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Tetraallylstannane and Weinreb amides: a simple 'green' route to *N*-protected homoallylic alcohols and allyl ketones

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Abstract

We have explored the addition of tetraallylstannane (**7**) to a variety of *N*-protected Weinreb amides (*N*-phthalimido and *N*-benzyl). Reactions were conducted in methanol and the ionic liquid, butylmethylimidazole tetrafluoroborate (bmim[BF_4]), yields of the corresponding *N*-protected allylketones were moderate to good. Allylation of the corresponding aminoaldehydes gave excellent yields of homoallylic alcohols (68–94%) and moderate to good diastereoselectivities (50–86%). © 2000 Published by Elsevier Science Ltd.

Keywords: Weinreb amides; tetraallylstannane; green chemistry; homoallylic alcohols; allyl ketones.

Over the past few years the allylation of α-amino aldehydes has been exploited as a key step towards the stereoselective synthesis of statine and hydroxymethylene dipeptide isosteres.[1] We too have been involved in this area recently reporting the *syn*-diastereoselectivity in the high-pressure addition of allyltrimethylstannane to *N*-protected α-aminoaldehydes.[2]

More recently we have been keen to develop organostannanes as reagents for green chemistry.[3] Our main criteria for such reagents are:

- Reactions should be conducted in environmentally benign solvents, or in the total absence of solvent.
- They should be high yielding reactions with high atom efficiency.

Our previous report of the high pressure addition of allyltrimethylstannane **2** is typical of an organostannane based reaction, in that the reaction is moderately efficient and only a small proportion of the atoms present on the reagent are found in the final product, Scheme 1.

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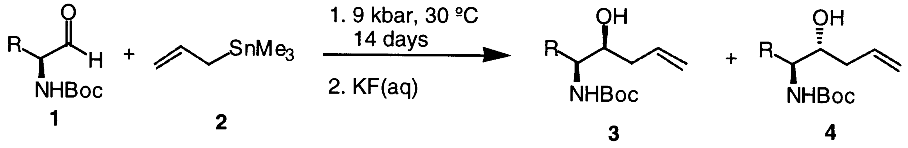


1 **2** **3** **4**

Scheme 1.

We have previously shown that allylations using **2** proceed under the influence of high pressure.[2] More recently we have also demonstrated that similar allylations with **7** proceed rapidly in methanol,[4] water,[3] and the ionic liquids bmim[BF_4] and bmim[PF_6],[5] especially in the case of aliphatic aldehydes. Ionic liquids are perhaps the ideal solvent, possessing no vapour pressure, are tunable to the requirements of the reaction, have a wide range operating temperatures (−100 to +400°C with the correct choice of ionic liquid), and importantly are easily recycled. The most commonly utilised ionic liquids are those based on 1-methyl imidazole,[6] see Fig. 1. With tetraallylstannane it is possible to obtain excellent yields in the case of ketones at methanol reflux. However, we have been unable to successfully allylate esters. Herein, we wish to report our recent development in the use of tetraallylstannane (**7**) as a reagent for green chemistry.

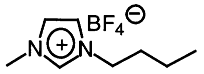
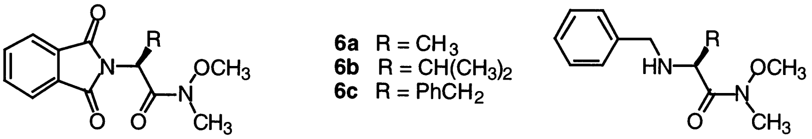

bmim[BF_4]

Figure 1.

Weinreb amides have been widely used as one of the key steps in the stereoselective synthesis of statine and hydroxymethylene dipetide isosteres.[1] It occurred to us that we may be able to allylate the parent amide and by varying the amine protecting group, and in the case of the corresponding aldehydes, influence the stereochemical outcome of the procedure. In conducting these reactions we limited our choice of solvent to methanol and bmim[BF_4].

Our initial studies on the parent Weinreb amides (Fig. 2) proved fruitless, no reaction was observed either in methanol or bmim[BF_4] after stirring at 30°C for 24 hours.

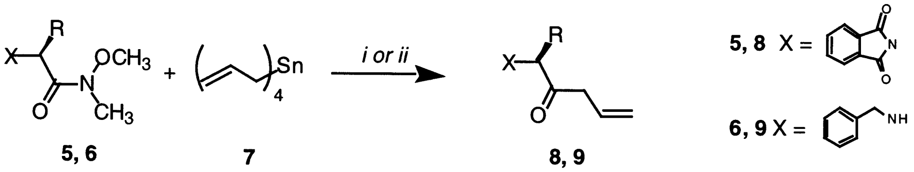


5a R = CH_3
5b R = $CH(CH_3)_2$
5c R = $PhCH_2$

6a R = CH_3
6b R = $CH(CH_3)_2$
6c R = $PhCH_2$

Fig. 2.

However, at methanol reflux after 2 hours we detected low yields of the corresponding *N*-protected allylketones (**8**, **9**), Scheme 2. Prolonged reflux, 5 days, afforded moderate to good yields. Stirring in bmim[BF_4] for 5 days at 50°C had a similar result, Table 1.

