Journal of Catalysis 285 (2012) 216–222

Contents lists available at SciVerse ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Rasta resin as support for TBD in base-catalyzed organic processes

Simona Bonollo, Daniela Lanari *, Tommaso Angelini, Ferdinando Pizzo, Assunta Marrocchi, Luigi Vaccaro *

Laboratory of Green Synthetic Organic Chemistry, CEMIN – Dipartimento di Chimica, Università di Perugia Via Elce di Sotto, 8, Perugia, Italy

ARTICLE INFO

Article history:
Received 2 September 2011
Revised 22 September 2011
Accepted 24 September 2011
Available online 9 November 2011

Keywords:
Heterogeneous catalysis
Solvent-free conditions
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)
Polymer-supported organocatalysts

ABSTRACT

Although its intriguing features, such as uniform functionalization through the entire beads and a very high-loading capacity are suitable candidates for solid-phase synthesis and reagent-scavenging, the use of Rasta resin as support for organocatalysis has been little explored. In this contribution, Rasta polymer has been used to preparation of high-loading Rasta-TBD. This catalyst has been able to efficiently promote several organic transformations with constantly good and promising results.

1. Introduction

Over the last decades, fast-growing development of polymer-supported reagents and catalysts led to a fascinating combination of chemical efficiency and environmental sustainability [1]. To have highly active and recoverable solid catalysts is certainly highly desirable in order to minimize the waste associated with a chemical process [2]. Anyway, an accurate choice must be made to select the ideal support considering its cost and commercial availability, its degree of functionalization and its influence on the catalyst stability and efficiency. The reaction medium plays a crucial role and its interactions with the support strongly influence the efficiency of the solid catalyst. Representatively, it is well known in the case of insoluble polymers, the access of reactants to the catalytic sites is closely related to the ability of the reaction medium to swell the matrix facilitating or hampering the process [3].

We have contributed to the development of efficient procedures based on the use of metal-free catalysts supported on Merrifield resins [4], proving that resin swelling problems can be overcome by eliminating the reaction medium [4]. Adoption of solvent-free conditions (SolFC) have led to a markedly increased efficiency of the anchored catalyst that was recovered and reused and generally allowed the use of stoichiometric amounts of reactants with consequent minimization of the waste associated with the processes [4]. To further reduce E-factor [2], our approach induced us to set cyclic continuous-flow protocols operating in SolFC or highly concentrated conditions running on multigram scale [4a–c,4e]. These results have proved that the combination of SolFC and polymer-supported organic catalyst is a promising approach to realize green and efficient synthetic protocols.

Moving forward, we have directed our interest toward the development of novel polymer supports to be used as alternatives to classic Merrifield resins and more suitable for being used in SolFC and in continuous-flow processes. At this purpose, high-loading material is desirable to facilitate stirring in solvent-free heterogeneous reaction conditions.

We have directed our attention to a new class of polymer-supported material, namely RASTA resins **1**, that have been developed by Hodges et al. by using living free radical polymerization (LFRP) of TEMPO methyl resin **2** with functionalized styrenyl monomers **3** (Scheme 1) [5].

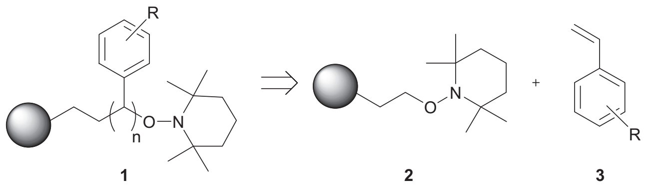
Rasta resins **1** are often depicted as in Fig. 1 by a cartoon structure **4** to indicate that polymer chains emerge from the cross-linked polystyrene core (as hair like appendages), or alternatively by **5**, wherein the shaded inner circle represents the original cross-linked polystyrene (PS) core and the outer clear circle represents new polymer growth. Studies on the macromolecular architecture showed that Rasta resins **1** are uniformly functionalized through the entire beads and have a very high-loading capacity [6]. Such properties make Rasta resins suitable candidates for solid-phase synthesis and reagent-scavenging [7]. For our purposes, we have envisaged in their peculiar architectural structure a promising solid support for improving our approach to SolFC continuous-flow chemistry.

Lately, Merck Research Laboratories have developed a new microwave-initiated living free radical polymerization to deliver

---

* Corresponding authors. Fax: +39 075 5855560.
E-mail address: luigi@unipg.it (L. Vaccaro).

0021-9517/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcat.2011.09.032



Scheme 1. Rasta resin retro-synthesis.

Rasta resins [8]. Such technique allowed the rapid gram-scale synthesis of novel high-loading polymers such as Rasta amines [8].

On the other hand, an excellent work is being carried out by Toy et al. on the use of Rasta-based catalysts that were synthesized by thermal polymerization [9].

Besides Toy's work in this field, and despite great expectations hold by Rasta resins, we have found only few applications in literature so far, to our knowledge [7–9].

Herein, we report the synthesis of a novel Rasta resin catalyst where 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) is covalently linked to the solid support (**7a**–**c**) and the study on its use as a base in a variety of base-catalyzed reactions that proves its high efficiency in SolFC processes. TBD was chosen as a representative effective basic catalyst able to promote various transformations under SolFC [4a-b,4e,4g-h].

2. Experimental section

2.1. General remarks

All chemicals were purchased and used without any further purification.

