Stereoselective Preparation and Reactions of Cycloalkylzinc Compounds**

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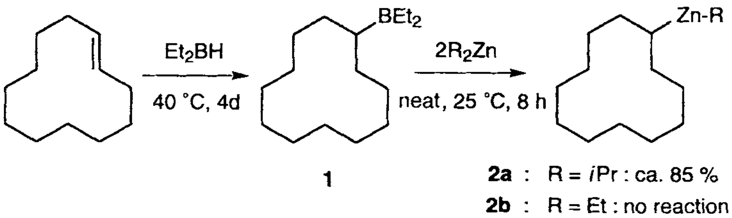
The preparation of chiral organometallic compounds with secondary alkyl substituents has been actively investigated over the past two decades. In the most successful studies the corresponding organolithium compounds[1, 2] were prepared bearing a heteroatom in α-position to the carbon–lithium bond, which ensures that these reagents can be handled easily and are configurationally stable. In contrast, organometallics having a more covalent carbon–metal bond display higher configurational stability even in the absence of an α-heteroatom, and it has been shown[3] that organozinc halides are configurationally stable over a wide temperature range.

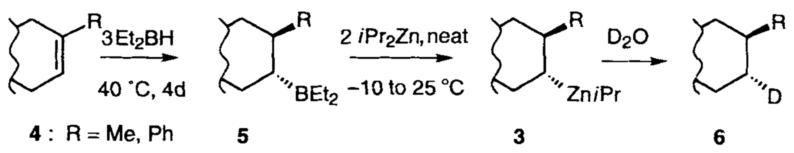
Unfortunately, a general method was not available previously for converting a chiral precursor stereoselectively into a chiral organozinc species. Thus, zinc metal inserts into stereochemically pure, secondary alkyl iodides by a radical mechanism and a mixture of stereoisomeric organozinc derivatives usually results.[3, 4] Recently we have found that organoboranes obtained by the hydroboration of alkenes can be converted to diorganozinc derivatives by treatment with diethylzinc (Et_2Zn). Although fast with primary organoboranes, this exchange is sluggish with secondary organoboranes and not stereoselective.[4, 5] Thus, the reaction of diastereomerically pure *trans*-2-diethylboryl-1-methylcyclohexane with Et_2Zn (large excess, neat, 25 °C, 40 h) produces a 1:2 mixture of *cis*- and *trans*-2-methylcyclohexylzinc derivatives in moderate yield.

We report herein that the boron–zinc exchange reaction is dramatically accelerated when diisopropylzinc ($i\text{Pr}_2\text{Zn}$)[6] is used instead of Et_2Zn and that this experimental procedure results in the first preparation of stereochemically pure, cycloorganozinc species which react with several classes of electrophiles with retention of configuration. Thus, the reaction of diethylborylcyclododecane (**1**) with $i\text{Pr}_2\text{Zn}$ (2 equiv, neat, 25 °C, 8 h) gave the mixed isopropylcyclododecylzinc (**2a**) in about 85% yield (as determined by iododolysis experiments). When Et_2Zn was used instead of $i\text{Pr}_2\text{Zn}$, the corresponding zinc reagent **2b** did not form under the same experimental conditions (Scheme 1).



Scheme 1.

With $i\text{Pr}_2\text{Zn}$ we could generate diastereomerically pure cycloorganozinc compounds of type **3** for the first time starting from the corresponding olefin of type **4**. The hydroboration of **4** with diethylborane (3 equiv, 40 °C, 90 h) produced the *trans*-diethylborylcycloalkane (**5**) (>99% *trans*). The reaction of **5** with $i\text{Pr}_2\text{Zn}$ (2 equiv) furnished as expected the desired zinc reagent **3**, which was quenched with D_2O in THF at −78 °C to provide the *trans*-monodeuterated products **6** (Scheme 2, Table 1).[7]

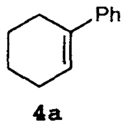


Scheme 2.

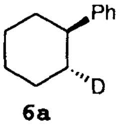
Table 1. Yields of **6** as well as conditions of the boron–zinc exchange.

