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Fluorous reagents and scavengers versus solid-supported reagents and scavengers, a reaction rate and kinetic comparison

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Summary

Reactions using fluorous reagents and scavengers are compared side-by-side with their solid-supported counterparts. Fluorous triphenylphosphine is used in the bromination reaction of alcohols, fluorous thiol is used as an electrophile scavenger for α-bromoketones, fluorous isatoic anhydride is used as a nucleophile scavenger for primary and secondary amines. Reactions involving fluorous reagents and scavengers occur in homogeneous media with solution-phase reaction kinetics. Reactions with solid-supported reagents and scavengers occur in a heterogeneous media, and the reaction kinetics is greatly affected by the nature of the solid-support and reaction environment. Significantly larger amounts of reagents and longer time are usually needed to complete the solid-supported reaction.

Keywords

fluorous reagents; fluorous scavengers; solid-supported reagents; solid-supported scavengers; triphenylphosphine; isatoic anhydride; thiol; reaction rate; reaction kinetics

Introduction

With the increasing practice of combinatorial and parallel synthesis to generate large numbers of compounds for biological screening, there are continuous needs to improve the efficiency of both the reaction and separation aspects of organic synthesis. An efficient way to improve the low conversion of reactions is to use reagent in excess. But this excess has an adverse effect on the efficiency of the product purification. To facilitate product purification, immobilized reagents and scavengers have been introduced in so called solid-supported solution-phase synthesis [1]. Excess reagents and scavenged byproducts on the solid support are readily separated from the reaction mixture by filtration. Since solid-supported solution-phase reactions are performed in a heterogeneous media, the advantage of easy separation can be counterbalanced by slow reaction, limitation on solvent selection, and the need to use large excess of the solid-bound reagent because not all the active sites on the solid-support are equally accessible.

The recent success of fluorous technologies has provided synthetic chemists opportunities to combine the advantages of solution-phase reactions and solid-phase separations [2]. Perfluoroalkyl chains instead of solid-supports are employed as “phase tags” to attach to substrates, reagents, or scavengers. The electronic effect of the perfluoroalkyl chain is minimized by insertion of an ethylene or propylene spacer between the tag and the functional group. Fluorous tags play a role similar to solid-supports in controlling the purification. Unique

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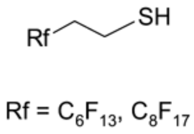
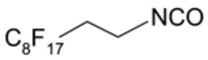
fluorous liquid-liquid extractions or fluorous silica gel-based solid-phase extractions efficiently separate fluorous molecules from non-fluorous molecules [3]. In addition to high solubility in organic solvents, fluorous tags are chemically inert and have good thermal stability for reactions conducted under microwave irradiation [4,5a].

The development of fluorous scavengers for electrophiles, nucleophiles, and dienophiles has been accomplished by the Curran group at the University of Pittsburgh [5], the Lindsley group at Merck [6], and our group at Fluorous Technologies, Inc [7]. We have recently reported the synthesis of fluorous thiol [7b], fluorous isocyanate, and fluorous isatoic anhydride [7c] and their applications to scavenge activated halides and amines, respectively. We found that only a slight excess amount of scavengers was needed in fluorous scavenging. The quenched materials were efficiently separated by fluorous solid-phase extraction to give products in 90% or even higher purities. Our preliminary results also indicated that fluorous scavenging is faster than the solid-supported scavenging [7b]. We report herein quantitative comparisons of two fluorous scavengers with their solid-bound counterparts in terms of reactivity and conversion rate. The experiments described in this paper focus on the quenching step of the scavenging reactions. Results on post-reaction workup and separation, reaction yields, and product purities associated with the scavenging reactions have been reported in the previous papers [7b–c].



