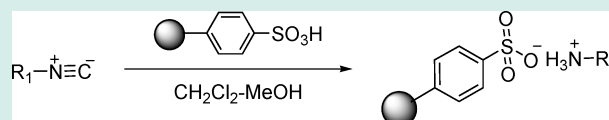


# Supported *p*-Toluenesulfonic Acid as a Highly Robust and Eco-Friendly Isocyanide Scavenger

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**ABSTRACT:** We document here the use of polymer-supported *p*-toluenesulfonic acid as a highly effective, robust, economical and eco-friendly isocyanide scavenger. The herein described strategy circumvent the intense and repulsive odor of volatile isocyanides, enabling simplified and odorless workup and purifications. The usefulness of the new scavengers has been validated in a set of diverse isocyanide-based organic transformations and this approach is also amenable to parallel synthesis techniques.

**KEYWORDS:** isocyanide, scavenger, supported reagents, Ugi reaction



## INTRODUCTION

The unusual structure and reactivity of isocyanides has attracted the scientific community since their discovery in the mid-1800s.<sup>1</sup> The isocyanide carbon behaves as a nucleophile or an electrophile depending on the reaction conditions, reagents, and the substituents present.<sup>2</sup> Isocyanides exhibit an exceptional ability to form  $\alpha$ -adducts, in an irreversible and exothermic transformation ( $\alpha$ -addition) in which C<sup>II</sup> is oxidized to C<sup>IV</sup>, which make these molecules extremely attractive starting materials for the rapid generation of chemical diversity.<sup>3</sup> This distinctive reactivity is usually complemented by excellent functional group tolerance that generally provides high levels of chemo-, regio-, and stereoselectivity.<sup>3</sup> The reactions in which these compounds participate are quite varied and include free radical additions,<sup>4</sup> organometallic transformations,<sup>5</sup> and polymerizations.<sup>6</sup> Beyond these diverse applications, isocyanides have proven to be particularly prolific in the development of multicomponent reactions (MCRs).<sup>7,3</sup>

The widely recognized contribution of isocyanides to the development of multicomponent reactions notwithstanding, their role as a reactive partner in simple organic transformations has been comparatively less explored.<sup>8</sup> In this context, recent reports<sup>9–12</sup> have documented the coupling reactions of isocyanides with molecules bearing acid groups that lead to the formation of *N*-formylamides, *N*-formylthioamides, or sulfamides. Despite its theoretical and experimental relevance, as well as the large literature available, we certainly do not know yet all facets of the chemistry of isocyanides, probably because these are not trivial substrates to work with. The potential of this functional group in synthesis has partially been hampered by limited commercial availability and, most importantly, by the intense and repulsive odor of these compounds (described as overpowering and extremely distressing by Hofmann and Gautier)<sup>1</sup>—a fact that has discouraged many potential contributors to this field.<sup>13</sup> Such a piercing

odor is critical for volatile compounds, some of which have been investigated as nonlethal weapons,<sup>14</sup> whereas higher-molecular-weight compounds are often odorless. The majority of these volatile compounds are commercially available and they are usually employed during process development/optimization. As a result, the unpleasant odor frequently makes the workup and purification of the reaction products highly tedious and distressing, particularly when applied to high-throughput organic synthesis operating in parallel mode.

