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Journal Name

ARTICLE

A new, efficient and recyclable [Ce(*L*-Pro)]$_2$(Oxa) as a heterogeneous catalyst used in Kabachnik-Fields reaction

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Herein we introduce a new catalyst for the Kabachnik-Fields reaction, the [Ce(*L*-Pro)]$_2$(Oxa), in a very accessible, simple and efficient methodology for α-aminophosphonates synthesis using some aromatic aldehyde, aromatic amine and diphenyl phosphite. This procedure was developed inserting a low catalytic loading of cerium (III) prolinate and it has allowed the recycle of the catalyst.

Introduction

Organophosphorus compounds are useful building blocks for their medicinal applications. Among them, the aminophosphonic acids are one class of organic compounds that had attracted the attention of many researches groups around the world because frequently this class has presented some biological properties such as antibacterial, antithrombotic agent, anti-inflammatory agent, carcinogenic drugs, pesticides and HIV protease.[1-2] Besides, the synthesis of aminophosphonic derivatives has received a considerable importance due to their structural analogy to the aminoacids.[3] For this reason, several methodologies have been developed aiming the synthesis of α-aminophosphonates. Among them, Kabachnik-Fields reaction is one of the easiest and most direct approaches, for being carried out using aldehyde, amine and diphenyl phosphite.[4] Usually, this reaction could be catalysed by Lewis acids, such as, $SnCl_2$, $SnCl_4$, $ZnCl_2$ and $MgBr_2$, but these reactions cannot be done as one-pot.[5] Among many synthetic approaches of the α-aminophosphonates synthesis, the nucleophilic addition of phosphites to imines is the most useful method. However, many imines are hygroscopic and are not stable for isolation.[6] Moreover, this procedure usually presents long reaction times, difficult procedures, low yields, the use of stoichiometric amounts of catalyst, difficulties of separation and the recycling and generally only dialkyl phosphite is used as phosphorus reagents.[7-8] Due to the biological potential of the α-aminophosphonates, the development of a new and simple method that enables the use of many types of phosphorus reagent, methodology that apply a reusable catalyst, mainly the less reactive such as aryl phosphites, using the one-pot methodology has become necessary.[9-10] It is observed that lanthanides have greater effects on the α-aminophosphonates reaction.[11] The first example using lanthanides complexes for the synthesis of α-aminophosphonates was described by Shibasaki[12] et al. by using lanthanum-potassium-BINOL, however, unfortunately, the authors described the use of high load of the catalyst (5-20 % mol). Furthermore, it is widely known that lanthanoids complexes used as catalysts represents an efficient method to produce high yields and high enantiomeric excess in reactions of α-aminophosphonates.[13] For these reasons, it is important to develop a new, efficient and green catalyst which may be inserted on the Kabachnik-Fields reaction. Our research group have worked with the application of some hybrid heterogeneous catalyst in many organic reactions *e.g.* thio-Michael reaction but all the catalyst had a zinc metal.[14] In order to modify the catalyst we preconize herein a oxalate cerate (III) - *N,O (L)*-prolinate or [Ce(*L*-Pro)]$_2$(Oxa) (Figure 1), as a heterogeneous catalyst in Kabachnik-Fields reaction. In other words, herein, we report an eco-friendly, easy and efficient methodology for the synthesis of α-aminophosphonates using [Ce(*L*-Pro)]$_2$(Oxa) catalyst. This catalyst can be separated by filtration and can be reused other times in the reaction and it is almost insoluble in any solvent.

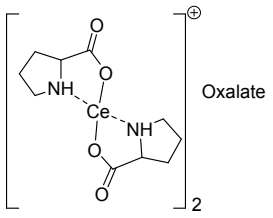

Figure 1. Purposed structure for [Ce(*L*-Pro)]$_2$(Oxa).