GC analyses were performed by using Hewett–Packard HP 5890 series II equipped with a capillary column SPB-5 (30 m, 0.25 mm), a FID detector and hydrogen as gas carrier. GC-EIMS analyses were carried out by using a Hewett–Packard HP 6890 Series GC system/5973 Mass Selective Detector equipped with a electron impact ionizer at 70 eV. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz or 400 MHz, and at 50.3 or 100.6 MHz, respectively, using a Bruker DRX-ADVANCE 200 MHz and a Bruker DRX-ADVANCE 400 MHz spectromers. Deuterated solvents were used with the residual peak as internal standard, or TMS in the case of $CDCl_3$. Chemical shift was reported in ppm and coupling constants in Hertz. All melting points were measured with Buchi Melting Point 510 apparatus and are uncorrected. Microanalyses were realized by using a Carlo Erba Elemental analyzer mod. 1106. Thin-layer chromatography analyses were performed on silica gel on aluminum plates, and UV and/or $KMnO_4$ were used as revealing systems. Column chromatographies were performed by using silica gel 230–400 mesh and eluting as reported below. Scanning Electron Microscopy (SEM) pictures of gold-coated polymers (instrument EMITECH K55OX SPUTTER COATER) were taken on a SEM XL30 PHILIPS. FTIR spectra were recorded on a Bruker ISF 28. Thermogravimetric (TG) and differential thermal analyses (DTA) analyses were performed on a STA 449 C Jupiter (thermal analyzer).

Rasta-TBD catalysts **7a**–**c** have been prepared starting from the corresponding Rasta-Cl (**6**). Their morphology was observed with SEM and compared with both starting Rasta-Cl **6** and commercially available PS-TBD **8** [10].

2.2. Preparation of catalysts ***7a***–***c***

2.2.1. Rasta-TBD ***7a***

In a round-bottomed flask equipped with a magnetic stirrer, TBD (2.0 g, 15 mmol) was dissolved in 1,4-dioxane (30 ml) and Rasta-Cl (50–100 mesh, 1% cross-linked, 0.587 g, 5.11 mmol Cl/g, 3.0 mmol) was added. The mixture was left under stirring at 60 °C for 24 h, then allowed to reach room temperature. The polymer beads were isolated by filtration, washed with methanol, dichloromethane, and acetone, and then dried under vacuum for 15 h at 60 °C. The degree of functionalization was determined to be 2.98 mmol TBD/g (Table 1, entry 4) by elemental analysis: C 76.00, H 8.20, N 12.66.

2.2.2. Rasta-TBD ***7b***

In a round-bottomed flask equipped with a magnetic stirrer, TBD (0.4 g, 3 mmol) was dissolved in 1,4-dioxane (30 ml) and Rasta-Cl (**6**) (50–100 mesh, 1% cross-linked, 0.587 g, 5.11 mmol Cl/g, 3.0 mmol) was added. The mixture was left under stirring at 60 °C for 24 h, then allowed to reach room temperature. The polymer beads were isolated by filtration, washed with methanol, dichloromethane, and acetone, and then dried under vacuum for 15 h at 60 °C. The degree of functionalization was determined to be 2.03 mmol TBD/g (Table 1, entry 6) by elemental analysis: C 68.92, H 7.14, N 8.53.

2.2.3. Rasta-TBD ***7c***

In a round-bottomed flask equipped with a magnetic stirrer, TBD (0.2 g, 1.5 mmol) was dissolved in 1,4-dioxane (30 ml) and Rasta-Cl (**6**) (50–100 mesh, 1% cross-linked, 0.587 g, 5.11 mmol Cl/g, 3.0 mmol) was added. The mixture was left under stirring at 60 °C for 24 h, then allowed to reach room temperature. The polymer beads were isolated by filtration, washed with methanol, dichloromethane, and acetone, and then dried under vacuum for 15 h at 60 °C. The degree of functionalization was determined to be 1.19 mmol TBD/g (Table 1, entry 7) by elemental analysis: C 73.19, H 6.92, N 5.01.

2.3. General procedure for the Michael addition of dimethylmalonate (***9***) to α,β-unsaturated ketones ***10a***–***c*** for the preparation of ***11a***–***c***

In a screw-capped vial equipped with a magnetic stirrer, Rasta-TBD (**7a**) (0.134 g, 0.4 mmol, 2.98 mmol/g), ketone **10** (2.0 mmol), and dimethylmalonate (**9**) (2.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 15 h, ethyl acetate was added, the catalyst was recovered by filtration, and the organic solvent was evaporated under vacuum to give pure product **11** in 92–97% yield (see Section 3).

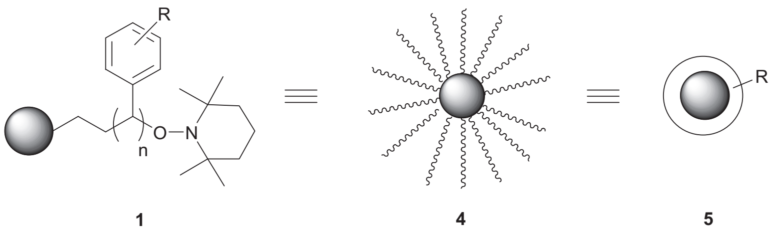
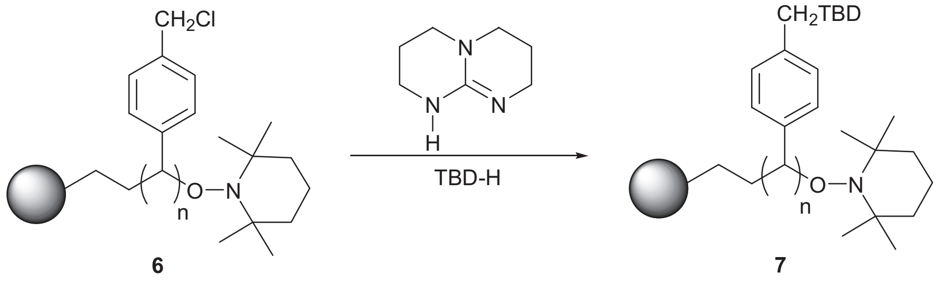


Fig. 1. Rasta resin cartoon architecture and shorthand representation.