F-thiols



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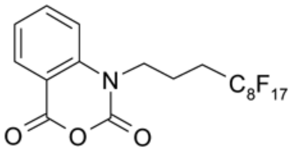

F-isatoic anhydride

Results and Discussion

In the thiol quenching study, the structural difference between the immobilized thiol and fluorous thiol was minimized by choosing fluorous 2-(perfluoroctyl)ethanethiol (F-thiol) **1** and silica gel-bound mercaptopropane (Si-thiol) **2**. Another commercially available polymer-bound thiol (PS-$CH_2NHCH_2CH_2SH$) was not selected because of significant structural difference (an amino group in the linker). The thiol quenching was performed by the reaction of 1.0 equiv of 2-bromo-4'-methoxyacetophenone **3a** with an excess amount of thiols **1** or **2** using diisopropylethylamine (DIPEA) as a base to promote the reaction and THF as the solvent. The reaction was carried out at room temperature. The reaction progress was monitored by taking aliquots from the reaction mixture at regular time intervals and was analyzed by GC with dodecane as an internal standard to determine the conversion of the bromide.

Results shown in Figure 1 demonstrate that when 1.5 equiv of F-thiol **1** was used (square-dot line), greater than 95% conversion was achieved in less than 40 min. The reaction with Si-thiol **2** (round-dot line) had much lower conversion; 50% of the halide was still unreacted even after 80 min. By doubling the amount of Si-thiol to 3.0 equiv, the reaction was significantly improved to gave 95% conversion after 60 min (diamond-dot line).

A similar study was conducted to compare reactions of F-isatoic anhydride **4** and PS-isatoic anhydride **5** [8] (cross-linked polystyrene with 1% DVB) with N-phenylpiperazine **7a**. Compound **6** bearing a C_8H_{17} group was synthesized by N-alkylation of isatoic anhydride and also included in the comparison experiment. Of course, compound **6** has no phase tag so it has no utility in actual scavenging applications; it only serves as a control to illustrate normal solution-phase reactivity. Reactions were performed in CH_2Cl_2 at room temperature. The data compiled in Figure 2 shows that reactions using 1.5 equiv of fluorous compound **4** (square-dot line) or non-fluorous compound **6** (triangle-dot line) were very similar. The fluorous reaction was slightly faster than the non-fluorous reaction. We attribute the fast reaction rate to the electronic-withdrawing effect of the fluorous tag which enhances the electrophilicity of compound **4** despite the propylene spacer [9]. A similar reaction with polymer-supported compound **5** proceeded much slower (round-dot line). Doubling the amount of **5** to 3.0 equiv increased the reaction rate (diamond-dot line), but it was still not as fast as either the reaction with 1.5 equiv of F-isatoic anhydride **4** or octylated isatoic anhydride **6**.

We have compared the reaction rate of different scavengers as the function of time (Figures 1 and 2). We also evaluated the performance of different scavengers with different substrates. Three α-bromoketones **3a–c** with different substituents on the benzene ring were selected to react with thiols and three amines **7a–c** including one primary and two secondary amines were selected to react with isatoic anhydrides.

Reactions of α-bromoketones **3a–c** with F-thiol **1** and Si-thiol **2** were performed under the same conditions: 1.0 equiv of **3** was reacted with 1.5 or 3.0 equiv of thiols **1** or **2** using DIPEA as a base and THF as a solvent. The reaction was carried out at room temperature for 1 h. The reaction mixture was analyzed by GC with dodecane as an internal standard to determine the conversion of α-bromoketones **3a–c**. The data compiled in Figure 3 are consistent with the results observed in the previous experiment. F-thiol **1** had better performance than Si-thiol **2** with all three substrates. Doubling the amount of Si-thiol **2** was necessary to catch up to the performance of the F-thiol **1**. The reaction of **3a** with F-thiol **1** was completion, but the reaction with Si-thiol **2** was only 50% complete and with 3.0 equiv of Si-thiol was only 97% complete. The reaction of α-bromoketone **3b** suggested that even 3.0 equiv of Si-thiol **2** was not enough to drive the conversion to completion in 1 h.

