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Intramolecular coupling between cyclohexadiene–Fe(CO)$_3$ complexes and pendant alkenes: formation of azaspiro[5,5]undecane derivatives

Anthony J. Pearson* and Xiaolong Wang

The Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106, USA

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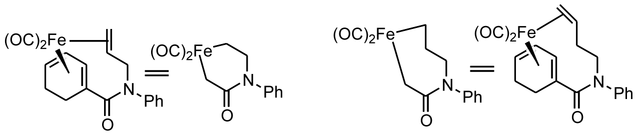
Abstract—A new methodology for making stereodefined 2-azaspiro[5,5]undecan-1-one (δ-lactam) derivatives was developed by intramolecular coupling between cyclohexadiene–Fe(CO)$_3$ moiety and pendant olefins. δ-Lactams were found more difficult to form than γ-lactams, thus resulting in poorer yields and requiring longer reaction times. By introducing an ester group on the pendant olefin, increased yield was achieved. © 2002 Elsevier Science Ltd. All rights reserved.

Stereoselective construction of quaternary[1] and spirocyclic[2] carbon centers remains a challenging problem in synthesis and continues to attract the attention of numerous researchers.[3] We have previously described an interesting and potentially useful cyclization reaction between cyclohexadiene–Fe(CO)$_3$ complexes and pendant alkenes to generate spiro-γ-lactams in excellent yield (Scheme 1, R = H).[4]

Unfortunately, this reaction suffers from pre- and post-cyclization rearrangement to give a pair of epimers and partial loss of absolute stereochemistry.[4a] By introducing a methoxy substituent at the 3-position (Scheme 1, **1**, R = OMe), a γ-lactam was produced stereospecifically after demetallation and hydrolysis of the cyclization product.[5]

In the synthesis of 2-azaspiro[5,5]undecane alkaloids, 2-azaspiro[5,5]undecan-1-one derivatives have frequently been used as intermediates,[6] which attracted our attention. While it seems trivial to construct spiro-δ-lactams similarly using our methodology, evaluation of the reaction mechanism shows that a seven-membered metallacycle is required for the desired δ-lactam formation (6-metallacycle for γ-lactam, Fig. 1). Since formation of seven-membered rings are generally much slower than six-rings,[7] side reactions may predominate during the δ-lactam cyclization. Herein, we report our recent work on azaspiro[5,5]undecane formation by intramolecular coupling between cyclohexadiene–Fe(CO)$_3$ complexes and pendant olefins.

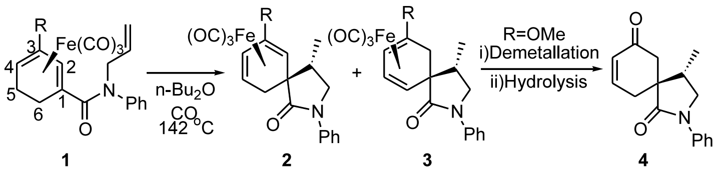
Amide complexes **6** were prepared in very good to excellent yield from acid complexes **5** and the corresponding butenylaniline[8] (Table 1). Heating **6a** under a CO atmosphere gave **7a** and **8a** in 70% yield (Table 2, entry 1). The stereochemistries of **7a** and **8a** were



5-spirolactam intermediate
6-metallacycle

6-spirolactam intermediate
7-metallacycle

Figure 1.



Scheme 1.

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* Corresponding author.

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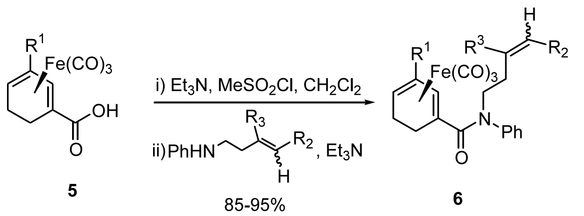
Table 1. Preparation of *N*-butenyl amide complexes

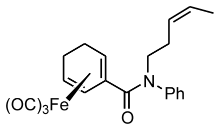


Entry	R$_1$, R$_2$, R$_3$	Amide **6**[a]	Yield (%)
1	H, H, H	**6a**	85
2	OMe, H, H	**6b**	95
3	H, Me, H	**6c**	86
4	OMe, Me, H	**6d**	89
5	H, CO$_2$Me, H	**6e**	89
6	OMe, CO$_2$Me, H	**6f**	94
7	H, H, Me	**6g**	89

[a] Double bonds in **6** are all *cis* except *trans* in **6e**.

determined by comparison of their ^{1}H NMR spectra with the corresponding azaspiro[4,5]decane prepared earlier.[4] Alternative reaction conditions were tested to improve the yield, but without success (Table 2, entries 2 and 3). 3-Methoxy-substituted amide complex **6b** cyclized to give **7b** and **8b** in a yield comparable to that of **6a** (Table 2, entry 4).

In order to test the generality of δ-lactam formation, substitution effects on the pendant double bond were studied. Cyclization of **6c** yielded **7c** and **8c** in only 35% combined yield (Table 2, entry 5) along with regioisomers (**9** and **10**) of **6c** from diene rearrangement. Extension of the reaction time to 48 h produced no appreciable increase in the yield, while **9** and **10** still remained. Reaction of **6d** gave a similar result (Table 2, entry 6).



