

Recoverable and reusable heterogeneous yttrium triflate for michael and diels-alder additions

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Introduction

Heterogeneous catalysts have many advantages over homogeneous ones, such as catalyst separation, recovery, regeneration, and reuse, even though the latter have higher selectivity and active sites accessibility. One strategy to blend the positive aspects of both is the immobilization of the homogeneous catalyst onto insoluble supports [1], such as porous silica (SiO₂) [2]. The different methods of immobilization comprise covalent binding, electrostatic interaction and adsorption. [2] While covalent binding is the most popular method and electrostatic interaction is used for ionic catalysts, adsorption-based methods are reported to be less preferred to the formers, because of the unstable catalysts obtainable. A negative feature of covalent binding methods is the strong chemical modification induced on the catalyst, which is generally accompanied by lower mass transfer efficiency, resulting in a lower activity and a poorer selectivity [3]. In this paper we focused the attention on Y(OTf)₃. Yttrium is a rare earth metal, and its triflate functions as a Lewis acid in promoting a variety of reactions [4] including Michael addition [5], Aldol reaction [6], Friedel–Crafts reaction [7], Diels–Alder cycloaddition [8]. While most Lewis acids are decomposed or deactivated in the presence of water, Y(OTf)₃, like lanthanide triflates [Ln(OTf)₃] and rare-earth metal triflates [RE(OTf)₃], proved to be stable and work as Lewis acid in water [9]. In addition, many nitrogen-containing compounds are successfully activated by a catalytic amount of Y(OTf)₃ [4,6b,10]. It has similar properties to other lanthanide triflates [Ln(OTf)₃]; however, it is often less reactive than the more commonly employed scandium triflate [Sc(OTf)₃] or ytterbium triflate [Yb(OTf)₃] [9,10] Lewis acids, with a few exceptions. Analogous to the other rare earth metal triflates, Y(OTf)₃ can be recovered easily after reactions and is regarded as an environment-friendly catalyst [9]. The model reactions studied in this work were the Michael addition between a Michael donor (indole) and a Michael acceptor (benzylidenemalonate) to produce a Michael adduct by creating a carbon-carbon bond [11] and the Diels–Alder cycloaddition between cyclopentadiene and (4S)-3-acryloyl-4-*tert*-butyloxazolidin-2-one [12]. The Diels–Alder

reaction is a [4 + 2] cycloaddition which, normally, implies the interaction of an electronrich diene with an electronpoor dienophile. The importance of this reaction was clear already from its first publication in 1928 [13], especially for the synthesis of complex compounds, similar or identical to natural products [14]. In fact, this reaction generates, starting from relatively simple reagents, molecule possessing a high complexity, in a regio- and diastereoselective way: in just one reaction step, a six membered ring is formed with the possibility to control the configuration of all the four new stereogenic centres [15]. This control is granted by the mechanism of the reaction which always implies a *cis* addition and usually favouring the *endo* product [16].

Unlike other RE elements, which are described in the literature anchored on different supports, with a variety of immobilization methods [17], to the best of our knowledge, supported Yttrium as a Lewis acid catalyst was never reported in the literature.

We wish to report here our findings on the preparation of heterogeneous Yttrium Lewis acid catalyst by exploiting an acid-base interaction, and its application in the Michael addition between indoles and benzylidene malonates and the Diels–Alder cycloaddition between cyclopentadiene and (4S)-3-acryloyl-4-*tert*-butyloxazolidin-2-one. Studies on the recovery and recycle of the catalyst are also reported.

