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Articles

Development of the Juliá−Colonna Asymmetric Epoxidation Reaction: Part 1. Preparation and Activation of the Polyleucine Catalyst

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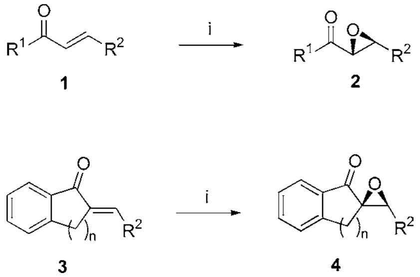
Abstract:

The preparation of silica-supported poly-L-leucine has been studied under a variety of reaction conditions leading to an efficient procedure for the preparation of material suitable for use in the Juliá−Colonna asymmetric epoxidation reaction.

Introduction

Alkene epoxidation is among the most widely used asymmetric transformations.[1] This reflects both the effectiveness of existing epoxidation protocols[2,3] and the versatility of epoxides as intermediates for biologically active target molecules. The Juliá−Colonna asymmetric epoxidation of (*E*)-α,*β*-unsaturated ketones, catalysed by polyamino acids such as poly-(L)-leucine, is one of the more commonly employed methods for epoxidation of electron-deficient substrates.[4] A wide range of (*E*)-enones **1** has been epoxidised using a variety of reaction protocols[5−9] to generate the corresponding trans-α,*β*-epoxyketones with good to excellent enantioselectivity.[4] In the case of substrate **1** (Scheme 1), R^1 and R^2 can be alkyl, aryl, heteroaryl or alkenyl. Moreover, certain trisubstituted olefins, derived from cyclic ketones (**3**, $n = 1-3$) have been reported to be epoxidised to provide compounds of type **4** with useful levels of enantioselectivity.[10] Certainly, with the recent advances made to this technology it is a mistake to suggest "that the reaction is only successful for chalcones".[11]

Scheme 1[a]



[a] Reagents and conditions: i. a) aq NaOH, aq H_2O_2, organic solvent, poly-(L)-amino acid, or b) DBU, urea−H_2O_2, organic solvent, polyamino acid, or c) Na_2CO_3·$1.5H_2O_2$, H_2O, DME, polyamino acid.

The application of the Juliá−Colonna protocol on a large scale is timely, as epoxyketones have proved to be useful intermediates in a number of syntheses of pharmacologically active molecules.[6,12−14] In this contribution it is demonstrated that a number of factors in the existing protocols for catalyst preparation need to be carefully defined to maximize the yield and quality of the Juliá−Colonna catalyst on a large scale.

Protocols and Preferred Catalysts for the Juliá−Colonna Reaction. Three protocols for the Juliá−Colonna reaction have been reported.[15] The original method employed

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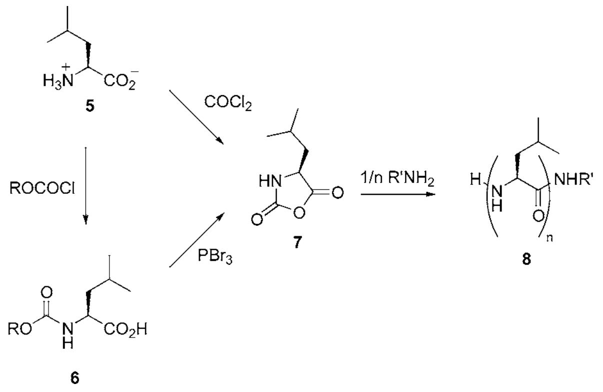
Scheme 2. **Polyleucine preparation**



