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A Protocol for Accessing the β-Azidation of α,β-Unsaturated Carboxylic Acids

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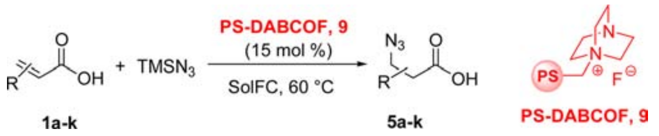
ABSTRACT



This contribution reports the preparation and use of a new immobilized catalyst, PS-DABCOF (9), which has been specifically designed to access for the first time the efficient β-azidation of α,β-unsaturated carboxylic acids.

The research on β-amino acids and β-peptides has grown dramatically in the past 15 years, since these compounds are endowed with a wide range of biological activities and pharmacological properties.[1]

There are different approaches for the synthesis of β-amino acids, including α-amino acid homologation,[2] addition of enolates or enolate equivalents to imines,[3] conjugate addition to electron-deficient olefins,[4] and nucleophilic ring-opening reaction of β-lactones.[5] Among these methods, aza-Michael addition is one of the most attractive and several procedures have been reported where amines[6] or N-nucleophiles[7] react with α,β-unsaturated carbonyl compounds. In particular, Michael addition of the azido ion is an attractive procedure to prepare β-amino acids, since azides can be easily converted into the corresponding amines. Moreover, β-peptides can be directly built with the so-called "azido acid approach",[8] exploiting the azido group as an *N*-protecting group for a β-amino acid.

Efficient methods for the Lewis acid or Lewis base catalyzed Michael addition of azides to α,β-unsaturated carbonyl compounds including unsaturated imides are known,[9] but there are no procedures for the azidation of α,β-unsaturated carboxylic acids.

The efficient Miller's procedure is based on the use of a tertiary amine as the catalyst which is responsible for the controlled production of hydrazoic acid (the effective azidation reagent) from a 1:1 mixture of $TMSN_3$ and AcOH.[9f]

We have reported the use of polystyrene-supported ammonium fluoride (Amberlite IRA900F, Amb-F, and

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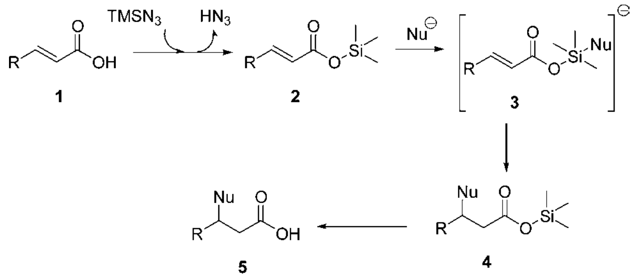
PS-DABCOF$_2$) to promote the β-azidation of α,β-unsaturated ketones under solvent-free conditions (SolFC),[10] through nucleophilic activation of the Si−N bond of trimethylsilylazide (TMSN$_3$) with the formation of a highly active silicon pentacoordinate species.[10]

Although the adoption of SolFC generally allows an increase in the reactivity of a catalyst,[11] our protocol does not work efficiently with unsaturated carboxylic acids or their methyl and ethyl ester derivatives.[10b] The efficient preparation of β-amino acids via β-azidation of α,β-unsaturated carboxylic acids is currently possible only if this process is performed on the corresponding pyrrolidinone derivative imide using a costly protection/deprotection procedure.[9d] The reduced electron-withdrawing ability of carboxylic or alkyl carboxylate groups may be ascribed as the main reason for the failure of the available procedures in the azidation of α,β-unsaturated carboxylic acids and esters.

Scheme 1. Strategy for the β-Azidation of α,β-Unsaturated Carboxylic Acids **1**



In the search for a solution to this issue we have found that, under SolFC, an equimolar mixture of a carboxylic acid **1** and TMSN$_3$ is immediately and quantitatively converted to the corresponding trimethylsilyl ester **2** producing 1 equiv of hydrazoic acid (Scheme 1). In the presence of an organic solvent this process is much less efficient, and **2** is formed very slowly (see Supporting Information (SI)). Ester **2** is an appropriate substrate to interact with a nucleophile (e.g., fluoride or azido ions) and form the pentavalent silicon species **3** that is effectively able to intramolecularly promote the attack of the nucleophile on **1**.