2. Results and discussion

2.1. Immobilization of Y(OTf)₃ and characterization of heterogeneous catalysts

In planning the immobilization of Y(OTf)₃ onto silica we were inspired by the work by Kobayashi and co-workers on the immobilization of a chiral Sc(III) catalyst through an acid-base interaction [18]. Heteropoly acids (HPA) were found to serve as anchoring agents between a support material, such as alumina, and the metal atom of a homogeneous catalytic complex [19,20]. However, it was found that, if inefficient interactions between the HeteroPoly Acid (HPA) and the support occurs, the metal catalyst can leach into solution, leading to

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heterogeneous catalyst deactivation [21]. Kobayashi and co-workers hypothesized that active and robust heterogeneous catalysts could be prepared if a strong interaction between the support and the HPAs could be achieved [22]. Given the strong Brønsted acidity of HPAs, they reasoned that a support having Brønsted basicity on the surface could tightly retain HPA through strong acid–base interactions (salt formation), thus preventing the leaching of the active metal species. Moreover, since HPAs bear multivalent anions, they are expected to form ion pairs with cationic metal complexes after salt formation. Mesoporous silica was chosen as a solid support material because of its large surface area, high mass transferability, tunable pore size, and potential for surface functionalization. Silica was functionalized with an aminopropyl silane reagent as a Brønsted base. On this basis, we designed the synthesis of heterogeneous Yttrium catalyst as depicted in Scheme 1.

A commercially available silica with regular dimensions was first reacted with aminopropyl silane reagents (APTMS = aminopropyl triethoxy silane, or APTMS = aminopropyl trimethoxy silane) to produce amino-functionalized silica (Scheme 2A). The obtained materials ($\text{SiO}_2\text{-NH}_2$) were reacted with heteropoly phosphotungstic acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$, PTA) in EtOH at room temperature to facilitate salt formation on the surface of the support (Scheme 2B). Then, immobilization of commercial $\text{Y}(\text{OTf})_3$ was performed in MeCN at room temperature for 1 h (Scheme 2C) [18].

Six heterogeneous catalysts (**HetCat 1–6**) were synthesized, using different amount of aminopropyl silane, PTA, and $\text{Y}(\text{OTf})_3$ according to Table 1.

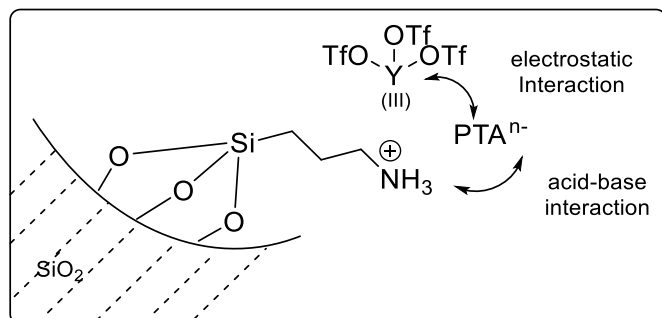
After the reaction, the solid was filtered, the supernatant was collected, and the solvent was removed. The real catalyst loading was determined using ICP-AES analysis on the washed-out residual Yttrium. The efficiency of the immobilization reaction %, Equation 1, was calculated by the following equation [18].

$$\text{Efficiency}\% = \frac{nY_{\text{used}} - nY_{\text{washed out}}}{nY_{\text{used}}} \bullet 100$$

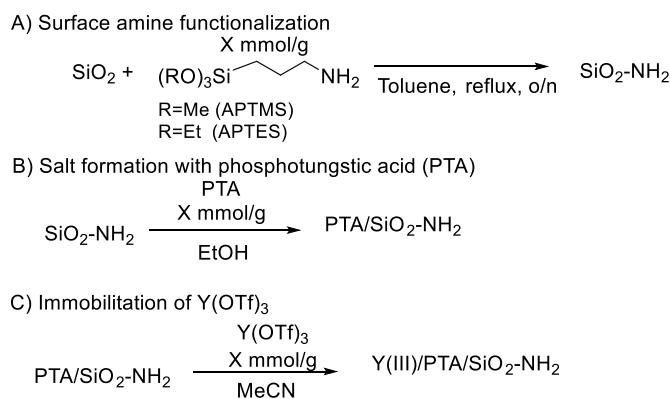
Equation 1: Immobilization Efficiency %

Y loading into the different heterogeneous materials is reported in Table 1. The Y loading determined by ICP-AES analysis ranged between 0.05 and 0.14 mmol Y/g silica, while the efficiency of immobilization ranged between 60 and 99 %. It is interesting to note that lower Y immobilization efficiency corresponds to higher amount of surface amine and PTA: we speculated that a higher amount of aminopropyl silane and PTA could lead to a more hindered silica surface inside the mesopores, that could prevent the electrostatic interactions between PTA and Lewis acidic Y. Kobayashi and co-workers actually demonstrated that each chemical modification takes place on the surface of silica material by measuring the surface area of each material by BET method [18].

