[Ce(L-Pro)2]2 (Oxa) as a heterogeneous recyclable catalyst: Synthesis of pyrazoles under mild reaction conditions

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We developed a novel and highly efficient protocol for the synthesis of important pyrazole derivatives by using some 1, 3-dicarbonyl compounds and phenyl hydrazines *via* one-pot protocol. As a recyclable heterogeneous catalyst, we used [Ce(L-Pro)$_2$]$_2$ (Oxa). In addition, the catalyst is recyclable, once the proline is economically viable and readily available in both enantiomeric forms and the catalyst is insoluble in almost all the solvents and may be easily filtered off from the reaction medium. Moreover, this new synthetic protocol is featured by high conversion, short reaction times, straightforward procedure and cleaner reaction profiles.

Introduction

Conventionally, organic chemistry includes the usage of many hazardous, toxic or inflammable chemicals which are very harmful to the environment, animals and humans. With regard to that, many researchers have tried to protect the environment through green approaches, which means to reduce to the minimum use such chemicals, and obtain the maximum conversion of reactants to the corresponding products.[1] In this perspective, we synthesized pyrazoles in the presence of (Ce(*L*-Pro)$_2$)$_2$ (Oxa) as a green recyclable catalyst. Pyrazoles and its derivatives are very significant class of heterocyclic compounds which play a crucial role in the context of drug therapies, and drug intermediates.[2] Most of the pyrazole derivatives are useful intermediates in synthetic organic and heterocyclic chemistry, as well as in medicinal chemistry.[3] These derivatives showed good medicinal properties such as anti-inflammatory, antipyretic, antibacterial, antidiabetic, analgesic and sedative-hypnotic activity.[4] Their analogues also find extensive use not only in the pharmaceutical industry (Viagra[5] and Celebrex[3]), but also in agrochemical industries (e.g. Tebufenpyrad insecticide[6,7]). Furthermore, pyrazoles are omnipresent as ligands in coordination chemistry and as building blocks in heterocyclic synthesis. [8] Herein, we proposed a catalyst structure as shown in Figure 1. And a few marketed drugs with pyrazole unit as a core moiety which is shown in Figure 2. However, several methodologies have been accomplished through the synthesis of pyrazoles derivatives such as J. Wu and his co-workers[9], who have developed the synthesis of pyrazoles by using hydrazines with various 1, 3-dicarbonyl compounds in pure water at rt mediated by efficient 12-Tungstophosphoric acid ($H_3PW_{12}O$) *via* one-pot protocol. S. Chandak and co-authors[10] reported the facile aqueous phase synthesis of pyrazoles catalyzed by amberlyst-70, by the condensation of hydrazines/hydrazides with 1, 3-diketones. R. S. Varma and his co-workers[11] demonstrated the synthesis of pyrazoles and diazepines by the condensation of hydrazines/hydrazides and diamines with 1, 3-diketones mediated by polystyrene supported sulfonic acid (PSSA) under aqueous condition at room temperature. S. Batra and co-workers[12] described the synthesis of pyrrolo-fused pyrazoles *via* one-pot protocol using halopyrazolecarbaldehydes and ethylisocyanoacetate in the presence of copper and a base. N. Haddad[13] *et al.* reported the synthesis of pyrazoles by using aryl benzophenone hydrazones with 1, 3-bifunctional substrates in the presence of Pd-catalyst.

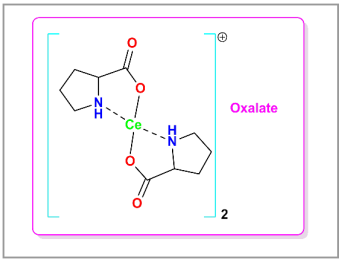

Figure 1. Proposed structure of the Ce-catalyst.

Recently, X-M Hu[14] and his co-authors reported the green synthetic protocol for the preparation of pyrazoles using phenyl hydrazines and various 1, 3-dicarbonyl compounds under glycerol and water used as mixture solvents at 90 ^{o}C.

