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The rate of elimination of a β-amino zinc reagent is *reduced* by using a *better* leaving group†

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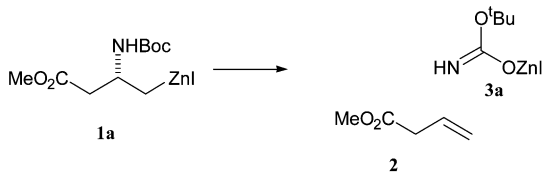
Replacing the *N*-Boc-protecting group on a β-amino organozinc reagent with a trifluoroacetyl group, which would be expected to make the nitrogen a better leaving group, results in a reagent that is more stable towards elimination.

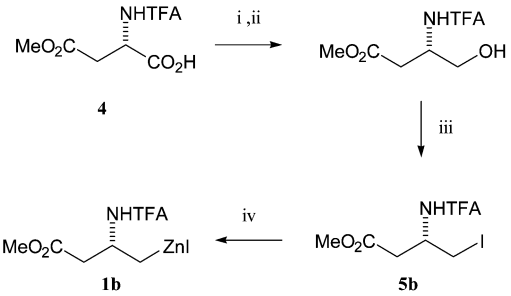
We have previously reported that the organozinc reagent **1a**, when prepared in either THF or DMF, decomposes *via* a well-behaved first-order process leading to methyl but-3-enoate **2**, as well as the presumed zinc salt **3a** (Scheme 1).[1] The rate of this elimination in DMF is sufficiently slow that good yields may be obtained in the palladium-catalysed cross coupling of organozinc reagent **1a** with aryl iodides, leading to a wide range of β-phenylalanine derivatives.[2] We have presented a range of circumstantial evidence that the mechanism of the decomposition is a *syn*-elimination (for example, the activation entropy is large and negative),[1] in which internal coordination of the carbonyl group to zinc is important.



Scheme 1 Elimination of β-amino zinc reagent **1a**.

With the primary aim of understanding the factors which influence this elimination reaction more completely, and with the secondary aim of improving the yields in the palladium-catalysed cross-coupling of zinc reagents related to **1**, we decided to explore the effect of changing the nature of the nitrogen protecting group. Although the nucleofugality of different leaving groups is not necessarily directly linked to the pK_a of the conjugate acid of the leaving group,[3] such a relationship can exist when the leaving groups are all of the same type (specifically, the same atom and charge).[4] Normally, a better leaving group, as indicated by a lower pK_a of the corresponding conjugate acid, would result in a faster rate of elimination. However, if the elimination reaction were dependent upon initial coordination of the leaving group to zinc, the opposite effect would be observed. Literature pK_a data determined for CF_3CONH_2 (17.15) and $EtOCONH_2$ (24.6)[5] indicate that a very significant difference is to be expected in their leaving group ability, with CF_3CONH^- a substantially better leaving group. With this in mind, we have explored the preparation and stability of the trifluoroacetyl-protected zinc reagent **1b** in DMF.

The precursor **5b** to the zinc reagent **1b** was prepared in a conventional manner from the known protected aspartic acid derivative **4**[6] (Scheme 2). Formation of the zinc reagent **1b** was achieved in d_7-DMF using a modification of our standard method.[1] Activation of zinc dust using chlorotrimethylsilane can be conveniently achieved by an adaptation of Hiemstra's protocol,[7] in which the solvent used during the activation, containing residual chlorotrimethylsilane and dissolved zinc chloride, is removed prior to use of the activated zinc. Thus, undeuterated DMF can be used in the first step, so that the amount of d_7-DMF that is required is reduced. This procedure has the advantage that it is possible to use a larger amount of chlorotrimethylsilane in the activation process, which results in greater reliability in the subsequent zinc insertion. It also resulted, somewhat unexpectedly, in a reduction in the elimination rate (*vide infra*).



Scheme 2 *Reagents and conditions*: i, *N*-Hydroxysuccinimide, DCC, EtOAc, 0 °C to room temp.; ii, $NaBH_4$, THF/H_2O, 0 °C; iii, PPh_3, I_2, imidazole, CH_2Cl_2; iv, Zn (activated with TMSCl), d_7-DMF, 0 °C.

The most striking feature of the ^{1}H NMR spectrum of **1b** in d_7-DMF is that the methylene group adjacent to zinc appears as a simple doublet, in sharp contrast to the corresponding Boc-protected derivative **1a** (Fig. 1). This provided circumstantial evidence that the interaction between the carbonyl group and the zinc had been suppressed.

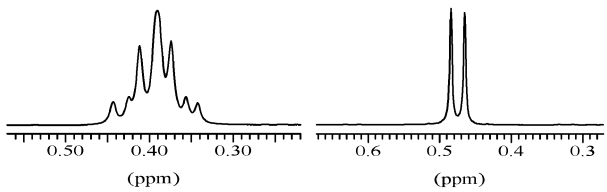


Fig. 1 Partial ^{1}H NMR spectra, showing signals due to CH_2ZnI for zinc reagent **1a** (left) and **1b** (right).

The decomposition of organozinc reagent **1b** was studied by ^{1}H NMR at 300 K. Two competing processes, namely elimination (the major pathway) to give methyl but-2-enoate **2** and protonation to give β-alanine **6** were observed (Scheme 3). The greater tendency for the organozinc reagent **1b** to protonate (compared with **1a**) is reasonably rationalized on the basis of the substantially lower pK_a of trifluoroacetamide,[5] although we have not unambiguously identified the source of the proton. The disappearance of zinc reagent **1b** followed simple first order kinetics, and the combined rate constant observed for the decomposition ($k = 0.31 \times 10^{-5}$) therefore represents an upper limit to the rate constant for the elimination reaction of **1b** to give methyl but-2-enoate **2**. This rate constant was approximately three-fold *lower* than that determined for the decomposition of the analogous Boc-derivative **1a** ($k = 0.87 \times 10^{-5}$) under identical conditions (Fig. 2).

