FULL PAPERS

DOI: 10.1002/adsc.201100705

Preparation and Use of Polystyryl-DABCOF₂: An Efficient Recoverable and Reusable Catalyst for β -Azidation of α , β -Unsaturated Ketones in Water

Tommaso Angelini,^a Daniela Lanari,^a Raimondo Maggi,^b Ferdinando Pizzo,^a Giovanni Sartori,^b and Luigi Vaccaro^{a,*}

^a Laboratory of Green Synthetic Organic Chemistry, CEMIN – Dipartimento di Chimica, Università di Perugia Via Elce di Sotto, 8; I-06123 Perugia, Italy

Fax: (+39)-075-5855-560; e-mail: luigi@unipg.it

^b "Clean Synthetic Methodologies Group", Dipartimento di Chimica Organica e Industriale dell'Università, and Consorzio Interuniversitario "La Chimica per l'Ambiente" (INCA), UdR PR2, Parco Area delle Scienze 17A, I-43124 Parma, Italy

Received: September 7, 2011; Revised: October 21, 2011; Published online: February 28, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100705.

Abstract: Novel solid fluorides were prepared to optimize the β -azidation of α , β -unsaturated ketones. The higher loading of these catalysts compared to that of commercially available fluorides has allowed the use of a smaller mass of catalyst helping the mixing of the reaction mixture. Porous polymeric supports have proved to be more efficient in the presence of water as reaction medium. Water has played a crucial role showing a beneficial effect on the reactivity by improving dispersion of the reaction mixture and also by avoiding organic fouling caused by the retention of the reaction mixture within the polymeric matrix. This has facilitated the recovery of the products from the catalyst. The protocol reported has allowed a significant reduction in the organic solvent required for the complete recovery of the pure product whilst leaving the catalyst clean and reusable. E-factors are in the range of 5.9-10.5 and therefore ca. 3 times smaller than previous procedures operating under solvent-free conditions. To further improve the efficiency of our approach we have developed a protocol operating in a continuous-flow manner that has allowed us to achieve an E-factor of 1.7-1.9, with a reduction of ca. 80% of the corresponding batch conditions. The continuous-flow protocol has allowed us to minimize the use of trimethylsilyl azide making the recovery and reuse of water and catalyst **5f** very efficient and simple. Finally, a novel reduction system using palladium on alumina (5 mol%) and equimolar amount of formic acid has been used in the presence of 1 equivalent of ditert-butyl pyrocarbonate to set a multistep protocol operating in continuous-flow conditions for the preparation of two representative N-Boc-β-amino ketones starting from the corresponding enones with E-factors of 3.2 and 2.7, respectively.

Keywords: azides; enones; green chemistry; polystyrene-supported catalysts; solvent-free conditions

Introduction

The conjugate addition of an N-nucleophile (e.g., N_3^-) to α,β -unsaturated ketones represents a well-established method for the preparation of β -amino carbonyl compounds^[1] which are versatile intermediates for the synthesis of a variety of target molecules including β -amino acids, pharmaceuticals, and natural products.^[2]

Among all the different nucleophiles, addition of azido ion and subsequent reduction is certainly a

useful approach for the selective introduction of a primary amino group. $^{\left[3\right] }$

Despite the large number of practical applications, efficient procedures for the preparation of β -azido carbonyl compounds are currently limited and generally they use a combination of sodium azide and a strong acid as hydrazoic acid source.^[4] Miller et al. reported an excellent protocol using a combination of trimethylsilyl azide (TMSN₃) and acetic acid as azido ion source and a tertiary amine as catalyst, developed in order to avoid the use of the highly toxic and explosive hydrazoic acid.^[5] Further similar examples



have been also reported^[6] and this approach has been exploited by Miller et al. for the realization of an asymmetric procedure.^[7]

We have been interested in the use of organic ammonium fluorides for activating Si–N and Si–O^[8] bonds and within this research we have reported an alternative protocol for the β -azidation of α , β -unsaturated ketones based on the use of recoverable Amberlite IRA900F as catalyst under solvent-free conditions (SoIFC).^[8c]

Our research program is committed to the optimization of synthetic procedures by employing ecofriendly reaction protocols, including the use of water,^[9] SolFC,^[10] and supported organocatalysts.^[11]

We have investigated the use of a polymer-supported organocatalyst under SolFC proving that this is a very attractive approach to realize efficient synthetic procedures with minimal waste production.^[8,11] In fact, while the adoption of SolFC is necessary to increase the efficiency of the polymer-supported recoverable catalyst, this approach imposes the use of strictly catalytic amounts of catalyst to avoid crucial issues relative to the mixing of equimolar amounts of reactants without employing a reaction medium. The resulting protocol is intrinsically characterized by a very high environmental efficiency.