Reactions of three different amines **7a–c** with F-isatoic anhydride **4** or PS-isatoic anhydride **5** were performed at 55 °C (Figure 4). The reaction of **7a** with F-isatoic anhydride **4** went to completion within 30 min whereas that with the PS-isatoic anhydride **5** only went 32% completion. Doubling the amount of **5** to 3.0 equiv only pushed the reaction to 64% completion. In all these three cases, 3.0 equiv of PS-isatoic anhydride **5** was not enough to drive the reaction to completion whereas only 1.5 equiv of F-isatoic anhydride **4** was enough to complete the reaction.

In addition to evaluation of supported scavengers, we also used triphenylphosphine (TPP) as an example to evaluated supported reagents. TPP has been involved in many important organic transformations such as Wittig, Mitsunobu, Staudinger reactions, halogenation reactions, and Pd-catalyzed reactions [10]. Separation of triphenylphosphine oxide from the TPP reaction usually requires chromatography. Recently, PS-TPP [11] and F-TPP [12] have been used to simplify the byproduct separation process. The Lindsley group studied the Staudinger reaction using F-TPP **8** and two polymeric TPPs with cross-linked polystyrene **9a** and cross-linked NovaGel™ **9b**, respectively [13]. In THF solution, it took 1 h for F-TPP **8** to convert the azide to the phosphoazide, an intermediate for the amine product, compared to 36 h for polymer-bound TPPs **9a** and **9b** to complete the same process. The reaction with F-TPP was not only faster than its resin-bound counterparts, it also gave 100% conversion with product purity greater than 98%. Polystyrene-bound TPP gave 26% conversion with >86% product purity and NovaGel-bound TPP gave 60% conversion with the same purity.

We conducted a comparison experiment by reaction of 1.5 equiv of different TPPs (F-TPP **8,** PS-TPP **9,** and normal TPP **10)** with 1.0 equiv of 2,4-dimethoxybenzyl alcohol **11** and 1.5 equiv of CBr_4 in toluene by following a literature procedure reported by the Sinou group [12h]. The reaction mixture was shaken at room temperature and monitored by GC using dodecane as an internal standard to determine the conversion of **11**. Results presented in Figure

4 shows reactions with F-TPP (square-dot line) were slightly slower than the normal TPP (triangle-dot line), but they have very similar reaction pattern; a 90% conversion was achieved after 180 min for both reactions. We were interested to find that during the first 10–15 min, the reaction with 1.5 equiv of PS-TPP **10** (round-dot line) proceeded a little faster than reactions with F-TPP or normal TPP. However, the reaction with PS-TPP slowed down and the conversion was less than 80% after 180 min. The reaction with 3.0 equiv of PS-TPP gave a significantly better result (diamond-dot line); the conversion was over 95% in less than 100 min.

The experimental results suggest that reaction kinetics with PS-TPP is different from that with fluorous and normal TPPs. The polymer-supported reagent does not always react slower than the fluorous counterpart at a given reaction time, but the conversion rate is low because not all functional groups on the polymer bead are easily accessible. Polymer-supported reagents are greatly affected by the nature of polymer support and reaction solvent system which made polymer-supported reactions less predictable. The influence of polymer supports on reaction rate and kinetics have been extensively studied [14].

Conclusions

These comparison experiments have demonstrated that when equal molar amounts of material are used, reactions with fluorous reagents and scavengers usually proceed faster and give higher conversion than reactions with solid-supported analogs. Fluorous reagents and scavengers are *real molecules*, they can be used in a stoichiometric manner and analyzed by standard methods such as LCMS and NMR. Solid-supported reagents and scavengers are *functionalized materials*, their chemical and physical properties such as loading, swelling, particle size, and percentage of cross-linking usually have a range of variation and are difficult to be assessed by the users. It is not uncommon that because of these uncertainties and unfavorable heterogeneous reaction kinetics, chemists use a large excess (3.0 equiv or even more) of solid-supported reagents and scavengers to “over kill” the reactions. This kind of practice results in high cost on reagents as well as high volume of solvent used for reaction and resin washes after the reaction. These are found not to be the issues in fluorous-supported reactions.