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b302564k/

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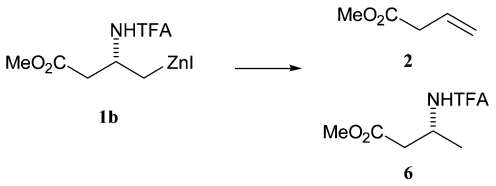


Scheme 3

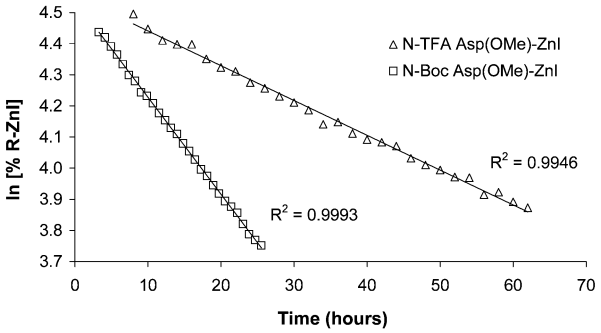
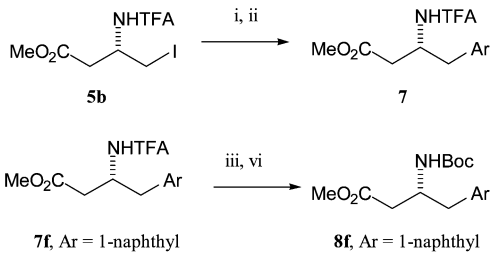


Fig. 2 Decomposition of the zinc reagents **1a** and **1b**.

It is notable that in our original determination of the rate constant for the decomposition of **1a**, in which residual zinc chloride and zinc bromide remained in solution, a higher value ($k = 2.6 \times 10^{-5}$ at 298 K) was observed.[1] Since, even in this case, the kinetics indicated a clean first order process, we believe that the outcome is not merely the result of zinc halides acting as external Lewis acids (which in an *anti*-elimination might be expected to promote the reaction by coordination to the leaving group, and whose concentration would increase during the course of the elimination), but rather as a source of chloride and bromide ions. One can speculate that the identity of the halide ion coordinated to zinc in **1a** has an influence on the rate of the elimination reaction, perhaps by modulating the strength of internal coordination of the carbamate carbonyl group to zinc. Strong support for this proposition is provided by the enthalpies of the oxygen–zinc bond in the adducts of zinc halides with DMF, which follow the sequence $ZnCl_2$·DMF (201 KJ mol^{-1}), $ZnBr_2$·DMF (184 KJ mol^{-1}) and ZnI_2·DMF (178 KJ mol^{-1}).[8] Thus, RZnCl is expected to be a stronger Lewis acid than RZnI, with the result that exchange of the initial iodide ligand in RZnI for chloride might lead to faster elimination.

In order to establish whether replacement of the nitrogen protecting group would influence the yields in palladium-catalysed cross-coupling, we investigated reactions of **1b** with a representative range of aryl iodides to give the corresponding aryl-coupled products **7** (Scheme 4). The results obtained, together with those previously obtained using **1a** for comparison,[2] are presented in Table 1. The main conclusion to be



Scheme 4 *Reagents and conditions*: i, Zn (activated with TMSCl in DMF), DMF, 0 °C; ii, ArI, $Pd_2(dba)_3$, P(o-tol)$_3$, r.t.; iii, NaOMe, MeOH, reflux; iv, Boc_2O, Et_3N, dioxane.

Table 1 Cross-coupling of organozinc reagent **1b**

Ar–I	Product **7**	Yield (%)[a]	Yield using **1a** (%)
4-MeC_6H_4	**7a**	64	73
4-$MeOC_6H_4$	**7b**	69	68
Ph	**7c**	72	73
4-CNC_6H_4	**7d**	77	—
4-$NO_2C_6H_4$	**7e**	65	89
1-Naphthyl	**7f**	70	61
4-BrC_6H_4	**7g**	53	58
4-FC_6H_4	**7h**	74	65

[a] Isolated yields refer to homogeneous material purified by flash chromatography.

drawn from these results is that the nature of the protecting group does not significantly influence the yield of the cross-coupling reaction. The adduct **7f** was converted into the corresponding free amine by treatment with NaOMe in methanol, and then reprotected as the known Boc derivative **8f**,[2] which allowed us to confirm that the adduct **7f** had been formed without detectable racemisation.

Despite the potential for elimination, and the high acidity of the N–H proton, the zinc reagent **1b** can be used efficiently in synthesis, extending the range of nitrogen protecting groups which is compatible with this chemistry. In this context, it should be pointed out that dimethyl malonate (pK_a of diethyl malonate is 16.4 in DMSO)[5] has been shown to be compatible with the formation of butylzinc iodide,[9] but the existence of the zinc reagent **1b** appears to extend the known tolerance of the carbon–zinc bond towards acidic protons within the organozinc reagent.

In summary, we have demonstrated that making the protected amine a "better" leaving group results in stabilisation of β-(acylamino) organozinc reagents towards elimination. This appears to be compelling further evidence that the key parameter in the elimination of these reagents is the ability of the nitrogen protecting group to coordinate to zinc. This result also suggests that the design of new reagents should be possible which will allow the already significant synthetic utility of functionalised organozinc reagents to be developed further.[10–12]

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