TEM analysis was performed on **HetCat-2**, to clarify the morphology of the catalyst (Fig. 1; see also Supporting information for more pictures). It was observed a regular dimension of silica particles (Fig. 1a–b), with the surface covered by the metal sites (dark dots, Fig. 1c). The area



Scheme 1. Design of heterogeneous catalyst.



Scheme 2. Step procedure for the synthesis of supported yttrium catalyst.

analysis showed the characteristic lines of silicon, oxygen, tungsten and yttrium; moreover, these elements are present in the same area of the material, thus supporting the interaction of the elements at the molecular level. (Fig. 1d).

2.2. Michael addition between indoles and benzylidene malonate promoted by heterogeneous yttrium

We tested the different heterogeneous catalysts in the Michael addition between indoles and benzylidene malonate, that is reported in literature using a complex of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ with a chiral ligand as a catalyst [11]. As model substrates we chose indole **1a** and benzylidene malonate **2a**, Scheme 3. The results are reported in Table 2.

Preliminary tests performed using commercially available, homogeneous $\text{Y}(\text{OTf})_3$ suggested methanol as the solvent of choice (81 % after 24 h), therefore it was used in the model reaction with supported $\text{Y}(\text{OTf})_3$ **HetCat1-6**. All the catalyst samples performed well in the model reaction, however, best results were obtained with **HetCat-2**, **HetCat-3** and **HetCat-6**, that allowed to recover the desired product **3a** in 73, 83 and 81 % yield respectively (entries 2, 3 and 6). It was found out that the catalyst preparation strongly influences the catalyst activity: we believe that a good catalyst activity derives from the right balance between the number of PTA/ NH_2 groups and immobilized Y on the silica surface.

The best performing catalysts were also tested in acetonitrile as the reaction solvent, affording similar or better results than methanol (see below). The model reaction promoted by **HetCat-2** in acetonitrile was also monitored by ^1H NMR during time. The ^1H NMR yield vs time graph is reported in Fig. 2, and it shows that NMR yield remained low for the first 8 h, yield <20 %, while it rapidly increased until reaching 95 % after 24 h.

Leaching tests were performed to determine whether $\text{Y}(\text{OTf})_3$ was released into the solution during the reaction. The Michael addition was first conducted using a fresh catalyst in the presence of 1,3,5-trimethoxybenzene as an internal standard. After 24 h reaction time, the catalyst was removed from the reaction mixture by filtration and ^1H NMR analysis on the filtrate was done to determine the reaction yield. Then, fresh indole and benzylidenemalonate were added to the filtrate and the reaction was run for 24 h; after this reaction time, ^1H NMR analysis on the reaction mixture was done. We found out that, when methanol was used as a reaction solvent, the reaction yields of the Michael addition performed with **HetCat-2** and **HetCat-3** were increased by about 20 % over the filtrate, thus demonstrating that some Yttrium leaching is possible in methanol. The same test was conducted using acetonitrile as a reaction solvent with **HetCat-2** and **HetCat-3**, and in both cases no significant increase in reaction yield was observed, thus indicating that no Yttrium leaching happened in acetonitrile as the solvent. For this reason, catalyst recycling tests were conducted using acetonitrile.

Table 1
Catalyst loading and Efficiency %.