a triphasic system, consisting of the insoluble catalyst (generally polyalanine or polyleucine), a solution of the enone in an organic solvent (such as hexane, carbon tetrachloride, or toluene), and an aqueous layer containing H_2O_2 and NaOH (herein known as the triphasic protocol).[5] More recently, Drauz, Roberts, et al. have reported two protocols that lead to greatly reduced reaction times and a significantly expanded substrate range. The first, referred to as the biphasic protocol, consists of the insoluble catalyst and a solution of the substrate in THF, DBU, and H_2O_2 (added in the form of anhydrous urea−H_2O_2).[6] The second, carried out in a homogeneous solvent mixture of water and DME, utilises sodium percarbonate as both oxidant and base and is known as the percarbonate protocol.[7] All three protocols employ as catalysts simple polyamino acids such as polyleucine or polyalanine, typically with chain lengths of around 30 residues. However, in the case of the biphasic protocol it is also possible to utilise a form of the catalyst in which the insoluble polyamino acid is adsorbed onto silica.[8] The advantages of the silica-supported polyamino acid catalyst are the following: improved filtration properties, higher catalyst activity (allowing increased substrate loading), and improved catalyst recycling. In comparison, the filtration properties of the unsupported polyamino acid were unsuitable for large-scale work; even on the sub-gram scale filtration proved to be problematic due to the small particle size of the catalyst. For this reason the biphasic protocol, utilising silica-supported polyleucine, was the method of choice for optimisation. Polyleucine was preferred over the slightly more active poly*neo*pentylglycine[16] due to the greater cost of the nonproteinogenic monomer.

Preparation of Leucine *N*-Carboxyanhydride. Polymerisation of the amino acid *N*-carboxyanhydride (NCA)[17] represents the most efficient method for preparing polyamino acids, although stepwise solid-phase synthesis has also been utilised.[13] The polymerisation-based synthesis is a two-step procedure; first, the NCA **7** is prepared and, after purification, is treated with a sub-stoichiometric quantity of a suitable nucleophilic initiator to effect polymerisation (Scheme 2).

The most widely used method of preparation of NCA **7** is the Fuchs−Farthing approach which involves the treatment of the amino acid **5** with phosgene or a more easily handled equivalent such as trichloromethyl chloroformate[18] (diphosgene) or bis(trichloromethyl)carbonate (triphosgene).[19] Alternatively, the Luchs method can be employed, in which an amino acid carbamate **6** is cyclised by treatment with an activator such as PCl_5, PBr_3, $SOCl_2$.[17] Clearly, in terms of efficiency, the Fuchs−Farthing approach is the more attractive, and this method was chosen to provide the starting material for the present study.

On a small scale, the Fuchs−Farthing procedure most conveniently employed for the preparation of the NCA involves adding triphosgene to a stirred suspension of L-leucine **5** in anhydrous THF (75 g/L) at 45−50 °C.[19] After 4 h the reaction mixture is concentrated in vacuo, and the NCA **7** is purified by recrystallisation from THF/hexane. On a 30-g scale this procedure affords the NCA **7** in 73−92% yield. On a larger scale, condensed phosgene may be preferred to the more expensive triphosgene. Working with 525 g of leucine (4 mol) in THF (2.3 L) we found that the reaction with phosgene was complete after 2 h at 50 °C. The increase in scale was found to result in a decrease in the purity of the crude NCA with an attendant reduction in the ease of recrystallisation. Generally, the crystalline NCA was accompanied by a dark brown oil, which led to a reduction in both yield (40−60%) and purity. It was found that toluene/hexane was a more effective solvent mixture than THF/hexane; slow recrystallisation from toluene/hexane [NCA dissolved in the minimum amount of hot toluene (ca. 200 mL); hexane (ca. 2.5 L) added to promote crystallization] typically generated the NCA in 60% yield on the larger scale.

