

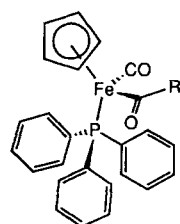
and also the fact that only very small weakly diffracting single crystals of these materials have been obtained so far. We are currently optimizing the crystallization of this and related materials. 3:  $C_6H_{10}NO_6Fe$ ;  $PI$ ,  $Z = 2$ ;  $a = 6.838(1)$ ,  $b = 7.058(1)$ ,  $c = 9.676(2)$  Å,  $\alpha = 103.29(1)$ ,  $\beta = 93.58(1)$ ,  $\gamma = 97.83(1)^\circ$ ,  $V = 448.1$  Å<sup>3</sup> ( $T = 22^\circ\text{C}$ );  $\rho_{\text{calc}} = 1.84$  g cm<sup>-3</sup>,  $M_{0\text{K}\alpha}$ ,  $\lambda = 0.71073$  Å,  $2^\circ < 2\theta < 52^\circ$ ; 1748 reflections (1659 with  $F > 6\sigma(F)$ ); Patterson synthesis (SHELXTL). An inversion center relates the two halves of the molecule. For 157 parameters  $R = 0.0351$  and  $R_w = 0.0394$ . Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-W-7514 Eggenstein-Leopoldshafen 2, on quoting the following number CSD-55936, the names of the authors, and the journal citation.

- [6] The assignment of the oxo and hydroxo bridges was made based on consideration of the geometry at each oxygen atom, and their number was confirmed by the results of the C,H,N,Fe-analysis. The elemental analysis is also consistent with the presence of four nitrate anions and sixty waters of crystallization in a unit cell containing one molecule of each of both 1 and 2.
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## New Chiral $\alpha$ -Benzyloxyacryliron(II) Complex for Asymmetric Synthesis of $\alpha,\alpha$ -Dialkyl- $\alpha$ -hydroxycarbonyl Compounds\*\*

By Felix Stolz, Peter Strazewski, Christoph Tamm,\* Markus Neuburger, and Margareta Zehnder

Davies et al. have shown<sup>[1]</sup> that a series of diastereoselective alkylations of carbonyl compounds can be performed with high selectivity by using an iron(II) complex of type 1 as chiral auxiliary. To our knowledge, in the past the only accessible enantiomerically pure starting materials for the preparation of derivatives was the acetyliron complex  $[(\eta^5\text{-C}_5\text{H}_5)\text{CO}(\text{PPh}_3)\text{Fe}(\text{COCH}_3)]$  (**1a**). Both the (*S*)-(+)- and the (*R*)-(–) forms are commercially available, but when their high molecular weight and the difficulty of regenerating the auxiliary in optically active form are taken in to account, they are rather expensive. Both configurations can also be



(*R*)-1

a: R = CH<sub>3</sub>

b: R = C(OCH<sub>2</sub>Ph)=CH<sub>2</sub>

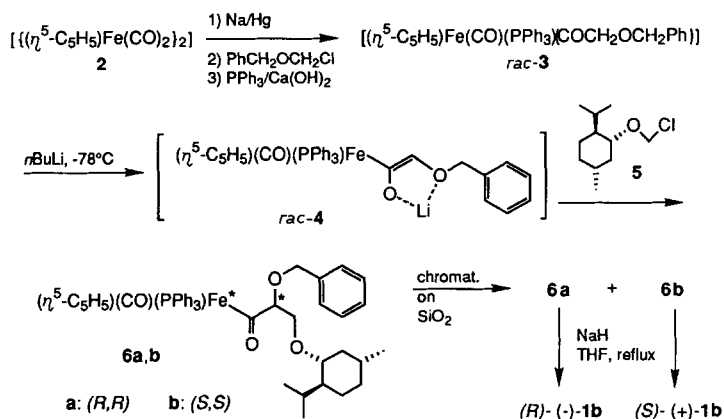
c: R = HC=CHCH<sub>3</sub>

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[\*\*] This work was supported by the Swiss National Science Foundation. We thank Ms. Gisela Umbricht and Dr. C. Bolm, Institut für Organische Chemie der Universität Basel for the GC and HPLC separations.

synthesized by the method of Brunner and Schmidt,<sup>[2]</sup> but an efficient procedure for their preparation is not yet available.

