



Imidazolium-modified poly(L-leucine) catalyst: an efficient and recoverable catalyst for Juliá–Colonna reactions

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ABSTRACT

A novel, easily recyclable imidazolium-modified poly(amino acid) catalyst was prepared. This catalyst exhibits high activity for the asymmetric epoxidation of α,β -unsaturated ketones without any pre-activation. The enantioselectivity was up to 99% ee for epoxidation of *p*-methoxychalcone. Compared to classical Juliá–Colonna catalysts, this insoluble, powdery catalyst can dramatically reduce the reaction time and can be easily recycled by a simple filtration after the reaction. More importantly, the recycled catalyst has been successfully reused for seven cycles without deterioration in catalytic efficiency.

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Chiral poly(amino acids) (PAA) such as polyleucine and polyalanine can be used as catalysts for asymmetric epoxidation of α,β -unsaturated ketones, as reported by Juliá and Colonna in the 1980s.¹ Juliá–Colonna enantioselective epoxidation subsequently attracted great interest since chiral, non-racemic epoxides can serve as building blocks for the synthesis of a wide variety of optically active compounds.² However, for practical applications there are at least three factors limiting the application of Juliá–Colonna catalysts: (1) relatively high catalyst loading (ca. 200 wt %); (2) long catalyst pre-activation and reaction times; and (3) it is difficult to recover the catalyst because of the voluminous gel-like catalyst formed after the reaction.

Many efforts have been devoted to solving these problems.^{3,2b} Roberts and co-workers prepared a simply recyclable PAASiCat (polyleucine adsorbed onto silica)⁴ with improved activity. We previously reported that silica gel-grafted poly(L-leucine) (PLL) via covalent bonding was an efficient and easily recoverable catalyst for Juliá–Colonna asymmetric epoxidation with high enantioselectivity.⁵ Although the silica gel-grafted immobilized PLL eliminates the trouble of handling voluminous gel-like catalyst during the work-up process, the amount of catalyst required for the reaction was still very large in terms of weight percentage (approximately 800 wt %).

Geller et al. reported a phase-transfer catalyst (PTC) mediated Juliá–Colonna epoxidation by using tetrabutylammonium bromide

or Aliquat 336 as a co-catalyst to increase the peroxide concentration in the organic phase.^{6,7} They also described another PLL catalyst which was polymerized at a higher temperature and led to a higher activity.⁷ These two protocols have the advantages of dramatically increasing Juliá–Colonna epoxidation reactivity, significantly decreasing the catalyst amount and reducing the pre-activation time (from 6 h to a few minutes).⁸ However, the problem of gel-like PAA in the recovery process still exists. Here, we report the preparation and application of a novel PLL catalyst for which amino acid polymerization is initiated by an imidazolium with a ω -amino group.

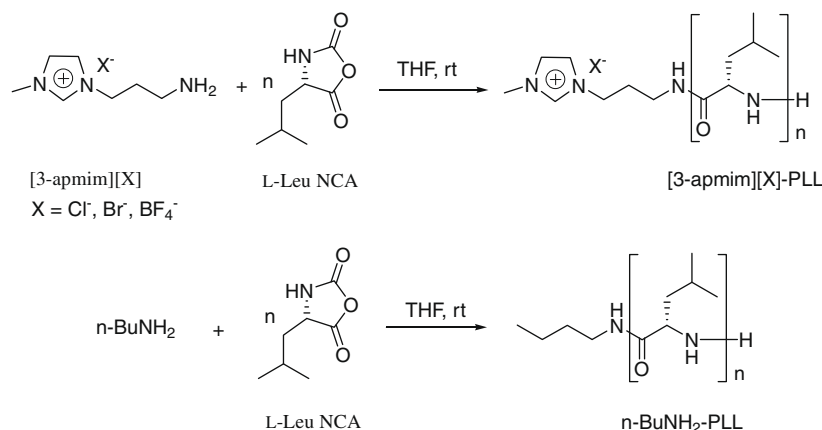
1-(3-Aminopropyl)-3-methylimidazolium⁹ ([3-apmim][X], X = Cl[−], Br[−], BF₄[−]) was used as a nucleophilic initiator for polymerization of the *N*-carboxyanhydride of L-leucine (L-Leu NCA¹⁰) with an initiator/L-Leu NCA ratio of 1:30 to afford the white powdery catalyst [3-apmim][X]-PLL.¹¹ The structure of the catalyst was characterized by ¹H NMR and IR. For comparison, the traditional catalyst *n*-BuNH₂-PLL was also prepared by using the same initiator/L-Leu NCA ratio (Scheme 1).