Entry	Catalyst	APTES mmol/g	APTMS mmol/g	PTA mmol/g	Y(OTf) ₃ mmol/g	Efficiency %	Loading mmol Y(OTf) ₃ /g silica
1	HetCat-1	1.0	/	0.1	0.05	99	0.05
2	HetCat-2	1.0	/	0.2	0.1	85	0.09
3	HetCat-3	/	4.1	0.1	0.1	91	0.09
4	HetCat-4	/	4.1	0.2	0.2	72	0.14
5	HetCat-5	/	6.0	0.1	0.1	60	0.06
6	HetCat-6	/	6.0	0.2	0.2	67	0.13

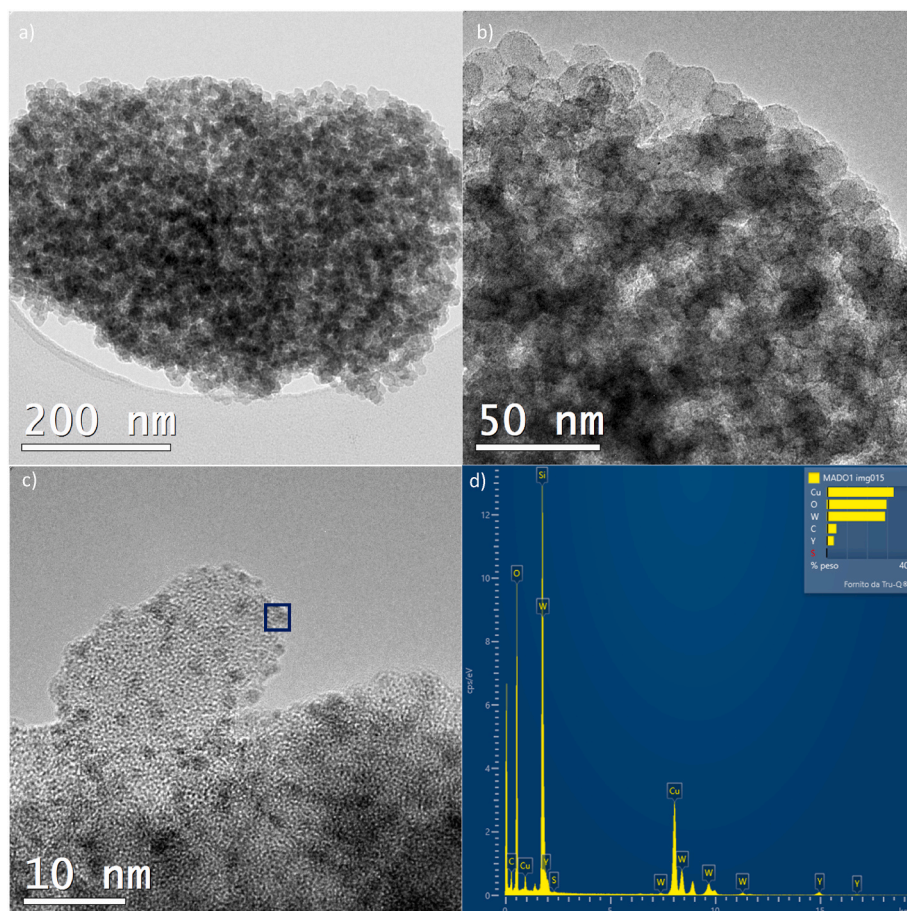
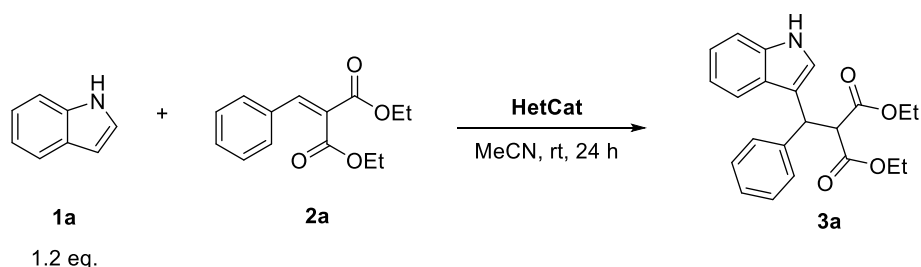


Fig. 1. TEM analysis on the HetCat-2. **a:** Supported catalyst at 200 nm; **b:** Supported catalyst at 50 nm. **c:** supported catalyst at 10 nm. **d:** TEM area analysis.