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Experimental Section

General methods:

All chemical reagents and solvents without any specific treatment. The respective reactions were monitored by Thin Layer Chromatography (TLC) MACHEREY-NAGEL (SIL G / UV_{254}). The purification of the compounds was performed by recrystallization solvent using Chloroform / Hexane to 65°C. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker (300 MHz and 75 MHz respectively) spectrometer. The infrared spectra were recorded on FT/IR 4100 type A spectrometer of Jasco.

Preparation of catalyst:

[Ce(*L*-Pro)]$_2$(Oxa) was synthesized using proline (2.7 mmol) in methanol (15 mL) and aqueous sodium hydroxide solution (2.7 mmol in 1mL) at room temperature for 10 minutes. After that, it was added cerium (III) cloride (1.4 mmol), the reaction crude was stirred by 45 minutes and it was added few drops of sodium oxalate solution (0.1g/mL) as precipitate agent. The semi-solid was centrifuged, washed with methanol and dried overnight at 40 °C and a pale yellow semi-solid was obtained.

General procedure for the preparation of α-aminophosphonates:

Aldehyde (2.2 mmol), aniline (2 mmol), diphenylphosphite (2 mmol) and [Ce(*L*-Pro)]$_2$(Oxa) catalyst (1 mol %) were added to magnetic stirrer in toluene (10 mL) at room temperature. The progress of the reaction was monitored by TLC (eluent: EtOAc/hexane, 10:90). After the reaction was completed the catalyst was separated by filtration.

After the product was purified by recrystallization (chloroform/hexane) the α-aminophosphonates were obtained.

Results and Discussion

First of all, we performed the synthesis of the catalyst using the same procedure described by Darben[14] here using a cerium salt ($CeCl_3.H_2O$) (see ESI for more information about the synthesis). After the reaction the semi-solid was analysed by FTIR and DRX and the data are presented on Figure 2 and 3 respectively.

By the analysis of the FTIR, we observed that for the $\nu_{C=O}$ for [Ce(*L*-Pro)]$_2$(Oxa) was shifted to a higher frequency (1636 cm^{-1}) which indicated that oxygen sp^3 was bonded to the cerium atom and this interaction increased the bond order on the carbonyl group. Furthermore, we observed the decreasing to of frequency for ν_{C-O} in cerium complex (from 1380 for proline to 1322 cm^{-1} for [Ce(*L*-Pro)]$_2$(Oxa) which indicated the same interaction previously described. At the end, we observed that the band at 780 cm^{-1} indicated the interaction between nitrogen and cerium. It is worth mentioning that the band at 3427 cm^{-1} is due to the presence of water in the catalyst's structure. All these results are in concordance with literature data for similar compounds containing cerium[13]. We also performed the X-Ray diffraction patterns by the analysis of all the starting materials and the [Ce(*L*-Pro)]$_2$(Oxa) and the data are presented at Figure 3. The results enabled us to

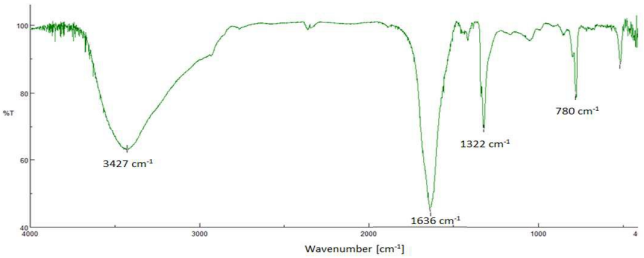

Figure 2. IR for Ce[(*L*-Pro)$_2$(Oxa)] in KBr spectroscopic.

observe that even proline and sodium oxalate are very well crystallized, and this diffraction peaks can be indexed as the references, respectively.[13] The starting materials and the catalyst presented a different pattern on X-ray diffraction, what indicated the successful of the synthesis. Besides, by the analysis of literature for a similar compound containing cerium and a different amino acid in the structure, we observed that the X-ray data were very similar.[15]

