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THE ASYMMETRIC SYNTHESIS OF β-LACTAMS. STEREOCONTROLLED ASYMMETRIC TANDEM MICHAEL ADDITIONS AND ALKYLATIONS OF α,β-UNSATURATED ACYL LIGANDS BOUND TO THE CHIRAL AUXILIARY $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$

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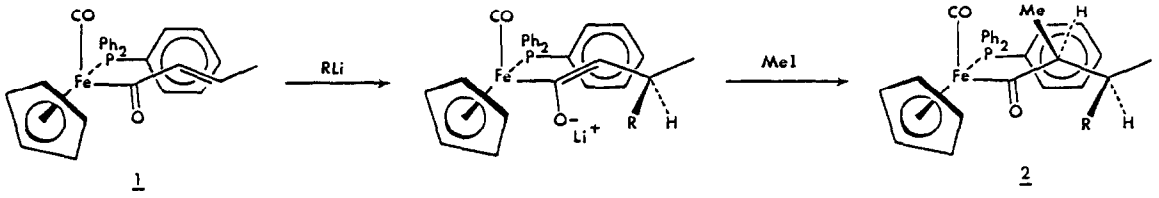
Summary: Michael addition of lithium benzylamide to the enantiomerically pure (S)-E-crotonyl complex of $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ followed by trapping of the resultant enolate with methyl iodide or methanol occurs with high diastereoselectivity and gives after decomplexation the essentially optically pure (3R),(4S)-(-)-3,4-dimethyl- and (4S)-(-)-4-methyl-N-benzyl-β-lactams respectively. Similarly, tandem addition of lithium benzylamide and methylation of the corresponding enantiomerically pure R-(-)-acryloyl complex gave after decomplexation the essentially optically pure (3S)-(-)-3-methyl-N-benzyl-β-lactam.

We have recently reported that the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ exerts powerful stereochemical control during the tandem Michael addition-alkylation reactions of an attached E-crotonyl ligand.[1] Thus, addition of an alkyllithium to the racemic E-crotonyl complex 1 followed by methylation of the resultant enolate gave the α,β-dimethylheptanoyl complex 2 with greater than 100:1:1:1 diastereoselectivity (as determined by 300MHz ^{1}H n.m.r. spectroscopy). Furthermore, it was established that complex 1 was reacting in the cisoid conformation with both the alkyllithium and the methyl iodide approaching from the face away from the bulky triphenylphosphine ligand i.e. overall cis addition to one of the diastereotopic faces of the original double bond.



