A new route to functionalised π-allyltricarbonyliron lactam complexes from aziridines and their use in stereoselective synthesis and oxidative conversion to β-lactams

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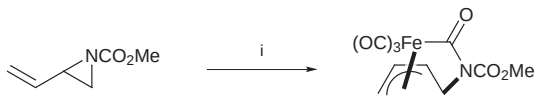
Aziridinyl enones can be converted in good yield into π-allyltricarbonyliron lactam complexes bearing ketone functionality in the side chain; addition of a variety of nucleophiles into the side chains of these complexes proceeds in good yield and excellent (> 95%) de to afford secondary and tertiary alcohols which on treatment with trimethylamine *N*-oxide form the corresponding β-lactams in good yield.

π-Allyltricarbonyliron lactam complexes have been previously investigated as precursors to stereodefined β- and δ-lactams,[1] and have been utilised in the synthesis of several natural products in our laboratory.[2] Previous preparation of these complexes involved the treatment of π-allyltricarbonyliron lactone complexes with a primary amine[3] or the sonochemical reaction of an alkenyl carbamate with $Fe_2(CO)_9$.[2a] In an isolated example, Aumann has also shown that UV irradiation of the vinyl aziridine **1** in the presence of $Fe(CO)_5$ leads to the formation of a π-allyltricarbonyliron lactam complex **2** in 71% yield (Scheme 1).[4]

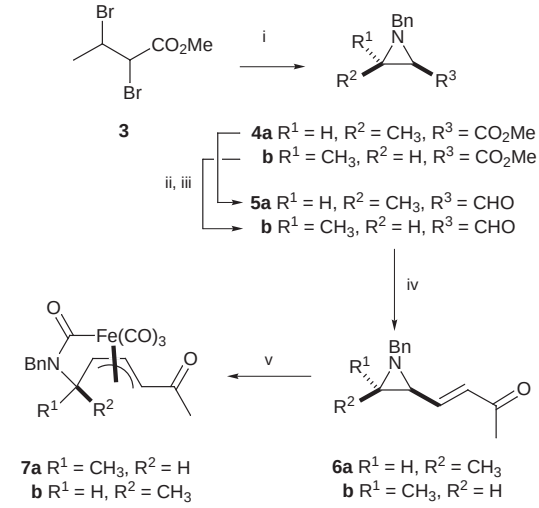


1 **2**

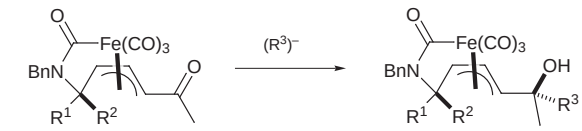
Scheme 1 *Reagents and conditions*: i, $Fe(CO)_5$, benzene, *hν*, 71%

We have additionally demonstrated that ketone functionalised π-allyltricarbonyliron lactone complexes, available from epoxy enone precursors, are versatile chiral templates for organic synthesis.[5] Here we show that the corresponding π-allyltricarbonyliron lactam complexes may be prepared from functionalised alkenyl aziridines by treatment with $Fe_2(CO)_9$ under ultrasonication.[6] This allows the rapid, large scale synthesis of π-allyltricarbonyliron lactam complexes bearing carbonyl functionality in the side chains and facilitates investigation into the potential of these lactam-tethered π-allyltricarbonyliron units as chiral templates. We also show that oxidative decomplexation of the stereodefined alcohols generated by diastereoselective addition of nucleophiles to ketone-bearing π-allyltricarbonyliron lactam complexes can be effected by treatment with trimethylamine *N*-oxide, providing an efficient route to highly functionalised β-lactams.