Scheme 3. Michael addition using supported catalyst HetCat-2 and HetCat-3.

2.3. Catalyst recovery and recycle

The model reaction between indole **1a** and benzylidene malonate **2a** was chosen to study the possibility to recover and recycle the heterogeneous catalysts. After the reaction, the mixture was filtered onto a Millipore glass funnel (pore size 0.1 μm): the solid was washed with

acetonitrile and dichloromethane and the filtrate was evaporated to afford the crude to be purified. The recovered solid was dried 1 h at 100 $^{\circ}\text{C}$ and reused in the subsequent reaction. Results are reported in Fig. 3.

Both the catalysts HetCat-2 and HetCat-3 were recycled four times affording the desired product **3a** in excellent yields, with a slight erosion

Table 2

Michael addition reaction between indole **1a** and benzylidene malonate **2a**, a mmol of Y(OTf)₃ on the heterogeneous catalyst with respect to the substrate **2a**; **b** isolated yield.

Entry	Catalyst	Catalyst loading ^a	Yield (%) ^b	
			Solvent: MeOH	Solvent: CH ₃ CN
1	HetCat-1	9 %	11	/
2	HetCat-2	15 %	73	95
3	HetCat-3	12 %	83	79
4	HetCat-4	27 %	20	/
5	HetCat-5	27 %	24	/
6	HetCat-6	13 %	81	65

from cycle 0 to cycle 4. It is worth noting that no treatment or reactivation was conducted on catalysts, which remained highly active until the 4th recycle, thus demonstrating the possibility of long-term use of the heterogeneous catalysts [23]. Moreover, both catalysts were recovered by filtration in high quantity after every recycle (see Fig. 4).

2.4. Substrate scope

With the developed optimized conditions, substrate scope was surveyed in both solvents, methanol and acetonitrile (Scheme 4).

At first, 5-substituted indoles were examined. The presence of halogen in 5 position of indoles afforded the target products **3b-3d** in satisfactory yields. The yield increased with the decrease of the atomic radius of the halogen atom. The presence of methoxy group in 5 position of indole gave **3e** in excellent yield. The compound **3f**, bearing a methoxy group on the aryl moiety of the malonate, was isolated in very low yield (10–15 %). Compound **3g** was obtained in moderate yield, while compound **3h**, bearing a bromine atom on the aryl moiety of the malonate, was achieved in good yield (67–72 %).

2.5. Diels-Alder cycloaddition

The HetCat-2 was used in the Diels-Alder cycloaddition between cyclopentadiene **4** and a dienophile bearing Evans' oxazolidinone as a chiral auxiliary, (4*S*)-3-acryloyl-4-*tert*-butyloxazolidin-2-one **5** [24].

