# Utilizing bound reagents & scavengers with microwave heating, an enabling strategy in medicinal chemistry

Shahnaz Ghassemi
Biotage, Discovery Chemistry Group1725 Discovery Drive Charlottesville, VA 22911

## Introduction

The utilization of bound reagents for the solution phase synthesis has become an important tool in synthesis of biologically active molecules. The disadvantage of this technique is the relative slow rate of reaction. Microwave irradiation has been used to overcome this problem and increase rate of reaction of solid-assisted solution phase synthesis. This presentation covers developing efficient and robust strategies for the preparation of an array of cyclic tertiary amines using microwave irradiation in conjunction with bound reagents and scavengers such as MP-cyanoborohydride.

**Reductive amination**:

Polymer bound borohydride, cyanoborohydride and triacetoxyborohydride (Figure 1) are versatile reducing agents used for the reduction of carbonyl compounds and imines, as in reductive amination of aldehydes and ketones. The resin bound borohydride reagent, in conjunction with some transition metal salts, can also be used for a number of other important reductive applications, such as reduction of oximes, azides and alkyl halides. The macroporous triacetoxyborohydride resin reacts with the water of condensation liberated on imine formation during reductive amination reactions.

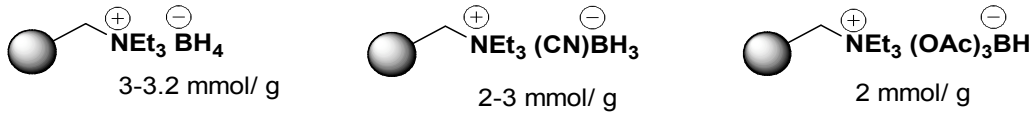



Figure 1

These reagents have received lot of attention due to following physical properties.

- Limited swelling
- Very little pressure build up under acidic conditions
- Masked toxicity
- Easy to handle and work-up

It has been reported that MAOS can shorten time required for the reaction of these bounded reducing agents (Figure 2 and Table 1).

Figure 2

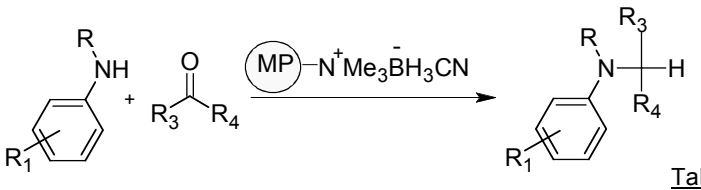



Table 1

| | Conventional | Microwave |
|---|---|---|
| Temp | RT | 110-130 ºC |
| Time | 16-24 h | 5-7 min |
| Solvent | THF/MeCN | DCM |
| % HOAC | 20 | 10-20 |

Biotage

**Reductive amination purification strategies**

Solid-supported scavengers are typically nucleophiles or electrophiles that interact and bind excess substrate or reagent, thus simplifying work-up and purification of solution phase chemistry. The concept was utilized in 1980 by Frechet, who utilized solid-bonded primary amines for selective removal of allergens present in natural oils. Later Carpino cleaved the 9-fluorenylmethyloxycarbonyl (Fmoc-) amino-protecting group utilizing solid-supported cyclic secondary amines which simultaneously scavenged the dibenzofulvene (DBF) liberated in the process. This concept was widely used in the parallel purification of solution phase combinatorial libraries. Here we report using of Polymer bound cyanoborohydride and triacetoxyborohydride in conjunction with microwave energy in rapid, reductive amination of aldehydes and ketones Table 3. In these process 1 equivalent of amines and 1.2 equivalent of carbonyl compounds where used. The resulting products were isolated from reaction mixture either using by ISOLUTE Si-TsOH in catch and release technique or Si-TS-Hydrazine is used for scavenging excess carbonyl group.

**"Catch and Release" Purification of Amines**

ISOLUTE Si-TsOH is a strong cation exchanger (SCX) for the "Catch and Release" purification of amines.Si-benzenesulfonic acid (Si-TsOH) can be used for fast isolation of reductive aminaton mixture through catch and release mechanism. ISOLUTE® Si-TsOH is stable to microwave heating and was reported s an excellent replacement to p-TsOH in both thermal and microwave assisted acid catalyzed reaction.