Results and Discussion: Large-Scale Preparation of Polyleucine

As summarised above, the documented protocols allowed large-scale preparation of leucine−NCA. This material was employed in our studies on the scale-up of the polymer formation and its downstream processing. Various reports in the literature have detailed a number of different initiators for the polymerisation reaction, such as water (in the form of water vapour acting on the solid NCA),[11] simple primary amines,[20] diamines and solid-supported amines (e.g., aminomethyl polystyrene).[21] Moreover, a variety of solvent systems has been reported, with THF being the solvent of choice for many studies. The catalyst utilised in the original Juliá−Colonna triphasic protocol was the crude polyamino acid. However, it has been found that this material is ineffective under the biphasic reaction conditions for the conversion of (*E*)-chalcone (**1**, $R^1 = R^2 =$ Ph) into *trans*-epoxychalcone (**2**, $R^1 = R^2 =$ Ph), requiring activation by stirring in a mixture of toluene and aqueous NaOH before use. It has also been shown that adsorbing the catalyst onto silica has a similar activating effect as well as producing the previously discussed improvements in filtration. Clearly, it was neces-

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Table 1. **Polymerisations in THF and with various catalyst activations**

entry	solvent	initiator	temp (°C)	time (d)	activation	support	conversion[a] (%, time)	ee[b] (%)
1	THF	DAP[c]	rt	7[d]	none	none	6 (30 min)	–
2	THF	DAP[c]	rt	7[d]	aq NaOH/toluene[e]	none	93 (30 min)	98
3	THF	DAP[c]	rt	7[d]	none	SiO_2[f]	45 (30 min)	91

[a] For the epoxidation of chalcone (**1**, $R^1 = R^2 =$ Ph) under biphasic conditions,[6] determined by HPLC. [b] For the epoxidation of chalcone under biphasic conditions,[6] determined by HPLC using a chiralpak AD chiral phase. [c] 1,3-Diaminopropane, 32 equiv of NCA per amino group. [d] A trace of NCA still remained after 7 days reaction. [e] Catalyst was stirred for 5 days, filtered, washed, and dried. [f] SiO_2: polyleucine 3.4:1.

Table 2. **Polymerisations in DME and with various catalyst activations**

entry	solvent	initiator	temp (°C)	time	activation	support	conversion[a] (%, time)	ee[b] (%)
1	DME	$PS{-}NH_2$[c]	rt	14 d	none	none	75 (120 min)	92
2	DME	$PS{-}NH_2$[c]	90	18 h	none	none	58 (60 min)	95
3	DME	$PS{-}NH_2$[c]	90	18 h	none	SiO_2[d]	98 (60 min)	97
4	DME	DAP[e]	90	18 h	none	none	73 (60 min)	96
5	DME	DAP[e]	90	18 h	none	SiO_2[d]	98 (60 min)	97

[a] For the epoxidation of chalcone under biphasic conditions,[6] determined by HPLC. [b] For the epoxidation of chalcone under biphasic conditions,[6] determined by HPLC using a chiralpak AD chiral phase. [c] Cross-linked amino methyl polystyrene, 32 equiv of NCA per amino group. [d] SiO_2: polyleucine 1.2–1.4:1. Silica was added directly to the polymerization reaction. [e] 1,3-Diaminopropane, 32 equiv of NCA per amino group.

sary to optimise the catalyst preparation, activation, and attachment to the support with a view to streamlining the procedure for large-scale work.

On a small scale, polymerisation of leucine–NCA is carried out in THF (~0.16 M) at room temperature using 1,3-diamino propane (DAP) as the initiator. A reaction time of >5 days is required for the polymerisation to reach completion. Under the biphasic reaction conditions the crude polymer is a very poor catalyst, with only a 6% conversion of chalcone (**1**, $R^1 = R^2 =$ Ph) into the epoxide (**2**, $R^1 = R^2 =$ Ph) being observed after 30 min (Table 1, entry 1). The catalyst's performance can be improved either by stirring in a mixture of 4 M aq NaOH (4 cm^3/g) and toluene (10 cm^3/g), filtering, washing with water, acetone, and hexane and then drying (98% ee for the chalcone test, Table 1, entry 2) or by adsorption onto silica as described by Roberts and Geller[8] (91% ee, Table 1, entry 3). As indicated above, the silica-adsorbed material is preferred because of its excellent filtration properties.