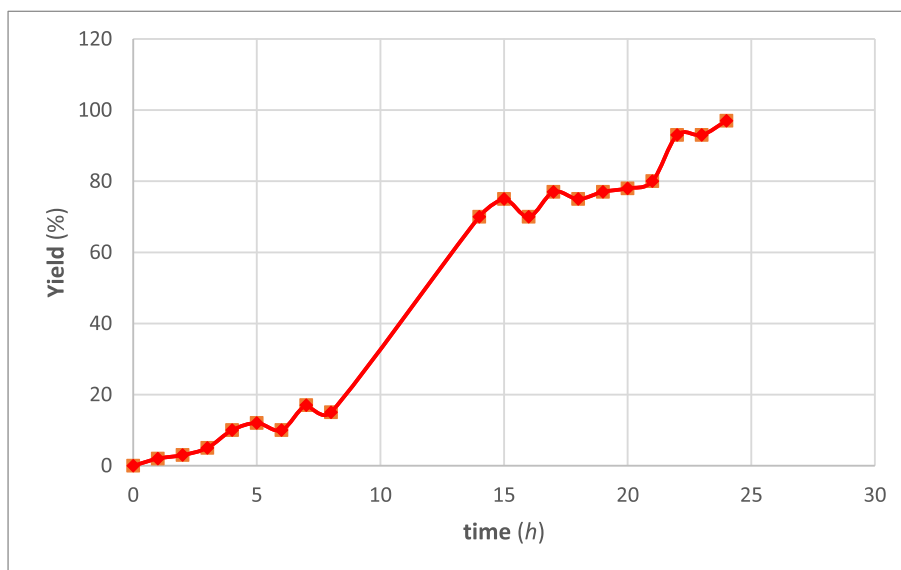


Fig. 2. Kinetic of Michael addition using HetCat-2 in MeCN monitored by ¹H NMR.

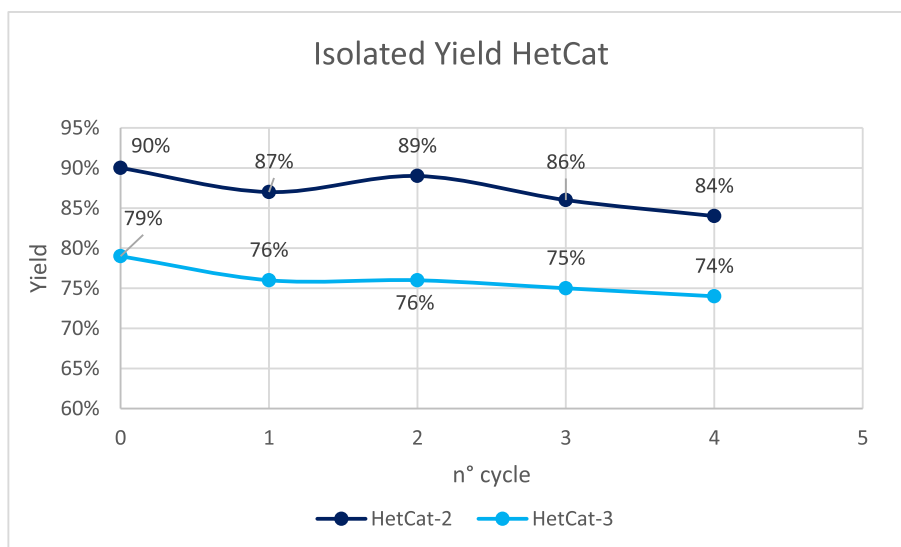


Fig. 3. Isolated yield using different heterogeneous catalysts.