Entry	4	6	T [°C]	t [h] [a]	trans:cis [b]	Yield [%] [c]
1	a	b	25	7	100:0	56
2	b	b	25	7	87:13	54
3	b	b	−10	10	98:2	56
4	c	c	25	7	88:12	47
5	c	c	−10	10	99:1	61
6	d	d	−10	10	97:3	60

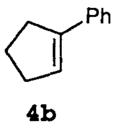
[a] Temperature and time required for the boron–zinc exchange reaction. [b] The *trans*:*cis* ratio was determined by ^{2}H NMR spectroscopy. [c] Overall yield (based on the olefin **4**) of analytically pure products.



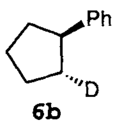
4a



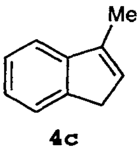
6a



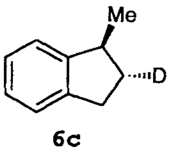
4b



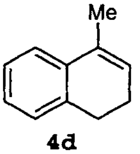
6b



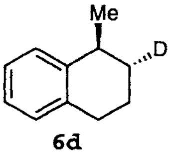
4c



6c



4d



6d

Phenylcyclohexene **4a** was converted by this sequence into pure *trans*-2-deuterio-1-phenylcyclohexane (**6a**), showing that the boron–zinc exchange and deuterolysis proceed with retention of configuration (Table 1, entry 1). Treatment of *trans*-isopropyl-(2-phenylcyclohexyl)zinc (**3a**) with CuCN·2LiCl[8] afforded an intermediate zinc–copper species which was deuterated to give **6a** with the same stereoselectivity. This implies that the zinc–copper transmetalation and deuterolysis of a zinc–copper reagent also occurs with retention of configuration. In the case of the conformationally flexible cyclopentane system, the stereoselectivity of the boron–zinc exchange was found to depend on the reaction temperature. Thus, by performing this reaction with *trans*-2-diethylboryl-1-phenylcyclopentane (**5b**) at 25 °C, we obtained **6b** in a *trans*:*cis* ratio of 87:13 after deuterolysis; however, when the same reaction was performed at −10 °C the *trans*:*cis* ratio was 98:2 (Table 1, entries 2 and 3). A similar result was obtained for 1-methylindene (**4c**) (entries 4 and 5). Interestingly, the deuterolysis of a secondary zinc reagent like *trans*-isopropyl-(2-phenylcyclopentyl)zinc (**3b**), which was stored for one week at 5 °C, proceeded with the same

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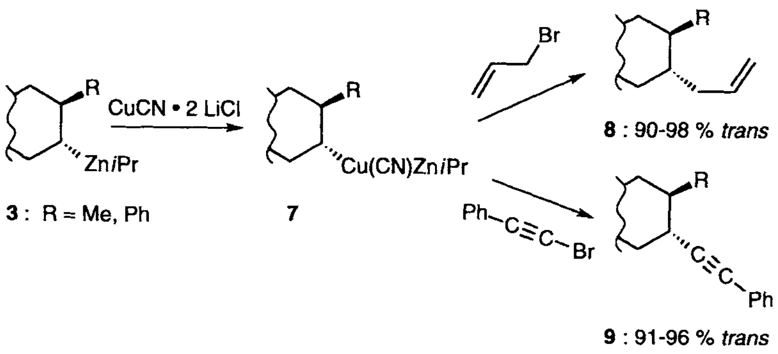
trans:*cis* selectivity (98:2); this shows that these organozinc compounds retain their configuration at this temperature for at least a week. The transmetalation of the secondary zinc reagents **3** with CuCN·2LiCl led to the zinc–copper species **7**, which were allylated and alkynylated to afford products **8** and **9**, respectively, with high retention of the *trans* configuration (Scheme 3 and Table 2).

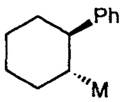


Scheme 3.

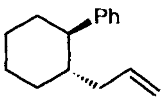
Table 2. Yields and *trans*:*cis* ratios of **8** and **9**, which were obtained by the stereoselective reaction of the zinc–copper reagents **7** with allyl bromide and 2-bromo-1-phenylacetylene, respectively.

