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Amino-modified Merrifield resins as recyclable catalysts for the safe and sustainable preparation of functionalized α-diazo carbonyl compounds

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ABSTRACT

Amino-functionalized polystyrene polymers derived from Merrifield resins were prepared and characterized. These basic materials were successfully employed as heterogeneous catalysts in the diazo transfer reaction to 1,3-dicarbonyl compounds, furnishing the corresponding diazo compounds in good to excellent yields and in relatively short reaction times. In addition, the work-up and purification protocols are simple and do not generate large amounts of waste, which are important features in sustainable catalysis and environmentally benign processes. The feasibility of the recovery and reuse of the amino-modified catalysts was also verified, since they can be employed up to five times without appreciable loss of catalytic activity. This straightforward procedure can be readily scaled up to gram scale, enabling the wide application of this method. The synthetic potential was demonstrated through the two-step preparation of 2-amino-N-dodecylacetamide (ANDA), a small molecule of commercial relevance.

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1. Introduction

Reported for the first time by Curtius in the nineteenth century [1], diazo compounds have become a powerful and convenient tool for a range of chemical transformations [2]. The loss of molecular nitrogen by thermal or photochemical processes induces the formation of highly reactive carbenoids or metallocarbenoids, which are intermediates in several chemo- and stereoselective reactions, such as C-H and C-X insertion, cyclopropanation, ylide formation, Wolff rearrangement, and 1,3-dipolar cycloaddition, leading to a variety of complex structures with biological and pharmaceutical properties [3]. In addition to their well-known synthetic versatility and tunable reactivity, diazo compounds have attracted the interest of the scientific community due to their unique application in the field of chemical biology for the modification of biomolecules [4].

The base-catalyzed diazo transfer reaction is one of the standard methods for the preparation of α-diazocarbonyl compounds [5]. However, the concerns associated with the use of potentially explosive tosyl azide (TsN_3) as the conventional diazo transfer reagent have led to a variety of inventive adaptations and improvements aimed at carrying out this transformation under safer conditions [6]. The use of *p*-acetamidobenzenesulfonyl azide ($ABSN_3$), for instance, is considerably less hazardous than TsN_3 and is a reagent of widespread application [7]. In addition, the removal of the solid sulfonamide formed as a byproduct of the diazo transfer is readily accomplished through trituration with hexane, thus furnishing the expected diazo product in high purity with no need for a further chromatography step [8].

On the other hand, the selection of a suitable base required to act as the catalyst for the diazo transfer reaction is not a trivial task and is a potential cause of unsuccessful transformations. Different organic bases have been reported to catalyze this reaction, including Et_3N, DBU, *i*-Pr_2NH and *t*-$BuNH_2$, which are usually employed in excess [8,9]. Even though these bases are of general application and relative efficiency, a subsequent aqueous work-up is commonly required to wash them out from the crude product, thus severely limiting the recovery of the catalyst and also generating large amounts of residues, which make these procedures less attractive from the green chemistry perspective [10].

The increase in environmental consciousness in both academia and industry has led to enormous efforts to develop more efficient and selective methods for chemical processes [11]. The use of

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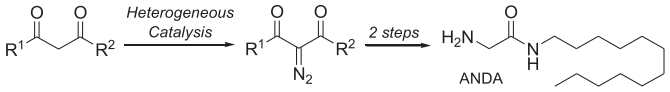
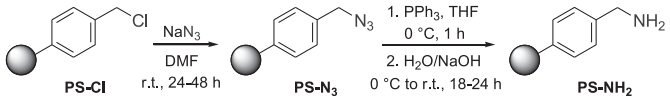


Scheme 1. Heterogeneous catalysis for the diazo transfer reaction and synthetic application.

heterogeneous catalysts as a sustainable resource has gained widespread acceptance as a powerful synthetic tool because these materials are readily recovered (usually by filtration) and thus can be reused instead of being disposed of as waste [12]. The use of basic heterogeneous catalysts for the diazo transfer reaction was first reported by Villemin and Alloum [13], who employed alumina-supported potassium fluoride, followed by Ferreira & cols [14] through the use of NaOH-treated natural clays, and more recently by our group [15], employing commercial molecular sieves and modified analogs. However, the reaction rates reported in these methods were slow (1–3 days) for most of the substrates studied. Therefore, the development of more efficient heterogeneous catalysts of basic character for the diazo transfer reaction is an important research theme.

In this regard, we became interested in developing catalysts based on divinylbenzene (DVB) cross-linked polystyrene [16], which is one of the most useful supports for catalysts in synthesis owing to its endurance and inertness [17]. Furthermore, the simple preparation, recyclability, environmental stability, low cost and insolubility of this polymer in both organic and aqueous solvents make it attractive as a versatile heterogeneous catalyst support. A simple and efficient polystyrene-supported basic catalyst for the diazo transfer reaction should achieve superior yields, low reaction times, broad substrate scope, high compatibility with functional groups embedded in both substrate and product, uncomplicated work-up and purification steps, and high recyclability. Herein, we report the synthesis of amino-functionalized heterogeneous catalysts anchored to a polystyrene polymer (Merrifield resin) and describe their behavior in the diazo transfer reaction to 1,3-dicarbonyl compounds. Furthermore, to demonstrate the synthetic application of this method, we describe for the first time the use of a readily accessed azido-substituted diazo ester for the straightforward preparation of ANDA (2-amino-*N*-dodecylacetamide), a long-chain amide [18] employed as a corrosion inhibitor [19] and molecular template for nanomaterials [20] (Scheme 1).



Scheme 2. Synthetic procedure for the preparation of catalysts **PS1-NH$_2$** and **PS2-NH$_2$**.

2. Results and discussion

2.1. Preparation and characterization of the heterogeneous catalysts *PS2-NH$_2$* and *PS1-NH$_2$*

The heterogeneous catalysts **PS1-NH$_2$** and **PS2-NH$_2$** were readily prepared in two-step procedures from commercially available Merrifield resins through a straightforward route as outlined in Scheme 2. Chloromethyl polystyrene resins **PS1-Cl** (2–3 mmol/g, 1% DVB cross-linked, 100–200 mesh) and **PS2-Cl** (1.26 mmol/g, 2% DVB cross-linked, 200–400 mesh) were treated with NaN_3 in DMF to give the azido intermediates **PS1-N$_3$** and **PS2-N$_3$** through the displacement of chlorine via an S_N2-type mechanism [21]. Subsequently, the azido-functionalized resins **PS1-N$_3$** and **PS2-N$_3$** were smoothly reduced with PPh_3 in an aqueous alkaline medium to generate the amino-modified catalysts **PS1-NH$_2$** and **PS2-NH$_2$** quantitatively, after separating out the triphenylphosphine oxide ($Ph_3P{=}O$), formed as a byproduct, with successive washing of the resins with a set of solvents of distinct swelling properties (see the Experimental Section).