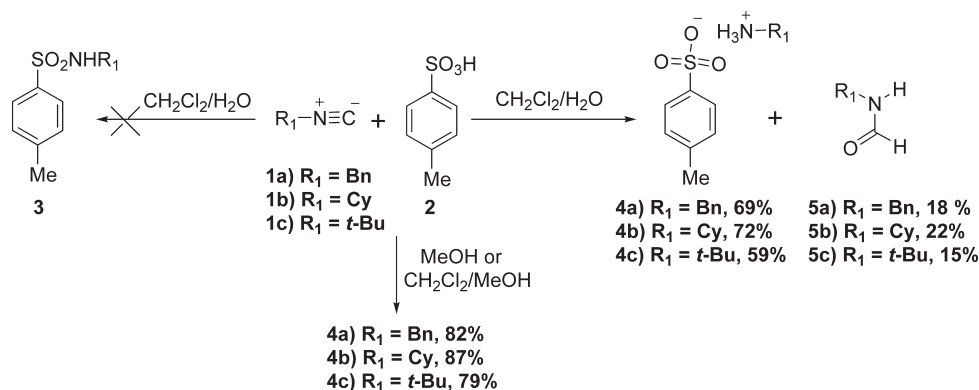
Contemporary attempts to circumvent the odor issue include the use of fragrant isocyanides<sup>15</sup> and the development of a plethora of polymer-supported isocyanides.<sup>16</sup> A strategy that has occasionally been employed involves treatment of reaction mixtures with acid,<sup>17</sup> to promote hydrolysis of the residual isocyanides. This hydrolytic quenching has several key drawbacks: it is not applicable to reactions that produce acid-sensitive substrates, isocyanides tend to polymerize<sup>2</sup> in strongly acidic media and, finally, such a quenching process produces the corresponding hydrolysis products, which must subsequently be removed from reaction mixtures. In concordance, these strategies do not provide general and practical solutions to address the unpleasant odor associated with the experimental manipulation of isocyanides. To the best of our knowledge, examples of the application of the scavenger concept<sup>18</sup> to such a problem have not been described. The experimental feasibility of this concept has been, probably, limited by the dearth of highly reliable transformations that can be employed as tools in the development of isocyanide scavengers.

The unique reactivity profile exhibited by isocyanides led us to incorporate this functional group into several of our in-house library generation programs. As experienced by practitioners of

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Scheme 1. Reaction of Representative Isocyanides and *p*-Toluenesulfonic Acid

isocyanide chemistry over the decades, the presence of unreacted isocyanides in the reaction mixtures, even in trace amounts, complicated the workup and purification of the target products considerably. Within the framework of this project, it was envisioned that the use of a polymer-supported reagent incorporating acidic functional groups would simultaneously promote isocyanide quenching and immobilize the isocyanide quenching products onto the polymeric matrix. These processes would avoid the tedious workup and purification stages encountered on working with this functional group. We document here the use of polymer-supported (polystyrene or silica) *p*-toluenesulfonic acid as a highly effective, robust, economical, and eco-friendly isocyanide scavenger. The usefulness of the new scavengers has been validated in a set of diverse isocyanide-based organic transformations and this approach is also amenable to parallel synthesis techniques.