ISOLUTE Si-TsOH is a strong cation exchanger (SCX) for the "Catch and Release" purification of amines. When a solution containing an amine is passed through a Si-TsOH (SCX-3) column the amine is retained or "caught" by the SCX-3. Non-basic impurities are not retained and are further removed by washing the column with an organic solvent, such as methanol, acetonitrile or THF. The product is subsequently "released" from the column by elution with a solution of ammonia in methanol. Amine salts of weak conjugate acids (e.g. acetate and trifluoroacetate) are exchanged onto the silica and are released as the free amine during the ammonia/methanol wash (Figure 3).

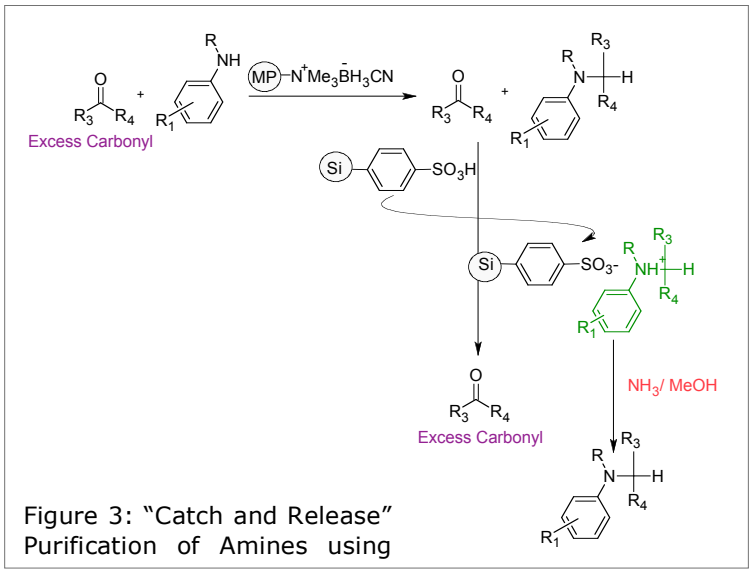
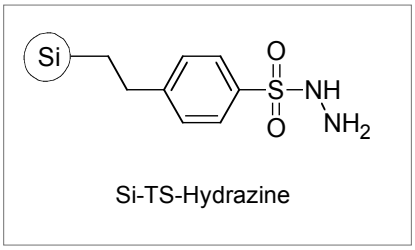



Figure 3: "Catch and Release" Purification of Amines using




Si-TS-Hydrazine

**Si-TS-Hydrazine in rapid purification of reductive amination products**

2-(4-Toluenesulfonyl hydrazine) ethyl functionalized silica (Si-TS-Hydrazine) is a silica supported equivalent of p-toluenesulfonyl hydrazine. This bonded reagent is an excellent scavenger for aldehydes and ketones (figure 5).

Biotage

The best rate of scavenging of aldehydes was achieved when 5% of acetic acid was added to the solvent (THF) also microwave irradiation has shown to increase the rate of scavenging at a shorter time (figure 4 Table 2).

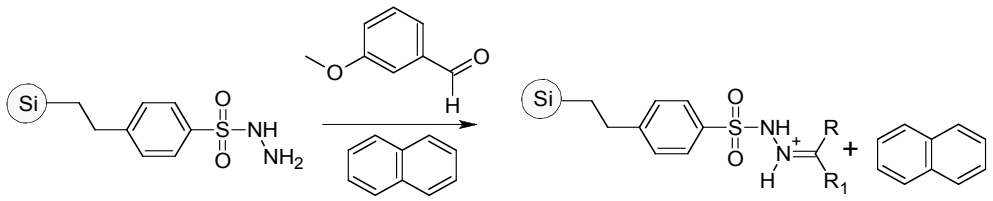


Figure 4: Scavenging aldehyde by Si-TS-Hydrazine

Table 2

| Solvent | THF | THF + 5% HOAc | THF + 5% HOAc |
|---|---|---|---|
| Condition | 30 min. R.T. | 30 min. R.T. | μW, 5 min. 100 ºC |
| Scavenged | 82 % | 90 % | 98 % |