The azido-functionalized intermediates **PS-N$_3$** and the amino-modified resins **PS-NH$_2$** were characterized by means of Fourier transform infrared (FT-IR) spectroscopy. In the case of **PS2-N$_3$**, the incorporation of the azido group in the first step of the route was confirmed by the presence of a characteristic strong band at 2089 cm^{-1} (Fig. 1). The absence of this band in the IR spectrum of **PS2-NH$_2$**, together with the appearance of a broad band at around 3400 cm^{-1}, which is typical of the N–H bond in amino groups, support the successful installation of the amine function in the resin through the mild reduction of the corresponding azido-loaded resin **PS2-N$_3$** with PPh_3/H_2O (Fig. 1; IR data for **PS1-N$_3$** and **PS1-NH$_2$** are given in the Supporting Information).

The determination of the percentages (by weight; wt%) of carbon, hydrogen and nitrogen in the polymeric amino catalysts **PS1-NH$_2$** and **PS2-NH$_2$** and their azido precursors **PS1-N$_3$** and **PS2-N$_3$** also confirmed the incorporation of the expected nitrogenated functionalities (Table 1). As expected, the amount of attached azido groups in the **PS1-N$_3$** resin (nitrogen weight = 12.4%, entry 1) was superior to that found for **PS2-N$_3$** (nitrogen weight = 5.2%, entry 3) due to the higher loading of active chlorine in the starting

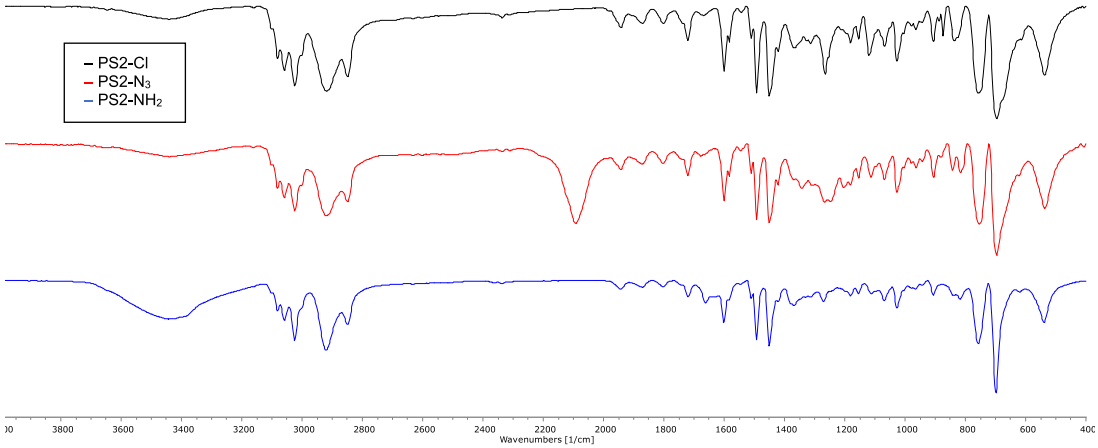


Fig. 1. FT-IR spectra for the 2% cross-linked Merrifield resin (**PS2-Cl**, black), azido-functionalized intermediate **PS2-N$_3$** (red), and amino-modified catalyst **PS2-NH$_2$** (blue).

Table 1
Elemental analysis results for the functionalized resins **PS-N_3** and **PS-NH_2**.

#	PS-resin	Loading[a]	C (wt%)	H (wt%)	N (wt%)
1	PS1-N_3	2–3	81.1	7.1	12.4
2	PS1-NH_2	2–3	85.3	6.6	4.2
3	PS2-N_3	1.26	87.0	7.3	5.2
4	PS2-NH_2	1.26	89.4	7.8	1.9

[a] Loading (mmol/g) based on the starting Merrifield resins **PS1-Cl** and **PS2-Cl**.

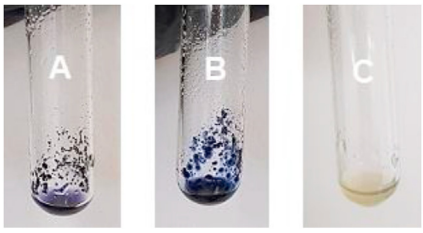


Fig. 2. Ninhydrin colorimetric tests: positive for **PS1-NH_2** (A) and **PS2-NH_2** (B), and negative for **PS1-Cl** (C).

Merrifield resin employed in the former case (2–3 mmol/g) compared to the latter (1.26 mmol/g). After the reduction to the amino-substituted resins **PS1-NH_2** and **PS2-NH_2**, the nitrogen percentage (respectively, 4.2% and 1.9%, entries 2 and 4) decreased to around one-third of the corresponding azido-functionalized resins **PS1-N_3** and **PS2-N_3** (respectively, 12.4% and 5.2%, entries 1 and 3), which is entirely in accordance with the expected nitrogen ratio of 3:1 for azide (R-N_3) to amine (R-NH_2).

Finally, submitting each resin **PS1-NH_2** and **PS2-NH_2** to the classic colorimetric assay with ninhydrin and phenol (Kaiser test) [22] gave blue-violet beads in a blue solution, which is a positive test for the presence of amino groups in the polymeric framework (Fig. 2).

2.2. Catalytic activity of *PS1-NH_2* and *PS2-NH_2* in the diazo transfer reaction

Initially, the designed amino-functionalized heterogeneous resins **PS1-NH_2** and **PS2-NH_2** were applied in the diazo transfer to 1,3-diketones **1a-e** (Table 2, entries 1–5). In the case of acetylacetone (**1a**, entry 1), benzoylacetone (**1b**, entry 2), and dibenzoylmethane (**1c**, entry 3), the formation of the corresponding diazo compounds **2a-c** was achieved with either **PS1-NH_2** or **PS2-NH_2** as the catalyst, although with distinct catalytic profiles. Thus, better yields for the expected diazo diketones **2a-c** were observed for **PS2-NH_2**, while shorter reaction times were attained with **PS1-NH_2**. Also, the **PS1-NH_2**-catalyzed diazo transfer to diketones **1b** and **1c** led to the formation of significant amounts of the acyl cleavage product **3**, which was detected in the ^{1}H NMR analysis of the crude product (characterized by a singlet at 5.91 ppm, assigned to the HC=N_2 framework) [23] and could be isolated by column chromatography (Scheme 3). In these particular cases, it is possible that the domino process involving amino-catalyzed diazo transfer to 1,3-dicarbonyls followed by aminolysis of the pre-formed diazo compound, as previously reported by our group [8], is also operating here. On the other hand, the cyclic 1,3-diketones **1d** and **1e** furnished the expected diazo compounds **2d** and **2e** (entries 4 and 5) in nearly quantitative yields without detectable traces of a byproduct originating from aminolysis. Once again, reactions with **PS1-NH_2** as the catalyst led to shorter reaction times. It is also important to note that dimedone (**1d**) was very reactive regardless of the type of catalyst employed, allowing the use of a reduced amount of **PS2-NH_2** without compromising the excellent yield (compare entries 4 and 4').

Both catalysts also performed well in the diazo transfer to Meldrum's acid (**1f**), a cyclic diester analog of cyclic ketones **1d,e**, furnishing the expected diazo **2f** in 76-67% yield after 2 h (Table 2, entry 6) [24]. However, the acyclic diester **1g** was found to be much less reactive than the 1,3-diketones and cyclic substrates, irrespective of the catalyst under study, giving the diazomalonate **2g** in modest yield (up to 60%) due to incomplete conversion rates even after prolonged reaction times (entry 7).