## RESULTS AND DISCUSSION

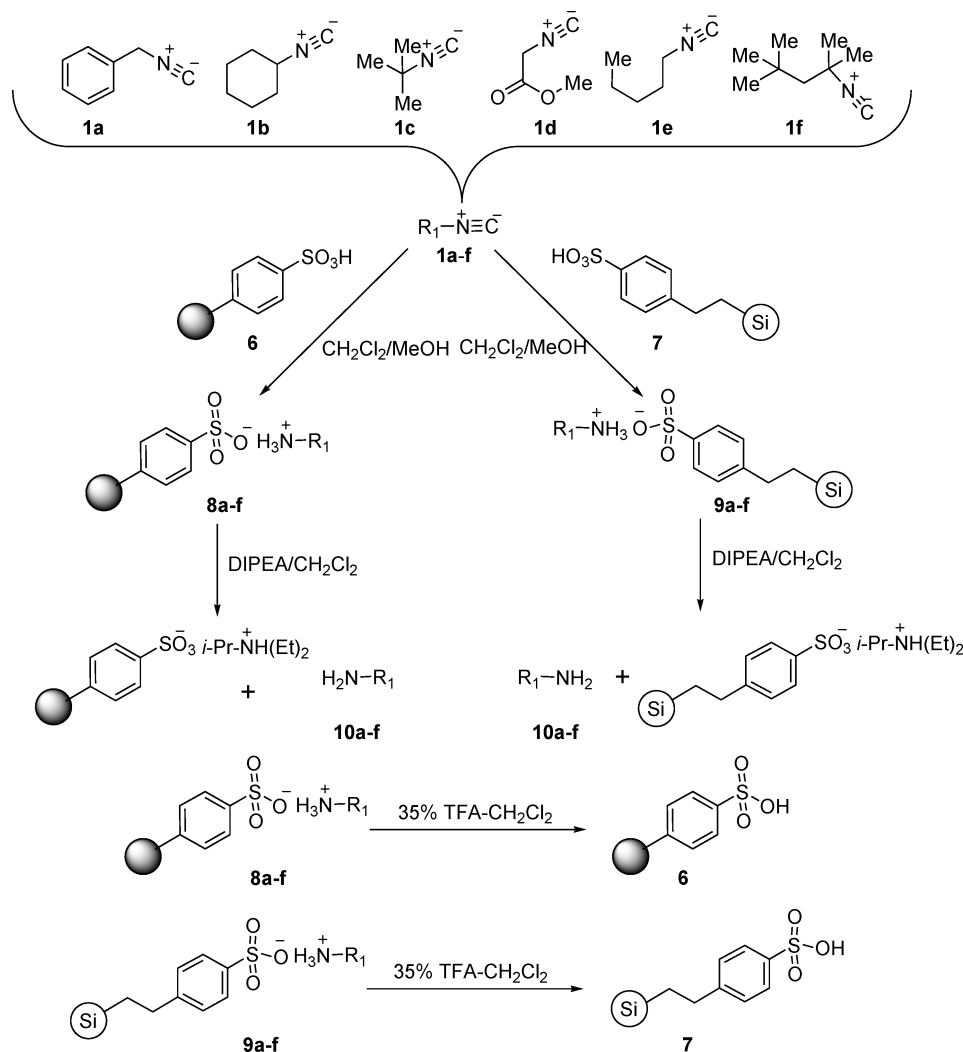
The recent breakthroughs on the two-component coupling reactions of isocyanides with molecules bearing acid groups<sup>9–12</sup> inspired the development of the scavenging strategy documented here. An in-depth analysis of recently published results on this topic would enable a range of approaches to be considered. In light of the efficiency and reliability of the two-component carboxylic acid/isocyanide coupling,<sup>9</sup> the most obvious approach to develop a selective scavenger for the isocyanide functional group is the use of a polymer-immobilized carboxylic acid. Such an approach would enable the selective attachment of the isocyanide onto the polymeric matrix as a *N*-formylamide. However, the main drawback associated with this approach is the harsh thermal activation (typically 150 °C for 30 min) required to promote the 1,3-O→N acyl transfer.<sup>9a</sup> An interesting and experimentally milder alternative to carboxylic acids is the use of thiocarboxylic acids, which showed satisfactory reactivity profiles in coupling reactions with isocyanides at room temperature.<sup>10</sup> Unfortunately, the limited commercial availability of polymer-supported thioacids restricts the feasibility and applicability of this strategy. In this scenario, a paper<sup>11</sup> attracted our attention as it documents a robust, room-temperature coupling of isocyanides and sulfonic acids to afford sulfonamides. These precedents, in conjunction with the cheapness, commercial availability, and applications described for supported *p*-toluenesulfonic acids,<sup>19</sup> fulfilled our expectations.

In a solution-phase proof of concept, *p*-toluenesulfonic acid **2** was reacted with three representative commercially available isocyanides (**1a–c**) at room temperature under published experimental conditions (Scheme 1).<sup>12</sup> Complete consumption of

the starting materials was observed within relatively short reaction times. Nonetheless, in our hands, the excellent reactivity profile was not complemented by the selectivity and efficiency levels claimed by the authors (Scheme 1). Analysis of the resulting products showed that the reaction of *p*-toluenesulfonic acid (**2**) and isocyanides **1a–c** did not afford sulfonamides **3**, but gave *p*-toluenesulfonate salts (**4**) together with variable amounts (15–22%) of formamides (**5**). These new structural assignments are supported by examination of published<sup>12</sup> spectroscopic and analytical data and by comparison with our own data and previous independent literature reports<sup>20</sup> on **3** and **4**.