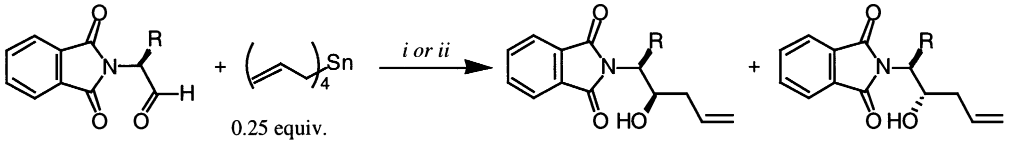


5, 6 **7** **8, 9**

Scheme 2. Conditions: (*i*) Methanol reflux, 5-days; (*ii*) bmim[BF_4], 50°C, 5-days

Table 1
Yields of *N*-protected allyl ketones after treatment of *N*-protected Weinreb amides, **5** and **6**, with **7**

Amide	Allylketone yield (%)	Amide	Allylketone yield (%)
5a	33	**6a**	42
5b	39	**6b**	46
5c	55	**6c**	56



10 **7** *syn* - **12** *anti* - **13**

10a R=CH_3; **10b** R=$CH(CH_3)_2$; **10c** R=$PhCH_2$

Scheme 3. Conditions: (*i*) Methanol 30°C, 24 h; (*ii*) bmim[BF_4], 30°C, 24 h

In a typical procedure, the Weinreb amide (10 mmol) was dissolved in methanol (5 mL) and to this was added **7** (0.705 g, 2.5 mmol) in methanol (5 mL) and the homogeneous mixture set to reflux for 5 days. After this time the cloudy mixture was cooled, poured onto water (50 mL), extracted with dichloromethane (3×25 mL), dried over Na_2SO_4, and the solvent removed to yield the crude product. With bmim[BF_4] the reaction is essentially identical, using 2 mL and adding **7** directly via a syringe, and the clear mixture warmed to 50°C for 5 days, followed by extraction with diethylether (bmim[BF_4] is miscible with dichloromethane).

A slight modification of the procedure was required in the case of the more reactive *N*-protected aminoaldehydes. In these instances the reactions were conducted at 30°C for 24 hours and then worked up as before. In all instances the expected homoallylic alcohols, Scheme 3, were generated in good to excellent yields, see Tables 2 and 3.

Table 2
Observed diastereoselectivity after addition of **7** to *N*-phthalimido protected aminoaldehydes, **10a–c**[a]

Entry	Compound	R	Ratio of *syn*-(**12**):*anti*-(**13**)[7]	Yield (%)	Yield (%)	d.e. (%)[b]
				Bmim[BF_4]	MeOH	
1	**10a**	CH_3	75:25	82	94	50
2	**10b**	$CH(CH_3)_2$	89:11	56	68	78
3	**10c**	$PhCH_2$	91:9	45	80	82

[a] L-amino acids were used in the generation of the Weinreb amides, followed by $LiAlH_4$ reduction.
[b] Determined by ^1H and ^{13}C NMR on a Varian AMX 300 MHz spectrometer.

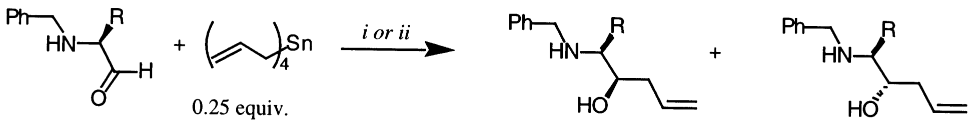
Table 3
Observed diastereoselectivity after addition of **7** to *N*-benzyl protected amino aldehydes, **11a–c**[a]

Entry	Compound	R	Ratio of *syn*-(**14**):*anti*-(**15**)[7]	Yield (%)	Yield (%)	d.e. (%)[b]
				Bmim[BF_4]	MeOH	
1	**11a**	CH_3	82:18	72	87	64
2	**11b**	$CH(CH_3)_2$	93:7	70	74	86
3	**11c**	$PhCH_2$	93:7	73	82	86

[a] L-amino acids were used in the generation of the Weinreb amides, followed by $LiALH_4$ reduction.
[b] Determined by ^1H and ^{13}C NMR on a Varian AMX 300MHz spectrometer.

Disappointingly, we found no evidence of improved diastereoselectivity on using bmim[BF_4] as the solvent of choice, indeed using this system we achieved identical d.e.'s but with lower chemical yields. We believe that the lower yields were a result of two factors. Firstly, product extraction is slightly more difficult with the ionic liquid, and secondly the lower reaction temperature. We are currently examining a wide-range of ionic liquids to determine the most suitable system for this type of reaction, these results will be presented in due course.

We also conducted the equivalent transformations using the mono-*N*-benzyl-protected Weinreb amides (Scheme 4), these reactions proceeded exactly as the phthalimido series had, and the results are shown in Table 3.



11 **7** *syn* - **14** *anti* - **15**

11a R=CH_3; **11b** R=$CH(CH_3)_2$; **11c** R=$PhCH_2$

Scheme 4. Conditions: (*i*) Methanol 30°C, 24 h; (*ii*) bmim[BF_4], 30°C, 24 h

Examination of Tables 2 and 3 suggest that the observed diastereoselectivity, is therefore a function of both the amino acid, with Leu and Phe showing the best selectivity (Tables 2 and 3, entries 2 and 3, respectively), and the *N*-benzyl protecting group yielding the best d.e. = 86% (Table 3, entry 3).

These results show significant improvement upon, in a number of ways, our previous report of Boc-protected amino aldehydes and reaction with allyltrimethylstannane. In those instances the best d.e. observed was 76%. However, access to a high-pressure reactor was required. Thus, in addition to increasing (albeit modestly) the diastereomeric excess of this type of reaction, it is now considerably simpler, able to be conducted in any basic laboratory. Additionally we have achieved a considerable increase in the atom efficiency of the process, only the Sn-atom of **7** is not transferred to the product. Judicious choice of the solvent allows for a simple, environmentally benign solvent being used, or in the case of the ionic liquid, a solvent that can be easily recycled.

Acknowledgements

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7. *Syn*:*anti* ratios were assigned on the basis of the ^{13}C chemical shift data for each species, see ref 2 and references cited therein.