1 2

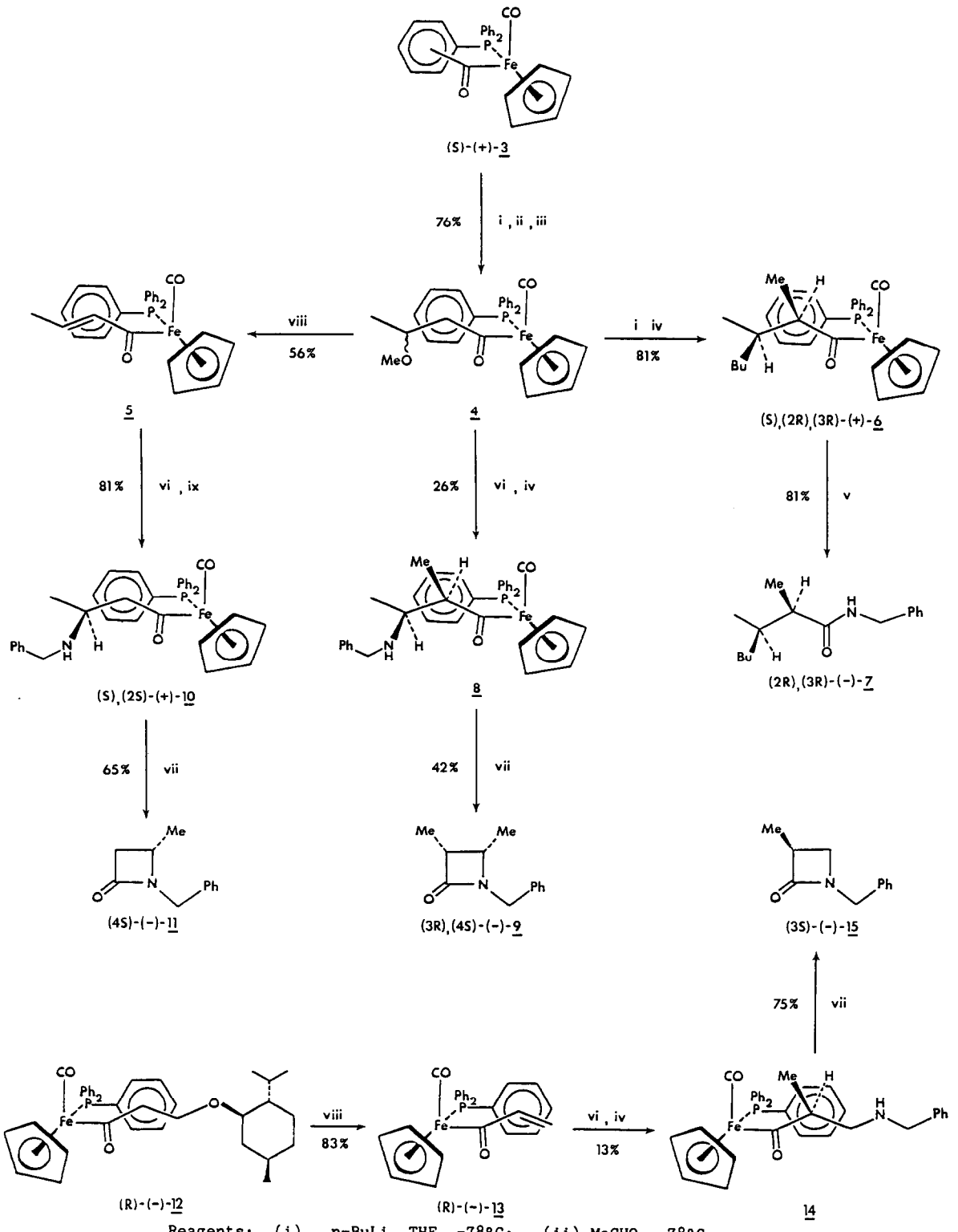
These results have subsequently been confirmed by Liebeskind and Welker[2] who also extended the reaction to the diastereoselective but racemic synthesis of β-amino iron acyl complexes, known precursors of β-lactams,[3] by the Michael addition of lithium amides followed by alkylation.

We describe in this letter our own results in this area in which the highly diastereoselective Michael addition of lithium benzylamide to and subsequent electrophilic quenching of enantiomerically pure α,β-unsaturated acyl complexes is utilised in the synthesis of 3-methyl, 4-methyl and cis-3,4-dimethyl-N-benzyl-β-lactams both of high optical purity and known absolute configuration.

The optically pure (S)-(+)-acetyl complex 3, whose absolute configuration we have unambiguously assigned,[4] was treated successively with n-butyllithium and acetaldehyde to give an essentially 1:1 diastereoisomeric mixture of the corresponding β-hydroxy complexes. Clean O-methylation with sodium hydride - methyl iodide gave the β-methoxy complexes 4. Treatment of this mixture of complexes 4 with two equivalents of n-butyllithium followed by methyl iodide at -78°C in THF gave upon work-up the (S),(2R),(3R)-(+)-2,3-dimethylheptanoyl complex 6[1] {$[\alpha]_D^{24}$ + 228.0° (c 0.29, C_6H_6)} in a diastereoisomeric ratio of greater than 100:1:1:1. The formation of (S),(2R),(3R)-(+)-6 is consistent with the tandem Michael addition - methylation occurring to the E-crotonyl complex 5 in the anti (acyl to carbonyl) and cisoid conformation from the unhindered face.[1] Complex 5 is presumably generated in situ via n-butyllithium-induced elimination of methanol. Oxidative decomplexation of complex 6 with bromine in dichloromethane at -78°C and in the presence of benzylamine gave (2R),(3R)-(-)-N-benzyl-2,3-dimethylheptanamide 7 {$[\alpha]_D^{24}$ - 5.3° (c 1.23, C_6H_6)}. The amide 7 was diastereoisomerically pure by ^1H n.m.r. spectroscopy and confirmed that the decomplexation procedure had occured with complete retention of stereochemistry at the α-centre in agreement with previously reported cases.[5] It thus follows that (2R),(3R)-(-)-7 must have an optical purity of greater than 100:1 and the absolute configuration as stated.