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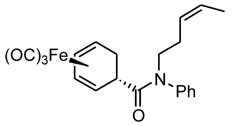

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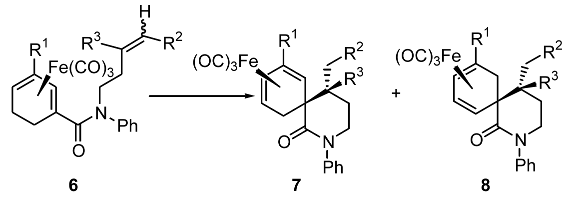
Cyclization products of **6g** gave surprising results. The only expected cyclization product was **7g** (**8g** is actually the enantiomer of **7g**, Table 1, entry 10), which should have two singlets in ^{1}H NMR, each corresponding to one CH$_3$ group. The reaction (n-Bu$_2$O, CO, 142°C, 8 h) gave a pair of epimers as cyclization products, and ^{1}H NMR of the major epimer showed two methyl doublets. Careful examination of its IR spectrum revealed the formation of a γ-spirolactam (1697 cm^{-1}) instead of δ-lactam (around 1660 cm^{-1}), and the ^{1}H NMR was consistent with structure **11**. Thus, isomerization of the pendant double bond, a known process,[4b] followed by cyclization led to **11** and **12** (ratio/2:1) in 30% yield (Scheme 2).

Table 2. Cyclization of **6a**–**g** (R^1, R^2, R^3 as in Table 1)



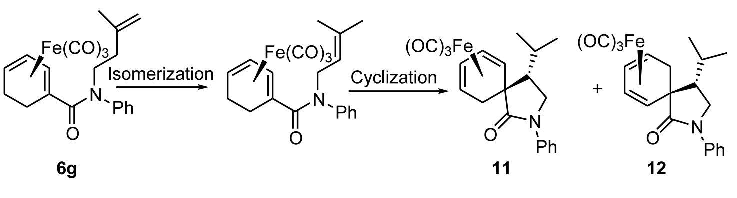
Entry	Reactant	Rxn. cond.[a] (h)	Products[b]	Ratio (**7**:**8**)	Yield: (**7**+**8**)/%
1	**6a**	A (8)	**7a**, **8a**	4:3	70
2	**6a**	B (2.5)			0
3	**6a**	C (24)	**7a**, **8a**	4:3	20
4	**6b**	A (8)	**7b**, **8b**	5:2	65[c]
5	**6c**	A (8)	**7c**, **8c**	1.8:1	35
6	**6c**	B (2.5)			0
7	**6d**	A (8)	**7d**, **8d**	3:1	20
8	**6e**	A (8)	**7e**, **8e**	3:2	80
9	**6f**	A (8)	**7f**, **8f**	2:1	53[d]
10	**6g**	A (8)	**7g**, **8g**		0

[a] A: n-Bu$_2$O, CO, 142°C; B: Rayonet, 350 nm; C: 1.7 equiv. Me$_3$NO, benzene, then CO for 12 h.

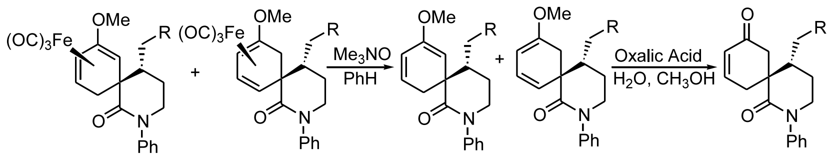
[b] Cyclization products as inseparable mixtures, single recrystallization gave **7**.

[c] Including 5% demetallated product.

[d] Including 13% demetallated product.



Scheme 2.



R = H, **7b** **8b** **13**
R = CO$_2$Me, **7f** **8f** **14**

Scheme 3.

The δ-lactam formation is therefore quite sensitive to substitution on the pendant double bond, and does not compete well with γ-lactam formation, or diene rearrangement. Iron carbonyls form more stable complexes with electron deficient olefins than with ethylene or electron rich olefins.[9] We argued that if we add an electron withdrawing group on the pendant olefin, more efficient coordination to diene–Fe(CO)$_2$ might ameliorate the steric hindrance from the introduced group. Gratifyingly, by introducing an ester group on the terminal position of pendant double bond, cyclization of **6e** gave **7e**, **8e** in 80% yield (Table 1, entry 8) and **6f** gave **7f**, **8f** in 53% yield (Table 1, entry 9), respectively, a good improvement over those of **6c** and **6d**. Moreover, the ester group provides a means of introducing further substitution into the product molecules. Cyclization products from **6b** and **6f** were converted to enones **13** and **14** in about 70% yield (Scheme 3).[5]

In this paper, intramolecular coupling between alkene and diene–Fe(CO)$_3$ moieties to produce azaspiro[5,5]undecane derivatives was shown to be successful. Improved yield was achieved by adding an ester group to the olefin and complete stereocontrol was also demonstrated (**13**, **14**), all of which bodes well for future applications of this chemistry.

Acknowledgements

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