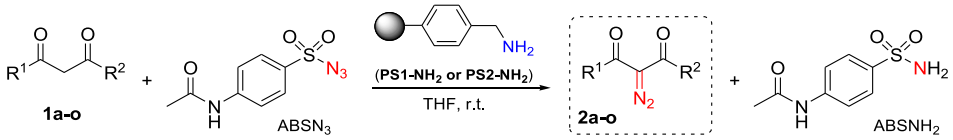
The scope of the **PS-NH_2**-catalyzed diazo transfer reaction was extended to a variety of β-ketoesters (Table 2, entries 8–15). In the presence of **PS2-NH_2**, simple acetoacetates **1h,i** gave moderate-to-good yields (65-58%) of the corresponding α-diazo-β-ketoesters **2h,i**, but at the expense of prolonged reaction times (8 h). On the other hand, the catalyst **PS1-NH_2** was more effective than **PS2-NH_2** in these transformations, giving the expected α-diazo-β-ketoesters **2h,i** in higher yields (62–80%) and shorter times (3–4 h, entries 8 and 9). For the homologous propionylacetate **1j**, comparable results were observed with both catalysts **PS1-NH_2** and **PS2-NH_2** regarding the chemical yield, while **PS1-NH_2** once more led to a faster transformation (entry 10). The diazo transfer to the arylated substrate **1l** was also successfully achieved with both catalysts under study and, as expected, **PS1-NH_2** gave better results than **PS2-NH_2** with respect to yield and reaction rate (entry 12). Remarkably, the presence of sensitive functional groups, such as chlorine, nitro, and C-C unsaturation (double or triple bonds), did not have a negative effect on the reaction outcome (entries 11, 13–15), with good-to-high yields being observed in these cases. It should also be noted that the formation of 2-diazoacetophenone (**3**) or any other byproduct that can arise from acyl cleavage, such as those observed for the diazo transfer to 1,3-diketones, was not detected during the studies with β-ketoesters **1h-o**.

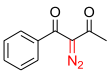
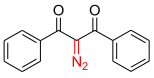
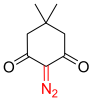
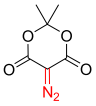
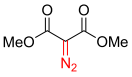
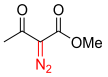
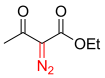
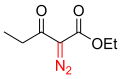
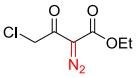
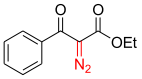
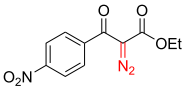
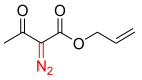
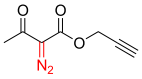
To evaluate the synthetic utility and scalability of this procedure, a gram-scale preparation of diazodimedone (**2d**) employing catalyst **PS2-NH_2** was performed. Starting from 1.19 g (8.5 mmol) of dimedone (**1d**), the target diazo **2d** was obtained after 2 h in 90% yield, indicating the potential application of the **PS-NH_2**-catalyzed diazo transfer reaction in the synthetic industry.

In addition to being an efficient and inexpensive method to access a structurally diverse set of representative diazo 1,3-dicarbonyls in good-to-high yields and chemoselectively, another advantage of the diazo transfer reaction developed in this study lies in the simplicity with which the work-up is performed. This consists of filtering off the heterogeneous catalyst, evaporating the volatiles, and triturating the crude product with hexane to separate out the solid sulfonylamide (ABSNH_2) that is formed as a byproduct (see the Experimental section). In most cases, the diazo product **2** is obtained in high quality and no further purification is required. Consequently, the generation of large amounts of residues through tedious and laborious separation stages is avoided. Moreover, the heterogeneous catalysts **PS-NH_2** were shown to be reusable after filtration (see discussion below), which is an important feature in the search for sustainable catalysis and environmentally benign processes.

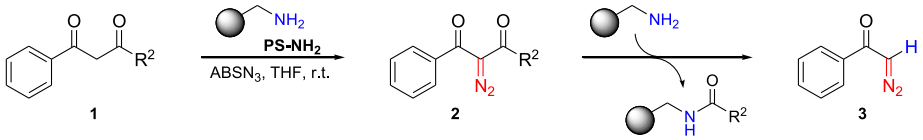
In order to amplify the scope of the **PS2-NH_2**-catalyzed diazo transfer reaction with respect to substitution patterns, a set of different substrates, shown in Scheme 4, was also included in this study. However, by applying the conditions outlined in Table 2 for the trifluoromethyl-substituted diketone **1p** and the tricarbonylated derivative **1q**, no desired diazo compound could be isolated. Instead, in both cases, a mixture of compounds was detected in the ^{1}H NMR monitoring of the crude reaction, including, among others, the unreactive starting materials **1** and 2-diazoacetophenone (**3**). This observation indicates that the elusive diazo products **2p** and

Table 2
Diazo transfer reaction using heterogeneous catalysis.

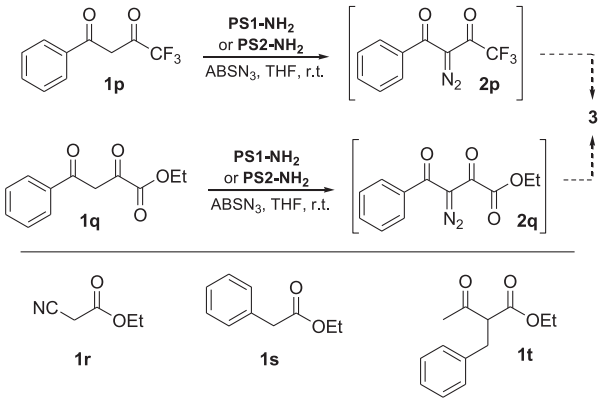


#	2	Product[a]	Mass PS-NH_2 (mg)	PS1-NH_2		PS2-NH_2	
				Yield (%)[b]	Time (h)	Yield (%)[b]	Time (h)
1	**a**		200	61	1.5	90	3
2	**b**		200	73	4	84	8
3	**c**		300	-[c]	8	65	16
4	**d**		200	96	1	94	2
4′	**d**		100	–	–	96	2
5	**e**		200	86	3	68	5
6	**f**		200	76	2	67	2
7	**g**		300	57	24	59	24
8	**h**		300	62	3	65	8
9	**i**		300	80	4	58	8
10	**j**		300	65	8	81	16
11	**k**		300	77	4	79	8
12	**l**		200	91	5	73	8
13	**m**		300	–	–	87	5
14	**n**		300	–	–	69	3
15	**o**		300	–	–	63	3

[a] Condition: compound **1** (1.0 mmol), $ABSN_3$ (1.2 mmol) and **PS-NH_2** in THF (6 mL/mmol) at room temperature.
[b] Isolated yield.
[c] Mixture of diazo diketone **2c**, 2-diazoacetophenone (**3**) and starting diketone **1c** (1.7:2.5:1 ratio).