Table 1
Optimization of Rasta-TBD synthesis.



Entry	TBD (eq)	Solvent (M)	T (°C)	t (h)	L[a] (mmol TBD/g)
1	2	1,4-Dioxane	60	24	2.57
2	2	1,4-Dioxane	110	24	2.52
3	2	1,4-Dioxane	110	70	2.70
4	5	1,4-Dioxane	60	24	2.98
5	10	1,4-Dioxane	60	24	3.10
6	1.0	1,4-Dioxane	60	24	2.03
7	0.5	1,4-Dioxane	60	24	1.19
8	10	MeOH/1,4-Dioxane	90/110	120	1.69
9	10	/	130	21	2.63
10	8	1,4-Dioxane[b]	180[b]	1	2.73
11	10	DMSO[b]	180[b]	1	2.38

[a] Loading of TBD calculated by elemental analysis.
[b] Microwave-assisted reaction (250w).

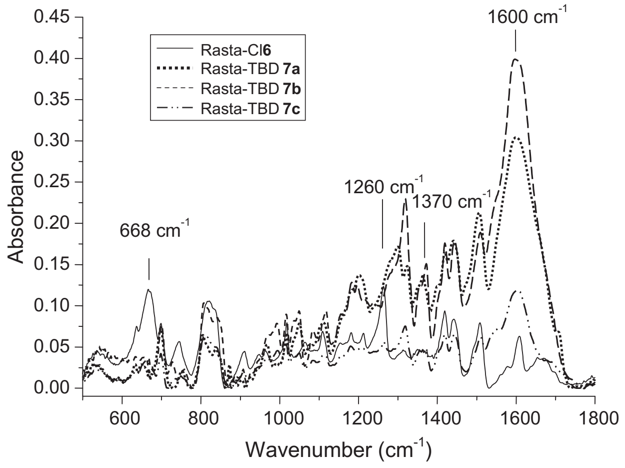


Fig. 2. FTIR spectra of Rasta-Cl 6 and Rasta-TBD 7.

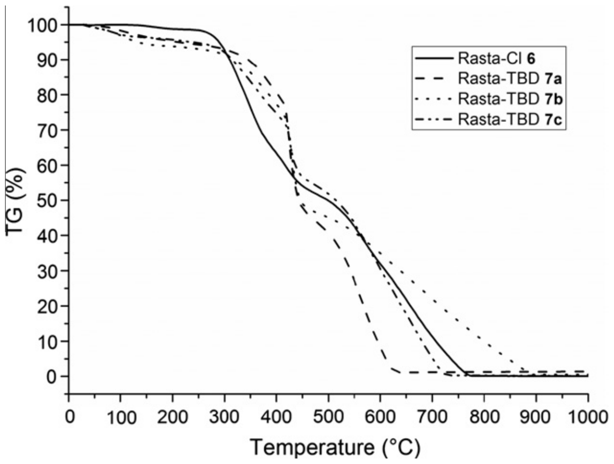


Fig. 3. TG curves of Rasta-Cl (**6**) and catalysts **7a**, **7b**, and **7c**.

2.4. General procedure for the Michael addition of nitroalkanes *12a–c* to α,β-unsaturated ketones *10a–c* for the preparation of *13–21*

In a screw-capped vial equipped with a magnetic stirrer, Rasta-TBD (**7a**) (0.134 g, 0.4 mmol, 2.98 mmol/g), ketone **10** (2.0 mmol), and nitroalkane **12** (2.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 30 or 60 °C. After 3-30 h, ethyl acetate was added, the catalyst was recovered by filtration, and the organic solvent was evaporated under vacuum. The reaction mixture was purified by silica gel column chromatography (95/5 Petroleum ether/EtOAc, 100/1 silica/sample) to give the corresponding pure product (**13**–**21**) in 80–95% yield (see Section 3).

2.5. General procedure for the ring-opening of phenyl glycidyl ether (*22*)

In a screw-capped vial equipped with a magnetic stirrer, Rasta-TBD (**7a**) (0.084 g, 0.25 mmol, 2.98 mmol/g), phenyl glycidyl ether (**22**) (0.678 ml, 5.0 mmol), and nucleophile (**23a** or **23b** or **23c**) (5.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 30 or 60 °C. After conversion of **22** was complete, ethyl acetate was added, the catalyst was recovered by filtration, and the organic solvent was evaporated under vacuum to give the corresponding pure products (**24–26**) in 89–100% yield (see Section 3).

2.6. Procedure for the tandem Michael–Henry reaction leading to nitrochromene *29*

In a screw-capped vial equipped with a magnetic stirrer, Rasta-TBD (**7a**) (0.067 g, 0.2 mmol, 2.98 mmol/g), trans-β-nitrostyrene (**27**) (0.149 g, 1.0 mmol), and salicylaldehyde (**28**) (0.107 ml, 1.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 80 °C.