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Despite, aforementioned reports suffer from one or more disadvantages such as lesser yield of products, environmental toxicity, and the use of transition metal catalysts, anhydrous organic solvents, long reaction times, non-recyclable catalysts and moisture sensitive reagents. Therefore, in view of these shortcomings, there is a need to develop a mild and atom-economic synthetic protocol for the synthesis of pyrazole derivatives by replacing flammable toxic or carcinogenic organic solvents.

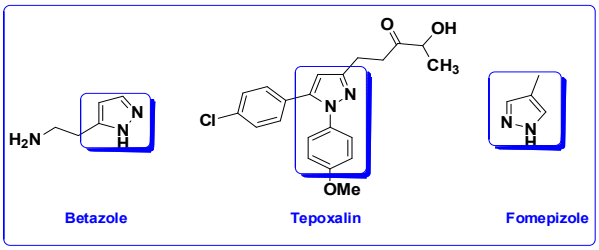
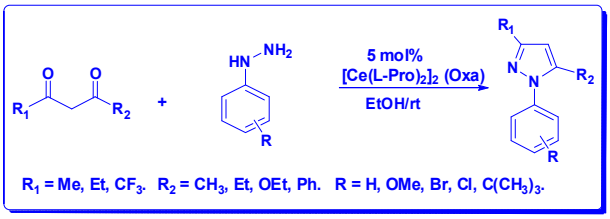


Figure 2. Some marketed drugs which are having pyrazoles skeleton.

Results and discussion

We presented $[Ce(L\text{-}Pro)_2]_2$ (Oxa) as an efficient and eco-friendly heterogeneous catalyst which is showed in +3 oxidizing state. Herein, the catalyst is non-toxic, easily handling, and can be easily filtered off from the reaction medium because it is insoluble in organic and inorganic solvents and it is chemically stable at high temperatures. In this research, we aimed to develop at rt. a new green and efficient synthesis of pyrazole derivatives by using various 1, 3-diketones and several phenyl hydrazines in the presence of $[Ce(L\text{-}Pro)_2]_2$ (Oxa) as a heterogeneous catalyst with EtOH used as a green solvent (Scheme 1).[17] Therefore, in order to optimize the reaction conditions, firstly, we performed the reaction between acetyl acetone (1.0 mmol), and phenyl hydrazine (1.0 mmol) under ethanol used as a solvent in the absence of any catalyst at room temperature. The corresponding product yield was obtained in very low percentage along with un-reacted starting materials after prolonged reaction times, which is shown in Table 1. After that, we carried out the same procedure by using EtOH (10 mL) as a green solvent, with $[Ce(L\text{-}Pro)_2]_2$ (Oxa) (5 mol %) used as a heterogeneous catalyst for the first time in the synthesis of pyrazoles at room temperature, for 2-3 hrs. The corresponding product was obtained in 88% yield (Table 1). All the remaining reactions were carried out under these conditions. Moreover, the present protocol was screened with different solvent systems such as EtOH, $CHCl_3$, CH_2Cl_2, THF, toluene and H_2O, in room temperature and reflux conditions as shown in Table 1. After several experiments, EtOH was proven to be the best choice, since the other solvents furnished low yields. Furthermore, the present reaction was successfully screened with different catalyst loadings such as 2.5 mol%, 5 mol%, and 10 mol% respectively. After several reactions, we found 5 mol% was the best catalyst loading among them.

On the other hand, phenyl hydrazines bearing electron donating group such as -OMe, and electron withdrawing groups such as -Cl, and –Br etc, at the *para* position of the substrates did not influence on the reaction medium and the yields of the corresponding products (Table 2) were excellent. It is worth mentioning that the other reactants such as 1, 3-dicarbonyl compounds containing -Me, -Et, -OEt and $-CF_3$ groups also furnished good yields as shown in Table 2.



Scheme 1. Synthesis of pyrazole derivatives.