We have also been interested in useful applications of continuous-flow chemistry.^[12] Accordingly, to further reduce the E-factor^[13] we have also reported the use of cyclic continuous-flow reactors operating in SolFC or highly concentrated conditions running on a multigram scale.^[8a,11a] Highlights of these protocols are the recovery of the product with a minimal amount of organic solvent, as well as recovery and reuse of the solid catalyst without decreasing the efficiency.

In our previous report on the β -azidation of α , β -unsaturated ketones catalyzed by Amberlite IRA900F, we have highlighted that the adoption of SolFC was necessary to achieve the maximum efficiency of the process. Although satisfactory E-factor values were achieved (*ca.* 22), we also noticed that in this process the reaction mixture showed an evident tendency to stick with the polymer resin. Therefore compared to other processes studied by our group, larger amounts of organic solvent were needed to isolate the products.^[8c]

We have decided to design a novel fluoride source supported on polystyrene featuring a higher loading compared to that of commercially available fluorides in order to use a smaller mass of catalyst and help mixing of the reaction mixture.

In addition to this and considering our experience in the use of water as reaction medium,^[9] we have decided to prepare solid fluoride catalysts suitable for being used in the presence of water. Our intention is to exploit water as medium to increase the reactivity of the system but also to improve dispersion of the reaction mixture. The use of a specific porous solid support in water should avoid the organic fouling^[14] caused by the sticking of the reaction mixture within the polymeric matrix, allowing a better catalytic efficiency and facilitating the recovery of the products from the catalyst.

Results and Discussion

In this paper, we report our results on the design and preparation of a novel ammonium fluoride supported on polystyrene, and its application for the development of a chemically and environmentally efficient procedure for the β -azidation of α , β -unsaturated ketones executable on a large scale and featuring a low E-factor.

We have focused our attention on 1,4-diazabicyclo-[2.2.2]octane (DABCO, 1), an interesting diamine moiety that, if supported on a polymer resin, may carry a high-loading of fluoride as counter ion to two ammonium functionalities (Table 1).

Starting from different types of polystyrene (PS)-Cl 2, the DABCO moiety was introduced to form the corresponding mono-ammonium chlorides 3 that were subsequently transformed into the bis-ammonium iodides 4 that, after treatment with potassium fluoride, gave the desired bis-fluoride PS-DABCOF₂ catalysts 5.

Besides the experimental details available as Supporting Information, it should be pointed that the conversion of the mono-ammonium salt **3** to the corresponding bis-ammonium iodide **4** with MeI in toluene, has been performed by using a continuous-flow procedure, because under normal stirring (although very gentle) the solid porous catalyst was immediately pulverized making very difficult its manipulation.

All the polymer-supported ammonium salts **3**, **4**, and **5** have been fully characterized. The fluoride loadings for the catalysts **5a–f** prepared are reported in Table 1.

These catalysts have been tested in the representative reaction of (*E*)-hept-3-en-2-one (**6a**) and TMSN_3 (1.5 equivalents) by using different reaction media at 60 °C. The results are reported in Table 2.

We were pleased to find that water has a beneficial influence on the process allowing us to achieve better results than those obtained in the presence of an organic medium (Table 2, entries 8 and 9).

All the catalysts 5a-f efficiently promoted the conversion of 6a to 7a using water as reaction medium (Table 1, entries 1–6). Better results were obtained in the case of catalysts 5d-f. (Table 1, entries 4–6) that were prepared by using a porous support, confirming

Table 1. Preparation of PS-DABCOF₂ catalysts 5.