Experimental section

Procedure for reactions of halides 3 with thiols 1 or 2

Fluorous thiol **1** (Fluorous Technologies, Inc. 72.3 mg, 0.15 mmol) was dissolved in 1.0 mL THF in a vial. The internal standard dodecane (23.0 μL, 0.14 mmol), diisopropylethylamine (26.0 μL, 0.15 mmol), and 2-bromo-4’-methoxyacetophenone **3a** (23.0 mg, 0.1 mmol) were added. The mixture was shaken on a MS 1 Minishaker at 600 rpm. Prior to the addition of the base, an aliquot of 10.0 μL was taken, diluted in 300 iL of THF and injected into GC to obtain the ratio of α-bromoketone to the standard from the peak areas. This ratio was taken as the starting point ($t_0 = H_0/S_0 = X_0$; where H_0 = peak area of the α-bromoketone and S_0 = peak area of the standard, and X_0 = ratio). Aliquots of 10.0 μL were taken at given time intervals, diluted in 300 μL of THF and injected into the GC for ratio analysis. The ratio of the α-bromoketone to the standard at subsequent time ($t_n = H_n/S_n = Y_n$) was used to calculate the remaining amount of α-bromoketone as a percentage $(Y_n/X_0)100 = Z_n\%$ which gives the reaction completion $(100 – Z_n)\%$. GC conditions: 100% dimethylpolysiloxane, 30m x 0.32 mm, 25 micron column; initial time 1 min at 150 °C, 100 to 250 ºC at 20 °C/min, remain at 250 ºC for 10 min. Similar reactions and data collection processes were applied to silica-supported thiol **2** (Aldrich cat # 53808-6, 200–400 mesh, 0.3–0.9 mmol S/g, average loading 0.6 mmol/g was used for calculations). The percent completion was plotted against time (min) to give the graphs in Figure 1. Comparison reactions of thiols **1** or **2** with different bromides

3a–c were conducted at room temp under stirring. Reaction mixtures were analyzed at 60 min. The conversion data were collected and presented in Figure 4.

General procedure for the reaction of amine 7 with isatoic anhydrides 4–6

F-isatoic anhydride **4** (Fluorous Technologies, Inc., 144.0 mg, 0.23 mmol) was dissolved in 1.0 mL of CH_2Cl_2 in a vial. The internal standard dodecane (24.0 iL, 0.14 mmol) and phenyl piperazine **7a** (24.0 μL, 0.15 mmol) were added and the reaction mixture was shaken on a MS 1 Minishaker at 600 rpm at room temperature. Prior to the addition of the amine, an aliquot of 30.0 μL was taken out, diluted with 1.0 mL of CH_2Cl_2 and injected into the GC to obtain X_0. At intervals of 30 minutes an equal amount of aliquot is taken out from the reaction vial and subjected to GC analysis to obtain Y_n. Same GC analysis and data collection methods as described above were used in this experiment. Similar reactions with PS-isatoic anhydride **5** (Aldrich, part # 51,437–3, 1% DVB, 200–400 mesh, 2.0–2.5 mmol N/g, average loading 0.23 mmol was used for calculations) and N-octyl isatoic anhydride **6** were conducted. The data of the percent completion were collected and plotted against time (min) to give the graphs in Figure 2.

Reactions of isatoic anhydrides **4** or **5** with different amines **7a–c** were conducted at 55°C under stirring. Reactions with **7a** and **7c** were analyzed at 30 min while the reaction with **7b** was analyzed at 60 min because of low reactivity of this substrate. The conversion data is presented in Figure 4.

General procedure for reactions of 2,4-dimethoxybenzyl alcohol 11 with triphenylphosphines 8, 9a, or10

Fluorous triphenylphosphine **8** (Fluorous Technologies, Inc., 318.0 mg, 0.45 mmol) was dissolved in 2 mL of toluene in a vial. The internal standard dodecane (25.0 iL, 0.15 mmol), 2,4-dimethoxybenzyl alcohol (50.0 mg, 0.30 mmol), and CBr_4 (149.0 mg, 0.45 mmol) were added at room temperature. The reaction mixtures were shaken on a MS 1 Minishaker at 600 rpm. Prior to the addition of CBr_4, an aliquot of 30 μL was taken out, diluted with 1.0 mL of toluene and injected into the GC to obtain X_0. At different reaction time, an equal amount of aliquot is taken out from the reaction vial and subjected to GC analysis to obtain Y_n. Same GC analysis and data collection methods described above were used in this experiment. Similar reactions with PS-triphenylphosphine **9a** (Argonaut, part # 800378, 2.1 mmol/g) and normal triphenylphosphine **10** were conducted. The data was collected and plotted against time (min) to give the graphs in Figure 5.