We were interested in the enantiomerically pure  $\alpha$ -benzyloxyacryliron(II) complex (**1b**), because Michael addition and subsequent alkylation of the intermediate enolate leads to  $\alpha,\alpha$ -dialkyl- $\alpha$ -hydroxycarbonyl derivatives, a class of compounds that are difficult to prepare in optically active form. We therefore developed a process that yielded the two optical antipodes (*R*)-**1b** and (*S*)-**1b** in gram quantities from inexpensive starting materials in good yield (Scheme 1).



Scheme 1. Synthesis of  $\alpha$ -benzyloxyacryliron(II) complexes (*R*)-**1b** and (*S*)-**1b**.

Compound *rac*-3 was prepared by a known procedure from  $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2]_2$  (**2**) in 42% overall yield.<sup>[1b,3]</sup> Deprotonation with *n*-butyllithium followed by a highly stereoselective alkylation of the intermediate enolate *rac*-4 with chloromethyl (–)-menthyl ether (**5**) afforded **6a** (less polar) and **6b** (more polar). The relative configuration of the centers Fe\* and  $\alpha$ -C\* were assumed to be (*R*\*,*R*\*) or *l* (like) on the grounds of the presumed configuration of the (*E*) lithium enolate **4** (cf. Davies et al.<sup>[1b–c]</sup>). The *u*-diastereomers [*R*\*,*S*\*] or unlike are in principle also possible, but were not observed in the <sup>1</sup>H NMR spectrum of the product mixture. A single flash-chromatographic separation on silica gel (toluene/ether/pentane 90:5:5) furnished the virtually enantiomerically pure products in 43 (**6a**) and 42% (**6b**) yield. The elimination of (–)-menthol from **6a** and **6b** was achieved with sodium hydride under retention of configuration at the iron atom. After filtration over a short column (neutral Al<sub>2</sub>O<sub>3</sub>), precipitation of the only iron complex

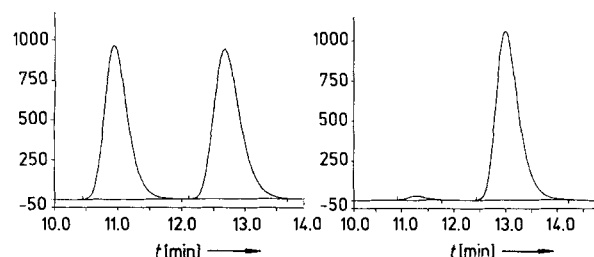


Fig. 1. Resolution of (*R*)-**1b** and (*S*)-(+)-**1b** by HPLC on a chiral stationary phase. The y axis represents the UV absorption at  $\lambda = 277$  nm [mV]. Mobile phase: 2-propanol/*n*-hexane 1.5:98.5. Derivatization of the stationary phase: cellulose carbamate (Chiralcel OD® by Daicel). Enantiomeric excess of (*S*)-(+)-**1b**: 96.1% *ee*. Enantiomeric excess of the (–)-menthol (Fluka) used for the synthesis of (*R*)-(-)-**1b** and (*S*)-(+)-**1b**: 98.75% *ee* (determined by gas chromatography with (–)-menthyl acetate on permethylated  $\beta$ -cyclodextrin.)

present with *n*-pentane yielded (*R*)-(-)-**1b** or (*S*)-(+)-**1b** (from **6a** and **6b** respectively) in preparative amounts as amorphous, air- and moisture-insensitive solids in 87–92% yield (Fig. 1).<sup>[14]</sup>

The crystal structure of racemic **1b** has been solved (Fig. 2). As in the corresponding (*E*)-crotyliron complex **1c**,<sup>[14]</sup> it reveals that the  $\beta$  carbon atom is oriented *s-cis* to the carbonyl oxygen atom of the same ligand. The *anti* arrangement of the two carbonyl oxygen atoms is the only possible one for steric reasons.<sup>[14d–e]</sup>