Entry	Resin ^[a]	Catalyst (F mmol g ⁻¹) ^[b]
1	gel -type (1% DVB cl) 100–200 mesh	5a (2.42) ^[c]
2	gel -type (2% DVB cl) 200–400 mesh	5b $(4.69)^{[c]}$
3	gel -type (2% DVB cl) 200–400 mesh	5c $(6.29)^{[d]}$
4	porous (5.5 DVB cl) 16–50 mesh	5d $(4.28)^{[c]}$
5	porous (5.5 DVB cl) 16–50 mesh	5e $(6.20)^{[d]}$
6	porous (5.5 DVB cl) 16-50 mesh	5f (7.39) ^[d]

^[a] DVB cl=divinyl benzene cross-linked.

^[b] **5** was prepared by washing **4** with aqueous KF in continuous-flow until after treating the eluted solution with AgNO₃ no precipitation of AgCl was observed. **4** was prepared by using 5 equiv. of MeI in toluene for 1 day at room temperature in continuous-flow (see Supporting Information).

^[c] Conditions for the preparation of **3**: 2 equiv. of DABCO (**1**), 3 days, 80 °C.

. . .

^[d] Conditions for the preparation of **3**: 10 equiv. of DABCO (**1**), 5 days, reflux.

Table 2. β -Azidation of 6a using catalysts 5a-f.

0

6a -		Cat (20 mol%) ^[a]			
		TMSN ₃ (1.5 equiv.) 60 °C, 8 h	Ta		
Entry	Catalyst	Medium ^[b]	Conversion [%] ^[c]		
1	5a	H ₂ O	89		
2	5b	H_2O	90		
3	5c	H_2O	92		
4	5d	H_2O	>99 ^[d]		
5	5e	H_2O	>99 ^[d]		
6	5f	H_2O	>99 ^[d]		
7	5f	_	91 ^[e]		
8	5f	CH ₃ CN	67		
9	5f	CH_2Cl_2	74		
10	4f	H_2O	70		
11	5f	$H_2O^{[f]}$	60		

^[a] Referred to the amount of fluoride used.

^[b] 0.5 mL for 1 mmol of **6a**.

^[c] Conversion of **6a** to **7a** was measured by ¹H NMR analyses, the remaining material was the unreacted **6a**.

^[d] 91% of isolated yield of the pure product **7a** (see Experimental Section for further details).

^[e] Complete conversion to **7a** was achieved after 12 h.

^[f] By using NaN₃ and keeping the pH value between 3.0 and 4.0 by adding H_2SO_4 (see Supporting Information for details).

that, for our process, these resins are adequate to be used in the presence of water

Under SolFC the results were satisfactorily but the conversion of **6a** to **7a** was slower than in the presence of water (Table 2, entry 7).

According to our previous results,^[8a-c] the recovered catalysts resulted from the complete substitution of both fluoride ions by azido ions with formation of volatile trimethylsilyl fluoride, b.p. 16 °C. Therefore in the case of catalyst **5f**, it was recovered as the corresponding PS-DABCO(N₃)₂ that was still equally efficient (see below).

Also iodide 4f was an effective catalyst but less efficient than fluoride, and complete conversion was not reached even after longer reaction time. This is probably due to the formation of trimethylsilyl iodide (by azido/iodide exchange) that probably decomposes in water to form HI which causes the hydrolysis of TMSN₃.

The pH of the reaction medium is *ca.* 3.0 at the beginning of the process and becomes *ca.* 4.0 when the conversion of **6a** to **7a** is complete. It should also be noticed that the reaction does not proceed satisfactorily when NaN₃ was used as alternative source of azido ion (Table 2, entry 11).

Therefore, in agreement to our previously reported results,^[8c] it can be concluded that the reaction proceeds according to the plausible mechanism depicted in Scheme 1.

Although these preliminary reactions were conducted on a small scale (0.5-1.0 mmol), we have observed that, as we have envisaged, water has a positive influence on the dispersion of the reaction mixture facili-



Scheme 1. Plausible mechanism for the process involving PS-DABCOF₂ catalysts.



Scheme 2. Schematic representation of the small-scale protocol for the β -azidation of enone **6a** in water with recovery and reuse of catalyst **5f**.

tating the recovery of the catalyst and of the product **7a**.

In fact, when the reaction is performed in water, the catalyst **5f** remains dispersed in water while upon adding EtOAc (1.0 mLmmol^{-1}) to the reaction mixture the product is dissolved in the organic phase and therefore can be separated from aqueous layer by simple suction. The product can be isolated after evaporation. Both water and catalyst are therefore easily recovered and have been reused in further 10 runs with no change in the results. Under these conditions E-factor for **7a** is 7.4 (Scheme 2).