Similarly, addition of two equivalents of lithium benzylamide and then methyl iodide to 4 at -78°C in THF gave the 3-amino-2,3-dimethyl complex 8[2] as a single diastereoisomer by 300MHz ^1H and 63MHz ^{13}C n.m.r. spectroscopy. Without purification, complex 8 was decomplexed with bromine in dichloromethane at -78°C to give the (3R),(4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactam 9 {$[\alpha]_D^{24}$ -29.2° (c 0.69, $CHCl_3$)}. Again, the cis stereochemistry[3] in the β-lactam is that predicted by Michael addition and methylation occurring to one face of the E-crotonyl ligand of the intermediate complex 5. As no trace of the thermodynamically more stable[6] trans isomer could be detected, neither epimerisation at the α- nor β-centres must accompany the decomplexation reaction. This when combined with the fact that the starting (S)-(+)-acetyl complex 3 was optically pure and that the derived complex 8 was formed with high diastereoselectivity (greater than 100:1:1:1) necessitates that (3R),(4S)-(-)-9, not previously known in optically active form, has an optical purity of greater than 100:1 and the absolute configuration as stated.

In order to confirm the intermediacy of complex 5 in the conversion of complex 4 to complexes 6 and 8, complex 4 was subjected to sodium hydride-induced elimination of methanol in THF.[7] The E-crotonyl complex 5 was isolated together with recovered starting material 4 which as an inseparable mixture was treated with lithium benzylamide in THF at -78°C followed by methanol. A single observable diastereoisomer of the (S),(2S)-(+)-3-amino-3-methyl complex 10 {$[\alpha]_D^{21}$ + 143.0° (c 0.44, C_6H_6)} was obtained as the sole product. Oxidative decomplexation of complex 10 gave the (4S)-(-)-4-methyl-N-benzyl-β-lactam 11 {$[\alpha]_D^{24}$ - 38.5° (c 2.1, MeOH), lit.,[8] $[\alpha]_D^{21}$ - 34.5° (c 3.0, MeOH)}. Since, by analogy with the formation of compounds 7 and 9, no racemisation is expected during the decomplexation step, (4S)-(-)-11 must have an optical purity of greater than 100:1 and the 4S absolute configuration.



Reagents: (i) n-BuLi, THF, -78°C; (ii) MeCHO, -78°C;
(iii) NaH, MeI, r.t.; (iv) MeI, -78°C;
(v) Br_2, $PhCH_2NH_2$, CH_2Cl_2, -78°C;
(vi) $PhCH_2NHLi$, THF, -78°C;
(vii) Br_2, CH_2Cl_2, -78°C; (viii) NaH, THF, r.t.;
(ix) MeOH, -78°C.

Finally, the diastereoisomerically pure (R)-(-)-β-menthoxy complex 12 of known absolute configuration[4] was treated with sodium hydride to generate the (R)-(-)-acryloyl complex 13 {$[\alpha]_D^{22}$ - 200.2° (c 0.11, C_6H_6)} whose use in asymmetric synthesis has already been demonstrated.[9] Sequential addition of lithium benzylamide and methyl iodide to complex 13 at -78°C gave the 3-amino-2-methyl complex 14 with greater than 100:1 diastereoselectivity which without purification was decomplexed to the (3S)-(-)-3-methyl-N-benzyl-β-lactam 15 {$[\alpha]_D^{21}$ -32.0° (c 0.33, $CHCl_3$)}, again presumably with an optical purity of greater than 100:1 and with the 3S absolute configuration.

The above results illustrate the potential of the chiral auxiliary [$(\eta^5-C_5H_5)Fe(CO)(PPh_3)$] for the asymmetric synthesis of β-lactams of high optical purity. Since a wide range of E-α,β-unsaturated ligands attached to the chiral auxiliary are available[7] and since many electrophiles can be used to quench the enolate generated by the Michael addition of lithiated primary amines, the scope of this reaction is extensive.

Acknowledgement

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