

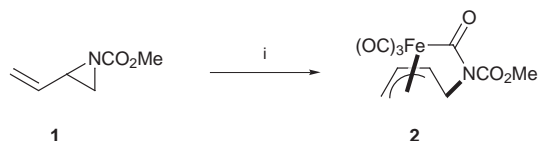
A new route to functionalised π -allyltricarbonyliron lactam complexes from aziridines and their use in stereoselective synthesis and oxidative conversion to β -lactams

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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.

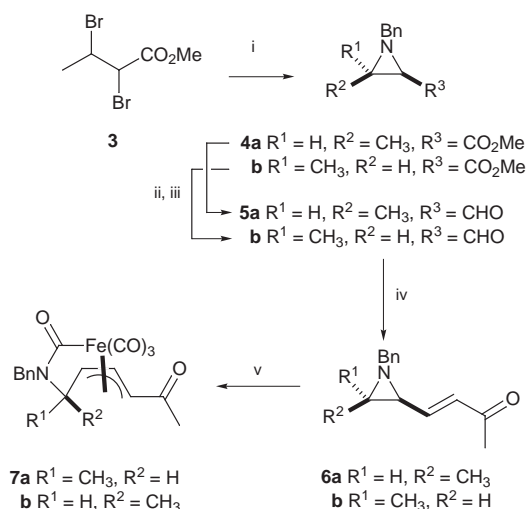
π -Allyltricarbonyliron lactam complexes have been previously investigated as precursors to stereodefined β - and δ -lactams,¹ and have been utilised in the synthesis of several natural products in our laboratory.² Previous preparation of these complexes involved the treatment of π -allyltricarbonyliron lactone complexes with a primary amine³ or the sonochemical reaction of an alkenyl carbamate with $\text{Fe}_2(\text{CO})_9$.^{2a} In an isolated example, Aumann has also shown that UV irradiation of the vinyl aziridine **1** in the presence of $\text{Fe}(\text{CO})_5$ leads to the formation of a π -allyltricarbonyliron lactam complex **2** in 71% yield (Scheme 1).⁴



Scheme 1 Reagents and conditions: i, $\text{Fe}(\text{CO})_5$, benzene, *h\nu*, 71%

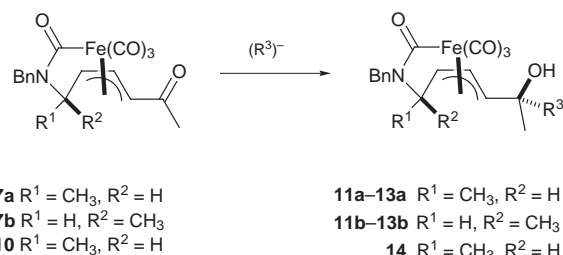
We have additionally demonstrated that ketone functionalised π -allyltricarbonyliron lactone complexes, available from epoxy enone precursors, are versatile chiral templates for organic synthesis.⁵ Here we show that the corresponding π -allyltricarbonyliron lactam complexes may be prepared from functionalised alkenyl aziridines by treatment with $\text{Fe}_2(\text{CO})_9$ 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 benzene⁸ afforded a 1:1 mixture of methyl esters **4a,b** which were separated by flash column chromatography. Reduction with LiAlH_4 and Swern oxidation⁹ of the crude product yielded the aldehydes **5a,b**. Horner–Wadsworth–Emmons coupling with diethyl (2-oxopropyl)phosphonate¹⁰ 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**



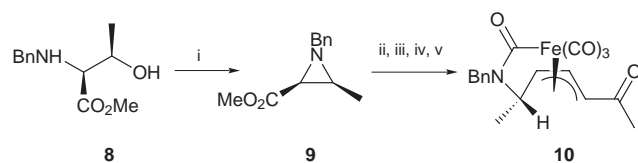
Scheme 2 Reagents and conditions: i, BnNH_2 , benzene, reflux, 16 h, then chromatographic separation, 35% (**4a**), 35% (**4b**); ii, LiAlH_4 , Et_2O , 0 °C, 2 h; iii, $(\text{COCl})_2$, Me_2SO , NEt_3 , CH_2Cl_2 , -70 °C, 3 h, 63% (**5a**), 56% (**5b**) (over 2 steps); iv, $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COMe}$,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