On the contrary, when the process is performed under SolFC or in an organic solvent, a filtration is needed to recover the catalyst and in the case of SolFC, the reaction mixture is strongly stuck on the solid catalyst. Therefore in these cases a larger amount of organic solvent is necessary (*ca.* 4.0 mLmmol^{-1}) for the recovery of the product and reuse of catalyst with an obvious increase of the E-factor.

In addition, PS-DABCOF₂ catalysts **5a–f** (in the reactions using water or organic solvent or SolFC) during the magnetic stirring are crunched into a fine powder that is rather difficult to be manipulated during filtration. The use of water as reaction medium offers a solution to this problem.

It is interesting to notice that by increasing the fluoride loading, the possible reduction of the efficiency of the catalyst due to crowding of the catalytic sites, was not observed. Therefore, highly loaded **5f** was chosen for the continuation of this study. The main advantage of the use of **5f** is the minimal amount of solid resin needed for running the reactions.

In Table 3 are summarized the results obtained in the reactions of α , β -unsaturated ketones **6a–j** catalyzed by 20 mol% of **5f** in water.

Reactions were carried out at 60 °C except in the case of enones **6c**, **6g** and **6h**, where the reactions were performed at 30 °C (Table 3, entries 3, 7 and 8) since these substrates decompose at higher temperature. Sterically hindered ketones **6e**, **6f** and **6i** react slowly and require a higher excess of TMSN₃ to complete the reaction (Table 3, entries 5, 6 and 9).

In all cases the E-factor obtained on a 1.0 mmol scale is low and *ca*. 3 times smaller than that of our previously reported procedure performed under SolFC and based on the use of Amberlite IRA900F as catalyst.^[8c]

To prove the efficiency of our approach we have also decided to perform the azidation of α , β -unsaturated ketones **6a**, **6f**, and **6h** on a large-scale setting in **Table 3.** PS-DABCOF₂-catalyzed β -azidation of enones **6** at 60 °C in water.

$R^{1} \xrightarrow{I}_{II} R^{2} \xrightarrow{I}_{H_{2}O, 60 \circ C} \xrightarrow{I}_{R_{3}} R^{1} \xrightarrow{I}_$								
Entry		Enone	Time [h]		Adduct	Yield [%] ^[a]	E ^[b]	
1	6a		8	7a	N ₃ O	91	8.6	
2	6b	₩ ↓	20	7b	N ₃ O V	95	6.7	
3	6c		16	7c	N ₃	93 ^[c]	10.2	
4	6d		18	7d	N ₃	97 ^[d]	5.9	
5	6e	-<	150	7e		95 ^[d,e]	6.5	
6	6f		24	7f	N ₃ O	89 ^[e]	9.7	
7	6g		24	7g	N ₃	80 ^[c]	10.5	
8	6h	°	18	7h	OL N ₃	95 ^[c]	7.8	
9	6i	0=	72	7i	0=	93 ^[e]	7.8	
10	6j		48	7j		97	7.0	

0

^[a] Isolated yield of the pure products **7** (see Experimental Section for further details).

^[b] E-factor.^[13]

^[c] Reaction performed at 30 °C.

^[d] 60/40 mixture of diastereoisomers.

^[e] 3.0 equivalents of TMSN₃ were used.

a continuous-flow reactor. According to our previous reports in this field, this reactor should be designed to optimize the recovery and reuse of the catalyst, to minimize waste and in particular the amount of organic solvent needed to isolate the final products.

In addition, in the context of this contribution, it is crucial to set the reactor in order to be able to recover and reuse the aqueous layer. Water can be a very expensive waste and the realisation of a procedure for its recovery and reuse is highly desirable especially in a large-scale protocol.

The schematic representation of the reactor is illustrated in Scheme 3 (thermostatted box is not shown for clarity).



Scheme 3. Preparation of β -azido ketones 7a, 7f and 7h using a cyclic continuous-flow reactor.

The mixture of water (20 mL) and reactants $(100 \text{ mmol of } 6a, 6f \text{ or } 6h, 1.2 \text{ equiv. of TMSN}_3)$ were charged into a glass column functioning as reservoir and equipped with a mechanical stirring system appropriately designed and built to fit the column. PS-DABCOF₂ (5f) (20 mol% measured on the ketone 6) was charged into a glass column and the reaction mixture was continuously pumped through it. In the cases of 6a and 6h the complete conversion to the corresponding 7a and 7h was achieved under the same conditions reported in Table 3. In the case of 6f a longer reaction time (72 h) was expectedly needed for the complete conversion to 7f due to the significantly reduced amount of TMSN₃ used (1.0 instead of 3.0 equivalents).