In light of these results, and in connection to previous reports in the carboxylic acid series,<sup>9</sup> we considered the feasibility and robustness of a hydrolytic scavenging process instead of the amidation approach. The evident mechanistic differences between the two immobilization processes have significant connotations, mainly in terms of reversibility and recycling issues. The hydrolytic scavenging strategy would be supported by the well-documented acid-catalyzed methanol-mediated conversion of isocyanides to amine salts.<sup>21</sup> With this aim in mind, a slight excess (1.20 equivalents) of *p*-toluenesulfonic acid (**2**) and model isocyanides (**1a–c**) were reacted at room temperature in either methanol or dichloromethane/methanol mixtures (Scheme 1). It was gratifying to observe that, under the new experimental conditions, hydrolysis of the isocyanide group required short reaction times (typically less than 30 min) and mild experimental conditions (room temperature) to afford the corresponding *p*-toluenesulfonic acids salts (**4**) in excellent yields. Despite the effectiveness of the process, small amounts of formamides **5** (ca. 5%) were also detected, most probably due to incomplete isocyanide hydrolysis. As experimentally verified the formation of formamides **5** in these transformations can be suppressed by simultaneously increasing the *p*-toluenesulfonic acid excess (e.g., 1.5–2.0 equivalents) and the proportion of methanol in the reaction mixtures.

Encouraged by these results, it was decided to investigate whether the use of a polymer-immobilized *p*-toluenesulfonic acid would still provide the excellent reactivity profile exhibited by the nonsupported substrate (**2**). In an attempt to address this issue and to optimize a multipurpose, robust isocyanide scavenger that is amenable to diverse solution phase protocols, we selected the commercially available *p*-TsOH immobilized on either polystyrene-divinyl benzene (PS-*p*-TsOH, **6**) or silica (Si-*p*-TsOH, **7**) matrixes for preliminary studies (Scheme 2). These two reagents differ not only in the polymeric matrix that supports the reactive

Scheme 2. Scavenging of Diverse Isocyanides with Polystyrene- Or Silica-Supported *p*-TsOH

sulfonic acid groups (polystyrene vs silica) and loading levels (2.60 mmol/g vs 0.59 mmol/g), but also in their solvent compatibility profile and price (€1.90/mmol vs €18.80/mmol). To further challenge these supported reagents (6 and 7) in the preliminary evaluation of their general applicability and robustness as isocyanide scavengers, a wider set of highly diverse isocyanides was selected (Scheme 2). All experiments were performed on a 1.0 mmol scale, employing a variable excess (1.1–2.5 equivalents) of the immobilized *p*-toluenesulfonic acid. The reactants were orbitally stirred at room temperature for variable times (30–90 min) and, depending on the solvent compatibility of each polymeric matrix, the effect of a range of solvent mixtures on the reaction outcome was also investigated [e.g., dichloromethane/methanol (3:1), dimethylformamide/methanol (2:1), dioxane/methanol (2:1), chloroform/methanol (3:1), or methanol/water (3:1)].

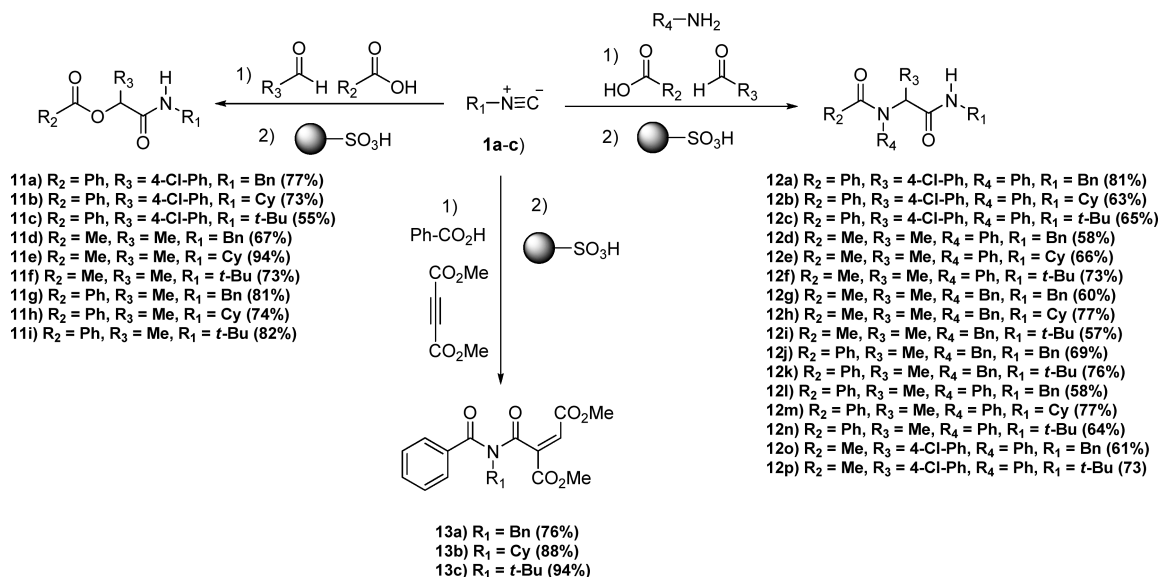
It was gratifying to find that room temperature incubation of representative isocyanides with supported *p*-TsOH (6 and 7) for relatively short reaction times (30–60 min) led to the complete disappearance of isocyanides from the starting solutions (Table 1). The transformation was successful regardless of the differences in the loading levels and polymeric matrixes present in the supported reagent. Two equivalents of the supported

