Conjugate Michael-additions with mixed diorganozincs

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Mixed diorganozincs ($RZnCH_2SiMe_3$; R = alkyl, aryl) undergo selective transfer of the R group in a 1,4-fashion to various Michael-acceptors.

Diorganozincs are a useful class of organometallic intermediates.[1] They can be readily prepared *via* iodine–zinc exchange[2] or boron–zinc exchange[3] and tolerate the presence of numerous functional groups.[1–4] In the presence of transition metal catalysts, they react with various electrophiles leading to polyfunctional products. Recently, we have found that a polar cosolvent like *N*-methylpyrrolidinone (NMP) allows the 1,4-addition[5] to proceed *in the absence of any copper or transition metal catalyst*. Unfortunately, only one organic group of the diorganozinc is transferred to an organic electrophile. However, we could show that mixed diorganozincs bearing a trimethylsilylmethyl group ($RZnCH_2SiMe_3$ **1**) can be readily prepared and characterized spectroscopically.[6] It was found that the CH_2SiMe_3 group plays the role of a non-transferable group which avoids the waste of an organic residue attached to zinc. This proves to be especially important for the performance of asymmetric additions to aldehydes.[6] In preliminary experiments we have shown that the reagents **1** add to cyclohexenone.[6] Herein, we wish to report that mixed diorganozincs of type **1** react with a variety of Michael-acceptors leading to 1,4-adducts of type **3** in good yields (Scheme 1 and Table 1).
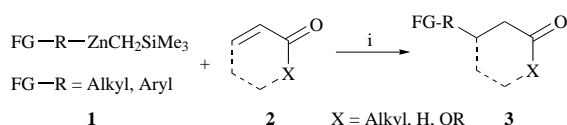
Scheme 1 *Reagents and conditions*: i, Me_3SiBr (2 equiv.), THF, NMP, −30 °C, 12 h

Thus, the reaction of 2-furyllithium with (trimethylsilylmethyl)zinc iodide in THF at −40 °C furnishes the mixed (trimethylsilylmethyl)(2-furyl)zinc which was allowed to react at −30 °C with hex-4-en-3-one **2a** (*ca.* 0.7 equiv.) in the presence of trimethylsilyl bromide[7] in NMP affording the Michael-adduct **3a** as sole product in 95% yield (see entry 1 of Table 1). Secondary zinc reagents or functionalized dialkylzincs like (4-chlorobutyl)(trimethylsilylmethyl)zinc can also be used with equal efficiency (see entries 2 and 3 of Table 1). In this case the mixed zinc reagent is best prepared by adding commercially available Me_3SiCH_2Li to 4-chlorobutylzinc iodide obtained by the direct insertion of zinc dust into 4-chloroiodobutane[1] in THF. The mixed reaction conditions involved in these Michael-additions allow the use of reactive vinyl methyl ketone **2b** which adds various aryl and alkyl zinc reagents in 74–92% yield (entries 4–6). Whereas the addition of organocuprates to unsaturated aldehydes often requires the use of highly polar cosolvents like HMPA,[8] the addition of the mixed zinc reagent to unsaturated aldehydes like 2-methylbut-2-enal **2c** (entries 7–8) or the reactive β-unsubstituted aldehyde 2-butylacryl-

aldehyde (**2d**; entries 9–10) occurs smoothly providing the functionalized aldehydes **2g**–**j** in 51–91% yield. No 1,2-addition products are observed (see Experimental section). Also, the conjugated addition to acrylic esters like butyl acrylate produces the expected Michael-adducts **3k**–**l** under similar reaction conditions (−30 °C, 3 h) in 76–86% yield (entries 11 and 12). The addition to acrylonitrile **2f** affords the conjugated addition product **3m** in which the trimethylsilyl group has been incorporated in the position α to the cyano group (**3m**: 54%; entry 13). Finally, addition to nitroolefins like 1-nitrobutene **2g** leads to nitroalkanes such as **3n** and **3o** in 64–76% yield (entries 14 and 15). In no case, was transfer of the trimethylsilylmethyl group observed.