At this point, still operating under mechanical stirring, the pump was left to run in order to recover the aqueous reaction mixture into the reservoir. The mechanical stirring was stopped and after some minutes water/organic phase separation occurred. Considering the amount remained adsorbed into the catalyst (*ca.* 40%), water was completely recovered into a separate reservoir. It should be noticed that the reaction progress includes the consumption of 1 equiv. of H₂O for the formation of the desired β -azido ketone **7** (see Scheme 1).

Then EtOAc was added $(3 \times 2 \text{ mL})$ to wash the catalyst and to isolate the pure product **7a**, **7f** or **7h**, after passing it through the dry column (10 g of Na₂SO₄) in 86, 85 and 92% yield, respectively (after evaporation of the organic solvent under reduced pressure). Additional use of EtOAc $(3 \times 2 \text{ mL})$ allowed the isolated yields of the pure products **7a**, **7f** and **7h** to be increased to 93, 91 and 96%, with a very low E-factor of 1.7, 1.9 and 1.8, respectively.

It is important to notice that the adoption of a cyclic continuous-flow procedure has allowed us to minimize the use of water and TMSN₃. In fact, to allow the complete fluoride-azido ions exchange occurring during the process, in the first run a 20 mol% excess of TMSN₃ has been used. Starting from the second run the E-factor slightly decreased because no more TMSN₃ was necessary for the ion exchange (see mechanism in Scheme 1) and strictly 1.0 equiv. of this reactant can be used. The catalytic system has been reused in three further runs with unchanged efficiency. In batch conditions the use of a stoichiometric amount of TMSN₃ was not possible and an incomplete conversion was observed due to a partial decomposition and loss of TMSN₃.

In order to define a protocol for a representative further manipulation of the intermediate β -azido ketones 7, we have searched for a procedure to directly reduce the azido group and prepare the corresponding β -amino ketones 8 (Scheme 4). In order to set-up a multistep procedure starting directly from α , β -unsaturated ketones 6, we focused our attention on a reductive method that could operate in the presence of water.

For this purpose, we directed our attention to the Pd-catalyzed reductive system that in our case, should be used in the presence of water with a hydrogen source alternative to H_2 . Formic acid or hydrazine are valuable options although in the literature their use is reported with a large excess (10–20 equiv.).^[15]

Pd-catalyzed reduction of azido group is a widely reported method in literature,^[4a,16] but to the best of our knowledge for this reaction, there are no reports on the use of Pd on alumina/formic acid or hydrazine systems.

Preliminary experiments confirmed that the direct reduction of β -azido ketones **7** to β -amino ketone **8** is not possible because these compounds are very unstable. In fact, after trying several sets of reaction conditions, running the reactions in water or in organic solvent, always only decomposition products were isolated. Actually, to the best of our knowledge compounds



Scheme 4. Preparation of N-Boc-β-amino ketones 9.

such as **8** are not known in the literature except as N-protected derivatives **9**.

For this reason we have directed our efforts to setup a procedure for the reduction of the azido group of **7** in the presence of the protective agent Boc_2O , as an amino protecting group N-Boc is a generally appreciable choice due to its easy manipulation and chemical stability.

In the representative case of **7a** we have devised an efficient procedure for its reduction to the corresponding **9a**. In water, by using 5 mol% of Pd/Al₂O₃ in the presence of just 1.0 equivalent of HCOOH and 1.0 equivalent of Boc₂O, the desired *N*-Boc- β -amino ketone **9a** was obtained in 80% yield.

The protocol defined is very efficient mainly because of the use of equimolar amounts of HCOOH, Boc_2O and **7a**. It should also be highlighted that the use of this ratio is also crucial for the success of the procedure, otherwise decomposition processes of both the β -amino ketone **8** and the protecting agent occur giving very discouraging results.

In addition, the reductive system showed no problem in the reduction of **7a** in clean water, but when in batch conditions we tried the one-pot protocol starting from **6a**, very poor results were obtained. This was ascribable to the excess of TMSN₃ used in the β azidation step in batch conditions that is responsible for the poisoning of the Pd catalyst.