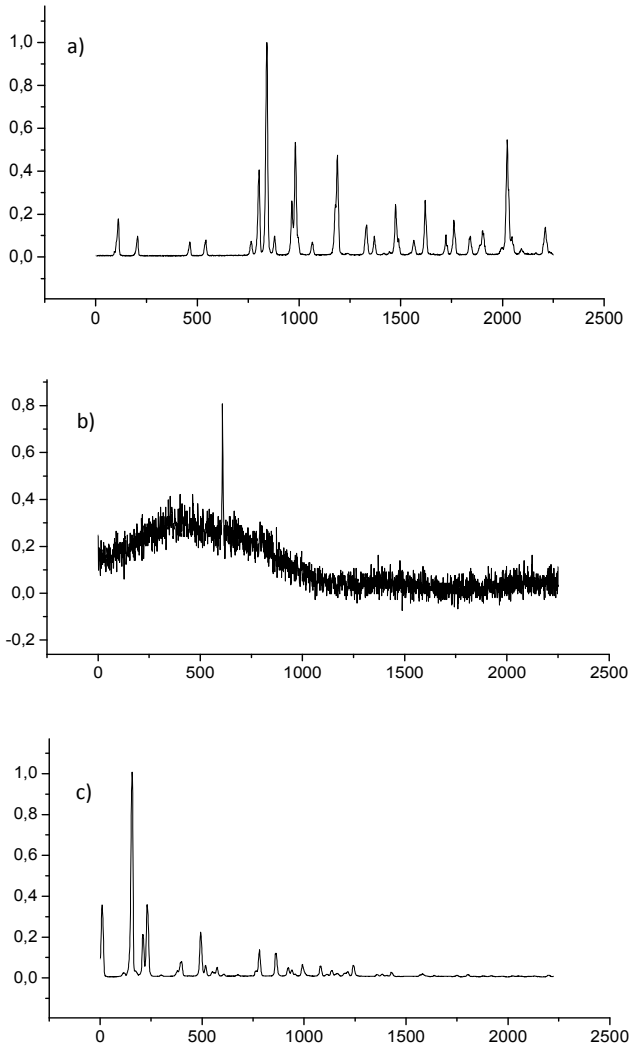

Figure continued....

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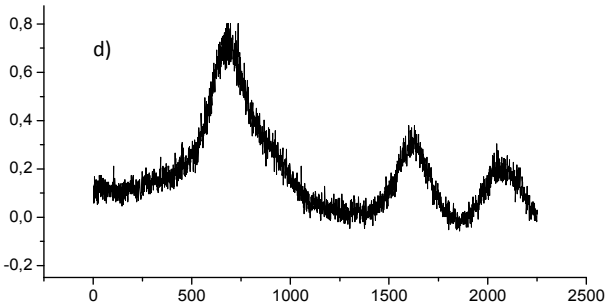
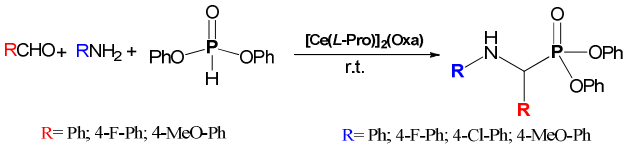


Figure 3. X-Ray diffraction patterns of proline (a), cerium chloride (b), sodium oxalate (c) and [Ce(*L*-Pro)]$_2$(Oxa) (d).

After these analysis, we inserted the [Ce(*L*-Pro)]$_2$(Oxa) on the Kabachnik-Fields reaction aiming to identify the optimum catalytic system. So, we carried out the standard reaction using aniline, benzaldehyde and diphenyl phosphite and [Ce(*L*-Pro)]$_2$(Oxa) in different solvents using the methodology described by Zhu and co-workers.[11] As shown in Table 1, the solvent have interfered directly over the yields. Moreover, we observed that the [Ce(*L*-Pro)]$_2$(Oxa) was compatible with many low polarity solvents. Thus, we established toluene as the best solvent of this reaction (96% of yield).