Table 1. Screening of different solvents on the synthesis of 3, 5-dimethyl-1-phenyl-1*H*-pyrazole catalysed by $[Ce(L\text{-}Pro)_2]_2$ (Oxa) (Table 2, entry 1).[a]

S. No	Solvent	T (°C)	Yield[b] (%)
1	EtOH	RT	88[c]
2	H_2O	Reflux	40[c]
3	$CHCl_3$	RT	51[c]
4	DCM	Reflux	55[c]
5	EtOH[d]	RT	-
6	THF	RT	39[c]
7	Toluene	RT	41[c]

[a]Reaction conditions: Acetyl acetone (1.0 mmol), and Phenyl hydrazine (1.0 mmol). [b]Isolated yields. [c]Presence of catalyst. [d]Absence of catalyst.

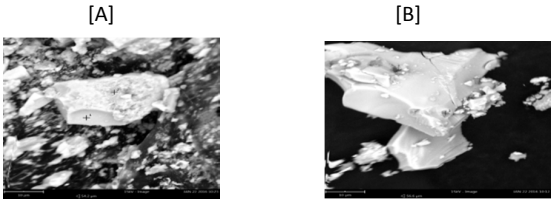


Figure 3. SEM images of [A] native Ce-catalyst and [B] Ce-catalyst after the reaction.

Further, we proposed a suitable mechanism for the preparation of pyrazoles: the catalyst is directly influenced on the reaction medium. Initially, the catalyst formed the hydrogen bonding between 1, 3-dicarbonyl compound which further formed an imine intermediate using phenyl hydrazine. The next steps were the cyclization followed by aromatization, which led us to the corresponding product as shown in Figure 4.

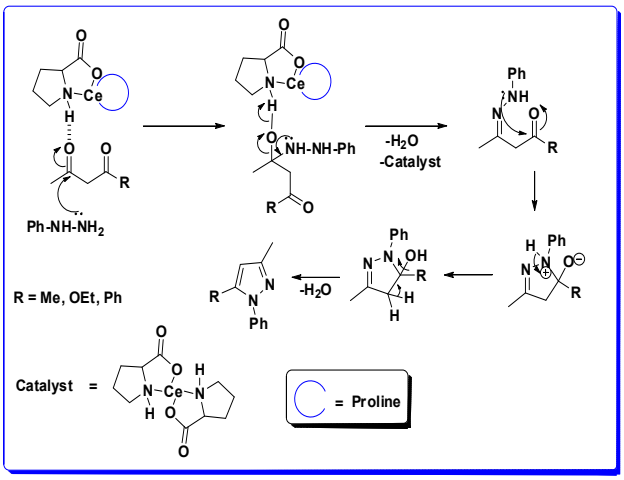
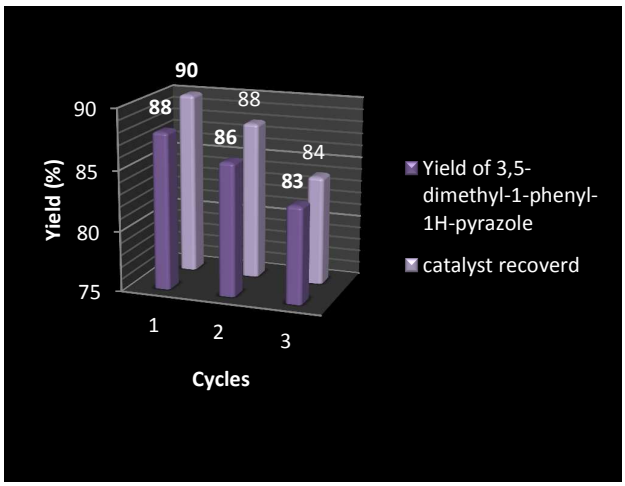