Asymmetric epoxidation of chalcones was carried out in DME using sodium percarbonate as an oxidant and base, and [3-apmim][Cl]-PLL, [3-apmim][Br]-PLL or [3-apmim][BF₄]-PLL as the catalyst (Scheme 2).¹² The results are summarized in Table 1.

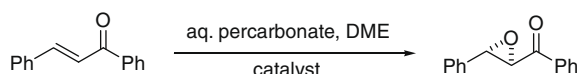
When the traditional catalyst *n*-BuNH₂-PLL was used, the enantioselectivity and yield were only 61% ee and 66% yield, respectively, after 54 h (Table 1, run 4). Under the same reaction conditions, the imidazolium-modified PAA [3-apmim]Cl-PLL catalyzed reaction can provide the product in 95% ee and 96% yield with a significantly reduced reaction time of 2 h (Table 1, run 1).

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Scheme 1. Preparation of catalysts [3-apmim][X]-PLL and *n*-BuNH₂-PLL.



Scheme 2. Juliá-Colonna epoxidation of chalcone.

Table 1
Chalcone epoxidation catalyzed by [3-apmim][X]-PLL^a

Run	Catalyst ^b	Time (h)	Yield ^c (%)	ee (%)
1	[3-Apmim][Cl]-PLL	2	96	95
2	[3-Apmim][Br]-PLL	7	93	94
3	[3-Apmim][BF ₄]-PLL	7	89	94
4	<i>n</i> -BuNH ₂ -PLL	54	66	61

^a Catalyst 20 mol % (based on chalcone).

^b *n*-BuNH₂-PLL pre-activated 24 h before use, [3-apmim][X]-PLL not pre-activated before use.

^c Isolated yield.

The other two modified PLL catalysts, [3-apmim]Br-PLL and [3-apmim]BF₄-PLL, also provided satisfactory results (Table 1, runs 2 and 3).

We postulated that addition of a terminal imidazolium group to PLL could improve the physical properties of the catalyst and allow its easy separation and recovery from the reaction system. More importantly, introduction of the quaternary ammonium moiety could provide the catalyst with phase transfer ability so that it can transfer more hydroperoxide (HOO[−]) from the aqueous phase to the reactive sites, thus improving the efficiency of the catalyst.

The reusability of [3-apmim]Cl-PLL was also investigated. The results are summarized in Table 2.

It took the initial reaction 2 h to go to completion. However, similar yield and enantioselectivity were obtained after only

Table 2
Reusability of catalyst [3-apmim][Cl]-PLL in chalcone epoxidation^a

Run	Time	Yield ^b (%)	ee (%)
1	2 h	96	95
2	15 min	94	95
3	15 min	98	95
4	15 min	99	95
5	15 min	99	96
6	15 min	99	94
7	15 min	99	95

^a The catalyst was used at 20 mol % based on chalcone and recovered by filtration and then washed with ethyl acetate.

^b Isolated yield.

Table 3
Influence of catalyst amount on chalcone epoxidation^a

Entry	Catalyst ^b (mol %)	Time (h)	Yield ^c (%)	ee (%)
1	20	0.25	99	95
2	10	12	99	91
3	5	12	99	86
4	1	12	94	75

^a Catalyst [3-apmim][Cl]-PLL recovered from run 7 described in Table 2.

^b Catalyst amount based on chalcone.

^c Isolated yield.

15 min in the second run for [3-apmim]Cl-PLL. It is possible that the catalyst was activated in the first run and the recycled catalyst was more efficient to catalyze the reaction in the second run. After each run, the powdery catalyst was almost completely recovered by a simple filtration. In all the seven cycles, both the yield and enantioselectivity had virtually no negative change (Table 2, run 7).

Since satisfactory enantioselectivity was obtained after only several minutes for 20 mol % of catalyst [3-apmim]Cl-PLL, we investigated the effect of decreasing the catalyst loading to 10, 5 and 1 mol %. The results are listed out in Table 3.

