we would like to present that alkenyl Fischer chromium carbene complexes react with

**Table 1.** Effect of Additives in the [3 + 2] Cycloaddition Reaction of Alkenyl Carbene Complex **2a** with Imine **1a**<sup>a</sup>

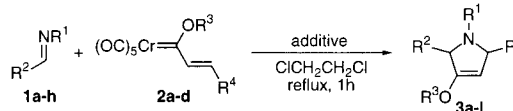
entry	additive	yield (%)	trans:cis <sup>b</sup>
1	none	55	84:16
2	ZnCl <sub>2</sub>	60	91:9
3	BF <sub>3</sub> ·OEt <sub>2</sub>	65	80:20
4	GaCl <sub>3</sub>	72	78:22
5 <sup>c</sup>	GaCl <sub>3</sub>	82	81:19
6	TMSOTf	69	78:22
7	Sn(OTf) <sub>2</sub>	68	80:20

<sup>a</sup> Molar ratio; **1a**:**2a**:additive = 1.0:1.0:0.1. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Molar ratio; **1a**:**2a**:additive = 1.2:1.0:0.2.

various kinds of simple imines to produce 3-pyrroline derivatives in the presence of a catalytic amount of GaCl<sub>3</sub>. This is the first example of the reaction of alkenyl Fischer carbene complex with imines leading to 3-pyrroline derivatives, which are important intermediate for the synthesis of natural and biologically active compounds.<sup>9</sup>

First, the reaction of alkenyl Fischer carbene complex **2a** (R<sup>3</sup> = Me, R<sup>4</sup> = Ph) with imine **1a** (R<sup>1</sup> = R<sup>2</sup> = Ph) was chosen as a model reaction (Scheme 1). When a mixture of **1a** (1.0 equiv)

#### Scheme 1



and **2a** (1.0 equiv) was allowed to reflux in 1,2-dichloroethane for 1 h, the corresponding cycloadduct **3a** was obtained in 55% yield as a mixture of diastereomers (84:16, determined by 400 MHz <sup>1</sup>H NMR, Table 1, entry 1). The regioselectivity was quite high, and no regioisomeric product was detected. It should be noted that the regioselectivity in the present reaction is quite different from that of the [4 + 3] cycloaddition reactions of alkenyl carbene complexes with 1-amino-1,3-dienes;<sup>7a,b</sup> the new C–N bond was formed between the  $\beta$ -carbon in the alkenyl carbene complex and the nitrogen in the imine. This fact rules out the initial attack of the nitrogen in the imine to the carbene carbon as proposed in the several reactions of Fischer carbene complexes with nitrogen-containing compounds.<sup>7b,d,10</sup> The stereochemistry of the major diastereomer of **3a** was unambiguously determined to be trans by an X-ray crystallographic analysis (see Supporting Information).

Next, to improve the yield, we have examined the effect of additives. Although transition metal compounds (10 mol %) such as RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (6%), [Rh(OAc)<sub>2</sub>]<sub>2</sub> (20%), PdCl<sub>2</sub>(PhCN)<sub>2</sub> (0%), and Cu(OTf)<sub>2</sub> (49%) were not effective as additives, addition of some Lewis acids greatly improved the yields (Table 1, entries 2–7). Among the Lewis acids examined, GaCl<sub>3</sub> (10 mol %) was the most effective; the yield was improved while maintaining the good diastereoselectivity (72%, trans:cis = 78:22, entry 4). TMSOTf and Sn(OTf)<sub>2</sub> were equally effective (entries 6 and 7). The highest yield was obtained when slightly excess amount of **1a** (1.2 equiv) and 20 mol % GaCl<sub>3</sub> were employed (82%, trans:cis = 81:19, entry 5).<sup>11</sup>

The [3 + 2] cycloaddition reaction of a variety of alkenyl Fischer carbene complexes with imines was carried out under

