Preparation of silyl substituted crotylzinc reagents and their highly diastereoselective addition to carbonyl compounds†

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Readily prepared β-silyl substituted crotylzinc reagents undergo highly selective allylation of carbonyl compounds leading to *syn*-homoallylic alcohols.

Allylation reactions of carbonyl compounds with allylic organometallic reagents are of huge importance in organic synthesis.[1] The allylation reaction is one of the best methods for the controlled synthesis of quaternary centres. Recently we have reported the use of zinc dust in the presence of lithium chloride in THF as a cheap and convenient method for the synthesis of substituted allylic zinc reagents from allyl chlorides or phosphonates.[2] Allylation reactions with carbonyl compounds at −78 °C provided mostly the *anti* isomers. To extend this methodology to the preparation of *syn*-homoallylic alcohols we have investigated the possibility of using steric hindrance on the 2-position of the allyl chloride, through the presence of a silyl group. The resulting allylic zinc reagents should undergo highly *syn*-selective allylation of aldehydes and ketones (Fig. 1). The use of silyl substituted allyl-chromium reagents has been investigated previously, however, moderate levels of diastereoselectivity were observed.[3]

We decided to concentrate our initial studies using a mixture of readily available trimethylsilyl substituted allyl chlorides[4] **1a** and **1b** (Scheme 1). In the presence of zinc powder (10 equiv.) and LiCl (3 equiv.), we observed a smooth insertion reaction in which complete consumption of the starting materials was observed in 18 h at 25 °C and provided organozinc species **2** in 78% yield as determined by iodometic titration. Remarkably, addition of 1.1 equiv. of this reagent to benzaldehyde (1 equiv.) at −78 °C gave the allylation product **3** as a single diastereomer as distinguishable by ^{1}H-NMR. Protodesilylation of the allylation product **3** via a carbon to oxygen silyl migration promoted by sodium hydride in THF/HMPA[5] gave the expected *syn*-homoallylic alcohol **4** in 86% yield (Scheme 1). The remarkable diastereoselectivity observed in this reaction must be attributed to the fact that only a single allylic zinc species (*E*-isomer) is formed during the insertion. This is highly unusual as previous examples of conformationally stable allylzinc reagents have relied upon either conformationally rigidity, coordination or stereoelectronic factors.[1,2,6]

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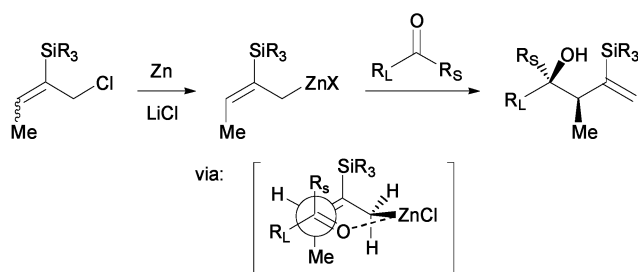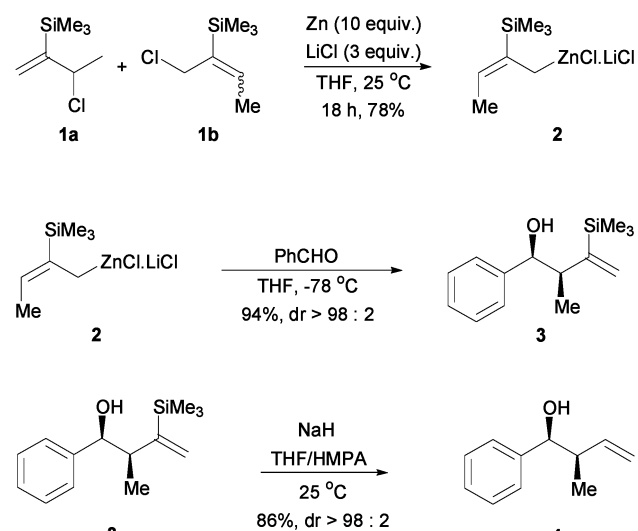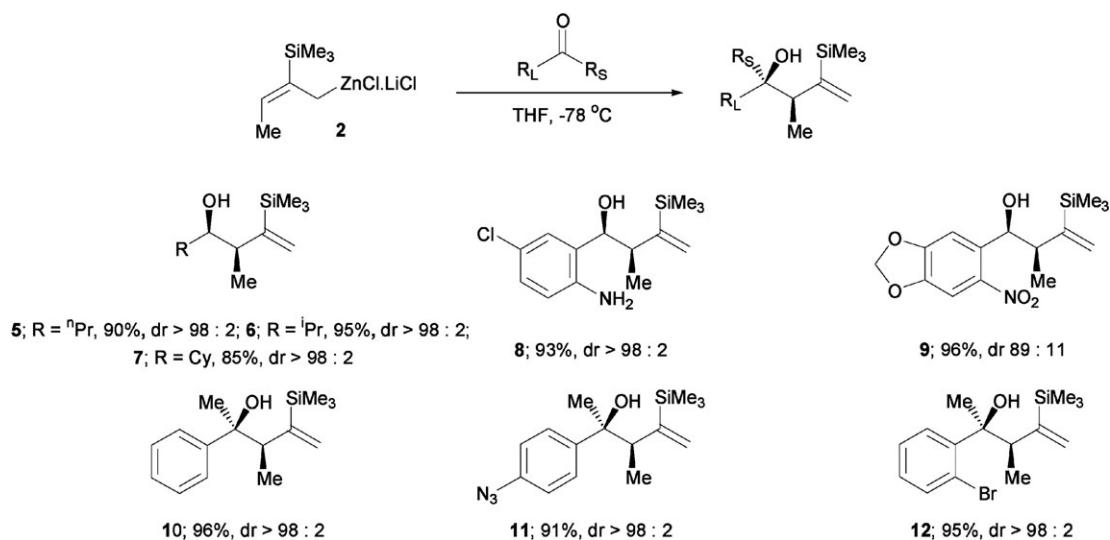