After 15 h, ethyl acetate was added, the catalyst was recovered by filtration, and the organic solvent was evaporated under

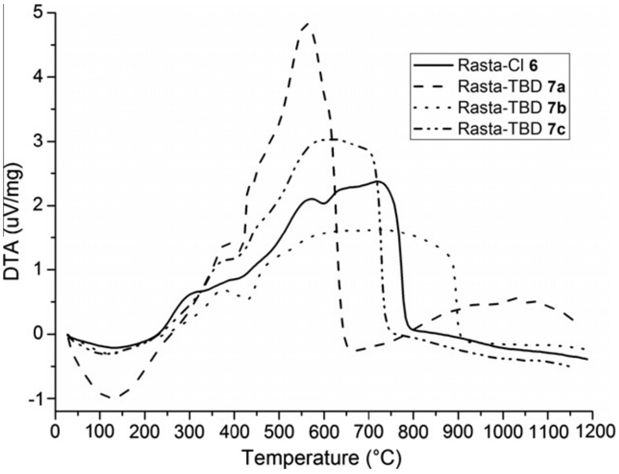


Fig. 4. DTA curves of Rasta-Cl (**6**) and catalysts **7a**, **7b**, and **7c**.

vacuum. The reaction mixture was purified by silica gel column chromatography (95/5 Petroleum ether/EtOAc, 40/1 silica/sample) to give 3-nitro-2-phenyl 2*H*-chromene (**29**) as a yellow oil (0.139 g, 55% yield).

Compounds **11a** [11], **11c** [12], **13** [4e], **14** [4e], **15** [4e], **16** [4e], **18** [13], **19** [4e], **20** [14], **21** [13], **24** [15], **25** [15], **26** [4b], **29** [16] are known compounds, while compounds **11b**, **17** are new compounds.

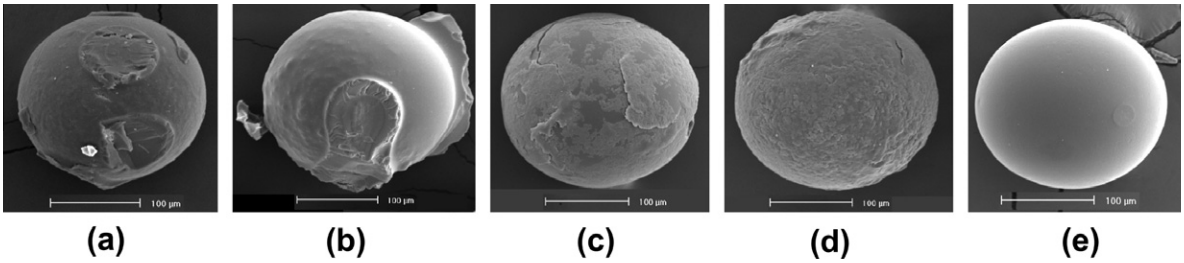
Characterization data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds (**11a**–**c**, **13**–**21**, **24**–**26** and **29**) are reported as Supplementary data.

3. Results and discussion

3.1. Catalysts preparation and characterization

Starting from Rasta-Cl resin **6,** we have tried different reaction conditions to yield the desired TBD-Rasta resin **7** with the highest loading possible in view of its use under SolFC. Microwave activation did not work as good as we expected [8]. (Table 1, entries 10, 11) and according to Toy's results thermal activation instead gave encouraging results [9]. 1,4-Dioxane proved to be the best solvent as it allowed a good polymer swelling and the setting of reaction temperature as high as 110 °C. The best results at the end were obtained at 60 °C when 5 eq of TDB were added to the chloromethylated Rasta resin **6** and Rasta-TBD **7** was obtained with a satisfactory 2.98 mmol TBD/g loading (Table 1, entry 4). A slightly better loading was obtained but only by using a larger excess of TBD (10 eq) (Table 1, entry 5).

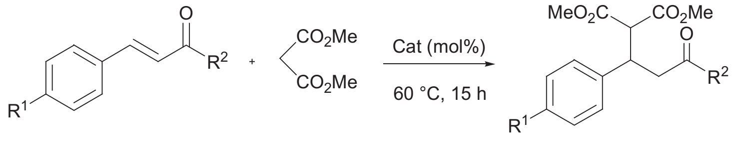
Afterward, three samples of Rasta-TBD (**7a**, **7b**, **7c**) with respective loading of 2.98 (**7a**) (Table 1, entry 4), 2.03 (**7b**) (Table 1, entry 6), and 1.19 (**7c**) mmol TBD/g (Table 1, entry 7) were prepared and characterized by elemental analysis, IR spectroscopy, Thermogravimetric (TG) and differential thermal analysis (DTA), and Scanning Electron Microscopy (SEM).



(a) (b) (c) (d) (e)

Fig. 5. SEM images of: (a) Rasta-Cl **6**. (b) Rasta-TBD **7c**. (c) Rasta-TBD **7b**. (d) Rasta-TBD **7a**. (e) PS-TBD **8**.

Table 2
Michael addition of dimethylmalonate (**9**) to α,β-unsaturated ketones (**10a**–**c**).