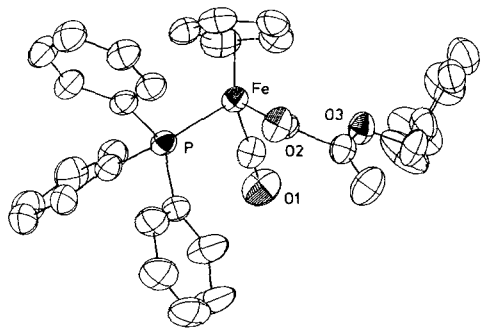


Fig. 2. Structure of (*R*)-**1b** in the solid state. Thermal ellipsoids represent 30% probability. Carbon atoms are complete ellipsoids; heteroatoms have a sector removed.

Compound **1b** was butylated in  $\beta$  position with *n*BuLi (two equivalents are required for complete conversion—cf. Davies et al.<sup>[14f]</sup>), and the resulting lithium enolate **7** trapped in situ with water, methyl iodide, or ethyl iodide (Scheme 2). The reaction mixture was filtered over a short column (neutral  $\text{Al}_2\text{O}_3$ ), and the alkylation products precipitated on addition of *n*-pentane. The yields determined at this stage lay between 76 (**10a,b**) and 88% (**8a,b**). The diastereoselectivity of the reactions was estimated from  $^1\text{H}$  NMR spectroscopy

and the preparative separation of the product mixture. The enolizable acyl derivatives **8**, like **6a,b**, were stable on silica gel, but **9** and **10** required separation on neutral  $\text{Al}_2\text{O}_3$ . The selectivity lay between 80 and 95% *ds*. In the case of **9a** and **b** (prepared from (*R*)-(-)-**1b**) the exact ratio (17:83) could be established by gas chromatography on permethylated  $\beta$ -cyclodextrin of the final product **14** formed on removal of the chiral auxiliary and the benzyl function. The ratio of **8a**:**8b** (7:93) was determined by HPLC (Si-60, 0.3% ether in hexane).

The racemic major product **9b** could also be crystallized. The crystal structure (Fig. 3b) shows that the *l* diastereomer was formed preferentially, as expected from the structure of **1b**. After methylation the acyl ligand rotated approximately  $180^\circ$  around the (OC)–( $\alpha$ -C) bond, allowing the smallest  $\alpha$  substituent, the methyl group to point in the direction of the triphenylphosphane ligand. Additional noteworthy features of the crystal structure are the changes in some angles ( $\text{O}\equiv\text{C}-\text{Fe}-\text{COR}$  is wider and  $\text{O}\equiv\text{C}-\text{Fe}-\text{PPh}_3$  narrower than in **1b**) and the remarkable rigidity of the pentyl side chain.<sup>[5]</sup> The chirality of the propeller geometry of the triphenylphosphane ligand follows the general rule in both crystal structures:<sup>[14e]</sup> the screw in the (*R*) complex is clockwise and in the (*S*) complex counterclockwise.

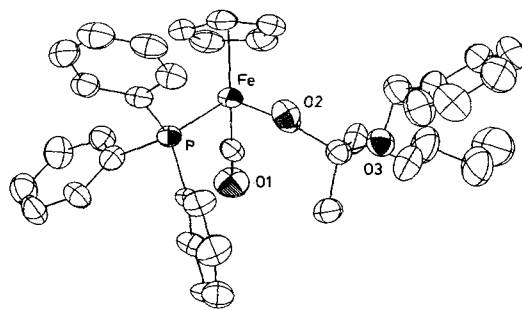
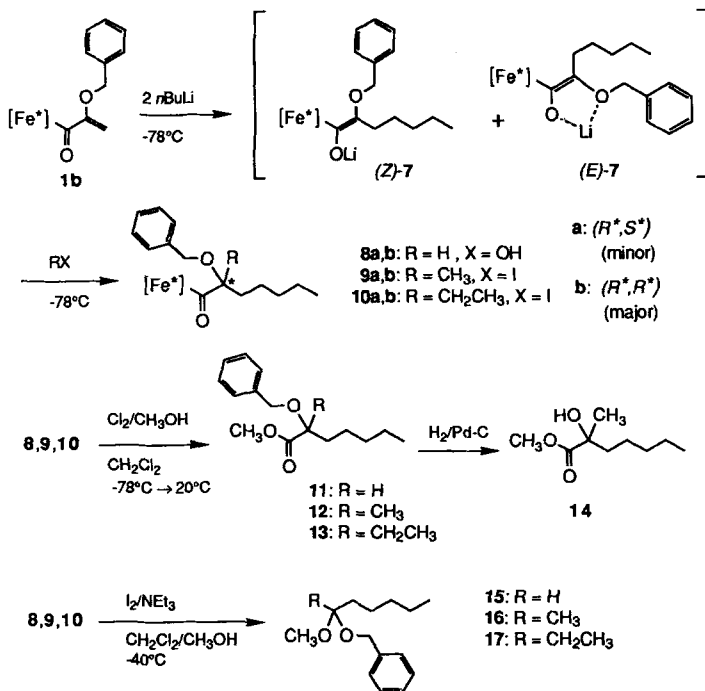