Whilst good epoxidation results were obtained using material prepared by these procedures, a number of limitations could be identified. First, both the polymerisation and activation times were prohibitively long. Second, of the two activated catalysts, the more readily filtered, silica-adsorbed material afforded the less efficient reaction. [Adsorption of activated material onto silica, generated a catalyst less active (78% conversion, 84% ee) than either the silica-adsorbed unactivated or the activated nonadsorbed material.]

To try to improve the quality of the catalyst, polymerisations were investigated in DME (Table 2). Polymerisation under similar conditions to those in THF led to a rather sluggish reaction with significant amounts of NCA still present (identified by IR spectroscopy) after 2 weeks' reaction. However, the catalyst generated (in an 86% yield, which suggests the average length of the polymer is 26 amino acids), proved to be significantly more active than the material isolated from the reaction in THF (Table 2, entry 1). In an effort to reduce the reaction time, the reaction was repeated at 90 °C; polymerisation was complete in 18 h using either aminomethyl polystyrene ($PS\text{-}NH_2$)[21] or DAP as the initiator. Both catalysts proved to be effective without any activation—the chalcone test reaction was >50% complete after 1 h with epoxide showing ee >95% (Table 2, entries 2 and 4). Moreover, both catalysts were further improved by supporting them on silica (Table 2, entries 3 and 5). The exact protocol for immobilisation involved cooling the polymerisation reaction to room temperature before adding silica to the suspension of the polyamino acid. The mixture was stirred for 3 days to allow adsorption of the catalyst onto the silica before filtering the solid (polyleucine coated silica). Overall, the two-step procedure of polymerisation in DME at 90 °C followed by adsorption onto silica generated a highly active polyleucine catalyst rapidly and efficiently, constituting a considerable improvement over the polymerisation in THF. Polymerisations were also undertaken in methyl *tert*-butyl ether (50 °C) and methyl isobutyl ketone (75 °C); however, in both cases, catalyst of poor quality was obtained.

A series of polymerisations was carried out in toluene (Table 3). At elevated temperatures, these reactions proved to be rather vigorous, with an observable effervescence occurring as the bath temperature reached 60 °C. Using the aminomethyl polystyrene initiator the catalyst prepared at 100 °C gave epoxyketone in 86% ee in the "chalcone test" (product of 90% ee was obtained when the catalyst was supported on silica, Table 3, entries 1 and 2). Under these conditions the DAP initiator generated a more effective catalyst; the chalcone test afforded epoxide (**2**, $R^1 = R^2 =$ Ph) of 91% ee (94% when supported on silica, Table 3, entries 3 and 4).

Direct comparisons of toluene and THF suggested that the polymerisations in the former solvent were considerably faster; indeed, it was found that on larger scales the evolution of carbon dioxide in reactions performed in toluene was quite rapid. Thus, later polymerisations were initiated at 0 °C and allowed to warm slowly to room temperature to produce a more controlled reaction. Under these conditions it was found that polymerisation was complete in 1 day; unfortunately,

Table 3. **Polymerisations in toluene and with various catalyst activations**

entry	solvent	initiator	temp (°C)	time	activation	support	conversion^a (%, time)	ee^b (%)
1	toluene	PS−NH$_2^c$	100	18 h	none	none	25 (60 min)	86
2	toluene	PS−NH$_2^c$	100	18 h	none	SiO$_2^d$ (direct)	62 (60 min)	90
3	toluene	DAP^e	100	18 h	none	none	33 (60 min)	91
4	toluene	DAP^e	100	18 h	none	SiO$_2^d$ (direct)	80 (60 min)	94
5	toluene	DAP^e	0 °C−rt	1 d	none	none	16 (30 min)	83
6	toluene	DAP^e	0 °C−rt	1 d	none	SiO$_2^f$	33 (30 min)	93
7	toluene	DAP^e	0 °C−rt	1 d	aq NaOH/toluene^g	none	86 (30 min)	97
8	toluene	DAP^e	0 °C−rt	1 d	aq NaOH/toluene^g	SiO$_2$	60 (30 min)	93
9	toluene	DAP^e	0 °C−rt	1 d	none	SiO$_2$ then water-wash	71 (30 min)	95
10	toluene	DAP^e	0 °C−rt	1 d	aq NaOH/toluene^g	SiO$_2$ then water wash	78 (30 min)	94
11	toluene	DAP^e	0 °C−rt	1 d	none	direct to SiO$_2$	25 (30 min)	89
12	toluene	DAP^e	0 °C−rt	1 d	none	direct to SiO$_2$ then water-wash	62 (30 min)	93