10a-c **9** **11a-c**

a R^1=H, R^2=Me; **b** R^1=Cl, R^2=Me; **c** R^1=H, R^2=Ph

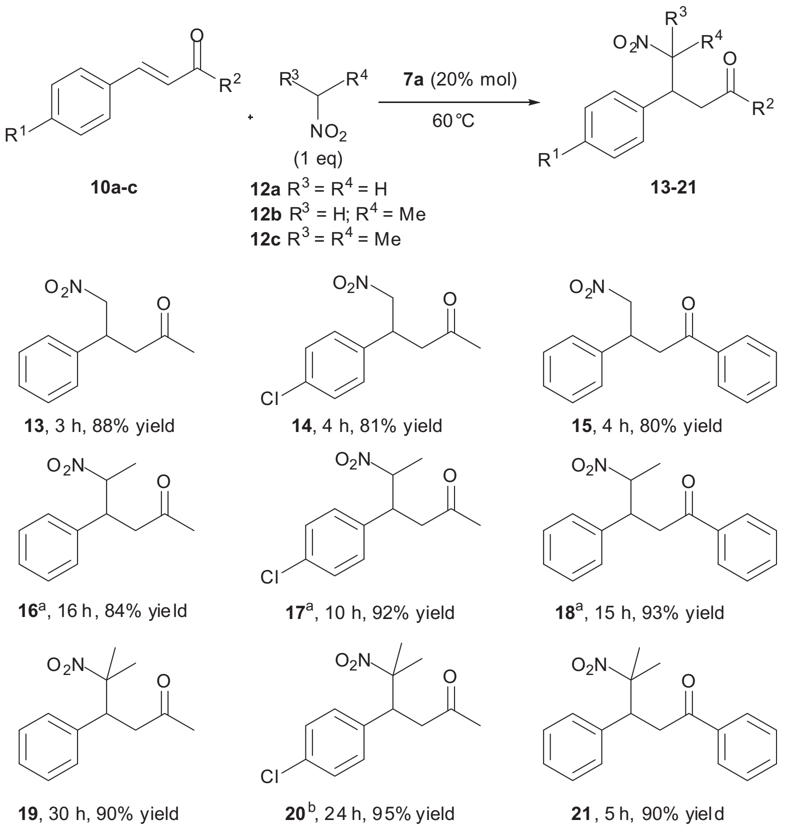
Entry	Ketone	Cat (mol%)	Medium	Conversion[a] (%)	Yield[b] (%)
1	**10a**	**7a** (20)	CH_3CN	39	–
2	**10a**	**7a** (20)	DCE	0	–
3	**10a**	**7a** (20)	1,4-Dioxane	13	–
4	**10a**	**7a** (20)	–	100	92
5	**10a**	**7a** (5)	–	39	–
6	**10a**	**6** (5)	–	0	–
7	**10b**	**7a** (20)	–	100	93
8	**10c**	**7a** (20)	–	100	97, 96,[c] 97[d]

[a] Measured by GLC analysis.

[b] Yield of the isolated pure product.

[c] Yield of the isolated pure product after first recycle.

[d] Yield of the isolated pure product after second recycle.



13, 3 h, 88% yield
14, 4 h, 81% yield
15, 4 h, 80% yield
16[a], 16 h, 84% yield
17[a], 10 h, 92% yield
18[a], 15 h, 93% yield
19, 30 h, 90% yield
20[b], 24 h, 95% yield
21, 5 h, 90% yield

The representative reaction of **10a** and **12a** in the presence of **6** gave no conversion at all.
[a] Reaction performed at 30 °C. [b] 2 equiv of nitroalkane were used.

Scheme 2. Michael addition of nitroalkanes.

FTIR spectra confirm the presence of the immobilized TBD moiety. By comparing the Rasta-TBD **7** spectra with that of the Rasta-Cl **6** is clearly visible the gradual disappearing of the 1260 cm^{-1} band corresponding to the CH_2Cl wagging vibration and the 670 cm^{-1} band corresponding to the C—Cl stretching vibration going from Rasta-Cl **6** to the more functionalized Rasta-TBD **7** (Fig. 2). Moreover, it can be noted the appearance of a strong peak at 1600 cm^{-1} relative to C=N stretching (the weak band observed at the same frequency for Rasta-Cl **6** spectrum is due to benzene skeleton) and a 1380 cm^{-1} band corresponding to C—N stretching. Elemental analyses were used to calculate the catalyst loading.

In Figs. 3 and 4 are shown Thermogravimetric (TG) and differential thermal analysis (DTA) curves of catalysts **7a**, **7b**, **7c** compared to starting material Rasta-Cl (**6**). It is clearly visible the different initial mass loss in the case of the TBD-containing catalysts (**7a**, **7b**, **7c**) and the starting chloride resin **6**.

Morphology of the Rasta-TBD samples (**7a**, **7b**, **7c**) was observed with SEM and compared with both starting Rasta-Cl **6** and commercially available PS-TBD **8** [10] (Fig. 5): the images, represented with equal magnification, show that particles size was on the micrometer scale, and Rasta resin beads are slightly bigger than PS ones.

3.2. Catalytic activity

The efficiency of the new base-supported organocatalyst **7a** has been tested in several fundamental organic transformations.

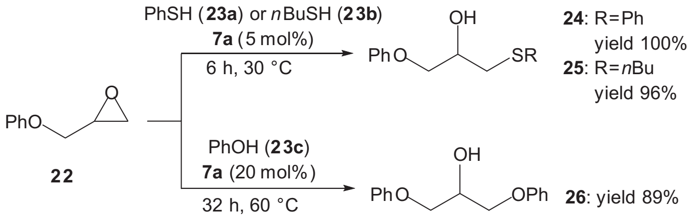
In the case of the Michael addition of dimethylmalonate (**9**) to (E)-benzylideneacetone (**10a**) (Table 2), poor results were obtained in the presence of 20 mol% of catalyst **7a** and of an organic reaction medium (Table 2, entries 1–3). On the other hand, by performing the reaction **10a** with **9** under SolFC at 60 °C, product **11a** was obtained in a 100% conversion and 92% isolated yield (Table 2, entry 4). The same reaction can be also performed under SolFC with smaller amount of catalyst (Table 2, entry 5).