Preliminary reactions performed on the representative substrate crotonic acid **1a** under SolFC and using TMSN$_3$ showed that Amb-N$_3$ and Amb-F were effective catalysts but allowing only 65 and 66% conversion, respectively, after 8 h (Table 1, entries 1 and 2). Completion of the reaction could not be achieved even after a prolonged reaction time due to the partial hydrolysis of **2**. The use of a tertiary base as the catalyst was also tried, and although this approach is also viable, conversion to the desired product **5a** was still unsatisfactory (Table 1, entries 3−5); also in this case complete conversion could not be reached. We have finally used simultaneously fluoride and tertiary amine based catalysts obtaining an improved conversion of 77% (entry 6), confirming that the combination of silicon and base activation is a promising approach.

Scheme 2. Synthetic Approach for the Preparation of Bifunctional Catalyst PS-DABCOF (**9**)

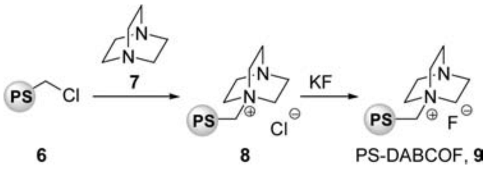
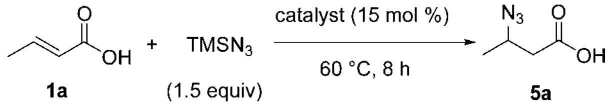


Table 1. Optimization of Representative β-Azidation of **1a**



entry	medium	base	conversion (%)[a]
1	SolFC	Amb-N$_3$	65
2	SolFC	Amb-F	66
3	SolFC	PS-CH$_2$N(CH$_3$)$_2$	33
4	SolFC	PS-DMAP	50
5	SolFC	PS-TBD	38
6	SolFC	Amb-F + PS-DMAP	77
7	SolFC	PS-DABCOF	95[b]
8	SolFC	PS-DABCOCl	41
9	SolFC	PS-DABCON$_3$	94
10	AcOEt[c]	PS-DABCOF	32
11	CH$_2$Cl$_2$[c]	PS-DABCOF	20
12	water[c]	PS-DABCOF	36

[a] Conversion to **5a** measured by GC-LC and ^{1}H NMR analyses; the remaining material was **1a**. [b] ≥99% conversion was reached after 12 h; product **5a** was isolated in 99% yield. [c] 0.5 M.

To access the β-azidation of α,β-unsaturated acids, we have then decided to prepare a bifunctional polystyrene-supported[12] catalyst **9** based on the DABCO moiety **7** featuring a basic moiety (tertiary amine able to interact with hydrazoic acid) and a quaternary ammonium functionality carrying a fluoride as a counterion able to interact with a silicon atom (Scheme 2). The polymeric support plays an important role in the strategy used for the preparation of **9**. In fact, while the use of a solid catalyst is desirable for its simple separation from the reaction mixture, in this case it is essential for achieving the

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(12) This product was purchased from Aldrich as "Merrifiled Resin" or "(Chloromethyl)polystyrene". See SI for further details.

formation of a monoammonium species **8** and the complete ion exchange from the Cl- to F-form (see SI).

The designed PS-DABCOF **9** resulted in being the most efficient catalyst allowing 95% conversion after 8 h at 60 °C (Table 1, entry 7) and, in 12 h, the complete conversion to **5a** which was isolated in 99% yield without any purification step (see SI).

The results obtained with catalyst **9** can be explained by the mechanism proposed in Scheme 3 that reflects the rationale used for the design of the bifunctional catalyst.

Initially, there are two fast exchange reactions. Under SolFC unsaturated acid **1** immediately forms the corresponding trimethylsilyl ester **2** with the formation of hydrazoic acid (as observed by GC-LC and ^{1}H NMR analyses). In addition PS-DABCOF **9** and $TMSN_3$ react to form PS-DABCON$_3$ **10** as previously reported in similar catalysts[10] and as confirmed by elemental analysis (see SI). The silicon atom in the ester works as a Lewis acid and coordinates the azido ion of the catalyst. This coordination seems to be crucial for the catalyst activity. In fact, in the resulting pentacoordinate silicon species the azido ion is sufficiently activated for the Michael addition giving the β-azido trimethylsilyl ester **4** as product. The process proceeds with the plausible assistance of the tertiary amine center that coordinates hydrazoic acid which furnishes the proton to the carbonyl and the azido ion to regenerate the catalyst. Compound **4** has not been observed because under the reaction conditions it is hydrolyzed to the corresponding β-azido acid **5**.