Scheme 3. Acyl cleavage through the aminolysis of the pre-formed diazo dicarbonyls **2**.



Scheme 4. Substrates that failed to produce the corresponding diazo compounds **2**.

2q may have been initially formed, as expected, but underwent partial aminolysis by the nucleophilic catalyst to give **3** through acyl cleavage [25], as represented in Scheme 3. Cyanoacetic ester **1r** was also tested as a substrate for the **PS1-NH$_2$** or **PS2-NH$_2$**-catalyzed diazo transfer reaction, but this resulted in the recovery of a low quantity of mass, consisting of a complex mixture of components. This lack of reactivity in the diazo transfer reaction was also observed for phenylacetate **1s** and α-substituted ketoester **1t**, which were recovered intact after prolonged periods (Scheme 4).

2.3. Substrate reactivity and catalyst activity

With these results in hand, some trends can be described regarding the relative reactivity of the substrates and the activity of the catalysts under study. The difference in the activity of the catalyst can be explained by the difference in the amino loading of the two resins, which is dependent on the loading of the two starting Merrifield resins. In general terms, a higher loading in the commercial chloromethyl polystyrene resin **PS-Cl** means a greater number of chlorine atoms that can be substituted by the azido group, which in turn is directly related to the number of amino groups present in the catalyst **PS-NH$_2$** after reduction of the azido intermediate **PS-N$_3$**. Accordingly, **PS1-NH$_2$** (synthesized from the **PS1-Cl** resin with 2−3 mmol/g loading) contains more amino groups per mass of resin compared to **PS2-NH$_2$** (prepared from **PS2-Cl** resin with 1.26 mmol/g loading), which is supported by the CHN elemental analysis (see Table 1). Therefore, the higher number of amino groups in **PS1-NH$_2$** compared to **PS2-NH$_2$** would lead to a high availability of basic sites in the catalyst, which is responsible for catalyzing the diazo transfer reaction through the extrusion of the acidic methylene hydrogens preceding the incorporation of the diazo function [5]. However, the higher availability of basic amino groups that makes catalyst **PS1-NH$_2$** more active than **PS2-NH$_2$** also leads to the undesirable behavior observed for more reactive substrates, such as 1,3-diketones, that is, the ability of the catalyst to act as a nucleophile, promoting the aminolysis of the pre-formed diazo diketones (as illustrated in Scheme 3). In contrast to the importance of the amino loading to the catalytic activity of **PS-NH$_2$**, the difference in the degree of cross-linking (1% for **PS1-NH$_2$** and 2% for **PS2-NH$_2$**) did not have a significant influence on the activity of the catalysts or their physicochemical properties.

The relative reactivity of the substrates seen in Table 2 can also be qualitatively correlated. The cyclic substrates **1d-f** (Table 2, entries 4−6) were the most reactive, followed by 1,3-diketones **1a-c** (entries 1−3), β-ketoesters **1h-o** (entries 8−15) and, lastly, malonate **1g** (entry 7) as the least reactive. This relative reactivity is in good agreement with the experimental pKa values found for active methylene compounds [26] (see Table S1 in the Supporting Information), which follows the decreasing order of acidity: cyclic 1,3-dicarbonyls > 1,3-diketones > β-ketoesters > 1,3-diesters. However, care must be taken to simplify the reactivity of a given substrate based solely on its relative Brønsted acidity, mainly because the diazo transfer reaction is a complex process that comprises many more steps than just the initial deprotonation of the active methylene compound. In addition, the heterogeneous **PS-NH$_2$**-catalyzed diazo transfer reactions were carried out in THF as the solvent, while the available experimental pKa values were obtained in water and/or DMSO [26]. Nevertheless, the lack of reactivity of ethyl phenylacetate (**1s**: pKa = 22.7) [26k] and the α-substituted β-ketoester **1t** (pKa c.a. 11.5−13) [26l,m] could be expected due to their comparatively poor acidity values.

2.4. Reutilization of *PS-NH$_2$* in the diazo transfer reaction

One of the most important properties of a heterogeneous catalyst is its ability to be readily recovered from the reaction mixture, with the possibility of reuse in subsequent reactions, thus minimizing the generation of waste. In the particular case of the amino-functionalized catalysts **PS1-NH$_2$** and **PS2-NH$_2$**, they can be recovered quantitatively through vacuum filtration with a Büchner funnel followed by successive washing with methanol and then dichloromethane, followed by drying under vacuum.

To reactivate the catalyst, the resin was suspended in DMF (a solvent with good swelling ability) and the suspension was treated with trifluoroacetic acid (TFA) for 30 min. The catalyst was then separated by vacuum filtration and neutralized with a solution of triethylamine (TEA) in DMF followed by washing using solvents with different swelling properties (see the Experimental section). After drying the catalyst under vacuum, it was ready for use in the next cycle.

In the case of the diazo transfer to dimedone (**1d**) with a pre-established time of 2 h, the catalyst **PS2-NH$_2$** maintained its activity for up to five cycles (>98% conversion), resulting in the expected diazodimedone (**2d**) in excellent yields (94-90%, Fig. 3). However, the yield dropped to 64% in the sixth cycle as the result of incomplete conversion (92%). On the other hand, the activity of the recovered catalyst **PS2-NH$_2$** with no further acid/base treatment for reactivation was found to be of limited application, due to a significant reduction in the conversion to the diazo **2d** after the second and subsequent cycles (results not shown).

A similar trend was observed for the **PS1-NH$_2$**-catalyzed diazo transfer to benzoyl acetate **1l** with the pre-established time of 5 h and acid/base reactivation between each cycle (Fig. 3). The catalyst could be used at least three times without appreciable loss of

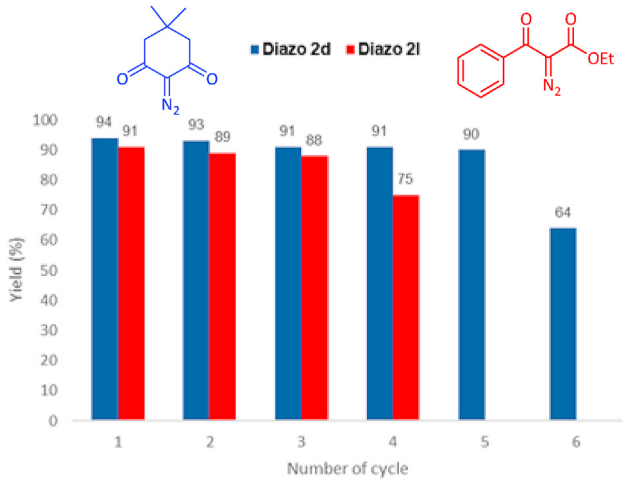


Fig. 3. Catalyst reuse. For **2d**: **PS2-NH$_2$** (200 mg/mmol **1d**), ABSN$_3$ (1.2 equiv), THF, r.t., 2 h. For **2l**: **PS1-NH$_2$** (200 mg/mmol **1l**), ABSN$_3$ (1.2 equiv), THF, r.t., 5 h.

catalytic activity (yields of 91-88% for the diazo **2l**), but in the fourth cycle a full conversion to **2l** was no longer achieved and extended reaction times were required to reproduce the yields observed for the first three cycles. Nevertheless, the yield of 75% for the diazo **2l** obtained in the fourth cycle is also synthetically expressive.