As expected, Rasta-Cl **6**, that does not contain any strong basic site, did not show any catalytic effect on the Michael addition of **9** to **10a** (Table 2, entry 6).

The use of **7a** (20 mol%) was extended to the addition of **9** to 4-(4′-chlorophenyl)-3-buten-2-one (**10b**) and *trans*-chalcone (**10c**), and also in these cases, conversions were quantitative and pure products **11b** and **11c** were isolated in 93% and 97% yields, respectively (Table 2, entries 7 and 8).

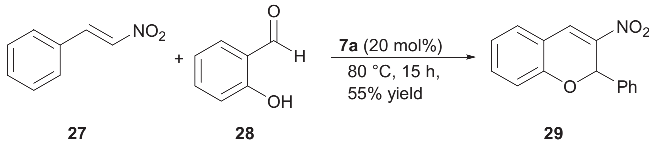
Rasta-TBD catalyst **7a** was also tested in Michael addition of nitroalkanes **12a–c** to α,β-unsaturated ketones **10a–c** (Scheme 2). Very good yields were obtained when 20 mol% of **7a** were used. Reactions with nitromethane (**12a**) and 2-nitropropane (**12c**) were run at 60 °C, the more reactive nitroethane (**12b**) required a lower temperature (30 °C). In this latter case, products **16–18** were isolated as 53/47, 52/48, and 56/44 diasteromeric mixtures, respectively.

Catalyst **7a** proved to be effective also in the representative nucleophilic ring-opening of phenyl glycidylether (**22**) by thiols **23a** and **23b** and by phenol (**23c**). Benzenethiol (**23a**) and *n*-butanethiol (**23b**) reacted at 30 °C in the presence of 5 mol% of **7a,** leading to the corresponding pure products **24** and **25**, respectively, in high yields. When phenol (**23c**) was employed as nucleophile, the reaction needed longer reaction time and 60 °C to reach complete conversion (Scheme 3). As expected [4b,17], the reactions proceeded with complete regioselectivity and it was



The representative reaction of **22** and **23a** in the presence of **6** gave no conversion at all.

Scheme 3. Ring-opening of phenyl glycidyl ether (**22**).



Scheme 4. Tandem Michael–Henry reaction for the synthesis of nitrochromene **29**.

Table 3
Efficiency comparison of solid catalyst Rasta-TBD **7a** and homogeneous Methyl-TBD (MTBD) (**30**) under SolFC.[a]

Entry	Substrates	Cat	*T* (°C)	*t* (h)[b]	Yield[c] (%)
1	**10a** + **9**	MTBD (**30**)	60	2	93
2	**10a** + **9**	Rasta-TBD (**7a**)	60	15	92
3	**10a** + **12b**	MTBD (**30**)	30	1	91[d]
4	**10a** + **12b**	Rasta-TBD (**7a**)	30	16	84
5	**10b** + **12b**	MTBD (**30**)	30	0.7	91[e]
6	**10b** + **12b**	Rasta-TBD (**7a**)	30	10	92
7	**10c** + **12b**	MTBD (**30**)	30	1	93[d]
8	**10c** + **12b**	Rasta-TBD (**7a**)	30	15	93
9	**22** + **23a**	MTBD (**30**)	30	0.5	100[f,g]
10	**22** + **23a**	Rasta-TBD (**7a**)	30	6	100[f,g]
11	**22** + **23c**	MTBD (**30**)	60	4	90[g]
12	**22** + **23c**	Rasta-TBD (**7a**)	60	32	89[g]

[a] Rasta-TBD (**7a**) and MTBD (**30**) were used in 20 amounts. Measured by GLC analysis.
[b] Time for the complete conversion to products.
[c] Yield of the isolated pure product (average over three experiments).
[d] Catalysts were used in 5 mol% amount.
[e] Diasteroisomeric ratio: 55/45.
[f] Diasteroisomeric ratio: 54/46.
[g] Only product coming from the C-3 attack was observed.

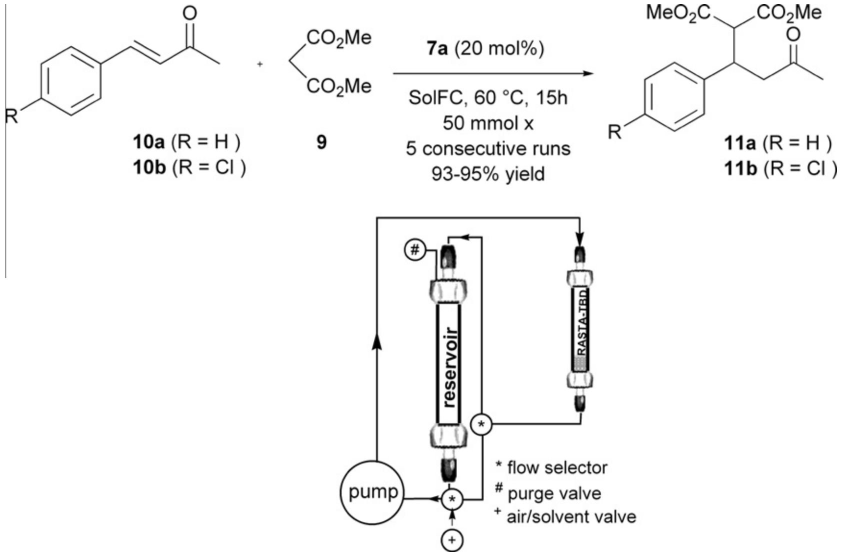
observed only the formation of the products coming from the attack of the nucleophile to the less substituted β-carbon (C-3).