Table 1. Optimization of the synthesis of α-aminophosphonates.



Solvent	Time	Yield[b]
Toluene	10	96
DCM	10	90
CH_3CN	10	55
THF	60	80
No solvent	60	0

[a] Reaction conditions: benzaldehyde (2.2 mmol), aniline (2.0 mmol) and diphenyl phosphite (2.0 mmol) and 1 % mol catalyst at room temperature. [b] Yield of isolated product.

Grate news related to the reaction time also surprised us. Zhu[11] described the Kabachnik-Fields reactions using a diethyl phosphite (a better nucleophile than diphenyl phosphite used by us) in 6h and our procedure has spent only 10 minutes (Table 1).We also studied the effect of catalyst load over yields of the standard reaction (Table 2). We observed that the best catalyst loading was 1 % mol (96% of yield). However, the reaction did not afford any product without catalyst (blank reaction). Furthermore, the increase of the catalyst loading did not furnished a substantial increase of the yields. Besides, we did not observe any sub-product as Pudovik reaction. After establishing all the general procedures for Kabachnik-Fields reaction using [Ce(L-Pro)]2(Oxa) as a heterogeneous catalyst, we extended the same protocol for several other reactions aiming to obtain some α-aminophosphonates by

Table 2. Examine the catalyst loadings for Kabchnik-Fieldsreaction using [Ce(*L*-Pro)]$_2$(Oxa) as a catalyst

Catalyst loading (% mol)	Yield (%)[b]
0	[c]
1	96
2	97

[a] Reaction conditions: benzaldehyde (2.2 mmol), aniline (2.0 mmol) and diphneylphosphite (2.0 mmol) at room temperature [b] Yields by recrystallization. [c] No reaction.

using various substituted benzaldehydes, substituted anilines, and diphenyl phosphite (Table 3). Concerned to benzaldehydes derivatives, we observed that the withdrawing groups bonded at *para*-position furnished the α-aminophosphonates in shorter reaction time whereas the donors groups furnished them in long ones, what was expected because the withdraw groups confers to the carbonyl carbon lower electronic density and it makes the carbonyl group more reactive (more electrophilic) when compared to the donor ones. So, the imine will be obtained quickly in such cases and also, and consequently, the α-aminophosphonates. This can be confirmed by the analysis of both entries 2 and 8 (nitro substituted), in which the change of the position of nitro group from *para*- to *meta*- increased twice the reaction time. Regarding to anilines derivatives, we observed that donors group bonded at the *para*-position (entries 18 – 20), contrary to what we expected, have produced the α-aminophosphonate in higher reaction time than anilines containing withdraw groups at *para*-position (entries 13 – 17).

As observed on the purposed mechanism, we concluded, with respect to cycle #1, that the catalyst affected this cycle making this step faster. We determine this when we used [Ce(*L*-Pro)]$_2$(Oxa) as catalyst in the imine reactions. In this case, the catalyst accelerated the reaction affording the imine in a lower reaction time when compared to data described in literature. For the second cycle, the catalyst affected the reaction by increasing the positive charge on the imine carbon as described in intermediate #8.

So, the strong withdrawing groups (NO_2 and F) will difficult this interaction higher than the moderate groups (Cl, Br and I) but both will activate the C=N. On the other hand, donors groups, despite the fact they decrease the electronic potential of nitrogen lone pair (more basic), they will not increase the eletrophilicity of carbonyl carbon in comparison to the previous ones (NO_2, F, Cl, Br and I). For this reason, for withdraw groups, the Kabachnik-Fields reactions using [Ce(*L*-Pro)]$_2$(Oxa) will be carried out at lower times than the ones with electron donors groups. We also performed the recycling of the catalyst for the reactions using *para*-anisaldehyde, aniline and diphenyl phosphite (entry 6, Table 2 - see procedure in ESI). By the analysis of the data, we concluded that the catalyst efficiency was decreased every reuse (Table 4 entries 1-3). But as described herein for this process using only 1% mol of the catalyst, its reusability did not depreciate this methodology.