2.5. One-pot preparation of γ-azido-α-diazo-β-keto ester **2u** and synthesis of ANDA

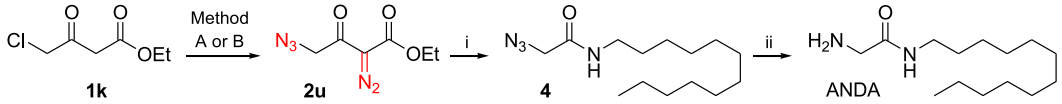
While the synthetic value of simple diazo compounds has been widely explored [2–4], the versatility of γ-functionalized-α-diazo-β-keto esters, such as **2u**, is of particular interest due to its importance as a building block for the preparation of a variety of multifunctionalized compounds [8,27]. Previous synthesis of γ-azido-α-diazo-β-keto ester **2u** required multistep routes involving the isolation and purification of intermediates, leading to low overall yields and large amounts of chemical waste. Recently, we presented a simple one-pot method to access **2u** from ethyl 4-chloroacetoacetate (**1k**) and commercially available reagents, consisting of the *in situ* generation of the diazo transfer reagent ABSN$_3$ from ABSCl followed by the transfer of the diazo portion and the displacement of chlorine by the azide anion [8]. Although this method involves the use of readily available and inexpensive *tert*-butylamine or diisopropylamine as the basic catalyst, they were used in equivalent amounts related to the substrates and, most importantly, it was not recovered at the end of the process, being disposed of as waste during the work-up and purification stages.

Therefore, we decided to adapt this one-pot strategy to heterogeneous catalysis using the **PS-NH$_2$**-catalyzed diazo transfer reaction developed herein. In this endeavor, two complementary methods were studied, one employing the previously prepared diazo transfer reagent ABSN$_3$ (method A) and the other involving the *in situ* generation of ABSN$_3$ from a combination of ABSCl and NaN$_3$ (method B, Scheme 5). The use of DMSO as the solvent (or cosolvent with THF) was found to be useful not only for solubilizing the polar reagents (in particular, NaN$_3$) but also for the good swelling ability related to the polystyrene-based catalysts **PS-NH$_2$**. As expected, the azido diazo ester **2u** was successfully obtained with both methods, but method B was more synthetically attractive due to the higher yield (61%) compared to method A (42–45%). In addition, the *in situ* generation of ABSN$_3$ in method B (instead of preparing it in a previous step as in method A) is not only a more convenient procedure but it is also safer and more environmentally benign, resulting in less solvent operations related to the work-up and isolation protocols.

Having established suitable conditions for the **PS-NH$_2$**-catalyzed one-pot preparation of γ-azido-α-diazo-β-keto ester **2u**, we sought to exploit its synthetic potential for the preparation of 2-amino-*N*-dodecylacetamide (ANDA). We found that the mild aminolysis [8] of **2u** in the presence of *n*-dodecylamine gave the azido amide **4** quantitatively, provided that a small excess of amine is added to speed up the conversion (Scheme 5). Equimolar amounts of **2u** and *n*-dodecylamine led to an incomplete conversion to the amide **4** even after prolonged reaction times (48 h). The subsequent reduction of the azido group in **4** could, in principle, be carried out with triphenylphosphine in aqueous medium, using the same strategy employed in the preparation of the **PS-NH$_2$** catalysts (see Scheme 2). However, the separation of the byproduct triphenylphosphine oxide from ANDA could not be achieved through column chromatography or solvent crystallization. To bypass the need for elaborate purification steps, we turned our attention to the widely employed palladium-catalyzed hydrogenation of azides to amines [28]. Gratifyingly, the use of Pd/Al$_2$O$_3$ as the heterogeneous catalyst under an atmosphere of hydrogen for 8 h cleanly furnished the expected ANDA, which was readily isolated after filtering off the catalyst and evaporating the solvent.

3. Conclusion

In summary, two heterogeneous catalysts **PS1-NH$_2$** and **PS2-NH$_2$** of basic character were readily prepared and successfully applied in the diazo transfer reaction to a wide variety of active methylene compounds. Besides being safe and furnishing the diazo compounds in good to excellent yields and in relatively short reaction times, the method offers operational simplicity, reduced production of waste and facile recovery of the catalysts. The reuse of the **PS-NH$_2$** catalysts after activation with TFA/TEA was also accomplished without significant loss of catalytic activity even after 5 cycles, which is an important feature in sustainable and environmentally benign processes. The one-pot synthesis of the highly valued azido-substituted diazo ester **2u** was also achieved by a straightforward procedure using the amino-modified catalysts **PS-NH$_2$**. Finally, the synthetic application of the versatile building block **2u** in the two-step preparation of ANDA was demonstrated for the first time. Further studies dealing with the catalytic properties of **PS1-NH$_2$** and **PS2-NH$_2$** as well as the synthetic potential of



Conditions:
Method A. **PS1-NH$_2$** or **PS2-NH$_2$** (200 mg/mmol **1k**), ABSN$_3$ (1.2 eq), NaN$_3$ (2.0 eq), DMSO, r.t., 5 h (42-45%).
Method B. **PS1-NH$_2$** or **PS2-NH$_2$** (200 mg/mmol **1k**), ABSCl (1.2 eq), NaN$_3$ (3.0 eq), β-CD (0.1 eq), THF:DMSO (2:1), r.t., 24 h (61%).
i. *n*-C$_{12}$H$_{25}$NH$_2$ (1.5 eq), THF, r.t., 20 h; ii. H$_2$, Pd/Al$_2$O$_3$, THF, r.t., 8 h (65%; two steps from **2u**).

Scheme 5. One-pot preparation of γ-azido-α-diazo-β-keto ester **2u** and short synthesis of ANDA.

functionalized diazo compounds are underway.

4. Experimental section

4.1. General information

Reagents employed in the experiments were commercially available and were used as received without further purification. The two Merrifield resins under investigation (**PS1-Cl**: 2–3 mmol/g, 1% cross-linked with DVB, 100–200 mesh; **PS2-Cl**: 1.26 mmol/g, 2% cross-linked with DVB, 200–400 mesh) were purchased from Sigma-Aldrich. All filtrations were proceeded in a vacuum system using Büchner funnel and low porosity filter paper. TLC analysis was performed in silica gel plates. Column chromatography was performed using silica gel (60 Å, 70–230 mesh) and hexane/ethyl acetate as the eluent. Melting points were determined using a hot plate apparatus and are uncorrected. Infrared spectra were acquired with a FT-IR spectrometer (range 4000-400 cm^{-1}) using KBr. ^{1}H NMR spectra were recorded at 400 MHz or at 200 MHz and $^{13}C\{^{1}H\}$ NMR spectra (fully decoupled) were recorded at 100 MHz or at 50 MHz. Coupling constants (*J*) are measured in Hertz (Hz). Chemical shifts were recorded in parts per million (ppm, δ) relative to TMS ($\delta = 0.0$ ppm) or solvent peak ($CDCl_3$ at 7.26 ppm for ^{1}H NMR and $CDCl_3$ at 77.16 ppm for ^{13}C NMR) as the internal standard. Multiplicities were given as s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplet), dq (doublet of quartet), ddt (doublet of doublet of triplet), bs (broad singlet), and m (multiplet). Elemental analyses of the commercial resins (**PS1-Cl** and **PS2-Cl**), polymeric intermediates (**PS1-N_3** and **PS2-N_3**), and catalysts (**PS1-NH_2** and **PS2-NH_2**) were conducted in a CHN microanalyzer. The ESI-QTOF mass spectrometer was operated in the positive ion mode at 4.5 kV and at a desolvation temperature of 180 °C. The standard electrospray ion (ESI) source was used to generate the ions. The instrument was calibrated in the range *m*/*z* 50–3000 using a calibration standard (low concentration tuning mix solution) and data were processed with the aid of computer software.