[a] For the epoxidation of chalcone under biphasic conditions,[6] determined by HPLC. [b] For the epoxidation of chalcone under biphasic conditions,[6] determined by HPLC using a chiralpak AD chiral phase. [c] Cross-linked amino-methyl polystyrene, 32 equiv of NCA per amino group. [d] SiO$_2$: polyleucine 1.5−1.6:1. [e] 1,3-Diaminopropane, 32 equiv of NCA per amino group. [f] SiO$_2$: polyleucine 3.4:1. [g] Catalyst was stirred for 6 days, filtered, washed, and dried.

filtration of the polymer was time-consuming, and the performance of the catalyst was modest, giving only a low conversion to epoxide of 83% ee in the chalcone test (Table 3, entry 5). However, this material could be significantly improved either by activation (97% ee, Table 3, entry 7), adsorption onto silica (93% ee, Table 3, entry 6), or a combination of both procedures (93% ee, Table 3, entry 8).

It has been found that silica−polyleucine of low catalytic activity (in terms of rate) can be activated by washing with water; the toluene-polymerised silica-supported catalysts were stirred in water for 48 h, filtered, washed with acetone, and dried in vacuo. In both cases, only a marginal improvement in ee was observed. However, the conversion figures at the 30-min time-point improved substantially when comparing the unactivated, silica-supported catalysts and the activated silica-supported catalyst (Table 3, entries 9 and 10).

A clear inefficiency in the above procedure is the filtration step between the catalyst synthesis and the silica adsorption, given the poor filtration properties of the first-formed poly-L-leucine. In an effort to circumvent this step, a polymerisation reaction was carried out in toluene, and then silica gel was added directly to the suspended catalyst without prior filtration; this mixture was then stirred for a further 2 days before removing the silica-supported catalyst by a fast, straightforward filtration. This catalyst proved less active than the other silica supported catalysts (25% conversion, 89% ee, Table 3 entry 11). However, once again, a simple water-wash served to improve the conversion rate, with the additional effect of raising the ee to levels similar to the other silica-supported catalysts (62% conversion, 93% ee, Table 3 entry 12).

In summary, the original reaction conditions for the preparation of silica-supported polyleucine, namely, NCA polymerisation in THF, filtration after 10 days, followed by adsorption onto silica may be replaced by one of two more efficient procedures. Polymerisation in DME requires heating to 90 °C, however at this temperature reaction is complete in less than 1 day, and after adsorption onto silica a catalyst of excellent quality is generated. Alternatively, polymerisation in toluene is more rapid, (avoiding the need for elevated reaction temperatures), and the product can be adsorped onto silica directly. However, the crude silica−polyleucine prepared in this way required a water-wash to increase the rate of the asymmetric epoxidation (Juliá−Colonna reaction) to acceptable levels. The optimised polymerisation conditions, in toluene, were performed on a 400-g scale.

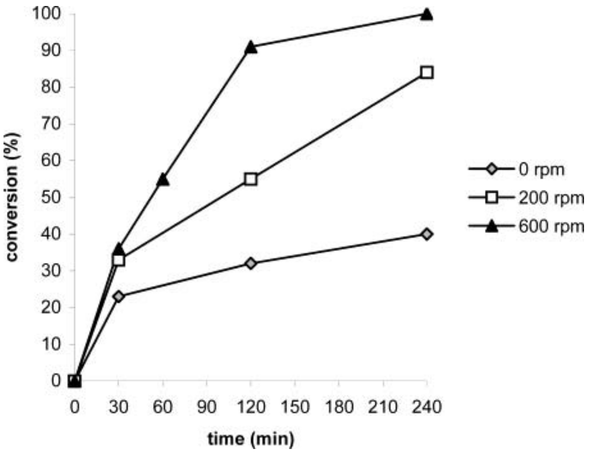

Figure 1. **The effect of stirring speed on the rate of chalcone (1, R^1 = R^2 = Ph) epoxidation using silica-poly-L-leucine under biphasic reaction conditions.**