Fig. 1

A variety of alkyl substituted aldehydes were investigated (**5–7**, Fig. 2). In all cases, we were delighted to observe very high diastereoselectivity and the steric properties of the aldehyde appeared to have no bearing on the diastereoselectivity. Reaction with functionalised benzaldehyde derivatives showed a high level of tolerance towards sensitive functional groups such as free amino, chloro and nitro groups (**8–9**, Fig. 2). In the cases involving nitro substituted, more electron deficient, aldehydes lower diastereoselectivity was observed (**9**, Fig. 2 and **15–16**, Scheme 2). The addition to acetophenones was also highly selective and again the tolerance towards sensitive functional groups was remarkable, with substrates containing azide and bromo functional groups proceeding smoothly (**10** to **12**, Fig. 2).

Reaction of 1.1 equiv of **2** with *p*-nitrobenzaldehyde gave homoallylic alcohol **15** in 89% yield with a diastereoselectivity
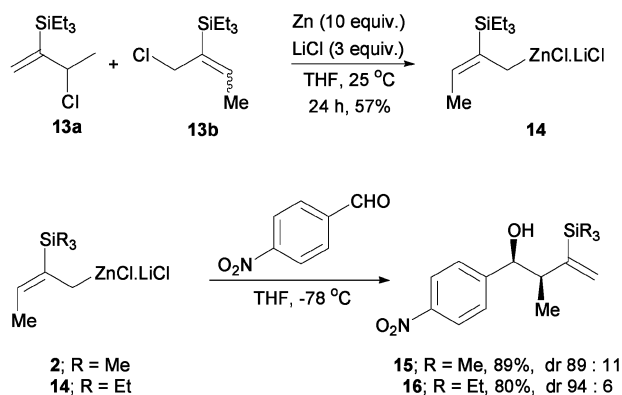

Scheme 1

Fig. 2 Addition of trimethylsilyl substituted allyl zinc **2** to functionalised aldehydes and ketones.[7]

Scheme 2

of 89 : 11 (Scheme 2). Careful recrystallisation from ethyl acetate and pentane gave only the major isomer which was identified as the *cis* isomer through X-ray analysis.‡ Formation of the triethylsilyl substituted allylic zinc **14** also proceeded smoothly (Scheme 2). Addition of **14** (1.1 equiv.) to *p*-nitrobenzaldehyde (1 equiv.) gave the allylation product **16** (Scheme 2) in 80% yield with a diastereoselectivity of 94 : 6. This increase in stereoselectivity may be best explained by the increased steric hindrance of the silyl group of **14** compared to **2** (Scheme 2).

In conclusion, we have demonstrated that the new β-silyl substituted allylic zinc reagent **2** undergoes highly diastereoselective additions to acetophenones and aldehydes. Further extensions of this methodology are currently under way in our laboratory.

Notes and references

‡ CCDC 673535.

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7 To further examine the scope of this methodology some further experiments were conducted. Reaction of **2** with 4-formyl-benzoic acid methyl ester gave the allylation product in 88% yield with a diastereoselectivity of 92 : 8. Reaction of **2** with *p*-anisaldehyde gave an unstable product which decomposed upon attempted isolation. Reaction of **2** with 4-acetyl-benzaldehyde gave a complex mixture of products containing the aldehyde allylation products and the α-addition product as the major contingent with traces of ketone allylation products. See ESI† for further details.