Highly diastereoselective synthesis of β-hydroxy carbonyl compounds using π-allyltricarbonyliron lactone complexes: a formal 1,7-asymmetric induction of chirality in a Mukaiyama aldol reaction

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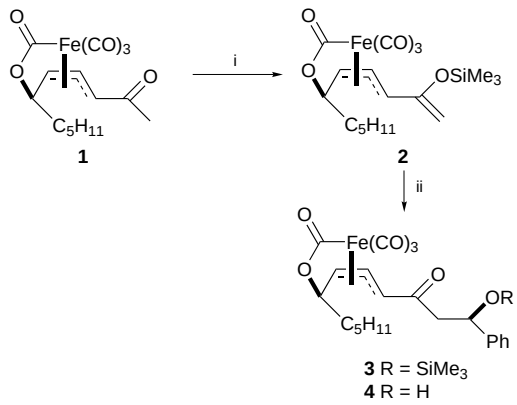
The reaction of π-allyltricarbonyliron lactone complex 2 with a variety of achiral aldehydes affords the corresponding aldol products in good yields and with good to excellent levels of stereocontrol.

The aldol reaction remains one of the most important C–C bond constructing processes in modern organic synthesis. While many methods towards the preparation of diastereoisomerically pure aldol products have been developed,[1] the direct synthesis of isomerically pure β-hydroxy ketones lacking an α-substituent has proved to be much more difficult, since the α-substituent is often a key stereocontrolling requirement in the addition event.[2]

We now report that a trimethylsilyl enol ether **2** appended to the side-chain of a π-allyltricarbonyliron lactone complex undergoes a Mukaiyama aldol reaction[3] with a range of achiral aldehydes, affording β-hydroxy ketone products in good yield and with good to excellent levels of stereocontrol. The reaction constitutes what is formally a 1,7-asymmetric induction of chirality[4] and as such is quite unprecedented in aldol chemistry.[5]

π-Allyltricarbonyliron lactone complexes bearing ketone functionality in the side-chain are readily prepared *via* a four-step sequence starting from an allylic alcohol.[6] The ketone group positioned in the side-chain of the allyl ligand preferentially adopts an s-*cis* conformation.[6] This, combined with the steric bulk of the tricarbonyliron moiety, ensures that nucleophiles add to the ketone to afford a single diastereoisomeric product.[6,7] Starting from (*E*)-oct-2-en-1-ol, the model methyl ketone complex **1** was prepared and treated with $Me_3SiOSO_2CF_3$ and Et_3N in CH_2Cl_2 at 0 °C to afford the remarkably stable trimethylsilyl enol ether **2** in excellent yield (Scheme 1). We envisaged that this silyl enol ether functionality would also adopt a preferred conformation and therefore might react with aldehydes producing the corresponding aldol products with some degree of stereocontrol.



Scheme 1 *Reagents and conditions*: $Me_3SiOSO_2CF_3$ (1.2 equiv.), Et_3N (1.4 equiv.), CH_2Cl_2, 0 °C, 1 h, 89%; ii, PhCHO (1.5 equiv.), $BF_3{\cdot}OEt_2$ (1.4 equiv.), Et_2O–CH_2Cl_2 (5 : 1), −78 °C, 5 h, then Et_3N (1.4 equiv.), −78 °C, 61% (**3**), 20% (**4**)

Addition of an ethereal solution of benzaldehyde and $BF_3{\cdot}OEt_2$ to a solution of silyl enol ether **2** at −78 °C afforded the aldol products **3** and **4** in good yield and, in both cases, mainly as one diastereoisomer (Scheme 1). Treatment of the crude reaction mixture with HF·pyridine allowed quantitative conversion of the silyl aldol product **3** to the free alcohol **4**† and subsequent determination of the overall diastereoselectivity of the aldol reaction by high field ^{1}H NMR analysis.‡

Encouraged by this result, we applied the same reaction conditions to a range of achiral aldehydes and the results are outlined in Table 1.§ Aldehydes with α-branching (entries 3–5) showed the best levels of diastereocontrol, with the sterically encumbered pivalaldehyde affording only one diastereoisomer as evidenced by ^{1}H NMR analysis on the crude reaction mixture. α,β-Unsaturated aldehydes reacted in high yield but showed decreased levels of diastereocontrol.