Table 1. Scavenging of Diverse Isocyanides with Supported *p*-TsOH

starting isocyanide	scavenger efficacy (%) <sup>a</sup>	
	PS- <i>p</i> -TsOH	Si- <i>p</i> -TsOH
1a	75	66
1b	91	73
1c	80	70
1d	93	81
1e	69	60
1f	76	66

<sup>a</sup> Calculated on the basis of the amine recovery after treatment with DIPEA.

*p*-TsOH led to complete transformation of the reactants under mild conditions in reasonable reaction times (ca. 30–60 min). A lower number of equivalents of the scavenger (i.e., less than 1.5 equivalents) was also acceptable, albeit with concomitant formation (<5%) of the corresponding formamide (5) and the need for longer scavenging times (e.g., 30–60 min with 2.0 equivalents versus 90–120 min with 1.2 equivalents for >95%

Scheme 3. PS-*p*-TsOH As an Isocyanide Scavenger in Diverse Organic Reactions

conversion at 25 °C). The effect of the solvent does not appear to be particularly critical, with most of the systems tested generally well tolerated, a (3–1) dichloromethane-methanol mixture was employed during process optimization. As shown in Scheme 2, the scavenging of structurally diverse isocyanides was efficient and was not influenced by the steric or electronic variations in the reacting substrates. Comparison of the results obtained with the two polymeric matrixes (polystyrene and silica) leads to the conclusion that polystyrene exhibits a slightly superior reactivity profile and efficacy (Table 1). In particular, the claimed intrinsic advantages of silica over polystyrene resins (i.e., no swelling or solvent compatibility issues) were not observed, most probably due to the fact that the latter can swell sufficiently in the solvents tested. Thus, the choice of **6** or **7** for extensive preparative applications would be mainly dependent on the loading levels, price, and the characteristics of the reaction in question. The use of Si-*p*-TsOH as scavenger could be particularly attractive in the context of recent reports on the acceleration of isocyanide-based multicomponent reactions in water.<sup>22</sup>

Experimental evidence supporting the occurrence of a hydrolytic process during the use of polymer-supported sulfonic acids **6** and **7** was found (Scheme 2). It can be seen that treatment of polymeric materials isolated once the scavenging of isocyanides (**1a–f**) had finished (**8** and **9**) with a dichloromethane solution of DIPEA led to the recovery of the corresponding amines (**10a–f**) from the reaction mixture (Table 1). These results provide further evidence to support a broader applicability for immobilized *p*-TsOH (**6** and **7**) in other facets of isocyanide chemistry. Thus, the hydrolytic isocyanide quenching strategy documented here could be attractive not only in the context of isocyanide scavenging, but also has potential in the implementation of catch and release<sup>23</sup> approaches during the synthesis of amines from isocyanides.<sup>24</sup>