Epoxidation Reactions. With significant quantities of catalyst in hand it was possible to start to investigate the efficiency of this bulk material for the epoxidation of chalcone (**1**, R^1 = R^2 = Ph). Three magnetically stirred reactions (3.25 mmol scale), identical apart from stirring rate, were carried out. The speed of the stirring was varied from 0 to 200 to 600 rpm. The enantioselectivity of the reactions proved to be independent of both the speed of stirring and of the rate of the epoxidation reaction—essentially no variation from 94% ee was observed with any of the samples of epoxyketone (**2**, R^1 = R^2 = Ph). On the other hand, the rate of the reaction was found to have a strong dependency on the speed of the stirring (Figure 1). For example, after 2 h, the conversions were 32% for the nonstirred reaction, 55% for the 200 rpm experiment, and 91% for that stirring at 600 rpm.

A further epoxidation reaction was performed with the magnetic stirrer bar being replaced with a mechanically stirred paddle of similar size and rotating at the same rate.

It was found that the change in the method of stirring led to a small improvement in the efficiency of the reaction, i.e., the paddle proved marginally more effective.

Obviously these results indicated that, in large-scale oxidations using silica-supported polyleucine, high stirrer speeds would need to be maintained. The large-scale synthesis of selected epoxyketones was based on these data and will be reported elsewhere.

Conclusions

Poly-L-leucine can be added to the list of natural[22] and nonnatural[23] oxidation catalysts that benefit from being supported on commercially available silica gel.

Experimental Procedures

General Procedures. *Polymerisation Procedure.* To a stirred 0.16 M solution of L-leucine NCA (**7**) in anhydrous solvent (THF, DME or toluene) under a nitrogen atmosphere was added initiator (0.0313 amino equivalents, either amino methyl polystyrene[21] or 1,3-diaminopropane). The course of the reaction was followed by IR spectroscopy and TLC. After polymerisation was judged complete, the reaction was filtered, and the solid poly-L-leucine was washed with further solvent and then dried in vacuo at 50 °C.

Activation Procedure for Nonsilica-Supported Catalyst. Poly-L-leucine was rapidly stirred in a mixture of toluene (10 cm^3/g) and 4 M aq NaOH (4 cm^3/g) for 6 days after which time the resulting paste was filtered. The activated polyamino acid was washed thoroughly with water, water/acetone, and acetone and then dried in vacuo at 50 °C.

Preparation of Silica-Supported Catalysts. The catalysts were supported on silica as previously described, except the preparation was carried in the solvent-type used to prepare the polyleucine.[8]

Activation of Silica-Supported Catalysts. Silica-supported poly-L-leucine was stirred in water (3 cm^3/g) for 2 days and then filtered, washed with acetone, and dried in vacuo at 50 °C.

General Epoxidation Procedure on a Small Scale. Epoxidations were carried out as previously described using either poly-L-leucine[6] or silica-supported poly-L-leucine[8] as the catalyst. Thus, in a typical process, a solution of the substrate (1 equiv) in anhydrous tetrahydrofuran was added urea. hydrogen peroxide (1.2 equiv), diazabicycloundecene (1.2 equiv) and poly-(L)-leucine (12 mol % optionally immobilised on silica [one part catalyst, three parts silica]). The mixture was stirred at room temperature until the reaction was complete (TLC). The catalyst was removed (by rapid filtration when supported on silica) and washed with ethyl acetate. The combined organic fractions were evaporated in vacuo to yield crude epoxide.

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