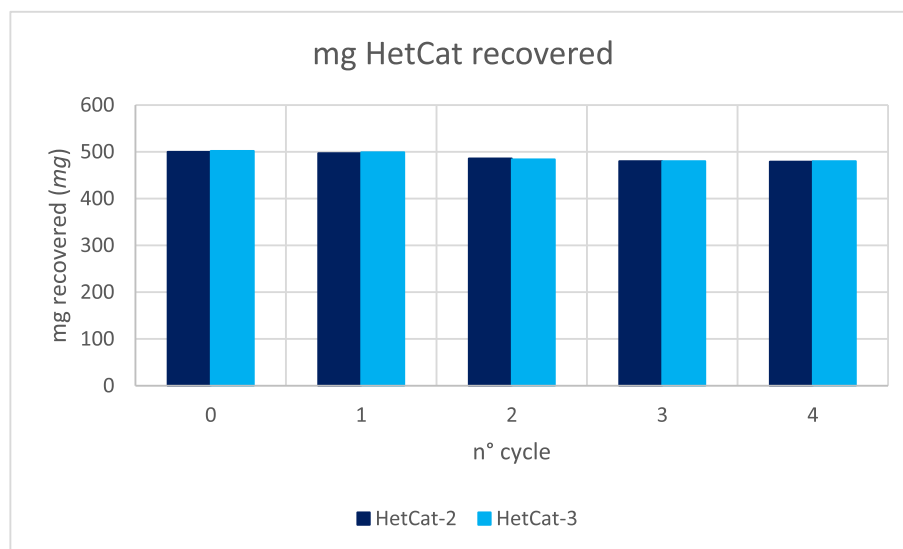
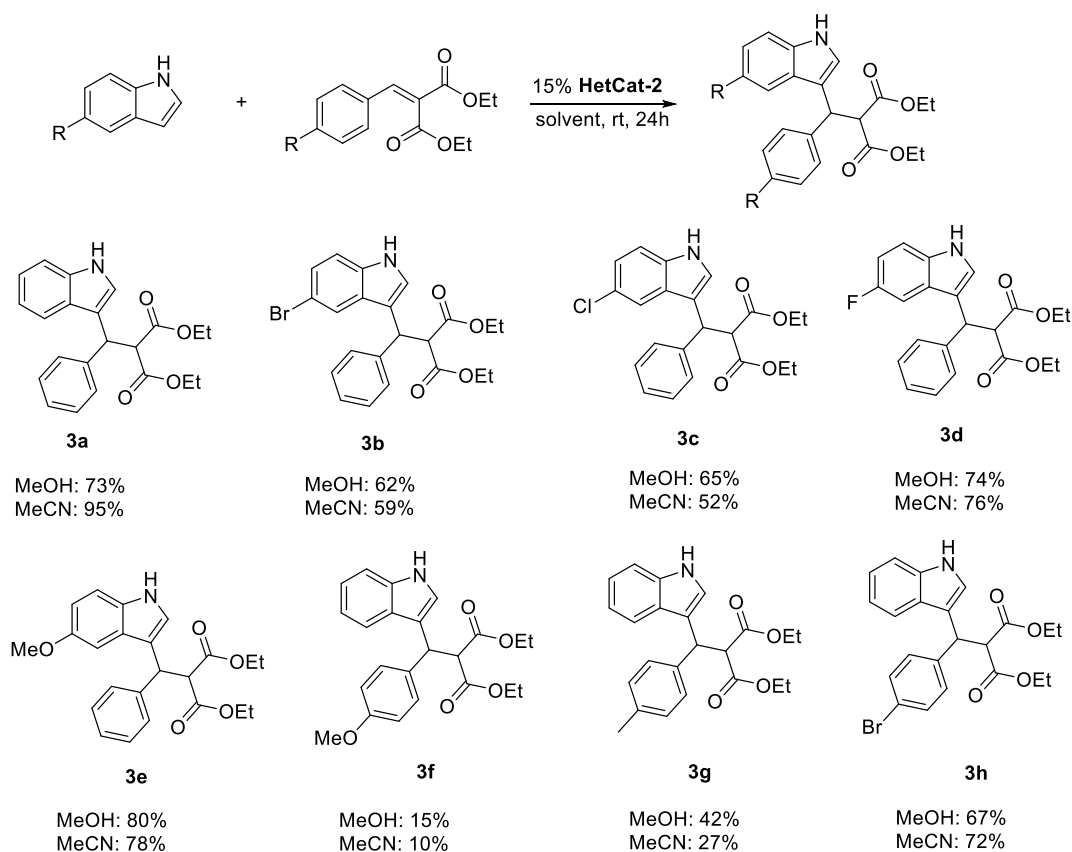


Fig. 4. Milligrams HetCat-2 and HetCat-3 recovered after every recycle.



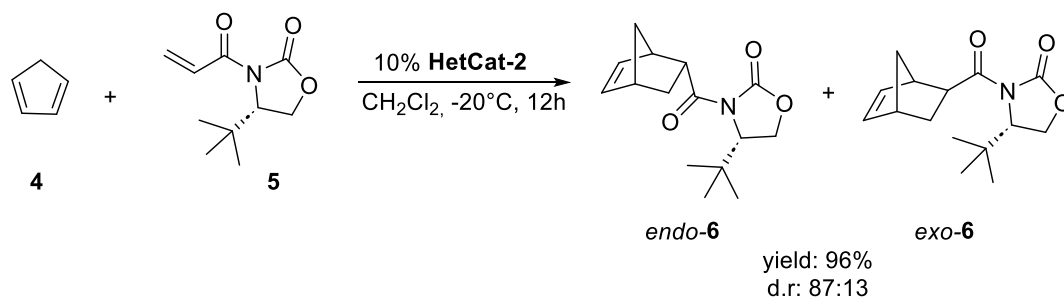
Scheme 4. Substrate scope.