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Table 3. Kabachnik-Fields reactions using [Ce(*L*-Pro)]$_2$(Oxa) as a catalyst.

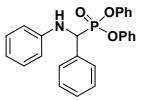
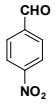
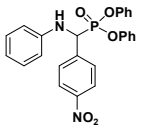
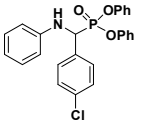
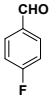
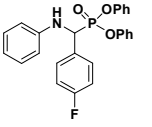
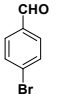
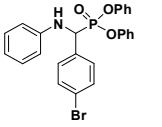
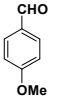
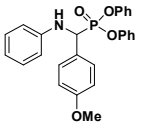
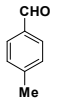
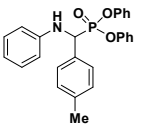
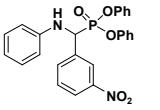
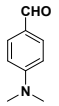
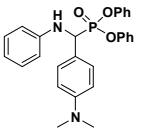
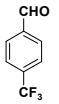
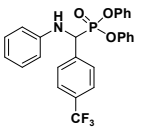
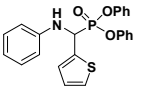
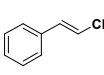
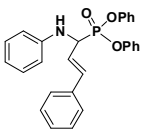
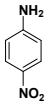
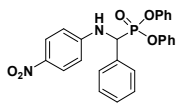
Entry	Aldehyde	Amine	Product	Time (min)	Yield[a] (%)
1				10	96
2				10	99
3				10	96
4				10	93
5				10	91
6				60	94
7				60	94
8				20	97
9				5	96
10				20	89
11				60	98
12				20	96

Table continued…

Entry	Aldehyde	Amine	Product	Time (min)	Yield[a] (%)
13				20	91
14				5	96
15				5	96
16				20	96
17				5	89
18				50	89
19				60	99
20				60	98

a. Yields by recrystallization

Aiming to analyse the catalyst's structure and trying to obtain some information able to confirm what is responsible for the decreasing of the yields in sequential catalysis cycles, we performed the SEM and EDS for the catalyst before and after the reaction (Figure 4). The data indicated that there were no changes neither on the morphology nor on the atomic percentage. Besides, we observed that there was a few loss of the catalyst loading per cycle (around 18%).

Table 4. Kabachnik-Fields reactions using [Ce(*L*-Pro)]$_2$(Oxa) recyclability.

Cycle	*Yield[a] (%)*	*ΔYield (per cycle)*
#1	94	-
#2	80	14
#3	65	15

[a] Yields by recrystallization.

