Stereospecific Allylation of a Serine-derived Zinc/Copper Reagent. Synthesis of Substituted Pipecolic Acid Derivatives

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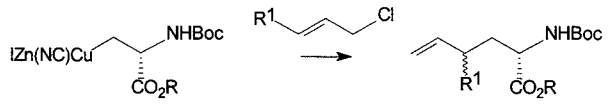
Abstract: Serine-derived zinc/copper reagents **1** and **2** add to enantiomerically pure (η^3-allyl)iron tetracarbonyl salts in fair to good yield in a stereospecific fashion. The vinylsulfones **10-12** can be converted into 4-methylpipecolic acid derivatives **19-21** in a two-step process comprising epoxidation and Zn/TMSCl mediated cyclisation.

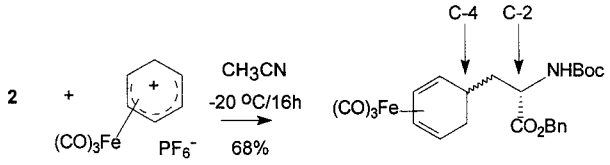
Reaction of the serine-derived zinc/copper reagents **1** and **2** with allylic halides is a straightforward method for the synthesis of unsaturated amino acids **3** (Scheme 1).[1] While the stereochemical integrity of the α-centre is completely preserved during this process, reaction with prochiral electrophiles always resulted in a mixture of diastereoisomers (generally in a ratio close to 1:1). This indicates that the intrinsic chiral discrimination of the zinc/copper reagents **1** and **2** is low.



1, R = Me
2, R = Bn

3

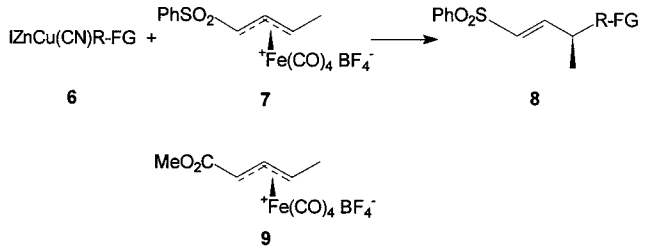
We have already demonstrated that the zinc/copper reagent **2** can add to tricarbonyl(η^5-cyclohexadienyl)iron salts **4** to give addition products such as **5** (again with no stereochemical induction from C-2 to C-4),[2] and we were therefore interested in exploring the reactivity of our zinc and zinc/copper reagents towards stereochemically defined (η^3-allyl) cation equivalents with a view to controlling the stereochemistry at the newly created asymmetric centre.



4

5

The recent report by Enders on the addition of zinc/copper reagents **6** to enantiomerically pure (η^3-allyl)iron tetracarbonyl salts **7** to give the adducts **8**[3] appeared to offer an ideal solution. Complex **7**,[4] and the corresponding ester complex **9**,[5] were each prepared from methyl lactate using literature procedures.



6

7

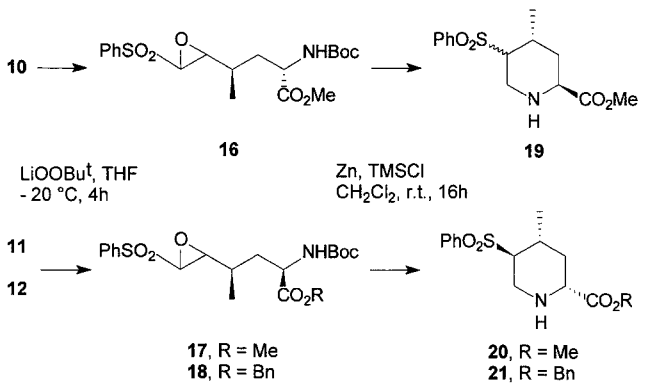
8

9

Addition of 1.5 equivalents of the copper reagents **1**, *ent*-**1** and *ent*-**2** to the iron salts **7** and **9** at -78 °C and gradual warming to -20 °C, followed by oxidative removal of the iron tetracarbonyl unit with ceric ammonium nitrate, gave the diastereoisomerically pure α-amino acids **10-15** (Table 1).[6] The substantially higher yield obtained in the preparation of **11** is probably a reflection of the larger scale (3 mmol) on which this reaction was carried out. The availability of both diastereoisomeric derivatives (*e.g.* **10**[7] and **11**[8]) allowed the stereospecificity of the reaction to be established. As unambiguous proof of stereochemistry, the X-ray crystal structure of the adduct **11** was determined,[9] which confirmed the assignment based on the absolute configurations of the two components. This result also confirmed unequivocally the stereochemical outcome of the attack of nucleophiles on (η^3-allyl)iron tetracarbonyl salts, supporting the proposals and substantial previous precedent provided by Enders.[10]

It is worth noting that conducting the reaction at -20 °C gave far superior yields to those obtained by allowing the reaction mixture to reach room temperature, and are notable in that a relatively small excess of the valuable zinc/copper reagent **1** and **2** can be used. This tactic may also be applicable in the reactions of other, albeit less expensive, zinc/copper reagents for which a 5-fold excess has previously been recommended.[3]

