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PaaSicats: Powerful Catalysts for Asymmetric Epoxidation of Enones. Novel Syntheses of α-Arylpropanoic Acids including (*S*)-Fenoprofen

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Abstract: Application of the recently developed silica-adsorbed polyleucine catalysts to the enantioselective epoxidation of two enones is reported. Treatment of these epoxides with trimethylaluminium in moist dichloromethane generates the α-hydroxy-β-methyl-ketones, with inversion of configuration. Diastereoselective reduction of the ketone moiety followed by oxidative cleavage generates α-arylpropanoic acids.

Keywords: Aluminium and compounds; Asymmetric reactions; Epoxidation; Pharmacologically active compounds.

Juliá and Colonna showed that polyamino acids such as polyalanine and polyleucine catalyse the asymmetric epoxidation of enones.[1] This work has been developed further[2] and reviews on the usefulness of the methodology for the synthesis of optically active epoxides have appeared.[3]

Recently we disclosed that immobilisation of such polyamino acids (Paas) on silica affords catalysts (PaaSicats) that are robust, easily recovered and readily recycled, allowing the rapid preparation of epoxyketones of high optical purity.[4] Herein we show that these newly developed catalysts can be employed to prepare 2-arylpropanoic acids of high enantiomeric purity, for example the non-steroidal anti-inflammatory agent (*S*)-fenoprofen.

In exploratory studies it was established that polyleucine immobilised on silica rapidly catalysed the epoxidation of chalcone (**1**) to epoxychalcones (+)-**2** or (–)-**2** in high yield and excellent ee (scheme 1). The configuration of the epoxide is dictated, as expected, by the absolute configuration of the catalytic polymer. Treatment of the epoxyketone (+)-**2** with trimethylaluminium (2 equivalents) in dichloromethane containing water (1.2 equivalents) at -78 °C gave the hydroxyketone (+)-**3**, contaminated by a small amount of diastereomeric (+)-**4** (88% overall yield; 10:1 ratio of diastereomers as determined from the ^{1}H nmr spectrum). The major product is formed *via* inversion of configuration at C-3. Reduction of the mixture of **3** and **4** gave the diols (–)-**5** (94% ee) and (+)-**6** (94% ee) which were separated by column chromatography. A two stage oxidation protocol, namely oxidative cleavage using sodium periodate adsorbed onto silica,[5] followed by Jones oxidation, was

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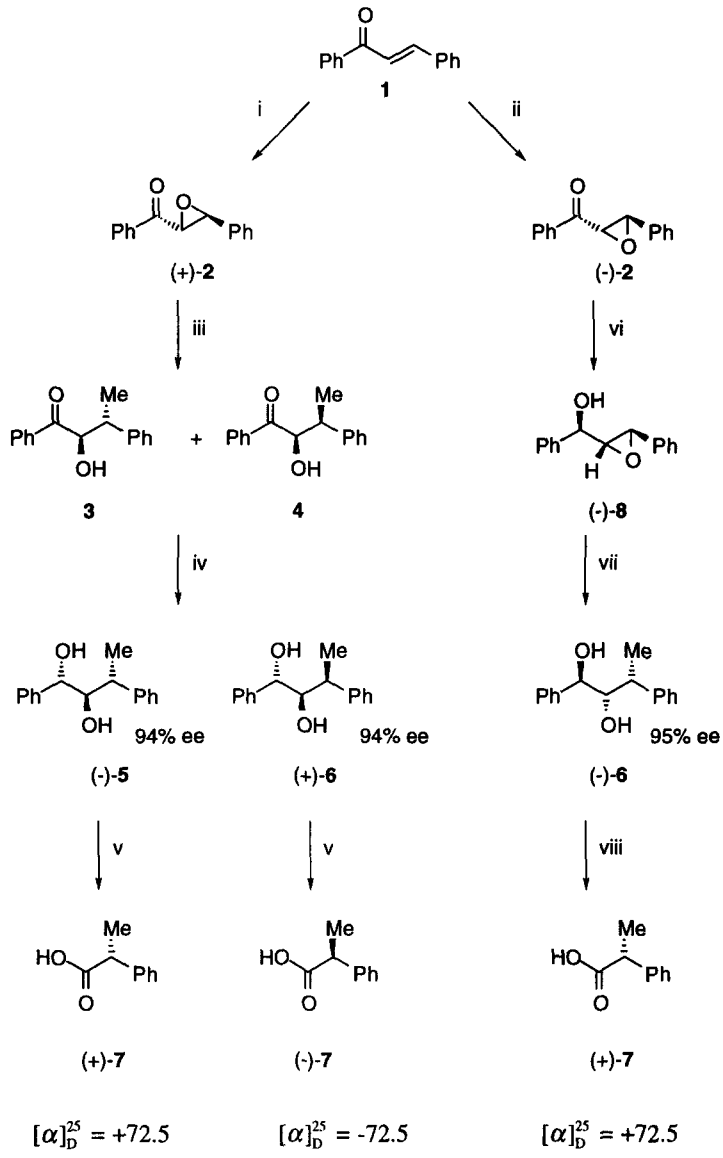
applied to the diol (–)-**5** and furnished (*R*)-(+)-phenylpropionic acid (+)-**7** $[\alpha]_D^{23}$ +72.5 (*c*=1, $CHCl_3$), [lit.[6] $[\alpha]_D^{25}$ +72.8 (*c*=1, $CHCl_3$)]. Oxidation of the diol (+)-(**6**) gave (*S*)-(-)-phenylpropionic acid (-)-**7** $[\alpha]_D^{23}$ -72.5 (*c*=1, $CHCl_3$) [lit.[7] $[\alpha]_D^{25}$ -72.2 (*c*=1, $CHCl_3$)].