Acknowledgements

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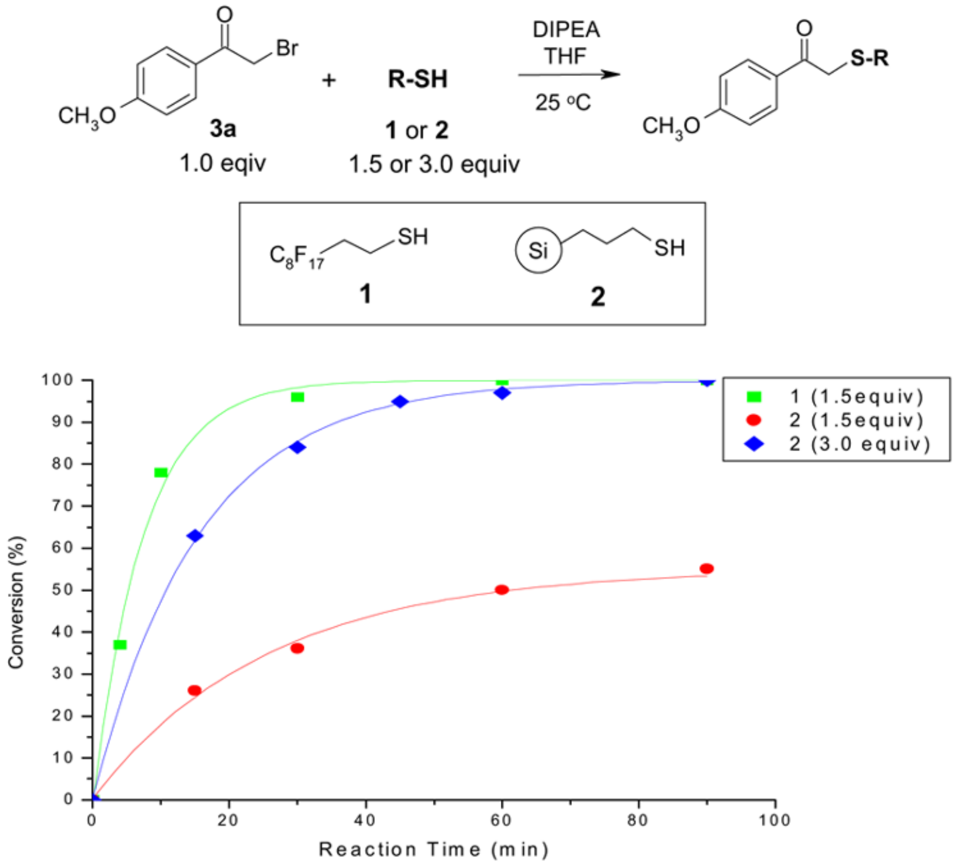


Figure 1.