The adoption of the continuous-flow protocol furnished the solution to this problem. In fact by operating in continuous-flow conditions a stoichiometric amount of $TMSN_3$ could be used and no poisoning of Pd catalyst could occur.



Scheme 5. Cyclic continuous-flow reactor for the preparation of *N*-Boc- β -amino ketones **9a** and **9b**.

We have then created a multistep continuous-flow reactor (Scheme 5) by adding a third column containing 5 mol% (calculated on 100 mmol of **6a**) of Pd on Al_2O_3 to the reactor previously described in Scheme 3.

At the end of the azidation process performed in continuous-flow according to the procedure described before, the air/solvent valve was opened and still under operating mechanical stirring, the pump was set to transfer the reaction mixture into the reservoir and empty the PS-DABCOF₂ (**5f**) column. EtOAc was added (6×2 mL) to wash the catalyst.

By setting appropriately the valves, Boc_2O (0.95 equiv.) was charged into the reservoir, HCOOH (0.95 equiv.) was added as a concentrated solution in H_2O (4 mL) into the column containing the Pd/Al₂O₃ and then the mixture was cyclically flowed through catalyst Pd/Al₂O₃ for 18 h at 30 °C until the reduction/ protection process was complete.

Similarly to the previously described reactor (Scheme 3), at this point and still under operating mechanical stirring, the pump was left to run in order to recover the aqueous reaction mixture into the reservoir. The mechanical stirring was stopped and after some minutes when water/organic phase separation occurred, water was recovered into a separate reservoir. The pure product was then flowed through a dry column (10 g of Na₂SO₄) to be recovered after organic solvent evaporation under reduced pressure. Additional use of EtOAC (3×2 mL) allowed the isolated yields of the pure products **9a** and **9b** in 74 and 77%, respectively with a very low E-factor of 3.2 and 2.7, respectively.

Conclusions

In conclusion, we have reported the preparation of novel solid fluorides **5a–f** to optimize the β -azidation of α , β -unsaturated ketones **6a–j**.

The catalysts have been designed to obtain a higher loading compared to that of commercially available fluorides allowing the use of a smaller mass of catalyst and help mixing of the reaction mixture. Gel-type and porous polymeric supports have been compared and more reticulated resins have proved to be more efficient in the presence of water as reaction mixture.

According to our expectations, water has proved to play a crucial role by increasing the reactivity and by improving the dispersion of the reaction mixture. The use of a porous solid support suitable for aqueous conditions has allowed us to avoid organic fouling caused by the sticking of the reaction mixture within the polymeric matrix, allowing a better catalytic efficiency and facilitating the recovery of the products from the catalyst. As an evident consequence, this approach has allowed to us minimize the use of the organic solvent needed for the complete recovery of product and leave the catalyst clean and reusable, while in the protocol performed under SolFC^[8c] the reaction mixture is strongly stuck on the solid catalyst requiring a larger amount of organic solvent for the isolation of the product. E-factors are in the range of 5.9–10.5 and therefore *ca.* 3 times smaller than our previous procedure operating under SolFC.^[8c]

To further improve the efficiency of our approach we have reported a protocol operating in a continuous-flow manner that has allowed to further reduce the E-factor to 1.7–1.9 (*ca.* 80% compared to our batch conditions and $93^{[8c]}$ –98% ^[8c] compared to literature procedures) for the representative substrates **6a**, **6f**, and **6h**. The continuous-flow protocol has allowed us to minimize the use of TMSN₃ making the recovery and reuse of water and catalyst **5f** very efficient and simple.

Finally a novel reduction system using Pd on Al_2O_3 (5 mol%) and equimolar amount of HCOOH has been used in the presence of 1 equiv. of Boc₂O to setup a multistep protocol operating in continuous-flow conditions for the preparation of representative *N*-Boc- β -amino ketones **9a** and **9b** starting from the corresponding enones **6a** and **6b** with an E-factor of 3.2 and 2.7, respectively.