In summary, we have shown that the mixed zinc reagents **1** undergo a conjugate addition to various Michael-acceptors. Extension of these reactions using other chiral non-transferable groups is underway.
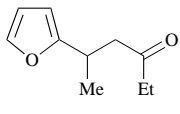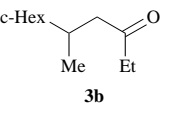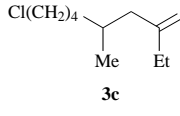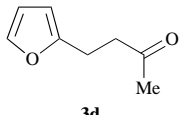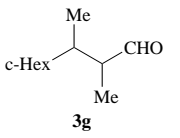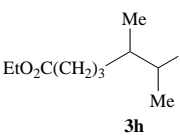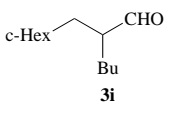
Experimental

Standard procedure: preparation of ethyl 6-(formyl)decanoate 3j
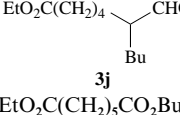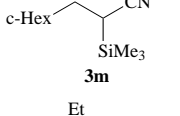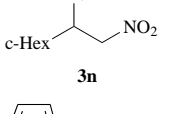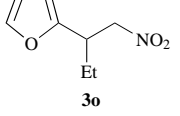1,2-Dibromoethane (0.2 cm³) was added dropwise to a stirred mixture of zinc dust (1.57 g, 24 mmol) in THF (6 cm³) at room temperature under argon, whilst heating with a heat gun to boil the solvent gently. Upon complete addition the mixture was cooled to room temperature and then trimethylsilyl chloride (0.2 cm³) was added dropwise over 5 min, again with gentle heating of the solvent. After complete addition, the mixture was stirred at room temperature for a further 5 min. Ethyl 4-iodobutanoate (1.45 g, 6 mmol) was added dropwise over 5 min, and then the reaction was heated at 50 °C for 3 h, and the zinc insertion reaction monitored by GC analysis. When the reaction was complete the reaction mixture was cooled to room temperature and the excess zinc dust allowed to settle for 15 min. The pale grey solution was transferred to a flame dried flask and cooled to −40 °C. A solution of trimethylsilylmethyl-lithium (6 mmol) in pentane (1.0 mol dm⁻³, 6.0 cm³) was added dropwise over 3 min to the zinc iodide solution and then stirred at −40 °C for one hour. NMP (1 cm³), trimethylsilyl bromide (1.0 cm³, 8 mmol) and then 2-butylacrylaldehyde **2d** (0.53 cm³, 4 mmol) were added to this reaction mixture at −60 °C. The reaction was warmed to −30 °C, and stirred at this temperature for 3 h. The reaction was poured into saturated aqueous ammonium chloride (50 cm³) and worked up as usual. The residue was further purified by column chromatography on silica using 15% diethyl ether–light petroleum as eluent to give the aldehyde **3j** (0.65 g, 71%) as a colourless oil.

Acknowledgements

Table 1 Michael-additions of the mixed diorganozincs **1** in THF–NMP mixtures

Entry	Michael-acceptor[a]	RZnCH$_2$SiMe$_3$	Product **3**	Yield (%)[b]
1	**2a**	2-Furyl	**3a**	95
2	**2a**	c-Hexyl	**3b**	87
3	**2a**	Cl(CH$_2$)$_4$	**3c**	71
4	**2b**	2-Furyl	**3d**	92
5	**2b**	EtO$_2$C(CH$_2$)$_3$	EtO$_2$C(CH$_2$)$_5$COMe **3e**	81
6	**2b**	Cl(CH$_2$)$_4$	Cl(CH$_2$)$_5$COMe **3f**	74
7	**2c**	c-Hexyl	**3g**	91
8	**2c**	EtO$_2$C(CH$_2$)$_3$	**3h**	51
9	**2d**	c-Hexyl	**3i**	68
10	**2d**	EtO$_2$C(CH$_2$)$_3$	**3j**	71
11	**2e**	EtO$_2$C(CH$_2$)$_3$	EtO$_2$C(CH$_2$)$_5$CO$_2$Bu **3k**	86
12	**2e**	Cl(CH$_2$)$_4$	Cl(CH$_2$)$_6$CO$_2$Bu **3l**	76
13	**2f**	c-Hexyl	**3m**	54
14	**2g**	c-Hexyl	**3n**	76
15	**2g**	2-Furyl	**3o**	64

[a] **2a**: Hex-4-en-3-one; **2b**: methyl vinyl ketone; **2c**: 2-methylbut-2-enal; **2d**: 2-butylacrylaldehyde; **2e**: butyl acrylate; **2f**: acrylonitrile; **2g**: 1-nitrobutene.
[b] Isolated yields of analytically pure products.

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