Reactions of α-bromoketone **3a** with thiols **1** or **2**

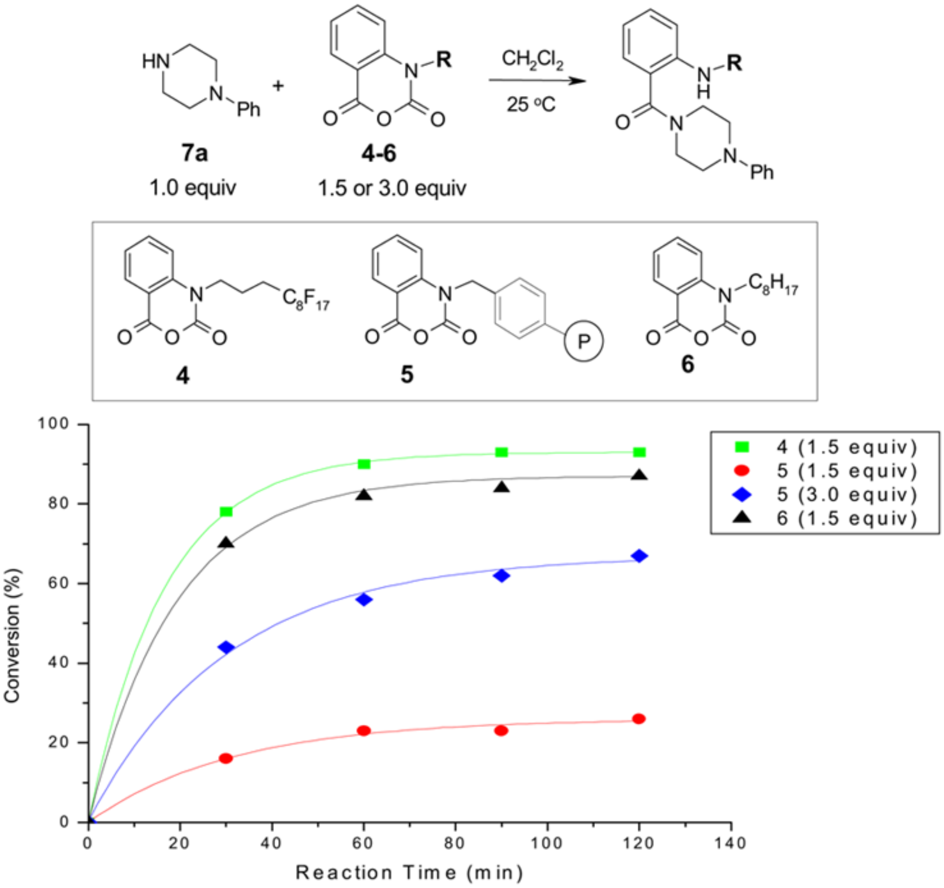


Figure 2.

Reactions of N-phenylpiperazine **7a** with isatoic anhydrides **4–6**

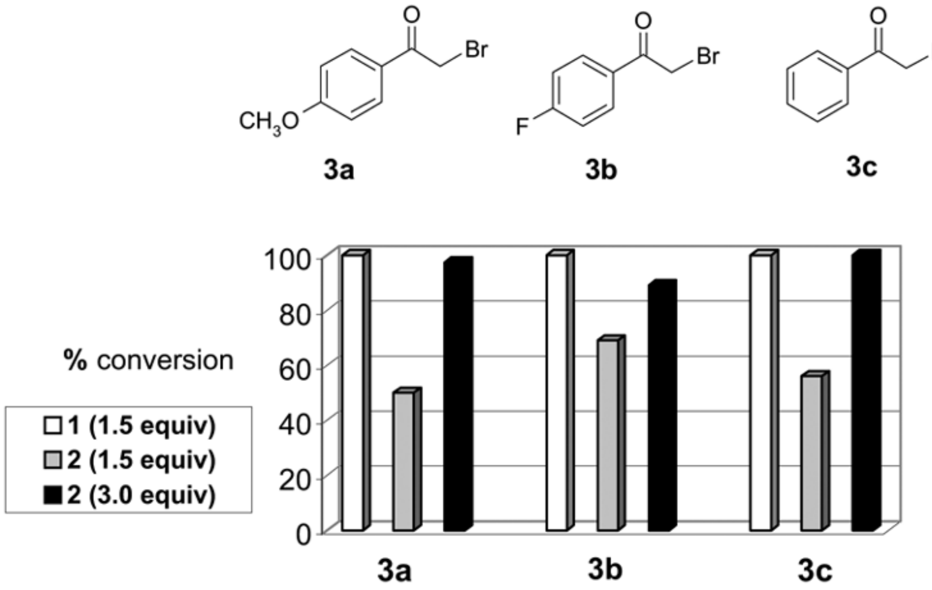


Figure 3.