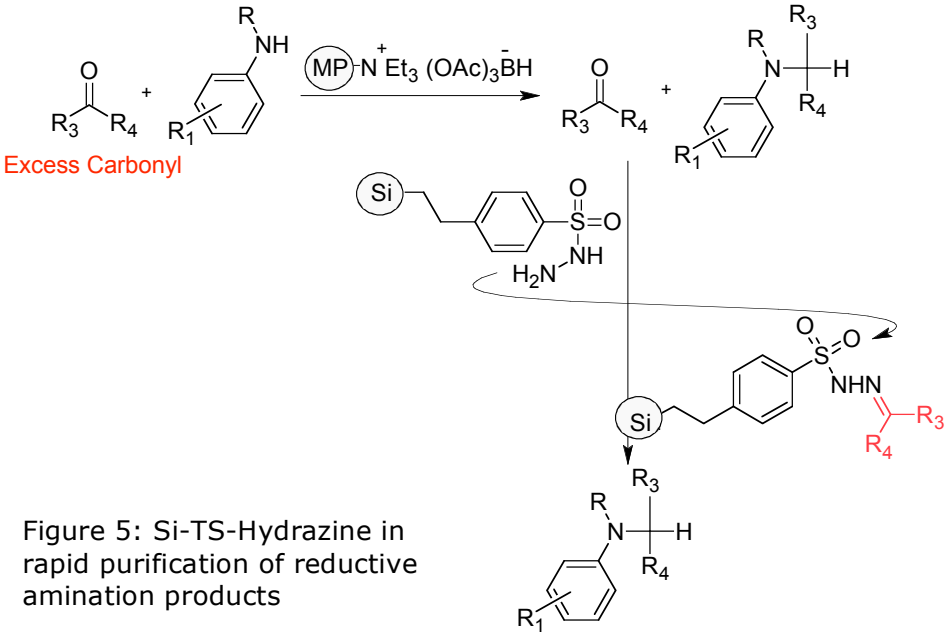
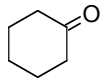
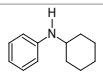
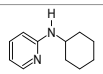
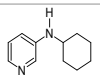
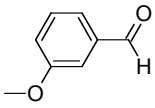
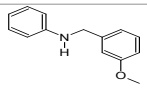
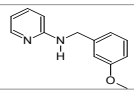
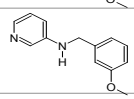
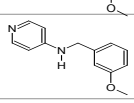
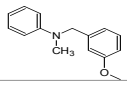



Figure 5: Si-TS-Hydrazine in rapid purification of reductive amination products

Biotage

Table 3: Isolated Yields, HPLC Purity

| Carbonyl | Amine | ISOLATED Yield | % HPLC purity |
|---|---|---|---|
|  |  |  95 | 100 |
| |  |  63 | 100 |
| |  |  67 | 100 |
| |  |  76 | 100 |
| |  |  73 | 88 |
|  |  |  71 | 100 |
| |  |  79 | 99 |
| |  |  73 | 100 |
| |  |  82 | 98 |
| |  |  84 | 98 |

## Conclusion

Solution phase synthesis employing solid supported reagents and scavengers in combination with MAOS has received greater importance and will become significant techniques in speeding up the drug development process, especially since in this protocol all aqueous washes and chromatography purification step have been eliminated.


**www.biotage.com**

**United States and Canada**
Tel: +1 434 979 2319
Toll-Free: +1 800 446 4752
ordermailbox@biotage.com

**United Kingdom, EIRE**
Biotage
Tel: +44 1992 501535
order@eu.biotage.com

**Sweden**
Biotage
Tel: +46 18 56 59 00
order@eu.biotage.com

**Japan**
Biotage
Tel: +81 422 281233
order@biotage.co.jp


Biotage