Fig. 3. Structure of (*R*)-**9b** in the solid state. The thermal ellipsoids represent 30% probability. Carbon atoms are complete ellipsoids; heteroatoms have a sector removed.



Scheme 2. Alkylation of (*R*)- or (*S*)-**1b**, followed by cleavage of the acyl ligands from iron. ( $[\text{Fe}^*] = [(\eta^5\text{-C}_5\text{H}_5)_2\text{CO}(\text{PPh}_3)_2\text{Fe}]$ ).

Both the extremely high diastereomeric selectivity of the alkylation of *rac*-**3** and the usually absolutely selective alkylations and protonations of comparable substrates<sup>[14,g]</sup> show that in complexes **1** the chiral auxiliary does not even permit sterically nondiscriminating electrophiles to attack from the triphenylphosphane side. The diminished stereoselectivity of the alkylation of **1b** thus requires a different explanation. The  $^1\text{H}$  NMR spectrum of **1b** suggests that in solution even at room temperature the complex exists virtually exclusively in the cisoid conformation, as in the solid state. Addition of *n*BuLi forces the enolate **7** into the (*Z*) configuration (Scheme 2). Then (*Z*)-**7** is alkylated stereospecifically to the *l* diastereomer. However chelation of the two oxygen atoms by a lithium ion in the (*E*) enolate **7** (as in enolate **4**) must lead specifically to the *u* diastereomer. Since two equivalents of *n*BuLi are required for complete conversion, it seems that the first equivalent of *n*BuLi merely coordinates to **1b**. The delayed onset of the red coloration typical of enolate formation supports this hypothesis. Apparently this type of activation is a prerequisite for the *n*-butylation of **1b** in  $\beta$  position. It is feasible that the presence of lithium ions simultaneously causes a partial isomerization to the transoid isomer of **1b**, which in turn reacts with the second equivalent of *n*BuLi to yield (*E*)-**7**. A greatly enhanced reactivity to *n*BuLi of the

mere traces of transoid conformer present would be another, but unlikely explanation.

The diastereoselectivity of the reaction presents no problem for synthesis, because the less polar side products **8a–10a** are separable by chromatography with minimum losses. Absolute diastereomeric purity of the products is attainable, and after cleavage of the acyl ligands enantiomerically pure  $\alpha$ -benzyloxy- $\alpha$ , $\alpha$ -dialkylcarbonyl compounds are obtained.

The oxidative cleavage of the  $\alpha$ -benzyloxyacyl ligands from the iron complex with bromine and methanol proved to be problematic at first. As Davies et al.<sup>[1c]</sup> had reported earlier, the bond between C(acyl) and  $\alpha$ -C tends to break instead of the Fe-C(acyl) bond, forming not the desired methyl esters **11–13**, but the benzyl methyl acetal **15** or the ketals **16, 17** that are shortened by one carbon atom. We therefore studied various cleavage conditions in order to bias the product composition. The most common cleavage reagent, bromine, yields varying mixtures of esters and acetals or ketals depending on the added mole equivalents of reagent and the reaction time. *N*-bromosuccinimide affords almost exclusively the acetal or ketal, but in poor yield. Iodine or bromine with added triethylamine furnishes exclusively the acetal or ketal (82% for **16**). However, with chlorine gas in dichloromethane the ester forms exclusively (54% for **12**).