Reactions of three α-bromoketones **3a–c** with F-thiol **1** and Si-thiol **2**. Bars in 3 different patterns represent 2 different thiols and different equiv. The first group represents the data obtained with **3a**, the second group obtained with **3b,** and the third, **3c**

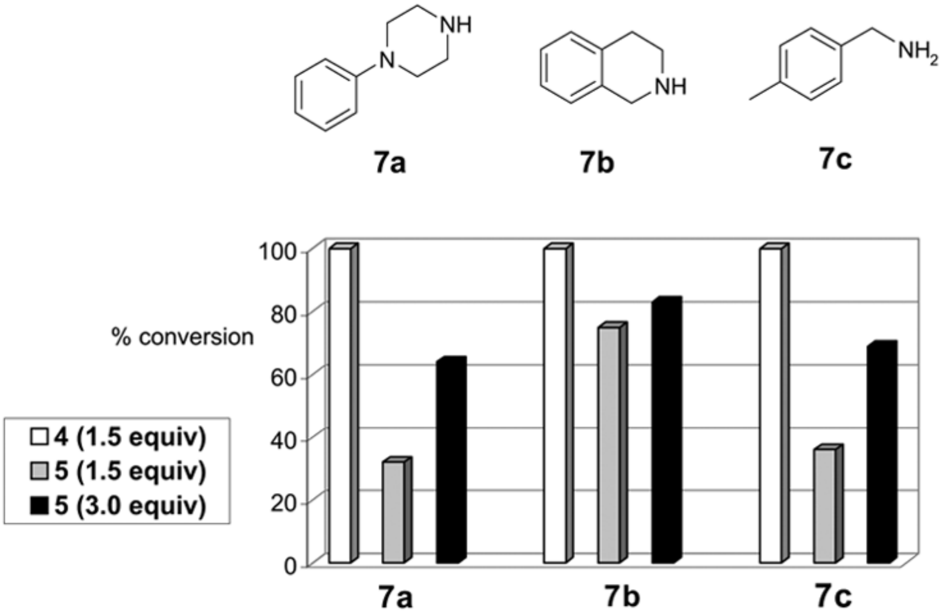


Figure 4.

Reactions of amines **7a–c** with F-isatoic anhydride **4** or PS-isatoic anhydride **5**. Bars in 3 different patterns represent 2 different thiols at different equiv. The first group represents the data obtained with **7a**, the second group obtained with **7b,** and the third, **7c**