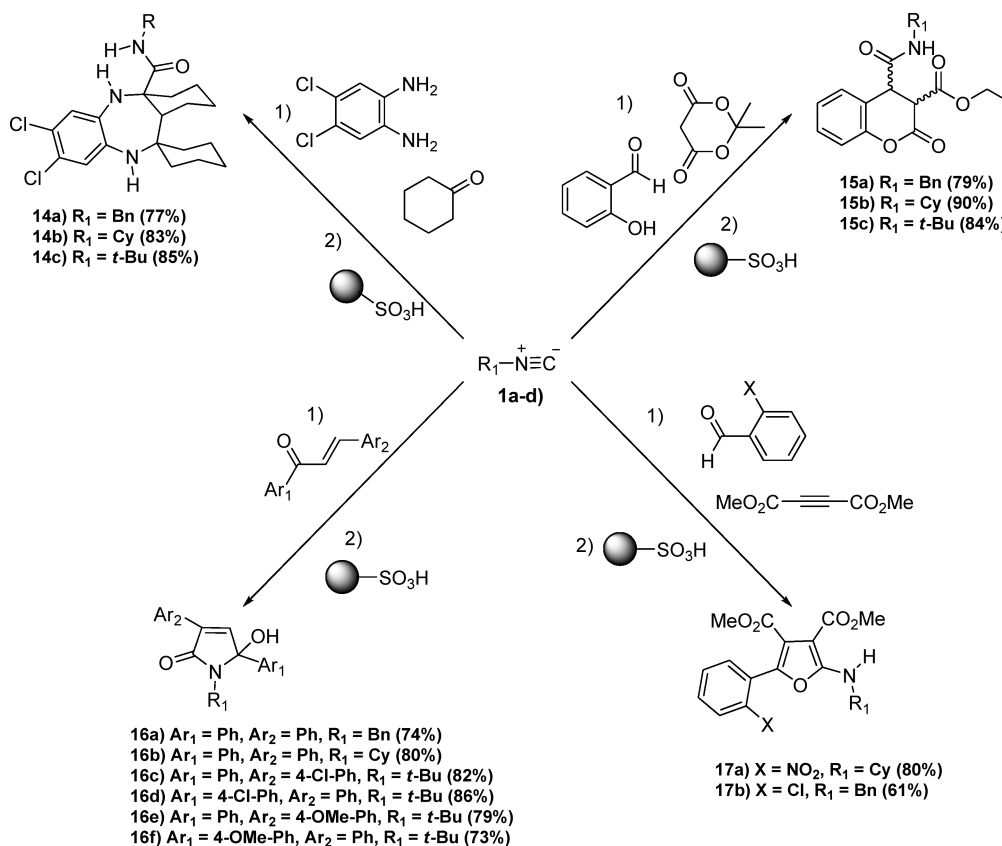
A remarkable feature of the isocyanide scavenging approach reported here concerns the recyclability. Since the optimized scavenging strategy is based on a highly reliable hydrolytic process, it was envisaged that it would be possible to regenerate the supported reagents for reuse in new experiments. The recyclability

of both polymer-supported *p*-toluenesulfonic acids (**6** and **7**) was examined for two model isocyanides (**1a** and **1c**). After appropriate washing protocols, the recovered sulfonate salts (**8** and **9**) were incubated in a 30% solution of trifluoroacetic acid in dichloromethane and submitted to orbital stirring for 30 min. It was verified that, once appropriately washed and dried under vacuum, the recovered immobilized *p*-toluenesulfonic acids can be reused at least five times in new scavenging experiments for the same isocyanide without dramatic yield loss and generating products with purities similar to those obtained in the first run.

Once the scavenging efficacy and recyclability of supported *p*-toluenesulfonic acids had been experimentally validated, a preliminary screening of the efficiency and robustness of polystyrene-immobilized *p*-toluenesulfonic acid (**6**) in diverse isocyanide-based reactions was carried out (Schemes 3 and 4). The main aim of the study was to assess the applicability of PS-*p*-TsOH in as diverse a range of organic reactions as possible. With this aim in mind, a set of transformations that highlight some of the most representative facets of isocyanides in organic synthesis was selected (Schemes 3 and 4). The experimental conditions were the same as those described in the original papers<sup>25–31</sup> and the scavenging process (2 equivalents of PS-*p*-TsOH) was integrated once it was verified that the reaction had finished.