Received: September 23, 1991 [Z4926 IE]  
German version: *Angew. Chem.* **1991**, *104*, 225

#### CAS Registry numbers:

(*R*)-**1b**, 138061-03-7; (*S*)-**1b**, 138230-57-6; *rac*-**1b**, 138230-58-7; *rac*-**3**, 111618-46-3; **5**, 26127-08-2; (*R,R*)-**6a**, 138061-04-8; (*S,S*)-**6b**, 138230-59-8; (*R\*,S\**)-**8a**, 138061-05-9; (*R\*,R\**)-**8b**, 138230-60-1; *rac*-**9a**(*R\*,S\**), 138061-06-0; (*R,S*)-**9a**, 138230-61-2; *rac*-**9b**(*R\*,R\**), 138230-62-3; (*R,R*)-**9b**, 138230-63-4; (*R\*,S\**)-**10a**, 138061-07-1; (*R\*,S\**)-**10b**, 138230-64-5; **12**, 138061-00-4; **14**, 138061-01-5; **1b**, 138061-02-6.

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[4] The same absolute configuration as that of **1a** was assigned on the assumption that the  $\alpha$ -benzyloxyacyl ligand does not reverse the optical rotation. (*R*)-(-)-**1b**:  $[\alpha]_D^{20} = -294$ ;  $[\alpha]_D^{20} = -191$  ( $c = 0.4$ ,  $C_6H_6$ ). (*S*)-(+)-**1b**:  $[\alpha]_D^{20} = +300$ ;  $[\alpha]_D^{20} = +192$  ( $c = 0.4$ ,  $C_6H_6$ ).

[5] *rac*-**1b** was crystallized from pentane at  $-20^\circ\text{C}$ .  $C_{34}H_{29}FeO_3P$ , triclinic space group space group *P1* (no. 2),  $Z = 4$  (2 independent molecules/asymmetric unit),  $a = 10.713(3)$ ,  $b = 15.395(8)$ ,  $c = 18.200(7)$  Å,  $\alpha = 83.17(6)$ ,  $\beta = 92.06(4)$ ,  $\gamma = 103.95(4)^\circ$ ,  $V = 2895.5(3)$  Å<sup>3</sup>,  $\rho_{\text{calc}} = 1.315$  g cm<sup>-3</sup>,  $F(000) = 1192$ . Collection of data at room temperature, CAD4 diffractometer, graphite monochromator,  $MoK_{\alpha}$  ( $\lambda = 0.71069$  Å),  $\omega$ - $2\theta$  scan,  $\theta_{\text{max}} = 28^\circ$ , 11973 independent reflections, 9235 of which with  $(F) > 2\sigma(F)$ . Solution by Patterson methods with subsequent weighted difference Fourier syntheses. Refinement: block matrix, least-squares method (SHELX-76) with anisotropic thermal parameters for all non-hydrogen atoms,  $R = 0.0590$ ,  $R_w = 0.0596$  for 704 parameters. *rac*-**9b** was crystallized in the dark from diethyl ether under a light stream of nitrogen at room temperature.  $C_{30}H_{44}FeO_3P$ , triclinic, space group (no. 2),  $Z = 2$ ,  $a = 8.126(4)$ ,  $b = 12.234(5)$ ,  $c = 16.465(9)$  Å,  $\alpha = 96.11(4)$ ,  $\beta = 93.48(5)$ ,  $\gamma = 92.85(3)^\circ$ ,  $V = 1622.0(3)$  Å<sup>3</sup>,  $\rho_{\text{calc}} = 1.320$  g cm<sup>-3</sup>,  $F(000) = 680$ . Data collection and structure determination as above, 5807 independent reflections, 3733 of which with  $(F) > 2\sigma(F)$ .  $R = 0.0749$ ,  $R_w = 0.0631$  for 403 parameters. Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, GB-Cambridge CB2 1EW on quoting the full journal citation.

