Stereoselective preparation and reactions of configurationally-defined mixed acyclic dialkylzincs

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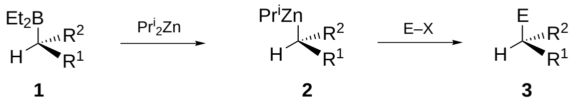
Mixed acyclic dialkylzincs are stereoselectively prepared from *E*- and *Z*-trisubstituted alkenes.

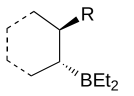
The preparation of configurationally defined reactive organometallics is of great interest,[1] since it offers the potential of transferring the stereochemical information at the α-carbon of the metal to a variety of organic compounds *via* reaction with various electrophiles. Recently,[2] we have shown that organoboranes **1** can be converted by an exchange reaction[3] with Pr^i_2Zn to configurationally stable[4] mixed diorganozincs **2**. These zinc reagents can be reacted with electrophiles like D_2O or allylic halides, providing products of type **3** (Scheme 1).



E–X = D_2O, allyl bromides

Scheme 1

In all these experiments, *trans*-cycloalkylborane derivatives **4** were used and converted to *trans*-cycloalkylzinc compounds **5**. To demonstrate the stereoselectivity of the boron–zinc exchange, the use of *cis*-cycloalkylboranes **6** would have been necessary. Since these molecules are not available by hydroboration with Et_2BH, we examined the hydroboration of open-chain trisubstituted *E*- and *Z*-olefins **7**. Herein, we report the stereoselective preparation of open-chain secondary dialkylzincs and their stereoselective deuterolysis and allylation.



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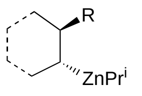

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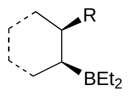

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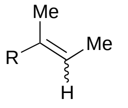


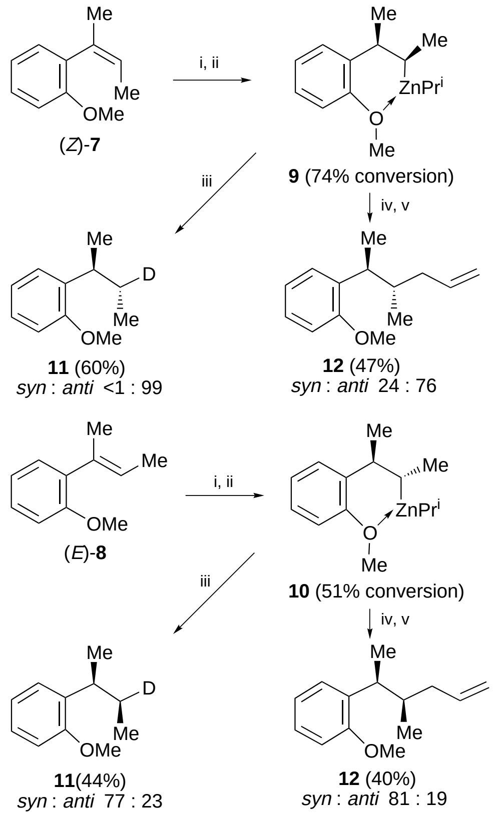
(*E*)- and (*Z*)-**7**

Thus, the hydroboration of *E*- and *Z*-styrene derivatives **8** with Et_2BH was complete after 14 h at 25 °C; the intermediate diethylorganoboranes were treated with Pr^i_2Zn, furnishing the mixed diorganozincs **9** and **10**, which were quenched with D_2O resulting in the formation of the deuterated product **11** (Scheme 2). The presence of the *o*-methoxy group was found to accelerate significantly the rate of the boron–zinc exchange reaction, allowing the completion of this exchange starting from (*Z*)- or (*E*)-**8** within 3 h at 0 °C. Under these conditions, the deuterolysis of **9** provides mainly the *anti*-deuterated product **11** (*syn* : *anti* < 1 : 99) whereas the deuterolysis of **10** furnishes the product **11** as a *syn* : *anti* mixture of 77 : 23. The *syn* : *anti* ratio of the deuterated products was determined by ^2H NMR spectroscopy. These experiments demonstrate for the first time the stereoselectivity of the boron–zinc exchange reaction for open-chain systems. It is interesting to note that performing the boron–zinc exchange at 25 °C instead of 0 °C leads to lower stereoselectivities, *i.e.* a *syn* : *anti* ratio of 22 : 78 starting from (*Z*)-**8** and 73 : 27 starting from (*E*)-**8**.

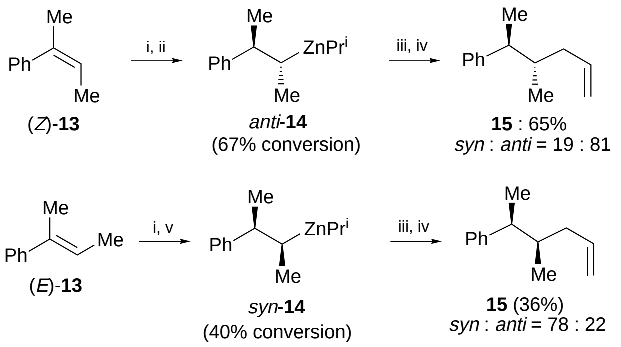
The mixed dialkylzincs **9** and **10** could also be transmetalated to copper–zinc compounds *via* reaction with CuCN·2LiCl, leading after treatment with allyl bromide to the desired allylated products **12** with a *syn* : *anti* ratio of 24 : 76 starting from the zinc intermediate **9** and 81 : 19 starting from the zinc reagent **10**. The lower stereoselectivity of the allylation of **9** compared to the deuterolysis may be due to a slow isomerization of **9** during the allylation reaction.†