Experimental Section

General Remarks

All chemicals were purchased and used without any further purification. All ¹H NMR and ¹³C NMR spectra were recorded at 400 MHz and 100.6 MHz, respectively, using a convenient deuterated solvent (reported in the characterization charts) and the residual peak as internal standard, or TMS in the case of CDCl₃. IR spectra were recorded with an FT-IR Bruker IFS 112 v spectrometer using CHCl₃ as solvent. Elemental analyses were realized by using a Fisons instrument EA 1108 CHN. SEM pictures of gold coated polymers (instrument EMITECH K55OX sputter coater) were taken on a Philips SEM XL30.

All polystyrene-supported ammonium salts **3a–f**, **4a–f**, **5a–f** are new compounds. All β -azido ketones **7**^[8c] and *N*-Boc- β -amino ketone **9a**^[4a] are known compounds while **9b** is a new compound.

All the detailed experimental procedures, characterization data of compounds **3a–f**, **4a–f**, **5a–f**, **7a–j** and **9a**, **b**, along with copies of the SEM images of **5f** as well as of the ¹H and ¹³C NMR spectra for compounds **7a–j** and **9a**, **b** are given in the Supporting Information.

Representative Batch Experimental Procedure

In a screw-capped vial equipped with a magnetic stirrer, PS-DABCOF₂ (**5f**) (0.014 g, 0.1 mmol, 7.4 mmolg⁻¹), water (0.250 mL), (*E*)-3-hepten-2-one (**6a**) (0.066 mL, 0.5 mmol)

and trimethylsilyl azide (0.100 mL, 0.75 mmol) were consecutively added and the resulting mixture was left under stirring at 60 °C for 8 h. Then, ethyl acetate (0.5 mL) was added, the mixture was stirred for 5 min, the organic phase was separated with a Pasteur pipette and the solvent evaporated under vacuum to give pure **7a**; yield: 0.071 g (91%). The aqueous phase and the catalyst remaining in the vial can be reused. E-factor: 7.4 [0.056 g (ketone)+0.086 g (TMSN₃)+0.450 g (AcOEt)-0.070 g (product)]/0.070 g (product).

Acknowledgements

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 and Parma for financial support.

References

- [1] a) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058–11076; b) G. Bartoli, M. Bartolacci, A. Giuliani, E. Marcantoni, M. Massaccesi, E. Torregiani, *J. Org. Chem.* **2005**, *70*, 169–174; c) S. Kobayashi, K. Kakumoto, M. Sugiura, *Org. Lett.* **2002**, *4*, 1319–1322; d) L. W. Xu, C. G. Xia, *Tetrahedron Lett.* **2004**, *45*, 4507–4510.
- [2] a) M. Arend, B. Westermann, N. Risch, Angew. Chem. 1998, 110, 1096–1122; Angew. Chem. Int. Ed. 1998, 37, 1044–1070; b) M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, J. Am. Chem. Soc. 1998, 120, 6615–6616; c) Y. Bandala, E. Juaristi, in: Amino Acids, Peptides and Proteins in Organic Chemistry, (Ed.:A. B Hughes), Wiley-VCH, Weinheim, 2009; d) D. C. Cole, Tetrahedron 1994, 50, 9517–9582.
- [3] a) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, Angew. Chem. 2005, 117, 5320–5374; Angew. Chem. Int. Ed. 2005, 44, 5188–5240; b) M. E. C. Biffin, S. J. Miller, D. B. Paul, in: The Chemistry of the Azido Group, (Ed.: S. Patai), Wiley-Interscience, London, 1971, pp 57–180; c) E. F. V. Scriven, K. Turbull, Chem. Rev. 1988, 88, 297–368.
- [4] a) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, J. Am. Chem. Soc. 2005, 127, 1313–1317;
 b) L.-W. Xu, C.-G. Xia, J.-W. Li, S.-L. Zhou, Tetrahedron Lett. 2004, 45, 1219–1221; c) L.-W. Xu, C.-G. Xia, J.-W. Li, S.-L. Zhou, Synlett 2003, 2246–2248.
- [5] D. J. Guerin, T. E. Horstmann, S. J. Miller, Org. Lett. 1999, 1, 1107–1109.
- [6] For other protocols using TMSN₃, see: a) I. Adamo, F. Benedetti, F. Berti, P. Campaner, Org. Lett. 2006, 8. 51–54; b) A. Dondoni, A. Marra, A. C. Boscarato, Eur. J. Org. Chem. 1999, 5, 3562–3572; c) A. Dondoni, A. Boscarato, A. Marra, Tetrahedron: Asymmetry 1994, 5, 2209–2212; d) R. Thiergardt, G. Rihs, P. Hug, H. H. Peter, Tetrahedron 1995, 51, 733–742.
- [7] a) D. J. Guerin, S. J. Miller, J. Am. Chem. Soc. 2002, 124, 2134–2136; b) T. E. Horstmann, D. J. Guerin, S. J.