Precursor PS-DABCOCl **8** was not effective as the corresponding fluoride **9** in the promotion of the reaction (Table 1, entry 8). In contrast, the recovered catalyst PS-DABCON$_3$ **10** (Scheme 3) showed the same efficiency as **9** (Table 1, entry 9). PS-DABCON$_3$ **10** is formed by the fluoride-azido ion exchange that occurs during the reaction with the formation of TMSF which is highly volatile (bp = 16 °C) (Scheme 3).[10] It has been also confirmed that in the presence of organic solvents or water the efficiency of the process significantly decreases (entries 10−12); this is presumably due to the low concentration of the trimethylsilyl ester **2** under these conditions.

We have also examined several crotonic acid derivatives **11**−**13**, in the presence of 1.5 equiv of $TMSN_3$ and 15% of PS-DABCOF **9** at 60 °C under SolFC (Table 2). Under these conditions, methyl crotonate **11** gave as expected a very poor yield (Table 2, entry 2). The more active 2,2,2-trifluoroethyl crotonate (**12**) and the very reactive Michael acceptor crotonyl oxazolidinone **13** reacted smoothly with satisfactory yields. As expected, in these latter cases, catalyst **9** could operate only as a monofunctional catalyst and the results obtained were comparable to those achieved by Miller using a tertiary amine as the catalyst[9f] or by our group using Amb-F as the catalyst.[10b−c]

Scheme 3. Plausible Mechanism of the β-Azidation of **1** Catalyzed by PS-DABCOF **9**

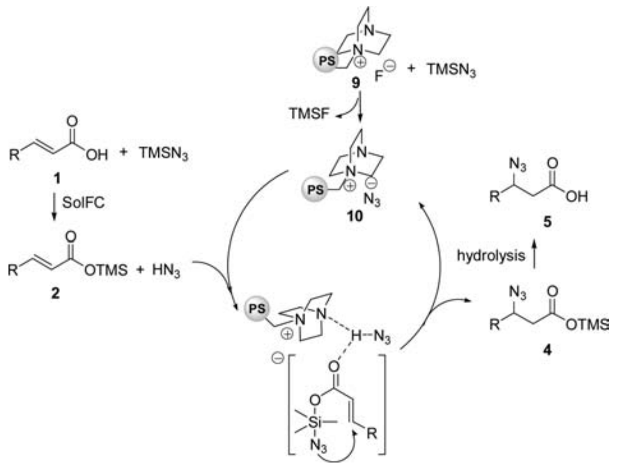
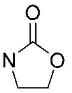


Table 2. β-Azidation of Crotonic Acid Derivatives **11**−**13** Catalyzed by PS-DABCOF (**9**)

entry	1a, 11-13, R	time (h)	product	yield (%)[a]
1	**1a**, OH	12	**5a**	>99
2	**11,** OCH_3	96	**14**	27
3	**12,** OCH_2CF_3	24	**15**	85
4	 **13,**	8	**16**	99

[a] Isolated yield of the products without any purification step except in the case of **14**.

In contrast, our procedure allowed improvement in the efficiency of the β-azidation from an environmental point of view, and this advantage can be quantified using the E-factor to compare the waste production associated with the processes.[13] In fact, considering a specific substrate like crotonyl oxazolidinone **13** (Table 2, entry 4), to obtain the corresponding azidation product **16**, we reached a very low 19.1 value for the E-factor compared to the value 474.6 obtained for the previously mentioned procedure.[9f,14]

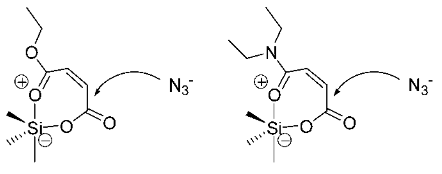


Figure 1. Plausible complex formed in the azidation of **1j** and **1k**.