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**Table 2.** [3 + 2] Cycloaddition Reactions of Alkenyl Carbene Complexes **2a–e** with Imines **1a–h** in the Presence of GaCl<sub>3</sub><sup>a</sup>

entry	imine <b>1</b>	R <sup>1</sup>	R <sup>2</sup>	complex <b>2</b>	R <sup>3</sup>	R <sup>4</sup>	time (h)	product	yield (%)	trans:cis <sup>b</sup>
1	<b>1a</b>	Ph	Ph	<b>2a</b>	Me	Ph	1	<b>3a</b>	82	81:19
2	<b>1a</b>	Ph	Ph	<b>2b</b>	Bn	Ph	1	<b>3b</b>	81	85:15
3	<b>1a</b>	Ph	Ph	<b>2c</b>	<i>i</i> -Pr	Ph	1.5	<b>3c</b>	80	86:14
4 <sup>c</sup>	<b>1a</b>	Ph	Ph	<b>2c</b>	<i>i</i> -Pr	Ph	2	<b>3c</b>	78	90:10
5	<b>1a</b>	Ph	Ph	<b>2d</b>	<i>i</i> -Pr	2-furyl	2	<b>3d</b>	77	81:19
6	<b>1a</b>	Ph	Ph	<b>2e</b>	<i>i</i> -Pr	2-styryl	2.5	<b>3e</b>	66	78:22
7	<b>1b</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ph	<b>2c</b>	<i>i</i> -Pr	Ph	1.5	<b>3f</b>	81	87:13
8	<b>1c</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ph	<b>2c</b>	<i>i</i> -Pr	Ph	1	<b>3g</b>	86	83:17
9	<b>1d</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ph	<b>2c</b>	<i>i</i> -Pr	Ph	2	<b>3h</b>	64	78:22
10	<b>1e</b>	Ph	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>2c</b>	<i>i</i> -Pr	Ph	1.5	<b>3i</b>	81	89:11
11	<b>1f</b>	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>2c</b>	<i>i</i> -Pr	Ph	1	<b>3j</b>	84	92:8
12	<b>1g</b>	Ph	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>2c</b>	<i>i</i> -Pr	Ph	2	<b>3k</b>	65	85:15
13	<b>1h</b>	Bn	Ph	<b>2c</b>	<i>i</i> -Pr	Ph	1.5	<b>3l</b>	70	79:21
14 <sup>c</sup>	<b>1h</b>	Bn	Ph	<b>2c</b>	<i>i</i> -Pr	Ph	1.5	<b>3l</b>	70	80:20

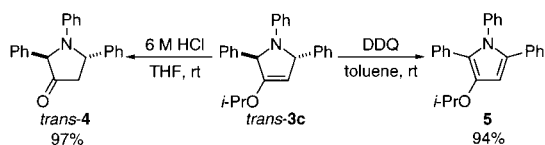
<sup>a</sup> Molar ratio; **1**:**2**:GaCl<sub>3</sub> = 1.2:1.0:0.2. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> One-pot reaction.

the optimized conditions described above (Scheme 1, Table 2).<sup>12</sup> It was found that bulkiness of the alkoxy substituents (OR<sup>3</sup>) slightly affected the diastereoselectivities in the reactions; bulkier alkoxy substituents exhibited the better selectivities (entries 1–3). Isopropoxy substituted complexes **2c–e**, being readily accessible, were used for further reactions. Replacement of the phenyl group on the β-carbon in the complex with either 2-styryl or 2-furyl groups also worked well to furnish the corresponding adducts **3d** and **3e** (entries 5 and 6). A variety of aromatic imines, derived from both *p*-substituted benzaldehydes and *p*-substituted anilines, could be used for the present [3 + 2] cycloaddition reactions. In all cases, the corresponding 3-pyrroline derivatives were obtained in high yields and with good diastereoselectivities (entries 7–12). In addition, the [3 + 2] cycloaddition reaction of *N*-benzyl imine **1h** was also found to be successful (entry 13).

Since it is synthetically convenient if imines were prepared *in situ* and were allowed to react with the complex under one-pot conditions, we examined to apply these reactions to one-pot, three-component synthesis of 3-pyrroline derivatives. As a result, it was found that the preparation of imines from benzaldehyde and aniline or benzylamine in the presence of MS4A in 1,2-dichloroethane followed by treatment of **2c** with 20 mol % GaCl<sub>3</sub> afforded the 3-pyrroline derivatives **3c** (entry 4) and **3l** (entry 14), respectively.