The amount of traditional catalysts required for Juliá-Colonna reaction is usually 20 mol % relative to the substrate. As shown in Table 3, when the loading of [3-apmim]Cl-PLL was decreased to 10 mol %, the enantioselectivity and yield remained almost unchanged (Table 3, entry 2 vs entry 1). On further decreasing the catalyst loading to 5 mol % and 1 mol %, the corresponding enantioselectivity decreased to 86% ee (Table 3, entry 3) and 75% ee (Table 3, entry 4). This reaction proceeds slowly in the absence of a catalyst, therefore the spontaneously produced racemic epoxide can be accounted for the decrease in enantioselectivity in the reactions with a low catalyst loading.

It is worth noting that the molecular weight of the imidazolium-modified PLL catalyst is much less than those of other inorganic or organic supported catalysts,⁵ therefore the weight percent of the catalysts is much less, even for a molar ratio of 20%.

The epoxidation of various (*E*)- α,β -unsaturated ketones was screened by using [3-apmim]Cl-PLL as the catalyst. Almost all the substrates gave the corresponding epoxides in excellent yield with high enantioselectivity, except for the *o*-methoxy-substituted chalcone (Table 4).

All the reactions proceeded rapidly within 15 min or less. For substrates bearing *p*-electron-donating substituents, excellent yields and enantioselectivity could be obtained (Table 4, entries 1 and 2). Their *p*-electron-withdrawing substituted counterparts afforded comparable results (Table 4, entries 4 and 5). Owing to

Table 4Enone epoxidation catalyzed by [3-apmim][Cl]-PLL^a

Entry	R ₁	R ₂	Time (min)	Yield ^b (%)	ee (%)
1	Ph	<i>p</i> -MeOC ₆ H ₄	15	90	97
2	<i>p</i> -MeOC ₆ H ₄	Ph	15	98	99
3	<i>o</i> -MeOC ₆ H ₄	Ph	15	24	77
4	<i>p</i> -ClC ₆ H ₄	Ph	10	96	94
5	Ph	<i>p</i> -ClC ₆ H ₄	7	98	93

^a [3-Apmim][Cl]-PLL: recovered from the reactions described in Table 3, 20 mol %.^b Isolated yield.

the steric effect, the *o*-substituted substrate gave a much lower yield (24%) with moderate enantioselectivity (77% ee) (Table 4, entry 3).

In conclusion, we developed a new type of imidazolium-modified PAA catalyst for asymmetric epoxidation of α,β -unsaturated ketones. This novel catalyst can effectively catalyze a highly enantioselective chalcone epoxidation without any pre-activation. The loading (weight percentage) of this catalyst was greatly decreased, compared to those of classical Juliá-Colonna catalysts. Furthermore, the better catalytic efficiency of this catalyst insured the significant reduction in reaction time. This insoluble, powdery catalyst also allows a simple recovery procedure. After seven cycles, no catalytic efficiency deterioration was observed in terms of either enantioselectivity or yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.127.

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- Synthesis of imidazolium-modified PLL catalyst*: L-Leucine NCA (16 mmol, 2.514 g) was dissolved in anhydrous tetrahydrofuran (60 mL) under a nitrogen atmosphere and [3-apmim][X] (0.5 mmol) was added as an initiator and the reaction mixture was stirred at rt for 72 h. The precipitate was filtered and successively washed thrice with tetrahydrofuran and diethyl ether and dried under vacuum to afford the asymmetric epoxidation catalyst [3-apmim][X]-PLL as a white solid. IR (KBr, cm⁻¹) 3312, 2958, 2871, 1658, 1548, 1468, 1385; ¹H NMR (500 MHz, CF₃CO₂D) for [3-apmim][X]-PLL (*n* = 10) ppm: 9.38 (1H, proton of imidazolium), 8.19 (1H, proton of imidazolium), 8.07 (1H, proton of imidazolium).
- Typical enone epoxidation procedure*: Enone (1 mmol) was dissolved in DME (7.5 mL) and water (7.5 mL). The percarbonate (1.5 mmol) and catalyst (20 mol %) were successively added and the reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC). The catalyst was recovered by rapid filtration and washed with ethyl acetate. The combined organic fractions were dried over anhydrous Na₂SO₄, and were then evaporated in vacuo and purified by silica gel column chromatography (AcOEt/petroleum 1:10–1:30) to afford the corresponding epoxide. The enantiomeric excess was determined by chiral-phase HPLC analysis on a Chiralpak AD column (eluent 10% *i*-PrOH in hexane, UV detection at 254 nm).