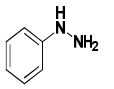
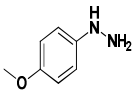
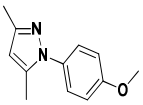
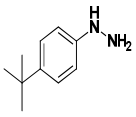
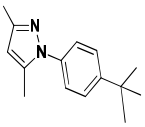
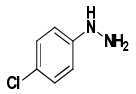
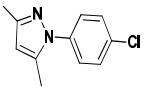
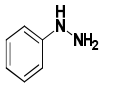
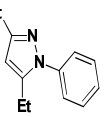
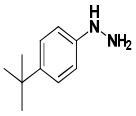
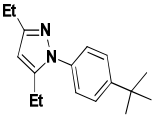
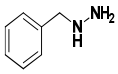
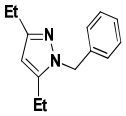
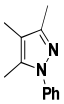
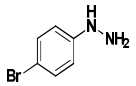
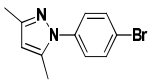
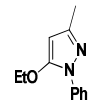
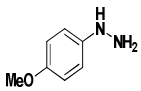
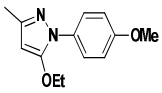
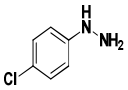
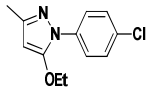
Figure 4. Proposed mechanism for the synthesis of pyrazoles.

Figure 5. Recyclability of the catalyst.



All the reactions were performed by using $[Ce(L\text{-}Pro)_2]_2$ (Oxa) as a catalyst, which could be recovered and reused. After completion of the reaction, the catalyst was filtered off and cleaned with diethyl ether and dried at 80 °C for 2h. The recovered catalyst was reused in the same substrates, and checked for the yields and catalytic activity as shown in Figure 5. It was observed that the yield of 3,5-dimethyl-1-phenyl-1*H*-pyrazole derivative reduced slightly after two to three cycles. The SEM images of the catalyst are given in Figure 3. All the products were purified, and characterized by ^{1}H, ^{13}C-NMR, and mass spectroscopic analysis.[9, 18]

Table 2. Synthesis of pyrazole derivatives using $Ce(L\text{-}Pro)_2]_2$ (Oxa) in EtOH.[a]

Entry	Substrate (1)	Substrate (2)	Product (3)	Yield[b] (%)
1				88
2				91
3				85
4				80
5				90
6				84
7				81
8				83
9				81
10				72
11				73
12				70
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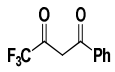
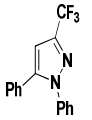
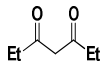
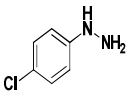
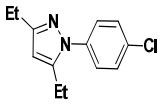
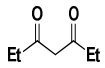
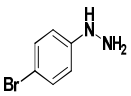
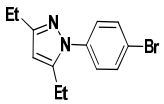
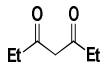
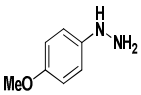
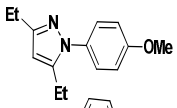
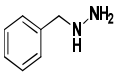
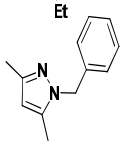
Entry	Substrate (1)	Substrate (2)	Product (3)	Yield[b](%)
14				80
15				80
16				79
17				81
18				80

[a]Reaction conditions: 1, 3-dicarbonyl compounds or β-keto esters (1.0 equiv), phenyl hydrazine (1.0 equiv), ethanol (10 mL), $[Ce(L\text{-}Pro)_2]_2$ (Oxa) (5 mol %), room temperature, 2-3h. [b]Isolated yields.

Conclusions

We have successfully accomplished the synthesis of pyrazole moieties, for the first time promoted by $[Ce(L\text{-}Pro)_2]_2$ (Oxa) in EtOH used as a green-solvent at room temperature. The catalyst can be recovered and reused after third cycle, with the loss of a small significant catalytic activity. In addition, this present protocol excludes toxic/hazardous solvents. This methodology involved shorter reaction times, good yields, besides being environmentally benign, inexpensive, and demanding mild reaction conditions.

Experimental

General Procedure for the synthesis of pyrazole derivatives: Round-bottomed flask (25 mL) was charged with 1, 3-dicarbonyl compound (1.0 mmol) and phenyl hydrazine (1.0 mmol) was taken in ethanol (10 mL), a catalytic amount of $[Ce(L\text{-}Pro)_2]_2$ (Oxa) (5 mol %) was added and the mixture was stirred under room temperature for appropriate time. The progress of the reaction was monitored by TLC. After the completion of the reaction was indicated by TLC, then the catalyst ($[Ce(L\text{-}Pro)_2]_2$ (Oxa)) was filtered off from the reaction mixture. The remaining solvent was evaporated under reduced pressure. Further, the crude product was purified by column chromatography over silica gel to afford the corresponding product yields were obtained in 70-91% as shown in Table 2.