The synthetic utility of *trans*-**3c** is exemplified as below (Scheme 2). Hydrolysis of *trans*-**3c** with 6 M HCl in THF afforded

### Scheme 2



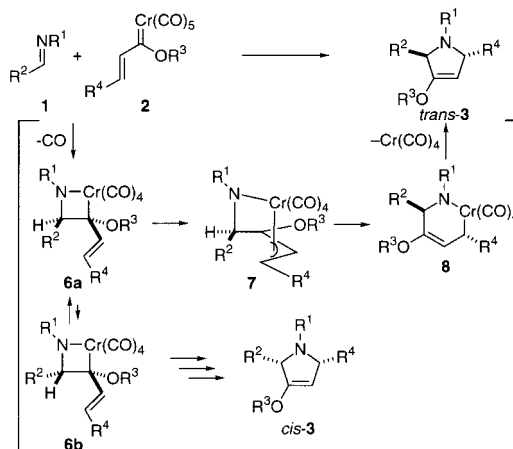
3-pyrrolidinone *trans*-**4** without any epimerization. In addition, *trans*-**3c** could be readily converted into the corresponding 3-isopropoxy pyrrole derivative **5** by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).<sup>13</sup> Although formation of pyrrole derivatives by use of Fischer carbene complexes has been described in several literatures,<sup>6a–f,h–1</sup> the present [3 + 2] cycloaddition reaction should provide a useful alternative route for synthesis of these compounds as well as 3-pyrroline derivatives.

At present, reaction mechanism including the role of Lewis acid is not clear. One of the tentatively proposed mechanisms is

(12) For all cycloadducts, except for **3d** and **3e**, the relative configurations were assigned on the basis of physical analogy with **3a**. The coupling constants ( $J(\text{H}^2-\text{H}^3)$ ) of the *trans* diastereomer of **3a** are 5.6 Hz, whereas those of the *cis* diastereomer of **3a** show smaller values of 2.1 Hz. In addition, the *trans* diastereomer is less polar than the *cis* isomer. The relative configurations of **3d** and **3e** were tentatively assigned since their physical properties were shown to be opposite to **3a**.

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### Scheme 3



outlined in Scheme 3.<sup>14</sup> The [2 + 2] cycloaddition reaction between the Cr–C double bond of the complex **2** and the C–N double bond of the imine **1** leads to two diastereomeric four-membered chromacycles **6a** and **6b**.<sup>15</sup> The fact that increasing the size of the alkoxy group at the carbene carbon improved the diastereoselectivity implies that **6a** would be formed preferentially over **6b**. Formation of a six-membered chromacycle **8** via the  $\eta^3$ -allyl complex **7**,<sup>3b,16</sup> followed by reductive elimination leads to *trans*-**3**.

In conclusion, we have found a novel [3 + 2] cycloaddition reaction of alkenyl Fischer carbene complexes with simple imines, a reaction which afforded 3-alkoxy-2,5-disubstituted-3-pyrroline derivatives in high yields and with good diastereoselectivities. We are currently investigating the substrate scope, the mechanism including the role of Lewis acid, and the development of an asymmetric version of this process.

**Acknowledgment.** Partial financial support from the Japan Society for the Promotion of Science is acknowledged (12740351). We thank Dr. Masato Nanjo (Gakushuin University) for the X-ray structural determination.

**Supporting Information Available:** Experimental procedures, characterization data for compounds **2b–e**, **3a–l**, **4**, and **5**, and X-ray structural information on *trans*-**3a** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA002225F

(14) One of the reviewers suggested another mechanism: A simple Michael addition of the nitrogen in the imine toward the β-carbon in the complex followed by ring closure. A detailed discussion will be presented in the future.

(15) Similar metallacycles had been proposed as reactive intermediates, see refs 5.

(16)  $\eta^3$ -Allyl chromium complexes have been suggested as intermediates in cyclopropanation reactions and [3 + 2] cycloaddition reactions of Fischer carbene complexes with alkenes: Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 8916–8921.