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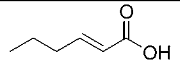
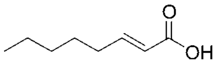
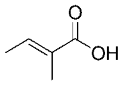
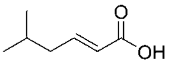
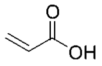
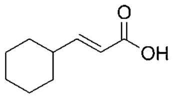
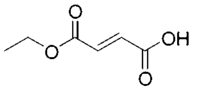
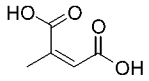
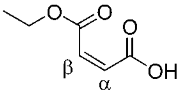
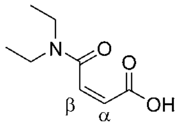
Table 3. β-Azidation of α,β-Unsaturated Carboxylic Acids **1b**–**k** Catalyzed by PS-DABCOF **9**

entry	acid	time (h)	yield (%)[a]
1	 **1b**	24	92
2	 **1c**	24	92
3	 **1d**	72	90[b]
4	 **1e**	72	80[b]
5	 **1f**	0.5	99
6	 **1g**	72	89[b]
7	 **1h**	24	65
8	 **1i**	24	68[c]
9	 **1j**	18	64[d]
10	 **1k**	18	77[d]

[a] Isolated yield of the corresponding pure products **5** without any further purification, except **5d**, **5e**, **5g** (see SI). [b] Reaction conditions: 80 °C, 3.0 equiv of $TMSN_3$, 30 mol % catalyst. [c] 2.5 equiv of $TMSN_3$ were used. [d] Yields of the mixture of α/β products. α/β ratio: 62/38.

The substrate scope has been extended to several α, β-unsaturated acids **1b**–**k** (Table 3). The products **5b**–**k** were obtained in satisfactory to good yields with E-factor values ranging from 19.0 to 33.2 (Table 3, entries 1–2, 5, 7–10).[14] Dicarboxylic acid **1i** reacted smoothly in the presence of 2.5 equiv of $TMSN_3$ (entry 8). Yet, acids **1d**–**e**, **g** (Table 3, entries 3, 4, 6) needed more drastic reaction conditions and a purification step to obtain the corresponding pure products **5d**–**e**, **g** in good yields.

The prevalent α-regioselectivity observed in the reaction of maleic acid derivatives **1j** and **1k** (Table 3, entries 9 and 10) can be explained evoking an intramolecular coordination of the silicon atom by the carbonyl oxygen, which makes the formal α-attack possible and competitive (Figure 1).

Finally, the recovery and reuse of the catalyst has been evaluated in the model reaction with crotonic acid (Table 1, entry 7). After the reaction has reached complete conversion, the crude mixture was filtered with ethyl acetate and the catalyst, after drying under vacuum pump, has been representatively reused in five subsequent runs maintaining the same efficiency.

In conclusion, we have prepared a new, efficient, and recoverable bifunctional supported catalyst, PS-DABCOF **9**, specifically designed to promote the β-azidation of α,β-unsaturated carboxylic acids. This catalyst features a nucleophilic and basic center that coordinates the substrate and activates the nucleophile at the same time, combining two different catalysts on a single structure. Moreover, the solid support is strategically used both for the synthesis of the appropriate catalyst and for facilitating its separation from the products. The use of SolFC is necessary to obtain a high level of efficiency for the process.

This novel synthetic tool allows direct access to β-azidation of α,β-unsaturated carboxylic acids avoiding costly protection/deprotection steps of the carboxylic functionality used in the previously reported procedures. Proof of the efficiency of such a new protocol resides obviously in the replacement of a three-step procedure with a one-step transformation. A quantitative measure of this advantage is given by the E-factor values achieved for the preparation of β-azido carboxylic acids **5**. In our protocol, an average value of 27 has been obtained that compared to the ca. 3400 associated with the three-step procedure available from the literature, corresponding to a dramatic 99.2% reduction of waste.

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Supporting Information Available. Complete experimental procedures, E-factor calculation, product characterization, SEM images of catalysts, copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For E-factor calculation, see SI.

The authors declare no competing financial interest.