Preparation of novel $[Ce(L\text{-}Pro)_2]_2$ (Oxa) catalyst: [15, 16]

(*L*)-Proline (2.7 mmol) was dissolved in 15 ml of methanol, then we added aqueous solution of sodium hydroxide (2.7 mmol in 1 mL) to it at room temperature and stirred the mixture for 10 minutes. Then cerium (III) chloride (1.4 mmol) was added to it, and the reaction mixture was stirred for 45 minutes and then few drops of sodium oxalate solution (0.1g/mL) were added to it. We used it as a precipitating agent. The semi-solid was centrifuged, washed with methanol and dried overnight at 40 °C and a pale yellow semi-solid was obtained.

3, 5-dimethyl-1-phenyl-1*H*-pyrazole (Table 2, entry 1)[1]: Light brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.46-7.33 (m, 4H), 7.29 - 7.19 (m, 1H), 5.90 (s, 1H), 2.25 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 148.1, 139.4, 138.4, 128.3, 126.4, 124.0, 106.4, 12.9, 11.8; MS (ESI): *m/z* = 173 $[M+H]^+$.

1-(4-methoxyphenyl)-3, 5-dimethyl-1H-pyrazole (Table 2, entry 2): brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.27 (d, 2H, *J* = 9.06 Hz), 6.90 (d, 2H, *J* = 9.06 Hz), 5.90 (s, 1H), 3.8 (s, 3H), 2.26 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 158.7, 148.0, 139.1, 132.7, 125.9, 113.7, 105.9, 55.1, 13.1, 11.7; MS (ESI): *m/z* = 203 $[M+H]^+$.

1-(4-tert-butylphenyl)-3,5-dimethyl-1H-pyrazole(Table 2, entry 3): brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.42 (d, 2H, *J* = 8.68 Hz), 7.32 (d, 2H, *J* = 8.68 Hz), 5.91 (s, 1H), 2.34 (s, 3H), 2.20 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 150.1, 148.4, 139.3, 137.3, 125.7, 124.5, 106.5, 34.8, 31.3, 13.5, 12.4; MS (ESI): *m/z* = 229 $[M+H]^+$.

1-(4-chlorophenyl)-3, 5-dimethyl-1H-pyrazole (Table 2, entry 4)[1]: thick brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.45(m, 4H), 5.95 (s, 1H), 2.29 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 148.7, 138.8, 137.7, 132.7, 128.7, 125.3, 107, 13.0, 12.0. MS (ESI): *m/z* = 207 $[M+H]^+$.

3, 5-diethyl-1-phenyl-1H-pyrazole(Table 2, entry 5): brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.42 (m, 5H), 6.08 (s,1H), 2.68 (m, 4H), 1.36-1.21(m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.7, 145.8, 140.2, 129.2, 127.3, 125.2, 103.2, 21.7, 19.6, 14.2, 13.15; MS (ESI): *m/z* = 201 $[M+H]^+$.

1-(4-tert-butylphenyl)-3, 5-diethyl-1H-pyrazole(Table 2, entry 6): brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.42 (d, 2H, *J* = 8.79 Hz), 7.33 (d, 2H, *J* = 8.05 Hz), 6.0 (s, 1H), 2.69-2.59 (m, 4H), 1.33 (s, 9H), 1.29-1.16 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 151.1, 147.3, 140.2, 136.2, 124.9, 119.2, 107.3, 40.2, 31.2, 23.1, 21.2 18.1; MS (ESI): *m/z* = 257 $[M+H]^+$.