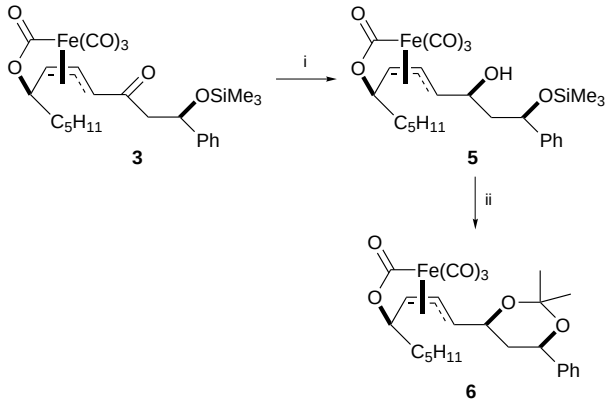
The relative stereochemical outcome of the aldol addition was determined as follows: reduction of the ketone group in **3** with $AlPr^n_3$ proceeded stereoselectively, in accord with earlier results, producing one diastereoisomer **5**.[6] Protection of the 1,3-diol unit as the acetonide **6** revealed a *syn* relationship between the alcohol functionalities as determined by characteristic shifts for the acetal carbon at δ 99.7[8] and the acetal methyl groups at δ 19.9 and 29.6 (Scheme 2).[9] By induction the relative configuration of the stereogenic centre formed in the aldol reaction to that at the lactone tether was determined.

In summary, the lactone tether imparts, *via* the tricarbonyliron moiety, a high degree of 1,7-induction of chirality in the Lewis acid-mediated reaction between silyl enol ether **2** and a wide range of achiral aldehydes. In general, the more sterically bulky the aldehyde, the greater the diastereoselectivity of the reaction. Such remote induction in an acyclic system is very unusual. The generated β-hydroxy carbonyl or *syn* 1,3-diol units are ubiquitous motifs in many biologically important molecules and since π-allyltricarbonyliron lactones are easily prepared in

Table 1 Mukaiyama aldol reaction of achiral aldehydes with π-allyltricarbonyliron lactone complex **2**

Entry	Aldehyde	Overall yield (%)[a]	Ratio of **3** : **4**[b]	De (%)[c]
1	PhCHO	81	75 : 25	86
2	$CH_3(CH_2)_4CHO$	74	23 : 77	82
3	$CH_3CH(CH_3)CHO$	66	39 : 61	94
4	$CH_3C(CH_3)_2CHO$	57	26 : 74	> 95[d]
5	cyclohexyl–CHO	75	57 : 43	91
6	$CH_3(CH_2)_3CH{=}CHCHO$	65[e]	72 : 28	79
7	$CH_3(CH_2)_4C{=}CCHO$	78	79 : 21	47

[a] Isolated yield after chromatography. [b] Determined from isolated yields of **3** and **4**. [c] De determined from the crude reaction mixture by 600 MHz ^{1}H NMR analysis after silyl deprotection. [d] Only one diastereoisomer was observable in the crude reaction mixture by 600 MHz ^{1}H NMR analysis. [e] Up to *ca.* 8% dehydration product was also isolated.