Racemic enones **6a**,**b** were synthesised in a four step sequence from a known common precursor, dibromo ester **3**[7] (Scheme 2). Treatment of **3** with excess $BnNH_2$ in boiling benzene[8] afforded a 1:1 mixture of methyl esters **4a**,**b** which were separated by flash column chromatography. Reduction with $LiAlH_4$ and Swern oxidation[9] of the crude product yielded the aldehydes **5a**,**b**. Horner–Wadsworth–Emmons coupling with diethyl (2-oxopropyl)phosphonate[10] afforded **6a**,**b** respectively in good yield. Sonication of **6a** in benzene in the presence of nonacarbonyldiiron afforded the *exo*-lactam complex **7a** in good yield, with only a small proportion of the chromatographically separable isomeric *endo* complex **7b** being formed (dr 14:1). Similarly, treatment of enone **6b** under the same conditions yielded a 10:1 ratio of **7b** and **7a** in 77% yield.



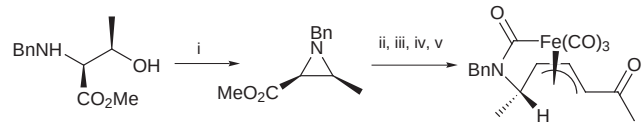
Scheme 2 *Reagents and conditions*: i, $BnNH_2$, benzene, reflux, 16 h, then chromatographic separation, 35% (**4a**), 35% (**4b**); ii, $LiAlH_4$, Et_2O, 0 °C, 2 h; iii, $(COCl)_2$, Me_2SO, NEt_3, CH_2Cl_2, −70 °C, 3 h, 63% (**5a**), 56% (**5b**) (over 2 steps); iv, $(EtO)_2P(O)CH_2COMe$, NaH, THF, 0 °C, 10 min, 91% (**6a**), 83% (**6b**); v, $Fe_2(CO)_9$, benzene, sonication, 30 °C, 3 h, 68% (dr 14:1) (**7a**), 77% (dr 10:1) (**7b**)



7a $R^1 = CH_3$, $R^2 = H$
7b $R^1 = H$, $R^2 = CH_3$
10 $R^1 = CH_3$, $R^2 = H$

11a–13a $R^1 = CH_3$, $R^2 = H$
11b–13b $R^1 = H$, $R^2 = CH_3$
14 $R^1 = CH_3$, $R^2 = H$

Enantiomerically enriched *exo* complex **10** could be synthesised in five steps from enantiomerically enriched methyl ester **9** (Scheme 3), accessible *via* cyclisation of the known L-threonine derivative **8**.[11] Reaction as above afforded *exo*



8 **9** **10**

Scheme 3 *Reagents and conditions*: i, PPh_3, CCl_4, MeCN, 25 °C, 16 h, 83%; ii, $LiAlH_4$, Et_2O, 0 °C, 2 h; iii, $(COCl)_2$, Me_2SO, NEt_3, CH_2Cl_2, −70 °C, 3 h, 59% (over 2 steps); iv, $(EtO)_2P(O)CH_2COMe$, NaH, THF, 0 °C, 10 min, 83%; v, $Fe_2(CO)_9$, benzene, sonication, 30 °C, 3 h, 68% (dr 18:1)

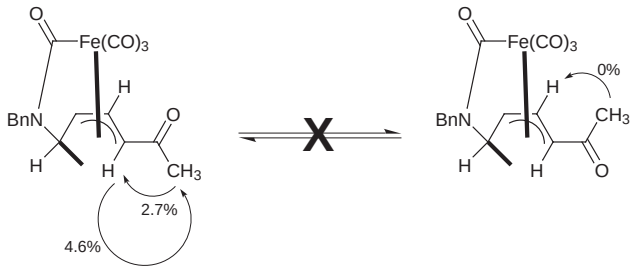


Figure 1 Selected NOE enhancements of complex **7b**

Table 1 Reaction of nucleophiles with π-allyltricarbonyliron lactam complexes bearing methyl ketone functionality in the side chain