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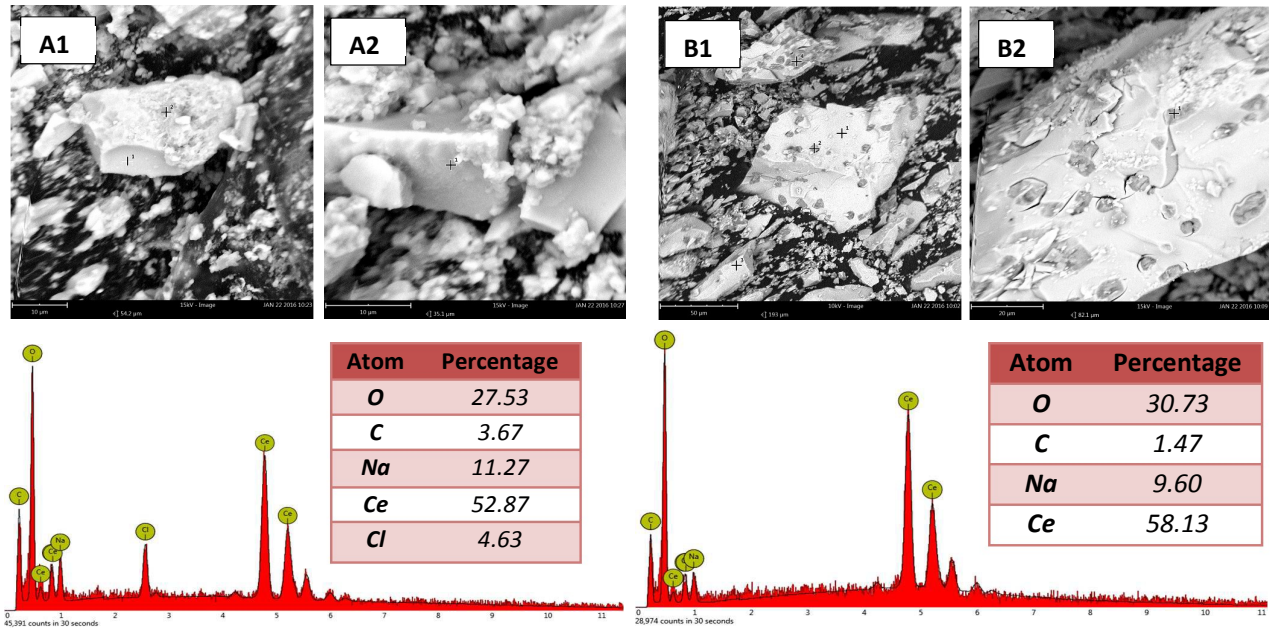
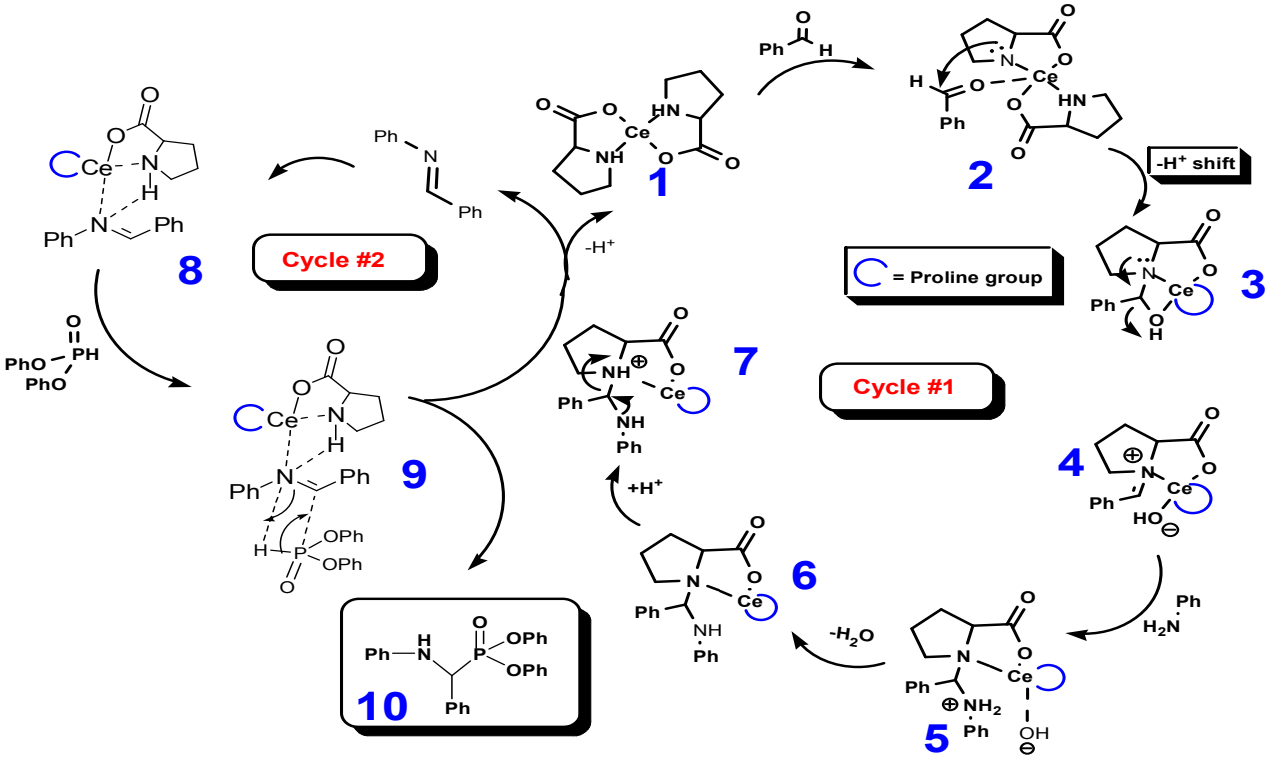