Caution: Organic azides are potentially explosive. Although we have never experienced any troubles, it must be handled with care.

4.2. Preparation of amino-modified polystyrene resins *PS-N_3* and *PS-NH_2*

4.2.1. Typical procedure for the azido-substituted polystyrene resin *PS1-N_3*

In a round bottomed flask equipped with a magnetic stirring bar were placed the 1% cross-linked Merrifield resin (**PS1-Cl**, 1.00 g, 2–3 mmol) and 10 mL of DMF. To the stirred suspension was added sodium azide (0.780 g, 12 mmol) and the reaction was magnetically stirred for 48 h at room temperature. The **PS1-N_3** resin was then separated by vacuum filtration, washed successively with DMF (10 mL), H_2O (15 mL), ethanol (15 mL), acetone (10 mL) and dichloromethane (10 mL), and dried under vacuum to give the product with a recovered mass of 94%. IR (KBr, cm^{-1}): $\nu_{max} = 3025$, 2921, 2850, 2091, 1601, 1491, 1450, 1244, 1024, 755, 689; CHN Analysis (wt%): C, 81.1; H, 7.1; N, 12.4.

4.2.2. Typical procedure for the azido-substituted polystyrene resin *PS2-N_3*

In a round bottomed flask equipped with a magnetic stirring bar were placed the 2% cross-linked Merrifield resin (**PS2-Cl**, 1.00 g, 1.26 mmol) and 10 mL of DMF. To the stirred suspension was added sodium azide (0.164 g, 2.52 mmol) and the reaction was magnetically stirred for 24 h at room temperature. The **PS2-N_3** resin was then separated by vacuum filtration, washed successively with DMF (10 mL), H_2O (15 mL), ethanol (15 mL), acetone (10 mL) and dichloromethane (10 mL) and dried under vacuum to give the product with a recovered mass of 98%. IR (KBr, cm^{-1}): $\nu_{max} = 3025$, 2915, 2850, 2089, 1599, 1491, 1446, 1265, 1024, 751, 691; CHN Analysis (wt%): C, 87.0; H, 7.3; N, 5.2.

4.2.3. Typical procedure for the amino-substituted polystyrene resin *PS1-NH_2*

The azido-substituted polystyrene resin **PS1-N_3** (1.0 g) prepared as above was suspended in 8 mL of THF and the resulting suspension was cooled in ice bath. Then, PPh_3 (2.75 g, 10.5 mmol) was added and the reaction mixture was magnetically stirred at 0–5 °C. After 1 h, H_2O (4 mL) and NaOH 1 M (0.9 mL) were added, the ice bath was removed, and the reaction was stirred for 24 h at room temperature. The **PS1-NH_2** resin was then separated by vacuum filtration, washed successively with THF (10 mL), H_2O (15 mL), ethanol (15 mL), acetone (10 mL) and dichloromethane (10 mL) and dried under vacuum to give the product with a recovered mass of 99%. IR (KBr, cm^{-1}): $\nu_{max} = 3382$, 3025, 2921, 2850, 1662, 1601, 1493, 1452, 759, 700; CHN Analysis (wt%): C, 85.2; H, 6.6; N, 4.2.

4.2.4. Typical procedure for the amino-substituted polystyrene resin *PS2-NH_2*

The azido-substituted polystyrene resin **PS2-N_3** (1.0 g) prepared as above was suspended in 8 mL of THF and the resulting suspension was cooled in ice bath. Then, PPh_3 (0.50 g, 1.9 mmol) was added and the reaction mixture was magnetically stirred at 0–5 °C. After 1 h, H_2O (4 mL) and NaOH 1 M (0.9 mL) were added, the ice bath was removed, and the reaction was stirred for 18 h at room temperature. The **PS2-NH_2** resin was then separated by vacuum filtration, washed successively with THF (10 mL), H_2O (15 mL), ethanol (15 mL), acetone (10 mL) and dichloromethane (10 mL) and dried under vacuum to give the product with a recovered mass of 99%. IR (KBr, cm^{-1}): $\nu_{max} = 3443$, 3025, 2921, 2850, 1601, 1493, 1450, 757, 698; CHN Analysis (wt%): C, 89.4; H, 7.8; N, 1.9.

4.3. General procedure for the synthesis of diazo carbonyl compounds ***2***

To a suspension of the amino-supported catalyst **PS1-NH_2** or **PS2-NH_2** (200 or 300 mg, see Table 2) in THF (3.0 mL) was added a solution of the 1,3-dicarbonyl compound **1** (1.00 mmol) in THF (3.0 mL). Next, $ABSN_3$ (0.288 g, 1.2 mmol) was added and the mixture was magnetically stirred at room temperature until the consumption of the starting material (monitored by TLC). Then, the solvent was removed under reduced pressure and the resulting residue was triturated with *n*-hexane to separate out the diazo product from the insoluble $ABSNH_2$ and the catalyst. The solid residue was separated by vacuum filtration and washed several times with *n*-hexane. The filtrate was concentrated under reduce pressure to give the diazo carbonyl compounds with satisfactory purity for subsequent synthetic applications, but they can be readily obtained with high degree of purity in 58–96% yield through a short column chromatography.

4.3.1. 3-Diazopentane-2,4-dione (***2a***) [6e]

Colorless oil. **PS1-NH_2**: reaction time = 1.5 h, yield 61% (76.8 mg); **PS2-NH_2**: reaction time = 3 h, yield 90% (113 mg). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.42 (s, 6H). IR (KBr, cm^{-1}): $\nu_{max} = 2931$, 2130, 1669, 1367, 1310, 1240, 1165.

4.3.2. 2-Diazo-1-phenylbutane-1,3-dione (***2b***) [6g]

Pale yellow solid, m.p. 54.6–55.8 °C (lit.: [6g] 54.9–61.0 °C). **PS1-NH_2**: reaction time = 4 h, yield 73% (137 mg); **PS2-NH_2**: reaction time = 8 h, yield 84% (158 mg). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67–7.43 (m, 5H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9

(C═O), 185.2 (C═O), 137.5 (C), 132.8 (CH), 129.1 (2 × CH), 127.5 (2 × CH), 29.3 (CH_3). IR (KBr, cm^{-1}): ν_{max} = 3107, 2929, 2123, 1656, 1640, 1322, 1234, 716. HRMS (ESI^+) calcd. for $C_{10}H_8N_2O_2Na^+$ $[M + Na]^+$: 211.0478, found: 211.0480.