[6] The experimental details of the syntheses for all compounds and their physical and spectroscopic characterization will be published later. They are part of the proposed dissertation of F.S.

## Enzymatic Preparation of Enantiomerically Pure *N*-alkyl Amino Acids\*\*

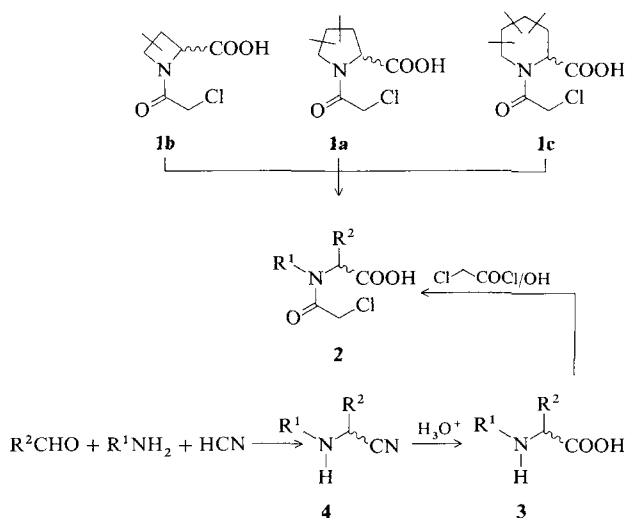
By Ulrich Groeger,\* Karlheinz Drauz, and Herbert Klenk

*N*-alkyl-L-amino acids **L-3**, and more particularly *N*-methyl-L-amino acids, are important building blocks of peptide and depsipeptide antibiotics.<sup>[1]</sup> They also occur free in biological material, as for instance, *N*-methyl-L-tryptophan in the seeds of *Abrus precatorius*.<sup>[2]</sup> Although preparation of optically inactive or racemic compounds **3** presents no problem, synthesis of the enantiomerically pure compounds **L-3** is laborious and sometimes provides unsatisfactory yields.<sup>[3]</sup>

One possible route to enantiomerically pure amino acids is the enantioselective hydrolysis of appropriate racemic *N*-acetyl amino acids catalyzed by an aminoacylase from *Aspergillus oryzae* or from porcine kidney (acylase I, EC 3.5.1.14), as for instance is used in an industrial process to prepare L-methionine or L-valine.<sup>[4]</sup> Although acylase I displays high selectivity for a wide spectrum of substrates, this system has limitations. Replacement of the hydrogen on the amine nitrogen atom by an alkyl group causes loss of enzymatic activity. Thus *N*-acylated secondary amines such as *N*-acylated proline (**1a**) or *N*-acylated *N*-alkylamino acids cannot be hydrolyzed by this method.<sup>[5]</sup>

Recently we isolated and characterized a new bacterial *N*-acyl-L-proline-acylase, whose high enantioselectivity ( $ee > 99.8\%$ ) makes it suitable for preparing L-proline from **1a**.<sup>[6]</sup> This enzyme also hydrolyses only the L-enantiomer of *N*-acetyl and *N*-chloroacetyl derivatives of azetidine-2-carboxylic acid (**1b**) and pipercolic acid (**1c**), thus enabling the enzyme-catalyzed resolution of these compounds.<sup>[7]</sup>

Compounds **1a–c** are *N*-acylated cyclic secondary amines. Ring-opening leads to the corresponding *N*-acylated, straight-chain secondary amines **2**. The precursors **2** can be prepared as racemates in good yield from **3** in a modified Strecker synthesis via *N*-alkylaminonitriles **4** (Scheme 1, Table 1).



Scheme 1. For  $R^1$ ,  $R^2$  see Table 1.

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[\*\*] Amino Acid Transformation, Part 8. This work was supported by the Bundesminister für Forschung und Technologie (0319007 A3). Part 7: K. Drauz, M. Kottenhahn, K. Makryaleas, H. Klenk, M. Bernd, *Angew. Chem.* **1991**, *103*, 704–706; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 712–714.