1-benzyl-3, 5-diethyl-1H-pyrazole(Table 2, entry 7): liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28-7.16 (m, 3H), 7.03 (d, 2H, *J* = 7.16 Hz), 5.82 (s, 1H), 5.20 (s, 2H), 2.60(q, 2H, *J* = 7.5 Hz), 2.41 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.55, 3H), 1.14 (t, 3H, *J* = 7.55); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 147.6, 141.2, 138.3, 129.5, 128.5, 127.3, 106.7, 53.5, 22.2, 20.1, 14.2, 12.6; MS (ESI): *m/z* = 215 $[M+H]^+$.

3, 4, 5-trimethyl-1-phenyl-1H-pyrazole (Table 2, entry 8): yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39- 7.31 (m, 5H) 2.10 (s, 6H),

1.96 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 148.4, 138.6, 135.9, 132.3, 129.0, 125.5, 113.6, 11.8, 10.9, 8.1; MS (ESI): *m/z* = 187 $[M+H]^+$.

1-(4-bromophenyl)-3, 5-dimethyl-1H-pyrazole(Table 2, entry 9)[3]: brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.52 (d, 2H, *J* = 8.3Hz), 7.36 (d, 2H, *J* = 9.0 Hz), 5.91 (s, 1H), 2.28 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 148.4 138.4, 137.3, 132.4, 128.5, 125.4, 107.8, 13.2, 12.2; MS (ESI): *m/z* = 251 $[M+H]^+$.

5-ethoxy-3-methyl-1-phenyl-1H-pyrazole (Table 2, entry 10): ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.68 (d, 2H, *J* = 7.74 Hz), 7.35 (t, 2H, *J* = 7.74 Hz), 7.17 (t, 1H, *J* = 7.74 Hz), 5.40 (s, 1H), 4.12 (q, 2H, *J* = 6.98 Hz), 2.42 (s, 3H), 1.44 (t, 3H, *J* = 6.98 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.6, 148.3, 138.8, 128.6, 125.5, 121.6, 86.1, 67.5, 14.6, 14.5; MS (ESI): *m/z* = 203 $[M+H]^+$.

5-ethoxy-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole (Table 2, entry 11): brown solid; mp.53-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (d, 2H, *J* = 8.78 Hz), 6.85 (d, 2H, *J* = 8.78 Hz), 5.37 (s, 1H), 4.08 (q, 2H, *J* = 6.83 Hz), 3.80 (s, 3H), 2.22 (s, 3H), 1.42 (t, 3H, *J* = 7.80 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 157.7, 154.4, 148.0, 132.2, 124.0, 113.8, 85.5, 67.2, 55.5, 14.6, 14.4; MS (ESI): *m/z* = 233 $[M+H]^+$.

1-(4-chlorophenyl)-5-ethoxy-3-methyl-1H-pyrazole (Table 2, entry 12): mp. 58-61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, 2H, *J* = 8.87 Hz), 7.47 (d, 2H, *J* = 8.87 Hz), 5.39 (s, 1H), 4.10(q, 2H, *J* = 6.98 Hz), 2.22 (s, 3H), 1.45 (t, 3H, *J* = 6.98 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 155.1, 148.9, 137.8, 132.4, 122.8, 118.7, 86.6, 68.0, 14.7, 14.6; MS (ESI): *m/z* = 237 $[M+H]^+$.

3-methyl-1, 5-diphenyl-1H-pyrazole (Table 2, entry 13): yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.37-7.19 (m, 10H), 6.28 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 148.7, 142.9, 139.7, 130.3, 128.2, 128.1, 127.9, 127.5, 126.4, 124.5, 107.5, 13.2; MS (ESI): *m/z* = 235 $[M+H]^+$.

1, 5-diphenyl-3-(trifluoromethyl)-1H-pyrazole (Table 2, entry 14)[2]: light yellow solid; mp. 86-90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.36-7.26 (m, 8H), 7.23 -7.18 (m, 2H), 6.71 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 144.8, 139.2, 129.0, 128.9, 128.7, 128.6, 128.3, 125.4, 105.5; MS (ESI): *m/z* = 289 $[M+H]^+$.