7a $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$
7b $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$
10 $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$
11a–13a $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$
11b–13b $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$
14 $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$

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*



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, $(\text{COCl})_2$, Me_2SO , NEt_3 , CH_2Cl_2 , -70 °C, 3 h, 59% (over 2 steps); iv, $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COMe}$, NaH , THF , 0 °C, 10 min, 83%; v, $\text{Fe}_2(\text{CO})_9$, benzene, sonication, 30 °C, 3 h, 68% (dr 18:1)

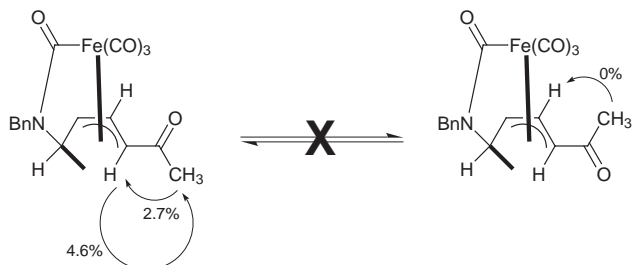


Figure 1 Selected NOE enhancements of complex **7b**

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

Starting material	Conditions	R ³	Product ^a	Yield (%) ^b
7a	NaBH ₄ , MeOH-CH ₂ Cl ₂ , -70 °C	H	11a	77
7b	NaBH ₄ , MeOH-CH ₂ Cl ₂ , -70 °C	H	11b	65
10^c	NaBH ₄ , MeOH-CH ₂ Cl ₂ , -70 °C	H	14^d	76
7a	AlBu ₃ , CH ₂ Cl ₂ , 0 °C	H	11a	77
7b	AlBu ₃ , CH ₂ Cl ₂ , 0 °C	H	11b	70
7a	AlEt ₃ , CH ₂ Cl ₂ , 0 °C	Et	12a (11a)	52 (26)
7b	AlEt ₃ , CH ₂ Cl ₂ , 0 °C	Et	12b (11b)	62 (32)
7a	Allyltritylbutyltin, BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , 0 °C	allyl	13a	86
7b	Allyltritylbutyltin, BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , 0 °C	allyl	13b	89

^a De determined by 600 MHz ¹H NMR, determined to be > 95%. ^b Figures in parentheses refer to isolated yield of reduction side product. ^c Ee > 95% [determined by 200 MHz ¹H NMR analysis in the presence of Pr(hfc)₃]. ^d Ee > 95% [determined by 600 MHz ¹H NMR analysis of the corresponding (*S*)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetyl ester].

complex **10** in >95% ee [determined by 200 MHz ¹H 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 -allyltricarboxyliron 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 NaBH₄ to form alcohol **14** proceeded in 76% yield without loss of enantiopurity, as determined by 600 MHz ¹H 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 Me₃NO 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 nitrate³ which

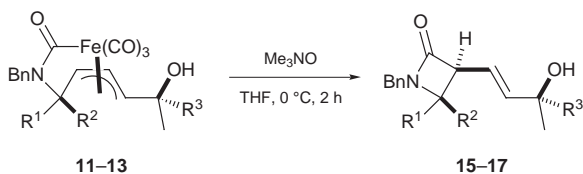


Table 2 Decomplexation of functionalised π -allyltricarboxyliron lactam complexes to β -lactams

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 Me₃NO 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 -allyltricarboxyliron 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 -allyltricarboxyliron complexes for natural product synthesis.

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Notes and References

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- Treatment of a solution of complex **11a** in MeCN with CAN (6.5 equiv.) at -20 °C in the dark for 2 h afforded β -lactam **15a** in 31% isolated yield after chromatography on Florisil.

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