As a further example of the versatility of Rasta-TBD catalyst **7a,** we studied the reaction of nitrostyrene (**27**) with salicylaldehyde (**28**) for the preparation of **29**. The initially formed Michael adduct gave intramolecular Henry reaction with subsequent water-elimination to form product **29** in 55% yield (Scheme 4). 3-Nitrochromenes such as **29** belong to an important class of heterocycles precursors of biologically active compounds [18].

In order to evaluate the influence of Rasta support on the efficiency of the processes herein investigated (specifically on the catalytic activity and selectivity), immobilized Rasta-TBD **7a** and the corresponding homogeneous catalyst methyl-TBD (**30**) have been compared and results are reported in Table 3.

The homogeneous MTBD (**30**) is a more efficient base than Rasta-TBD (**7a**) and as expected the use of the immobilized catalyst resulted in slower reactions. Anyway, the selectivity observed in the addition of nitroethane (**12b**) to enones **10a**–**c** was almost identical (52–56/48–44 for Rasta-TBD, vs. 54–55/46–45 for MTBD) and also the ring-opening of **22** with benzenethiol (**23a**) and phenol (**23c**) gave in all cases a complete C-3 selectivity. These data suggest that, although the catalytic efficiency of TBD nucleus is reduced by the presence of the polymeric support, the mechanisms of the reactions considered are not influenced, and Rasta supports allow to achieve the same regiochemical and stereochemical outcomes than the free homogenous catalyst.

We have also evaluated the recovery and reuse of **7a**. Both in the ring-opening of epoxides and in the Michael addition of dimethylmalonate (**9**) to α,β unsaturated ketones **10a**–**c**, we have not observed any decrease in its catalytic efficiency. The recovered catalyst has been analyzed by Elemental Analysis, confirming the un-



Scheme 5. Schematic diagram of the cyclic continuous-flow reactor in the reaction of **10a** or **10b** and **9** catalyzed by **7a**.

changed loading of TBD, and SEM image (see Supplementary data) showed some expected crunching of the beads due to the mechanical stirring used to perform the reactions.

Finally, to optimize the recovery and reuse of catalyst Rasta-TBD **7a** and to prove its application in continuous-flow processes operating under solvent-free conditions, we have defined an automated protocol for the representative reactions of **9** with **10a** and **10b** (Scheme 5).

According to our previous reports in this field, the reactor has been designed to minimize waste and in particular the amount of organic solvent needed to isolate the final products [4a–c,4e]. The schematic diagram of the reactor is presented in Scheme 5 (thermostated box is not showed for clarity). The equimolar mixture (50 mmol) of **9** and **10a** or **10b** was charged into a glass column functioning as reservoir. Catalyst **7a** (20 mol%, corresponding to 10 mmol of TBD) was charged into a glass column, and the reaction mixture was continuously pumped through it at 60 °C for 15 h, necessary for the complete conversion to **11a** and **11b**.

At this point, the pump was left to run in order to recover the reaction mixture into the reservoir. Then, EtOAc was added (5×2 ml) to wash the catalyst and to isolate the pure products **11a** or **11b** in 95% and 94% yield, respectively.

The same protocol was repeated for five consecutive runs, and the efficiency of the catalyst was unchanged. After 15 h, the conversion of **10a** or **10b** to **11a** or **11b** was always complete and the final products were recovered always in very high yields (93–95%).

It should be highlighted that by using the cyclic continuous-flow procedure, crunching of the catalyst was not anymore observed and the recovered catalyst almost conserved is physical integrity as showed by the SEM image reported in Supplementary data.

4. Conclusion

In conclusion, we have reported a study on the synthesis and applications of a novel TBD catalyst supported on a Rasta polymer **7a**. We have developed a simple and straightforward synthetic procedure to obtain the catalyst with a high-loading value, which is strategic for its use under SolFC. TBD on Rasta resin **7a** has been tested in a set of organic transformations giving constantly good results. The presence of the support has resulted in the reduction of the catalytic efficiency of TBD nucleus, but no significant changes have been observed in the regiochemical and stereochemical outcomes. We have also defined a continuous-flow protocol for the representative reactions of **9** with **10a** and **10b** operating under SolFC on a 50 mmol scale. Under these conditions, the same catalyst can be used for at least five consecutive runs with no decrease in its efficiency. This approach has allowed the physical integrity of the catalyst to be conserved and proves that combination of this Rasta-catalyst with SolFC is promising in view of its future application in environmentally-efficient continuous-flow chemistry.

Acknowledgments

We gratefully acknowledge the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) within the projects PRIN 2008 and "Firb-Futuro in Ricerca" and the Università degli Studi di Perugia for financial support. We also wish to thank FONDAZIONE Cassa di Risparmio di Perugia for financial support within the Project "Nuovi sistemi catalitici per la realizzazione di processi a flusso continuo" prot. 2008.031.0356.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcat.2011.09.032.