Entry	7 [a]	Product	*trans*:*cis* ratio [b]	Yield [%] [c]
1	**a**	**8a**	98:2	46
2	**a**	**9a**	91:9	44
3	**b**	**8b**	95:5	36
4	**b**	**9b**	96:4	41
5	**c**	**8c**	90:10	57
6	**c**	**9c**	93:7	42

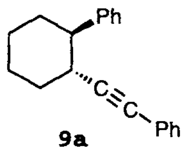
[a] M = Cu(CN)Zn*i*Pr. [b] The *trans*:*cis* ratio was determined by GC analysis and a ^{13}C NMR spectroscopy of the crude reaction mixture. [c] Overall yields (based on the olefin **4**) of analytically pure products.



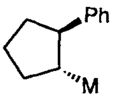
7a



8a



9a



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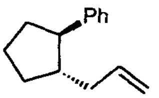

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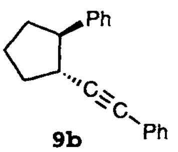

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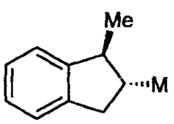
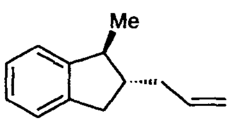


7c



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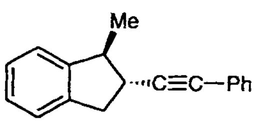

9c

The degree of configuration retention depends critically on the reaction conditions. When the alkynylation was conducted at temperatures above −50 °C, significant epimerization was observed. Although the *trans*-isopropyl-(2-phenylcyclohexyl)-zinc (**3a**) and its zinc–copper derivative are less sensitive to the reaction conditions used, it was noticed with **3b** that the presence of an extra equivalent of zinc bromide leads to extensive isomerization. The allylated product **8b** (Table 2, entry 3) was obtained with a 66:34 *trans*:*cis* ratio, in strong contrast with results obtained without zinc bromide (*trans*:*cis* ratio of 95:5).

We have described a new method for preparing stereoselectively chiral non-heteroatom stabilized cycloorganozinc compounds. We have demonstrated that these reagents react stereoselectively with several carbon electrophiles (allylation, alkynylation) in the presence of CuCN·2LiCl. Extension of this reaction to the preparation of diastereomerically pure aliphatic organozinc compounds as well as the study of the stereoselectivity of the trapping reactions of these organometallics are currently underway.

Experimental Section

Typical procedure: **9b**: A 50 mL, two-necked flask equipped with a rubber septum and an argon inlet was charged with the olefin **4b** (649 mg, 4.50 mmol). After the olefin had been degassed, diethylborane (prepared from triethylborane and borane/methyl sulfide complex (1.32 g, 13.5 mmol, 3 equiv)) was added dropwise by syringe at 25 °C. The resulting mixture was stirred for 4 d at 40 °C. Excess diethylborane was removed by distillation (25 °C, 2 h). $i\mathrm{Pr_2Zn}$ (1.36 g, 9.00 mmol, 2 equiv) was carefully added by syringe at 25 °C. The reaction mixture was immediately cooled to −10 °C and kept at this temperature for 10 h with exclusion of light. Meanwhile a mixture of CuCN (806 mg, 9.00 mmol, 2 equiv) and LiCl (763 mg, 18.0 mmol, 4 equiv) was dried in vacuo (130 °C, 3 h). The copper and lithium salts were dissolved in dry THF (9 mL) and the solution cooled to −78 °C. Then excess $i\mathrm{Pr_2Zn}$ was removed by distillation (25 °C, 1 h); the flask was covered with aluminum foil to exclude light. The flask was equipped with an internal thermometer and the organozinc compound was diluted with dry THF (2 mL) and cooled to −78 °C. The previously prepared CuCN·2LiCl solution was added. The reaction mixture was stirred at −78 °C for 15 min, and 2-bromo-1-phenylacetylene (1.63 g, 9.00 mmol, 2 equiv) in dry THF (5 mL) was added dropwise within 20 min while the temperature of the reaction mixture was kept below −70 °C. The reaction mixture was warmed up to 25 °C and worked up as usual. The crude product was purified by flash chromatography (hexanes), affording the compound **9b** (459 mg, 1.82 mmol, 41 % yield) as a pale yellow liquid.

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[7] The yields given in Table 1 (47–61 %) and Table 2 (36–57 %) are overall yields based on the corresponding olefins **4**. No significant amounts of side products could be isolated besides the compounds of type **6** and **8** or **9**.

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