We first focused on the well-documented Passerini and Ugi reactions (Scheme 3).<sup>25,26</sup> It was satisfying to find that the use of **6** led to a marked simplification of the workup and purification process required to isolate the coupling products (**11** or **12**). In a similar way, complete isocyanide scavenging and simplified processing was observed during the assembly of fumarates **13**.<sup>27</sup> An additional feature of supported *p*-toluenesulfonic acid during the implementation of simplified purification strategies for the Ugi reaction is derived from the electrophilic character of the immobilized reagent.<sup>19</sup> This characteristic means that supported *p*-toluenesulfonic acid not only scavenges the unreacted isocyanide (**1**) but also immobilizes residual amounts of several of the starting amines. A set of 4 isocyanide-based transformations enabling the assembly of



Scheme 4. PS-*p*-TsOH As an Isocyanide Scavenger in Diverse Organic Reactions

diverse heterocyclic scaffolds was selected to assess the potential of **6** in library production (Scheme 4).<sup>28–31</sup> The addition of PS-*p*-TsOH after completion of the reaction ensured complete fixation of unreacted isocyanides to the polymeric matrix, thus facilitating the isolation of the heterocycle.

In summary, the potential and versatility of supported *p*-toluenesulfonic acid as a highly efficient, selective and environmentally friendly isocyanide scavenger has been proven. The mild and simple experimental scavenging protocol is based on a highly reliable acid-catalyzed methanol-mediated hydrolytic process. The reversibility of this hydrolytic fixation protocol enables the simple and straightforward regeneration and reuse of the supported reagents. The convenience and robustness of the herein described strategy was demonstrated in a set of highly diverse isocyanide-based organic transformations.

## EXPERIMENTAL PROCEDURES

**Representative Procedure for the Hydrolytic Quenching of Isocyanides **1** Employing Supported *p*-TsOH.** To a Kimble vial containing 2.0 mmol of the polymer supported *p*-TsOH (PS-*p*-TsOH or Si-*p*-TsOH) in a 3:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  mixture (5 mL) was added the corresponding isocyanide **1** (1.0 mmol). The reaction mixture was submitted to orbital stirring at room temperature until the reactions reached completion (30–60 min). The polymer-supported salt was filtered off and successively washed [3 times (10 mL)].

**Representative Procedure for Amine Synthesis Employing PS-*p*-TsOH under the Catch and Release Sequence.** The recovered polymer-supported salt **8** (0.20 g) was added to a Kimble vial

containing 6 mL of a solution of *N,N*-diisopropylethylamine (2.0 mmol) in  $\text{CH}_2\text{Cl}_2$ . The reaction mixture was submitted to orbital stirring at room temperature for 2 h. The polymeric material was filtered off and washed [3 times (10 mL)] with MeOH, AcOEt, and  $\text{CH}_2\text{Cl}_2$ . The solvent was removed from the filtrates under vacuum to give an oily residue containing the amine **10**.

**Representative Procedure for the Regeneration of the Polymer-Supported *p*-Toluenesulfonic Acids (**6** and **7**).** The corresponding recovered polymer-supported salt (**8** or **9**) (0.20 g) was added to a Kimble vial containing 5 mL of a solution of 30% of trifluoroacetic acid in  $\text{CH}_2\text{Cl}_2$ . The reaction mixture was submitted to orbital stirring at room temperature for 2 h. The polymeric material was filtered off and successively washed [3 times (10 mL)] with MeOH, AcOEt and  $\text{CH}_2\text{Cl}_2$  and dried under vacuum for 12 h at room temperature. The recovered polymer-supported *p*-toluenesulfonic acid (**6** or **7**) was employed in either the direct reaction with isocyanides **1a** and **1b** or under the general conditions described herein for the Passerini and Ugi reactions or in reactions that allow the preparation of compounds **11a** and **12a**. These experiments showed that the recycled polymeric material exhibits similar efficacy as an isocyanide scavenger after 5 runs to afford products with similar yields and purity.

## ASSOCIATED CONTENT

**S Supporting Information.** Detailed experimental procedures, analytical and spectroscopic data for all compounds described (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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