Whilst the presence of the *o*-methoxy group of **8** facilitates the subsequent boron–zinc exchange, it is possible to extend the reaction to (*E*)- and (*Z*)-styrenes **13** with similar selectivities. This proves that the configurational stability of the organozinc intermediates does not depend on the presence of a heteroatom in close proximity. In this case, the deuterium signals after quenching of the intermediate zinc reagent **14** were not separated, so that the selectivity could not be determined. However, after transmetalation with CuCN·2LiCl and allylation the desired allylated product **15** was obtained stereoselectively. The *Z*-olefin **13** gave allylation product **15** with a *syn* : *anti* ratio of 19 : 81, whereas the *E*-olefin **13** gave a *syn* : *anti* ratio of 78 : 22 for **15** (Scheme 3).

The relative stereochemistry of the product **15** (*syn* : *anti* ratio of 78 : 22) was determined by converting it to 3,4-dimethyl-1-tetralone **18** by ozonolysis followed by oxidation of the

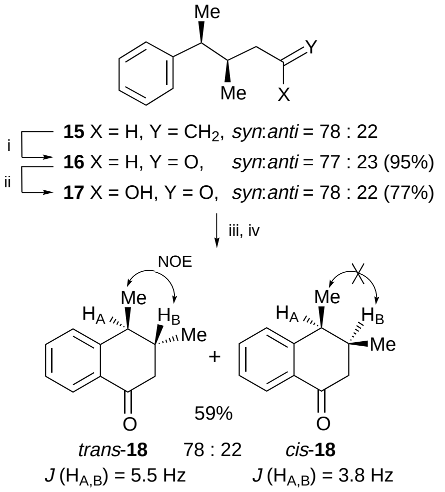


Scheme 2 *Reagents and conditions*: i, $HBEt_2$ (3 equiv.), 25 °C, 14.5 h; ii, Pr^i_2Zn (2 equiv.), 0 °C, 3 h; iii, D_2O, THF, −78 °C; iv, CuCN·2LiCl; v, allyl bromide, −78 to 25 °C



Scheme 3 *Reagents and conditions*: i, $BHEt_2$ (3 equiv.), 25 °C, 13 h; ii, $Pr^i{}_2Zn$ (2 equiv.), 25 °C, 3 h; iii, CuCN·2LiCl, −78 °C; iv, allyl bromide, −78 to 25 °C; v, $Pr^i{}_2Zn$ (2 equiv.), 25 °C, 4 h

resulting aldehyde **16** to the acid **17**. Friedel–Crafts cyclization of the corresponding acid chloride furnishes the *cis*- and *trans*-ketones **18** (*cis* : *trans* = 22 : 78). Both the major *trans* isomer and the minor *cis* isomer could be unequivocally identified by NMR spectroscopy (Scheme 4).



Scheme 4 *Reagents and conditions*: i, O_3, then Me_2S; ii, $NaClO_2$, $Me_2C{=}CHMe$, NaH_2PO_4, Bu^tOH, 25 °C, 1 h; iii, $SOCl_2$, 60 °C, 1 h; iv, $AlCl_3$ (1.25 equiv.), $ClCH_2CH_2Cl$, 25 °C, 4 h

In conclusion, we have shown that the boron–zinc exchange performed with $Pr^i{}_2Zn$ on open-chain secondary zinc reagents proceeds stereoselectively. Although the relative stereochemistry of the zinc reagents could not be directly determined, we assume that this exchange reaction proceeds with retention of configuration as well as the allylation (and deuterolysis),‡ since an overall retention of configuration is observed. Current work in order to improve the level of stereoselectivity and to extend the number of electrophiles that can quench stereoselectively the intermediate organozinc reagents is underway.

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Footnotes and References

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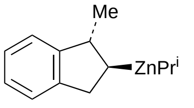
† We have observed in separate experiments that secondary copper–zinc reagents are more prone to epimerization than the organozinc precursors. Treatment of *trans*-1-methylindanyl)(isopropyl)zinc **19** (see ref. 2) with D_2O affords the corresponding *trans*-deuterated indane **20** with a *cis* : *trans* ratio of 1 : 99. Treatment of this zinc reagent with stoichiometric amounts of CuCN·2LiCl provides a copper–zinc reagent which was slowly warmed to 0 °C. After deuterolysis a *cis* : *trans* ratio of 11 : 89 was obtained. However, keeping this copper–zinc reagent at −78 °C and treating it with another equivalent of $ZnBr_2$ provides a *cis* : *trans* ratio of 1 : 99, showing that the zinc–copper reagent has good configurational stability at −78 °C and that, at this temperature, the zinc salts produced during the allylation reaction are not responsible for the epimerization reaction.



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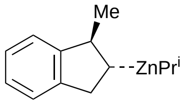

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‡ The relative configuration between the methyl group and the deuterium atom in **20** was proven to be *trans* by comparison of NOE measurements for dihydro-1-methylindane and **20**.

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