With the stereochemically defined adducts in hand, we have explored their potential application in the synthesis of cyclic amino acid derivatives. Epoxidation of each of the vinyl phenylsulfones **10**, **11** and **12** using lithium *tert*-butylperoxide in THF[11] gave the corresponding phenylsulfonyloxiranes **16** (99%), **17** (62%) and **18** (99%) as inseparable 1:1 mixtures of diastereoisomers. Each of these three oxirane mixtures was then separately treated with Zn/TMSCl in dichloromethane, a reagent system that has been successfully employed for the cyclisation of epoxy esters.[12] Rather than the expected pyrrolidines (which would arise from nucleophilic attack at C-3 of the oxirane), the only isolated products were the 5-phenylsulfonyl-4-methyl pipecolic acid derivatives **19** (49%), **20** (67%) and **21** (70%). Compounds **20** and **21** were isolated as single stereoisomers, whilst **19** was obtained as a 1:1 mixture of diastereoisomers (as determined by ^{1}H NMR).[13]



16

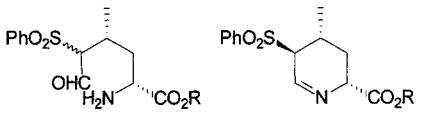
19

17, R = Me
18, R = Bn

20, R = Me
21, R = Bn

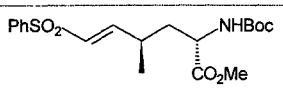
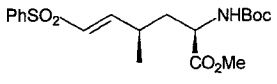
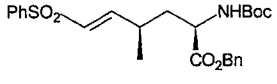
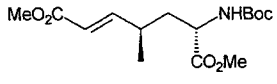
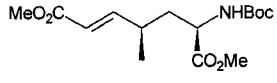
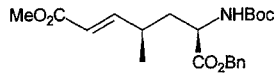
We believe that these compounds arise from an isomerisation of the phenylsulfonyloxirane to the corresponding α-phenylsulfonyl aldehyde **22** (presumably Lewis acid catalysed),[14] followed by an intramolecular reductive amination mediated by zinc.[15] The stereochemical outcome in the case of **20** and **21** is most likely the result of epimerisation at the

carbon atom bearing the phenylsulfonyl group to the all equatorial isomer in the presumed precursor imine **23**. In the precursor to **19**, there is no such driving force.



22 **23**

Table 1. Preparation of Unsaturated α-Amino Acids

Complex	RCu(CN)ZnI	Yield %	Product
7	1	47	 **10**
7	*ent*-1	75	 **11**
7	*ent*-2	54	 **12**
9	1	35	 **13**
9	*ent*-1	40	 **14**
9	*ent*-2	45	 **15**

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(6) The zinc/copper reagent **1** (0.75 mmol) in THF, prepared as previously described,[1] was carefully added *via* a syringe to the (η^3-allyl)iron tetracarbonyl salt **7** or **9** (0.5 mmol) at -78 °C (no additional solvent). The resulting mixture was stirred under argon and the temperature was allowed to rise to -20 °C. The reaction mixture was stirred overnight at this temperature. Ceric ammonium nitrate (55 mg, 0.6 mmol) in water (0.5 mL) was then added and the reaction was stirred for six hours. The reaction mixture was filtered and partitioned between diethyl ether (25 mL) and water (25 mL). The organic extracts were washed with saturated aqueous ammonium fluoride (10 mL), saturated sodium thiosulphate (10 mL), saturated sodium chloride (25 mL), and water (3 x 25 mL). Finally, the organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography using petrol:ethyl acetate (10:1).

(7) For compound **10**, colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (d, 3H, *J* 6.7), 1.41 (s, 9H), 1.52 - 1.72 (m, 1H), 1.84 - 1.95 (m, 1H), 2.45 - 2.55 (m, 1H), 3.71 (s, 3H), 4.20 - 4.22 (m, 1H), 4.98 (d, 1H, *J* 8), 6.36 (d, 1H, *J* 15), 6.89 (dd, 1H, *J* 8 & 15), 7.50 - 7.66 (m, 3H), 7.88 (m, 2H).

(8) For compound **11**, m.p. 104-106 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (d, 3H, *J* 6.7), 1.44 (s, 9H), 1.6 - 1.8 (m, 2H), 2.45 - 2.55 (m, 1H), 3.74 (s, 3H), 4.20 - 4.4 (m, 1H), 4.98 (d, 1H, *J* 8), 6.36 (dd, 1H, *J* 1 & 15), 6.89 (dd, 1H, *J* 7 & 15), 7.50 - 7.66 (m, 3H), 7.88 (m, 2H).

(9) Clegg, W.; Elsegood, M.R.J., unpublished results. Full details of the X-ray crystal structure determination will be published separately.

(10) For the most recent paper, and references to earlier work, see reference 5 above.

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(13) The structures of the piperidines **19**, **20** and **21** were established by spectroscopic means, specifically ^{1}H-^{13}C NMR correlation; N.H. Rees, unpublished results. Further details will be provided in a full paper.

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