References

[1] (a) T.E. Kristensen, T. Hansen, Eur. J. Org. Chem. (2010) 3179–3204;
(b) J. Lu, P.H. Toy, Chem. Rev. 109 (2009) 815–838;
(c) B.M.L. Dioos, I.F.J. Vankelecom, P.A. Jacobs, Adv. Synth. Catal. 348 (2006) 1413–1446;
(d) F. Cozzi, Adv. Synth. Catal. 348 (2006) 1367–1390;
(e) M. Benaglia, A. Puglisi, F. Cozzi, Chem. Rev. 103 (2003) 3401–3429.
[2] (a) R.A. Sheldon, Chem. Commun. (2008) 3352–3365;
(b) J. Augè, Green Chem. 10 (2008) 225–231;
(c) R.A. Sheldon, Green Chem. 9 (2007) 1273–1283;
[d] R.A. Sheldon, Chem. Ind. (1997) 12–15.
[3] D.C. Sherrington, Chem. Commun. (1998) 2275–2286.
[4] (a) D. Lanari, R. Ballini, S. Bonollo, A. Palmieri, F. Pizzo, L. Vaccaro, Green Chem., doi: 10.1039/C1GC15790F.;
(b) A. Zvagulis, S. Bonollo, D. Lanari, F. Pizzo, L. Vaccaro, Adv. Synth. Catal. 352 (2010) 2489–2496;
(c) F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, Green Chem. 12 (2010) 1301–1305;
(d) T. Angelini, F. Fringuelli, D. Lanari, L. Vaccaro, Tetrahedron Lett. 51 (2010) 1566–1569;
(e) R. Ballini, L. Barboni, L. Castrica, F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, Adv. Synth. Catal. 350 (2008) 1218–1224;
(f) F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, Eur. J. Org. Chem. (2008) 3928–3932;
(g) F. Fringuelli, F. Pizzo, C. Vittoriani, L. Vaccaro, Eur. J. Org. Chem. (2006) 1231–1236;
(h) F. Fringuelli, F. Pizzo, C. Vittoriani, L. Vaccaro, Chem. Commun. (2004) 2756–2757;
(i) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, J. Org. Chem. 69 (2004) 8780–8785.
[5] (a) J.C. Hodges, L.S. Harikrishnan, S. Ault-Justus, J. Comb. Chem. 2 (2000) 80–88;
(b) C.W. Lindsley, J.C. Hodges, G.F. Filzen, B.M. Watson, A.G. Geyer, J. Comb. Chem. 2 (2000) 550–559.
[6] S.R. McAlpine, C.W. Lindsley, J.C. Hodges, D.M. Leonard, G.F. Filzen, J. Comb. Chem. 3 (2001) 1–5.
[7] (a) G. Chen, L. Tao, G. Mantovani, J. Geng, D. Nyström, D.M. Haddleton, Macromolecules 40 (2007) 7513–7520;
(b) D. Founier, S. Pascual, V. Montembault, L. Fontaine, J. Polym. Sci.: Part A 44 (2006) 5316–5328;
(c) D. Fournier, S. Pascual, V. Montembault, D.M. Haddleton, L. Fontaine, J. Comb. Chem. 8 (2006) 522–530.
[8] (a) D.D. Winoski, W.H. Leister, K.A. Strauss, Z. Zhao, C.W. Lindsley, Tetrahedron Lett. 44 (2003) 4321–4325;
(b) J.M. Pawluczyk, R.T. McClain, C. Denicola, J.J. Mulhearn Jr., D.J. Rudd, C.W. Lindsley, Tetrahedron Lett. 48 (2007) 1497–1501.
[9] (a) J. Lu, P.H. Toy, Synlett (2011) 659–662;
(b) Y. Teng, P.H. Toy, Synlett (2011) 551–554;
(c) P.S.-W. Leung, Y. Teng, P.H. Toy, Org. Lett. 12 (2010) 4996–4999;
(d) P.S.-W. Leung, Y. Teng, P.H. Toy, Synlett (2010) 1997–2001.
[10] Stratospheres™ PL-TBD resin (50–100 mesh, 1% cross-linked) was purchased from Aldrich (product number 554812).
[11] N. Halland, P.S. Aburel, K.A. Jørgensen, Angew. Chem. 42 (2003) 661–665.
[12] M. Agostinho, S. Kobayashi, J. Am. Chem. Soc. 130 (2008) 2430–2431.
[13] B. Vakulya, S. Varga, T. Soós, J. Org. Chem. 73 (2008) 3475–3480.
[14] N. Halland, R.G. Hazell, K.A. Jørgensen, J. Org. Chem. 67 (2002) 8331–8338.
[15] W. Su, J. Chen, H. Wu, C. Jin, J. Org. Chem. 72 (2007) 4524–4527.
[16] D.-Q. Xu, Y.-F. Wang, S.-P. Luo, S. Zhang, A.-G. Zhong, H. Chen, Z.-Y. Xu, Adv. Synth. Catal. 350 (2008) 2610–2616.
[17] [a] F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, J. Org. Chem. 69 (2004) 8780–8785;
(b) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, J. Org. Chem. 68 (2003) 8248–8251;
(c) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, Green Chem. 5 (2003) 436–440;
(d) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, Tetrahedron Lett. 44 (2003) 6785–6787.
[18] (a) N. Ono, K. Sugi, T. Ogawa, S. Aramaki, J. Chem. Soc. Chem. Commun. (1993) 1781–1782;
(b) L. Rene, L. Blanco, R. Royer, R. Cavier, J. Lemoine, Eur. J. Med. Chem. 12 (1977) 385–386;
(c) M. Fatome, L. Andrieu, J.D. Laval, R. Royer, L. Rene, Eur. J. Med. Chem. 11 (1976) 81–82.