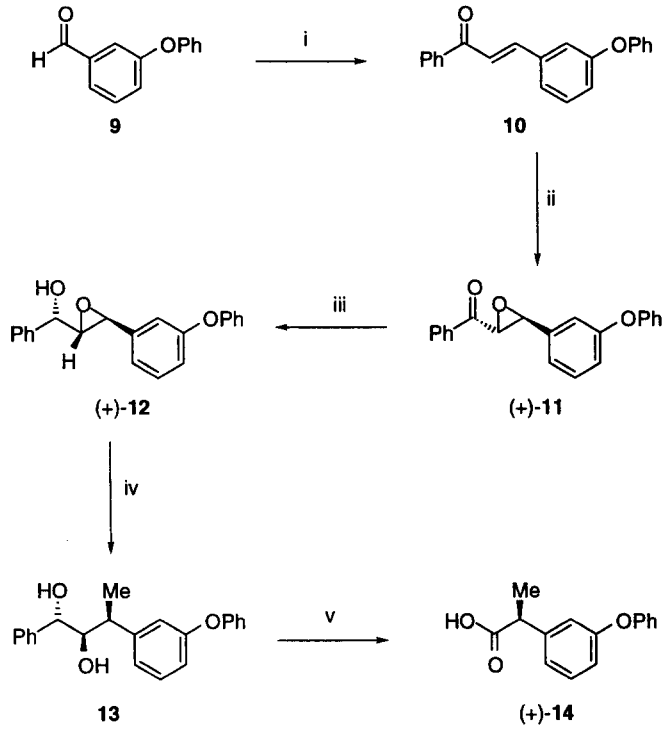


Scheme 1 *Reagents and conditions:* i) poly-L-leucine-SiO_2, urea-H_2O_2, DBU, THF, 30 min, 90%; ii) poly-D-leucine-SiO_2, urea-H_2O_2, DBU, THF, 30 min, 91%; iii) Me_3Al (2 equiv.), H_2O (1.2 equiv.), CH_2Cl_2, -78 °C, 3 h, 88%; iv) $Zn(BH_4)_2$ (0.3 equiv.), Et_2O, 0 °C, 2 h, overall yield 95%; v) $NaIO_4$-SiO_2 (1.2 mmol/g, 3 equiv.), CH_2Cl_2, then Jones oxidation, 71%; vi) $Zn(BH_4)_2$ (0.3 equiv.), Et_2O, 0 °C, 2 h, 95%; vii) Me_3Al (3 equiv.), hexane, -78 °C, 89%; viii) $NaIO_4$-SiO_2 (1.2 mmol/g, 3 equiv.), CH_2Cl_2, then Jones oxidation, 71%.

Reduction of the ketone (–)-**2** with zinc borohydride gave the epoxyalcohol (–)-**8**. Treatment of this compound with trimethylaluminium in hexane, according to the method of Oshima[8] gave the ring opened product (–)-**6**, (95% ee), with retention of configuration at the carbon undergoing alkylation, as expected.[9] Periodate and Jones oxidations provided a complementary route to (*R*)-(+)-phenylpropionic acid (+)-**7**.

These new findings can be applied to the synthesis of optically active non-steroidal anti-inflammatory agents (NSAIs). Prescription of the optically active NSAI ibuprofen has been common practice for some years.[10] Ketoprofen has been made available in single enantiomer form more recently.[11] Often resolution is the method of choice for the preparation of such homochiral NSAIs.[12] Such methodology is intrinsically wasteful and new asymmetric syntheses of optically active NSAIs are still of potential commercial importance.[13]

Aldol condensation of *m*-phenoxybenzaldehyde (**9**) and acetophenone provided the enone **10** which was used as a substrate for poly-L-leucine adsorbed onto silica (PLLSicat) (scheme 2). The silica-bound catalyst promoted oxidation efficiently and in a highly stereocontrolled manner to produce the epoxide (+)-**11** (98% yield, 94% ee).



Scheme 2 *Reagents and conditions:* i) $PhCOCH_3$, MeOH, NaOH, 18 h, 87%; ii) poly-L-leucine-SiO_2, urea-H_2O_2, DBU, THF, 2 h, 98%, 94% ee; iii) $Zn(BH_4)_2$ (0.3 equiv.), Et_2O, 0 °C , 3 h, 95%; iv) Me_3Al (3 equiv.), hexane, -78 °C, 80%; v) $NaIO_4$-SiO_2 (1.2 mmol/g, 3 equiv.), CH_2Cl_2, then Jones oxidation, 64%.

Reduction of the epoxide with zinc borohydride gave the alcohol (+)-**12** as the sole diastereomer. Reaction with trimethylaluminium (with retention of configuration at the participating centre), followed by a two-stage,

one-pot oxidation afforded (+)-(*S*)-fenoprofen (+)-(**14**) $[\alpha]_D^{23}$ +46 (*c*=1, $CHCl_3$), [lit.[14] $[\alpha]_D^{25}$ +45.7 (*c*=1, $CHCl_3$)].

In summary, we have developed the use of silica adsorbed polyleucine for the epoxidation of two enones and converted the resulting epoxides into α-arylpropionic acids, one of which is an important non-steroidal anti-inflammatory agent. By varying the order of the methyl addition and the diastereoselective reduction it is possible to generate either enantiomer of the α-arylpropionic acid using poly-L-leucine. It is anticipated that this route will prove to be a general approach to these pharmacologically significant targets.

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