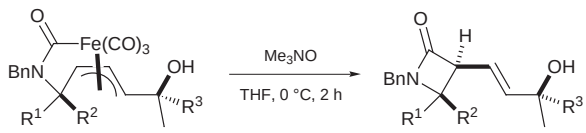
Starting material	Conditions	R^3	Product[a]	Yield (%)[b]
7a	$NaBH_4$, MeOH–CH_2Cl_2, −70 °C	H	**11a**	77
7b	$NaBH_4$, MeOH–CH_2Cl_2, −70 °C	H	**11b**	65
10[c]	$NaBH_4$, MeOH–CH_2Cl_2, −70 °C	H	**14**[d]	76
7a	$AlBu^i_3$, CH_2Cl_2, 0 °C	H	**11a**	77
7b	$AlBu^i_3$, CH_2Cl_2, 0 °C	H	**11b**	70
7a	$AlEt_3$, CH_2Cl_2, 0 °C	Et	**12a (11a)**	52 (26)
7b	$AlEt_3$, CH_2Cl_2, 0 °C	Et	**12b (11b)**	62 (32)
7a	Allyltributyltin, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C	allyl	**13a**	86
7b	Allyltributyltin, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C	allyl	**13b**	89

[a] De determined by 600 MHz ^{1}H NMR, determined to be > 95%. [b] Figures in parentheses refer to isolated yield of reduction side product. [c] Ee > 95% [determined by 200 MHz ^{1}H NMR analysis in the presence of $Pr(hfc)_3$]. [d] Ee > 95% [determined by 600 MHz ^{1}H NMR analysis of the corresponding (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester].

complex **10** in >95% ee [determined by 200 MHz ^{1}H NMR spectroscopy in the presence of the chiral shift reagent (+)-$Pr(hfc)_3$].[12]

In order that the addition of nucleophiles to the ketone group in the sidechain proceeds with high diastereocontrol, it is necessary that the tricarbonyliron group blocks one face of the carbonyl group, thus forcing approach of the nucleophile to occur from the opposite side, and that the ketone adopts only one reactive conformation. The solution conformation of complex **7b** was investigated by the use of NOE experiments. These results clearly show that the s-*cis* conformation is adopted preferentially (Fig. 1). These results are consistent with earlier studies carried out on π-allyltricarbonyliron lactone complexes.[5a] Reaction of complexes **7a**,**b** with a variety of nucleophiles (Table 1) afforded the addition products **11a–13a** and **11b–13b** in good yield and excellent diastereoselectivity (de >95%).[13] Reduction of enantiomerically enriched **10** with $NaBH_4$ to form alcohol **14** proceeded in 76% yield without loss of enantiopurity, as determined by 600 MHz ^{1}H NMR analysis of the ester formed with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[14]

Furthermore, it was discovered that treatment of complexes **11–13** with excess Me_3NO in THF at room temperature affords the functionalised β-lactams **15–17** in good yield (Table 2). This result is an improvement over the published method of oxidative decomplexation with ceric ammonium nitrate[3] which



11–13 **15–17**

Table 2 Decomplexation of functionalised π-allyltricarbonyliron lactam complexes to β-lactams

Starting material	R^1	R^2	R^3	Product	Yield (%)[a]
11a	Me	H	H	**15a**	63
11b	H	Me	H	**15b**	65
12a	Me	H	Et	**16a**	61
12b	H	Me	Et	**16b**	65
13a	Me	H	allyl	**17a**	54
13b	H	Me	allyl	**17b**	69

[a] Isolated yield after treatment with excess Me_3NO in THF at 0 °C for 2 h, followed by chromatography on Florisil.

has given markedly lower yields of β-lactams with this type of substrate.[15]

In summary, a convenient route to racemic and homochiral π-allyltricarbonyliron lactam complexes bearing ketone functionality in the side chain has been developed. It has been shown that the tethered tricarbonyliron moiety is able to direct nucleophilic attack on an appended methyl ketone group, affording complexes bearing secondary and tertiary alcohol functionality in good yield and with excellent diastereoselectivity. A novel oxidative decomplexation method allows the generation of highly functionalised β-lactams bearing stereodefined secondary and tertiary alcohol centres. These results should extend further the utility of π-allyltricarbonyliron complexes for natural product synthesis.

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Notes and References

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