Scheme 2 *Reagents and conditions*: i, $AlPr^n_3$ (2.4 equiv.), CH_2Cl_2, −78 → 0 °C, 1 h 75%; ii, HF·pyridine (3 equiv., *ca.* 2.25 mol dm^{-3} solution), THF, 25 °C, then pyridinium *para*-toluenesulfonate (PPTS) (0.05 equiv.), 2,2-dimethoxypropane (20 equiv.), DMF, 25 °C, 12 h, 71%

enantiomerically enriched form (> 95%),[7] and can be decomplexed to β-, γ- and δ-lactones,[10] (*E*,*E*)-dienes,[10] or alkenols,[10,11] we envisage that this addition to their chemistry will yet further extend their utility in natural product synthesis. Work exploring the scope of this reaction and possible reaction mechanisms is presently underway within our laboratory.

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Footnotes and References

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† *General procedure* for the aldol reaction: synthesis of **4**. A solution of PhCHO (0.035 cm^3, 0.35 mmol) and BF_3·OEt_2 (0.047 cm^3, 0.34 mmol) in Et_2O (1.0 cm^3) was added dropwise to a cooled (−78 °C) solution of silyl enol ether **2** (0.099 g, 0.23 mmol) in Et_2O–CH_2Cl_2 (1.5 cm^3, 2 : 1). After 5 h, Et_3N (0.047 cm^3, 0.34 mmol) was added dropwise with vigorous stirring. After 2 min, the solution was filtered through a pad of Celite, washing the residue with Et_2O–CH_2Cl_2 (50 cm^3, 4 : 1). Concentration of the filtrate *in vacuo* followed by treatment of the residue with a solution of HF·pyridine (0.69 mmol, 0.300 cm^3 of a *ca*. 2.25 mol dm^{-3} solution in THF) for 30 min afforded, after standard aqueous work-up and purification by flash column chromatography (silica, eluent: Et_2O–light petroleum, 7 : 3), aldol product **4** as a yellow oil (0.087 g, 81%); ν_{max}(film)/cm^{-1} 3458 (OH), 3031, 2928, 2858, 2088 (CO), 2016 (CO), 1667 (C=O), 1496, 1454, 1417, 1363, 1323, 1233, 1204, 1027, 760, 701, 654; δ_H(500 MHz) 0.88 (3 H, t, *J* 6.2, 12-H × 3), 1.23–1.62 (8 H, m, 8-H × 2, 9-H × 2, 10-H × 2, 11-H × 2), 2.96–3.19 (3 H, m, 2-H × 2, OH), 3.83 (1 H, d, *J* 11.3, 4-H), 4.34 (1 H, app q, *J* 5.6, 7-H), 5.03 (1 H, dd, *J* 8.3, 4.5, 6-H), 5.26–5.28 (1 H, m, 1-H), 5.59 (1 H, dd, *J* 11.3, 8.3, 5-H), 7.28-7.39 (5 H, m, Ph-*H*); δ_C(100 MHz) 13.9 (CH_3, 12-C), 22.4 (CH_2), 26.5 (CH_2), 31.5 (CH_2), 36.6 (CH_2), 51.7 (CH_2, 2-C), 65.5 (CH), 70.1 (CH), 77.0 (CH), 84.9 (CH), 92.0 (CH), 125.7 (CH), 127.9 (CH), 128.7 (CH), 142.5 (quat. C), 199.6 (CO), 202.4 (CO), 203.6 (CO), 204.4 (CO), 207.8 (CO); *m*/*z* (FAB) 457 (MH^+, 25%), 442 (17), 429 (6, MH − CO), 411 (15, MH − CO − H_2O), 399 (20, M − H − 2CO), 383 (13, M − H − 2CO − O), 373 (5), 353 (18), 345 (38, MH − 4CO), 327 (61, MH − 4CO − H_2O), 239 (33), 223 (37), 179 (48), 151 (50), 136 (100) [Found (MH^+): 457.0984. $C_{22}H_{25}FeO_7$ requires *M*H, 457.0950].

‡ Diastereoisomeric excess of the aldol products was determined by ^1H NMR analysis using a Bruker DRX-600 spectrometer.

§ All new compounds exhibited satisfactory spectral and mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

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