4.3.3. 2-Diazo-1,3-diphenylpropane-1,3-dione (**2c**) [6g]

Yellow solid, m.p. 106.3–107.1 °C (lit.: [6g] 107.8–108.2 °C). **PS1-NH_2**: reaction time = 8 h, mixture of **2c**, **3**, and **1c** (1.7:2.5:1 ratio); **PS2-NH_2**: reaction time = 16 h, yield 65% (162 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.5 Hz, 4H), 7.44 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.6 (2 × C═O), 137.1 (2 × C), 132.8 (2 × CH), 128.5 (4 × CH), 128.4 (4 × CH). IR (KBr, cm^{-1}): ν_{max} = 3054, 2113, 1636, 1593, 1261, 855, 716. HRMS (ESI^+) calcd. for $C_{15}H_{10}N_2O_2Na^+$ $[M + Na]^+$: 273.0634, found: 273.0630.

4.3.4. 2-Diazo-5,5-dimethylcyclohexane-1,3-dione (**2d**) [6c]

Yellow solid, m.p. 103.6–104.0 °C decomp. (lit. [6c]: 103–105 °C). **PS1-NH_2**: reaction time = 1 h, yield 96% (159 mg); **PS2-NH_2**: reaction time = 2 h, yield 94% (156 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 2.44 (s, 4H), 1.12 (s, 6H). IR (KBr, cm^{-1}): ν_{max} = 2962, 2189, 2136, 1673, 1636, 1307.

4.3.5. 2-Diazocyclohexane-1,3-dione (**2e**) [6e]

Pale yellow oil. **PS1-NH_2**: reaction time = 3 h, yield 86% (119 mg); **PS2-NH_2**: reaction time = 5 h, yield 68% (94 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 2.54 (t, J = 6.5 Hz, 4H), 2.08–1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5 (2 × C═O), 36.9 (2 × CH_2), 18.7 (CH_2). IR (KBr, cm^{-1}): ν_{max} = 2958, 2138, 1640, 1293.

4.3.6. 5-Diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (**2f**) [6b]

White solid, m.p.: 90.0–91.1 °C (lit. [6b]: 92–93 °C). **PS1-NH_2**: reaction time = 2 h, yield 76% (129 mg); **PS2-NH_2**: reaction time = 2 h, yield 67% (114 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 1.79 (s, 6H). IR (KBr, cm^{-1}): ν_{max} = 2990, 2183, 1726, 1336, 1167, 908, 757.

4.3.7. Dimethyl 2-diazomaloante (**2g**) [6g]

Colorless oil. **PS1-NH_2**: reaction time = 24 h, yield 57% (90.1 mg); **PS2-NH_2**: reaction time = 24 h, yield 59% (93.3 mg). ^1H NMR (200 MHz, $CDCl_3$): 3.83 (s, 6H). IR (KBr, cm^{-1}): ν_{max} = 2958, 2138, 1762, 1742, 1697, 1438, 1334, 1097, 761.

4.3.8. Methyl 2-diazo-3-oxobutanoate (**2h**) [9a]

Colorless oil. **PS1-NH_2**: reaction time = 3 h, yield 62% (88.1 mg); **PS2-NH_2**: reaction time = 8 h, yield 65% (92.4 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 2.45 (s, 3H). IR (KBr, cm^{-1}): ν_{max} = 2958, 2142, 1724, 1660, 1316, 1081.

4.3.9. Ethyl 2-diazo-3-oxobutanoate (**2i**) [6f]

Colorless oil. **PS1-NH_2**: reaction time = 4 h, yield 80% (125 mg); **PS2-NH_2**: reaction time = 8 h, yield 58% (90.5 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 4.24 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). IR (KBr, cm^{-1}): ν_{max} = 2984, 2140, 1720, 1660, 1318, 1075.

4.3.10. Ethyl 2-diazo-3-oxopentanoate (**2j**) [29]

Yellow oil. **PS1-NH_2**: reaction time = 8 h, yield 65% (110 mg); **PS2-NH_2**: reaction time = 16 h, yield 81% (138 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 4.28 (q, J = 7.0 Hz, 2H), 2.84 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 193.7 (C═O), 161.6 (C═O), 61.5 (CH_2), 33.8 (CH_2), 14.4 (CH_3), 8.4 (CH_3). IR (KBr, cm^{-1}): ν_{max} = 2982, 2134, 1720, 1660, 1301, 1026. HRMS (ESI^+) calcd. for $C_7H_{10}N_2O_3Na^+$ $[M + Na]^+$: 193.0584, found: 193.0584.

4.3.11. Ethyl 4-chloro-2-diazo-3-oxobutanoate (**2k**) [27a]

Yellow oil. **PS1-NH_2**: reaction time = 4 h, yield 77% (147 mg); **PS2-NH_2**: reaction time = 8 h, yield 79% (150 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 4.60 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). IR (KBr, cm^{-1}): ν_{max} = 2984, 2142, 1715, 1671, 1336, 1293, 1216, 1028.

4.3.12. Ethyl 2-diazo-3-oxo-3-phenylpropanoate (**2l**) [6f]

Pale yellow oil. **PS1-NH_2**: reaction time = 5 h, yield 91% (198 mg); **PS2-NH_2**: reaction time = 8 h, yield 73% (159 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.64–7.60 (m, 2H), 7.54–7.48 (m, 1H), 7.44–7.38 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.0 (C═O), 161.1 (C═O), 137.2 (C), 132.3 (CH), 128.4 (2 × CH), 127.9 (2 × CH), 61.7 (CH_2), 14.3 (CH_3). IR (KBr, cm^{-1}): ν_{max} = 3062, 2984, 2144, 1724, 1693, 1630, 1301, 1116, 938, 747. HRMS (ESI^+) calcd. for $C_{11}H_{10}N_2O_3Na^+$ $[M + Na]^+$: 241.0584, found: 241.0579.

4.3.13. Ethyl 2-diazo-3-(4-nitrophenyl)-3-oxopropanoate (**2m**) [15]

Pale yellow solid, m.p. 39.7–40.8 °C (lit. [6e,15]: colorless oil). **PS2-NH_2**: reaction time = 5 h, yield 87% (229 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 8.26 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 185.7 (C═O), 160.4 (C═O), 149.7 (C), 142.7 (C), 129.4 (2 × CH), 123.2 (2 × CH), 62.1 (CH_2), 14.3 (CH_3). IR (KBr, cm^{-1}): ν_{max} = 3080, 2984, 2148, 1720, 1630, 1601, 1524, 1314, 1118, 853. HRMS (ESI^+) calcd. for $C_{11}H_9N_3O_5Na^+$ $[M + Na]^+$: 286.0434, found: 286.0429.