Miller, Angew. Chem. 2000, 112, 3781–3784; Angew. Chem. Int. Ed. 2000, 39, 3635–3637.

- [8] a) F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, *Green Chem.* 2010, *12*, 1301–1305; b) F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem.* 2008, 3928–3932; c) L. Castrica, F. Fringuelli, L. Gregoli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* 2006, *71*, 9536–9539.
- [9] a) S. Bonollo, D. Lanari, F. Pizzo, L. Vaccaro, *Org. Lett.* **2011**, *13*, 2150–2152; b) S. Bonollo, D. Lanari, L. Vaccaro, *Eur. J. Org. Chem.* **2011**, 2587–2598.
- [10] For leading examples, see: a) D. Lanari, R. Ballini, A. Palmieri, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem.* 2011, 2874–2884; b) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, *J. Org. Chem.* 2004, 69, 8780–8785.
- [11] For leading examples, see: a) A. Zvagulis, S. Bonollo, D. Lanari, F. Pizzo, L. Vaccaro, *Adv. Synth. Catal.* 2010, *352*, 2489–2496; b) L. Soldi, W. Ferstl, S. Loebbecke, R. Maggi, C. Malmassari, G. Sartori, S. Yada, *J. Catal.* 2008, *258*, 289–295.
- [12] a) M. Baumann, I. R. Baxendale, S. V. Ley, *Mol. Diversity* 2011, *15*, 613–630; b) C. J. Smith, C. D. Smith, N. Nikbin, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem.* 2011, *9*, 1927–1937; c) M. O'Brien, N. Taylor, A. Polyzos, I. R. Baxendale, S. V. Ley, *Chem. Sci.* 2011, *2*, 1250–1257; d) C. Aranda, A. Cornejo, J. M. Fraile, E. García-Verdugo, M. J. Gil, S. V. Luis, J. A. Mayoral, V.

Martinez-Merino, Z. Ochoa Green Chem. 2011, 13, 983–990; e) V. Sans, N. Karbass, . M. I. Burguete, V. Compañ, E. García-Verdugo, S. V. Luis, M. Pawlak Chem. Eur. J. 2011, 17, 1894–1906; f) M. Baumann, I. R. Baxendale, M. Brasholz, J. J. Hayward, S. V. Ley, N. Nikbin, Synlett 2011, 1375–1380; g) L. J. Martin, A. L. Marzinzik, S. V. Ley, I. R. Baxendale, Org. Lett. 2011, 13, 320–323.

- [13] a) R. A. Sheldon, *Chem. Ind. (London, U.K.)* 1997, 12–15; b) R. A. Sheldon, *Green Chem.* 2007, 9, 1273–1283;
 c) J. Augé, *Green Chem.* 2008, 10, 225–231; d) R. A. Sheldon, *Chem. Commun.* 2008, 3352–3365.
- [14] http://www.dow.com/assets/attachments/business/ier/ ier_for_industrial_water_treatment/amberlite_ira900_cl/ tds/amberlite_ira900_cl.pdf.
- [15] a) A. Kulkarni, R. Gianattasio, B. Torok, Synthesis 2011, 1227–1232; b) K. Nadrah, M. S. Dolenc, Synlett 2007, 1257–1258; c) Z. Paryzek, H. Koeng, B. Tabaczka, Synthesis 2003, 2023–2026; d) N. A. Cortes, R. F. Heck, J. Org. Chem. 1977, 42, 3491–3494; e) A. Furst, R. C. Berlo, S. Hooton, Chem. Rev. 1965, 65, 51–68.
- [16] a) S. Chandrasekhar, S. J. Prakash, C. L. Rao, J. Org. Chem. 2006, 71, 2196–2199; b) H. Sajiki, Tetrahedron Lett. 1995, 36, 3465–3468; c) Y. Gaony, J. Org. Chem. 1994, 59, 6853–6855; d) E. J. Corey, J. O. Link, J. Am. Chem. Soc. 1992, 114, 1906–1908.