Preliminary tests performed using commercially available, homogeneous $Y(OTf)_3$ afforded the desired product **6** in 86 % yield 81:19 *endo-6:exo-6* diastereoisomeric ratio after 20 h at $-20\text{ }^\circ\text{C}$ in CH_2Cl_2 as a solvent.

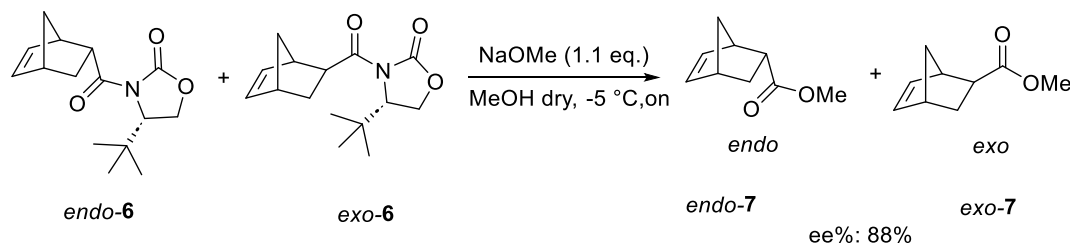
The reaction with **HetCat-2** was run in CH_2Cl_2 as a solvent, at $-20\text{ }^\circ\text{C}$ for 12 h, affording the desired product **6** in 96 % yield, in 87:13 *endo-6:exo-6* diastereoisomeric ratio (Scheme 5). The oxazolidinone moiety was then removed from the inseparable mixture of *endo-6* and *exo-6* under mild conditions, with NaOMe in MeOH at $-5\text{ }^\circ\text{C}$, in order to determine

the enantiomeric excess (Scheme 6).

The ee%, evaluated on compound **7** using HPLC on chiral stationary phase, was 88 % on the *endo-7* product, vs 96 % ee obtained with homogeneous $Y(OTf)_3$. Although the ee was somewhat lower than the ee obtained under homogeneous conditions, the supported catalyst **HetCat-2** showed a good catalytic activity in the Diels-Alder reaction.



Scheme 5. Diels-Alder cycloaddition between cyclopentadiene and (4S)-3-acryloyl-4-tert-butylloxazolidin-2-one.



Scheme 6. Deprotection reaction of (4S)-3-acryloyl-4-tert-butylloxazolidin-2-one 6.

3. Conclusions

Different heterogeneous catalysts were synthesized exploiting ionic interactions, and characterized with different analytic techniques. The catalysts were tested in the Michael addition between indoles and benzylidenemalonates obtaining satisfactory and reliable results. The catalysts afforded the desired products in high yield, with a simple reaction workup and product isolation. We proved that is possible to recover and recycle the catalysts at least four times with a small erosion of the catalytic activity, using acetonitrile as a solvent. In acetonitrile no catalyst leaching was detected. After every recycle, both **HetCat-2** and **HetCat-3** were recovered almost quantitatively. A small library of products with different indoles and benzylidenemalonates were synthesized using **HetCat-2**. In the end, the Diels-Alder cycloaddition between cyclopentadiene and (4S)-3-acryloyl-4-tert-butylloxazolidin-2-one were studied using **HetCat-2** obtaining excellent yield and good enantiomeric excess. This work demonstrated the feasibility of an efficient catalytic protocol using heterogenized, recyclable and precious rare earth element like Y(OTf)₃.

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CRedit authorship contribution statement

Emanuela Donato: Investigation, Methodology, Writing - original draft. **Fabrizio Medici:** Investigation, Methodology. **Valerio Chiroli:** Methodology. **Sergio Rossi:** Writing - review & editing. **Alessandra Puglisi:** Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tgchem.2023.100032>.

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