1-(4-chlorophenyl)-3, 5-diethyl-1H-pyrazole(Table 2, entry 15): liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.41-7.31 (m, 4H), 6.01 (s, 1H), 2.69-2.57 (m, 4H), 1.33-1.19 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.5, 145.4, 140.5, 128.9, 127.8, 125.9, 103.5, 21.5, 19.9, 14. 3, 13.3; MS (ESI): *m/z* = 235 $[M+H]^+$.

1-(4-bromophenyl)-3, 5-diethyl-1H-pyrazole (Table 2, entry 16): liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.55 (d, 2H, *J* = 8.79 Hz), 7.29 (d, 2H, *J* = 8.05), 6.05 (s, 1H), 2.70-2.59 (m, 4H), 1.33-1.20 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 151.8, 147.7, 140.1, 136.3, 124.4, 119.2, 107.0, 21.6, 20.4, 15.1, 14.2; MS (ESI): *m/z* = 279 [M+H].

3, 5-diethyl-1-(4-methoxyphenyl)-1H-pyrazole (Table 2, entry 17): brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.26 (d, 2H, *J* = 9.06 Hz), 6.81 (d, 2H, *J* = 8.3 Hz), 5.92 (s, 1H), 3.84 (s, 3H), 2.69-2.52 (m, 4H), 1.30-1.15 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 158.8, 148.3, 139.4, 133.5, 126, 114, 108, 55, 22.3, 19.8, 13.7, 12.8; MS (ESI): m/z = 231.15 $[M+H]^+$.

1-benzyl-3, 5-dimethyl-1H-pyrazole (Table 2, entry 18): liquid; ^{1}H NMR 200 MHz, $CDCl_3$) δ: 7.28-7.15 (m, 3H), 7.02 (d, 2H, *J* = 7.32), 5.85 (s, 1H), 5.14 (s, 2H), 2.22 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (50 MHz, CDCl3) δ: 147.2, 138.9, 137.2, 128.9, 127.5, 126.5, 105.7, 52.5, 13.5,11.3; MS (ESI): m/z = 187.16 $[M+H]^+$.

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Graphical Abstract:

$[Ce(L\text{-}Pro)_2]_2$ (Oxa) as a heterogeneous recyclable catalyst: Synthesis of pyrazoles under mild reaction conditions

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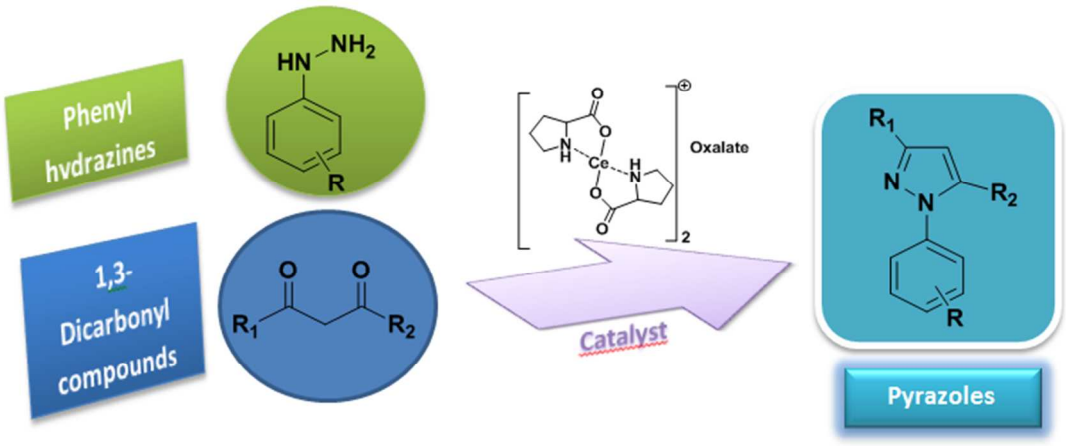

A highly efficient method for the synthesis of pyrazoles mediated by $[Ce(L\text{-}Pro)_2]_2$ (Oxa) as a heterogeneous catalyst.