4.3.14. Allyl 2-diazo-3-oxobutanoate (**2n**) [30]

Pale yellow oil. **PS2-NH_2**: reaction time = 3 h, yield 69% (116 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 5.92 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.33 (dq, J = 17.2, 1.3 Hz, 1H), 5.27 (dq, J = 10.4, 1.3 Hz, 1H), 4.71 (dt, J = 5.8, 1.3 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1 (C═O), 161.2 (C═O), 131.6 (CH), 119.2 (CH_2), 65.9 (CH_2), 28.3 (CH_3). IR (KBr, cm^{-1}): ν_{max} = 2952, 2142, 1720, 1658, 1369, 1314, 1067.

4.3.15. Prop-2-yn-1-yl 2-diazo-3-oxobutanoate (**2o**) [31]

Pale yellow oil. **PS2-NH_2**: reaction time = 3 h, yield 63% (104 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 4.81 (d, J = 2.5 Hz, 2H), 2.53 (t, J = 2.5 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8 (C═O), 160.7 (C═O), 77.0 (C), 75.8 (CH), 52.7 (CH_2), 28.3 (CH_3). IR (KBr, cm^{-1}): ν_{max} = 3284, 2952, 2144, 1724, 1658, 1318, 1069. HRMS (ESI^+) calcd. for $C_7H_6N_2O_3Na^+$ $[M + Na]^+$: 189.0271, found: 189.0267.

4.4. Reutilization of the catalyst **PS-NH_2**

At the end of the diazo transfer reaction, the catalyst was separated by vacuum filtration and was quantitatively recovered after exhaustive washings with methanol and dichloromethane followed by drying under vacuum. Next, 300 mg of the catalyst was suspended in 6 mL of DMF (2 mL/100 mg of catalyst) and ~3 mL of TFA was slowly added to the suspension. The mixture was magnetically stirred at room temperature for 30 min. Then the catalyst was filtered by vacuum using a Büchner funnel and thoroughly washed with a solution of TEA (2.0 mL) in DMF (20 mL) followed by successive washings with H_2O, methanol, acetone and dichloromethane. The recovered catalyst was dried under vacuum for 3–4 h before its utilization in the next cycle.

4.5. One-pot synthesis of ethyl 4-azido-2-diazo-3-oxobutanoate (**2u**) through the in situ generation of $ABSN_3$

To a suspension of the amino-supported catalyst **PS1-NH_2** (90 mg) in THF (1.3 mL) under magnetic stirring at 25 °C was added a solution of ethyl 4-chloroacetoacetate (49.3 mg, 0.3 mmol) in DMSO (0.7 mL). Then, ABSCl (84 mg, 0.36 mmol), NaN_3 (58.5 mg, 0.9 mmol), and β-cyclodextrin (34.5 mg, 0.03 mmol) were added to the reaction, and the mixture was stirred at room temperature for 24 h. Upon completion of the reaction, the catalyst was separated by vacuum filtration and washed with H_2O (10 mL) and methanol (15 mL). The filtrate was concentrated under reduced pressure and the residue was diluted in ethyl acetate. The organic phase was washed with H_2O (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum, furnishing a light-brown solid. The resultant solid was triturated with *n*-hexane to separate out the insoluble $ABSNH_2$ by decantation. The resulting supernatants were filtered and concentrated under reduced pressure to furnish the azido diazo ester **2u** [27a]. Yield: 61% (35.9 mg). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.38 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 186.6 (C═O), 161.0 (C═O), 62.1 (CH_2), 56.1 (CH_2), 14.4 (CH_3); IR (KBr, cm^{-1}): ν_{max} = 2984, 2144, 2103, 1713, 1662, 1310, 1224, 1030.

4.6. Synthesis of ethyl 4-azido-2-diazo-3-oxobutanoate (**2u**) with $ABSN_3$

To a suspension of the amino-supported catalyst **PS2-NH_2** or **PS1-NH_2** (300 mg) in DMSO (3.0 mL) under magnetic stirring at 25 °C was added a solution of ethyl 4-chloroacetoacetate (0.164 g, 1.00 mmol) in DMSO (3.0 mL). Then, $ABSN_3$ (0.288 g, 1.2 mmol) was added followed by NaN_3 (0.130 g, 1.5 mmol) and the final mixture was stirred at room temperature for 5 h. After the reaction was completed, the catalyst was separated by vacuum filtration and washed with water (15 mL), methanol (20 mL) and *n*-hexane (20 mL). The filtrate was concentrated under reduced pressure and the residue was diluted in ethyl acetate. The organic phase was washed with H_2O (2 × 10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a light brown residue, which was triturated with *n*-hexane to separate out the insoluble $ABSNH_2$ by decantation. The resulting supernatants were filtered and concentrated under reduced pressure to give the azido diazo ester **2u** [[27a]] as a pale yellow oil in 42% (82.5 mg, using **PS2-NH_2**) or 45% (88.4 mg, using **PS1-NH_2**) yield after column chromatography.

4.7. Aminolysis of ethyl 4-azido-2-diazo-3-oxobutanoate (**2u**) with n-dodecylamine

To a stirred solution of the azido-diazo compound **2u** (0.182 g, 0.92 mmol) in THF (5.0 mL) was added n-dodecylamine (318 μL, 1.38 mmol) and the reaction mixture was stirred at room temperature for 20 h. The final solution was evaporated and the resulting residue was diluted in ethyl acetate and carefully washed with 1.0 M HCl (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the amide **4** as a pale brown oil with high purity. Yield: 92% (228 mg). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.37 (bs, 1H), 3.96 (s, 2H), 3.25 (q, J = 6.2 Hz, 2H), 1.53–1.46 (m, 2H), 1.26–1.23 (m, 18H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5 (C═O), 52.9 (CH_2), 39.6 ($NHCH_2$), 32.0 (CH_2), 29.7–29.5 (7 × CH_2), 27.0 (CH_2), 22.8 (CH_2), 14.2 (CH_3); IR (KBr, cm^{-1}): ν_{max} = 2925, 2854, 2103, 1660; MS (EI): *m/z* (%) = 291.22 $(M + Na)^+$, 186.19 $(C_{12}H_{25}NH_3)^+$.

4.8. Preparation of 2-amino-N-dodecylacetamide (ANDA) through the reduction of 2-azido-N-dodecylacetamide (**4**)

To a stirred solution of the azido amide **4** (71.2 mg, 0.26 mmol) in 1.5 mL of THF was added Pd/Al_2O_3, 10 wt.-% (56 mg, 0.053 mmol). Then, a balloon containing hydrogen gas was connected to the reaction mixture and the stirring was continued at room temperature until the consumption of the starting material (monitored by TLC: 8 h). The reaction mixture was filtered through Celite and washed with AcOEt (15 mL) and MeOH (8 mL). The resulting filtrate was washed with aqueous NaClO (2 × 8 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give 2-amino-*N*-dodecylacetamide (ANDA) as light-brown solid. Yield: 65% (41.8 mg). Its physical and spectral data were consistent with the expected structure and the related literature [19]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.40–3.21 (m, 4H), 1.55–1.45 (m, 2H), 1.35–1.15 (m, 18H), 0.86 (t, J = 6.4 Hz, 3H).

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.tet.2021.132081.

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