Atom	Percentage
O	27.53
C	3.67
Na	11.27
Ce	52.87
Cl	4.63

Atom	Percentage
O	30.73
C	1.47
Na	9.60
Ce	58.13

Figure 4. SEM and EDS for [Ce(*L*-Pro)]$_2$(Oxa) before the reaction (A1, A2 and A3) and after the reaction (B1, B2 and B3).



Scheme 1. Proposed mechanism of the Kabacnick-Fields reaction catalyzed by [Ce(*L*-Pro)]$_2$(Oxa).

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Therefore, as we carried out the next cycles in the same flask and without any further catalyst charge and maintaining the same starting materials amount used on the first cycle, we can assign that this loss is strongly associated with the decrease of the subsequent reaction yields.

Conclusions

We have successfully developed a new versatile catalyst, the [Ce(*L*-Pro)]$_2$(Oxa), in Kabachnik-Fields reaction which have afforded high yields of α-aminophosphonates by the use of a very accessible, simple and efficient methodology of minimal of catalyst loading in short reaction time. In relation to its reusability, it was possible only in some cycles but this does not depreciate this procedure.

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Notes and references

Keywords: cerium • aminophosphonates • heterogeneous catalysis • proline

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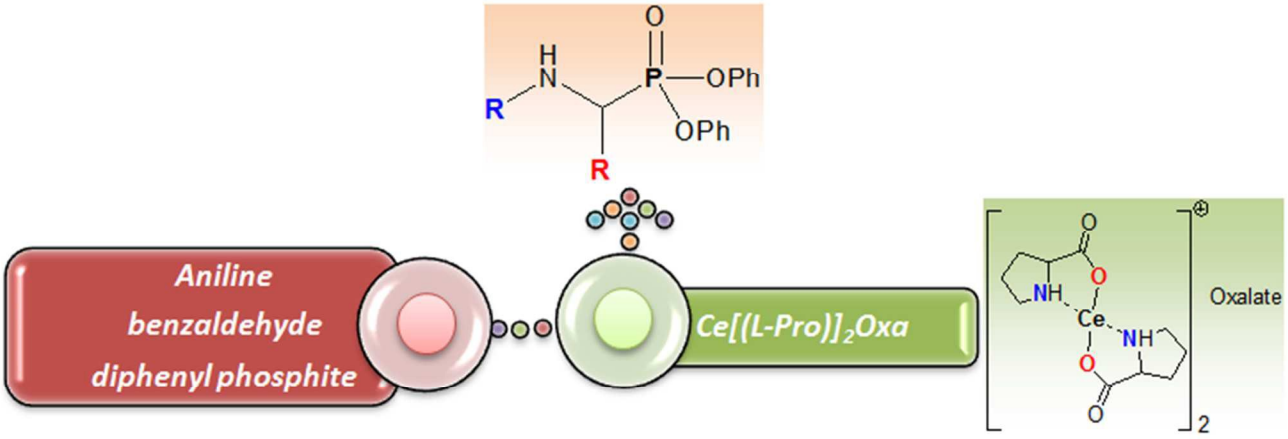

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