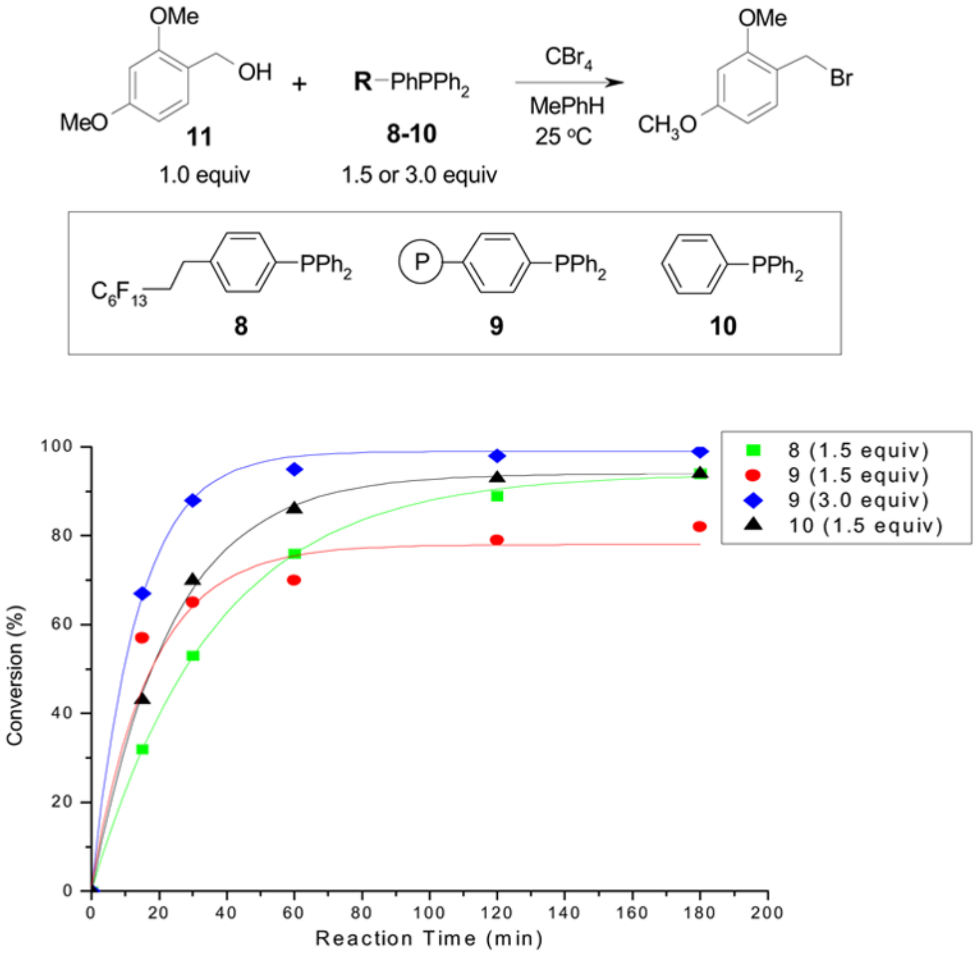
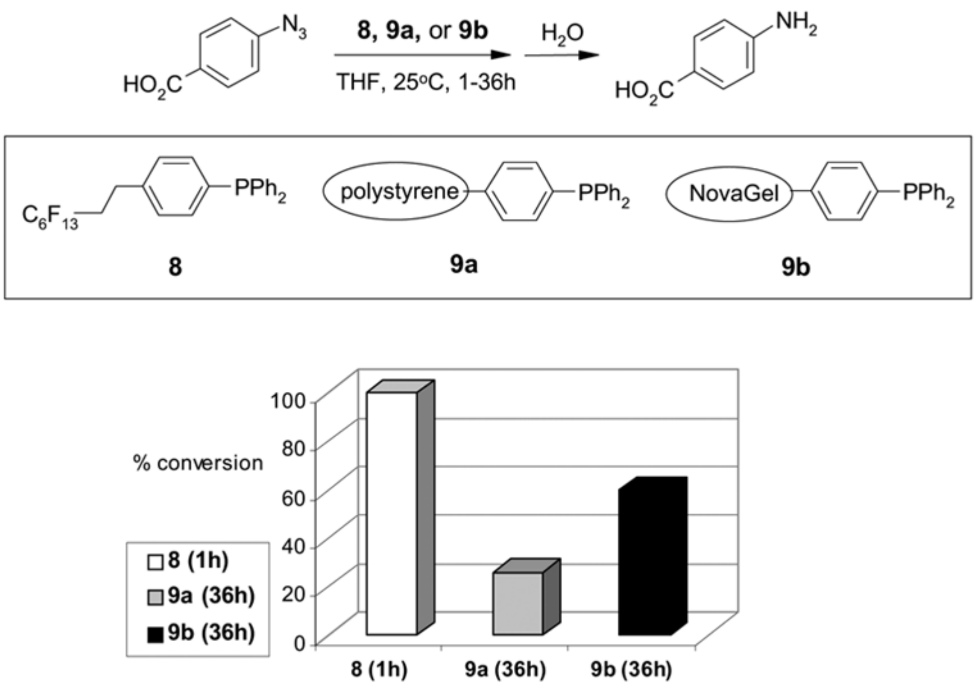


Figure 5.

Reactions of 2,4-dimethoxybenzyl alcohol **11** with triphenylphosphines **8–10** and CBr_4



Scheme 1.

Staudinger reactions with triphenyl phosphines **8**, **9a** and **9b**