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Catalytic Asymmetric Reductive Addition of Olefins to Aldehydes Mediated by Boron and Zinc Organometallics.

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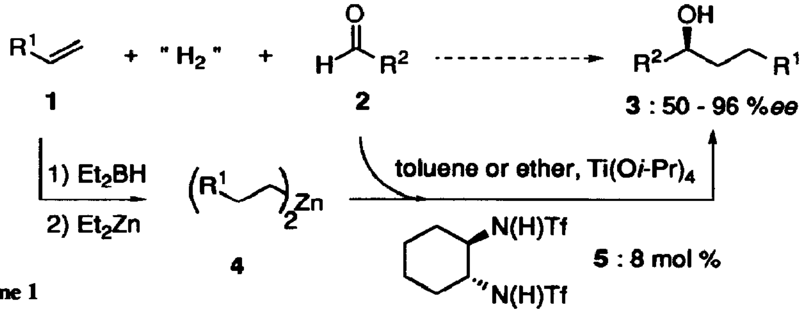
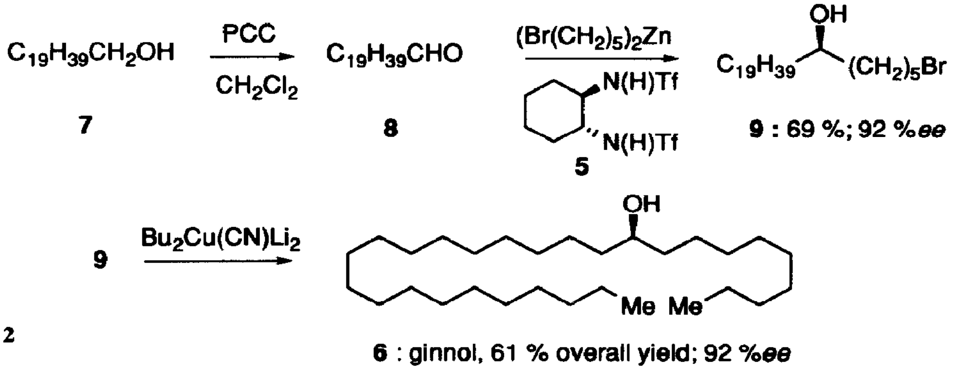
Summary: A procedure involving a hydroboration, boron-zinc exchange and asymmetric addition to an aldehyde allows the reductive addition of olefins to aldehydes in 50-96 % *ee*. A short and efficient 3 step synthesis of ginnol (61 % overall yield, 92 % *ee*) demonstrates the synthetic utility of the method.

The formation of carbon-carbon bonds with unactivated olefins constitutes an important olefin valorization and its performance in an asymmetric manner is of considerable synthetic and industrial importance. Several organometallic reagents effect these addition reactions in the presence of the appropriate catalyst with high enantioselectivity.[1] Recently, we have shown that the boron-zinc exchange reaction[2] is an excellent method allowing the preparation of polyfunctional dialkylzincs.[3] We wish to report herein that this reaction can be extended to a formal catalytic asymmetric addition of functional olefins **1** to aldehydes **2** leading to polyfunctional secondary alcohols of type **3** with high enantioselectivity (Scheme 1). Most organometallics which add enantioselectively to aldehydes are prepared form the corresponding alkyl halides which are usually obtained from an alcohol or an olefin. Our approach involved a direct one-pot conversion of the olefin to a dialkylzinc **4** *via* successive hydroboration with diethylborane,[4] boron-zinc exchange,[2,3] followed by a catalytic asymmetric addition of the dialkylzinc to an aliphatic, unsaturated or aromatic aldehyde using (1R,2R)-1,2-*bis*-(trifluoromethanesulfonamido)cyclohexane[5] **5** as catalyst. Thus, alkenes of type **1** are smoothly hydroborated with diethylborane[4] (1 equiv; -10 ° C to 25 °C, 0.5 - 1 h; 70-90 % yield). After evaporation of the volatiles, diethylzinc (2 equiv) was added at 0 °C and after 0.5 h the formed triethylborane was pumped off. The resultant dialkylzinc was treated in toluene or ether with the aldehyde **2** (1 equiv for 2-3 equiv dialkylzinc) at -20 °C for 5-10 h leading to the chiral alcohol **3** in 57-88 % yield and 50 to over 96 % *ee* (Table 1). Several oxygen containing functionalities (ester, silyl ether, acrylate) can be present in the starting alkene (entries 5-10). Especially interesting is the synthesis of *bis*-(5-carbethoxy-5-hexenyl)zinc (entries 9 and 10) which is prepared



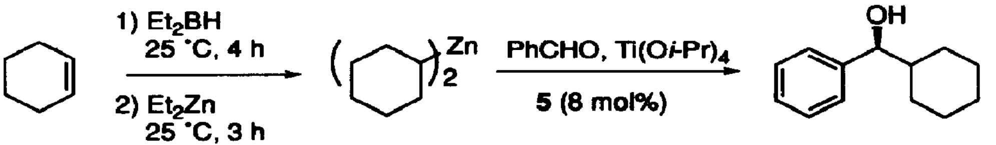
Scheme 1

by the selective hydroboration of ethyl 2-methylene-5-hexenoate with Et_2BH. Its smooth transmetalation with Et_2Zn provides a new dialkylzinc reagent containing a sensitive acrylate functionality. Its asymmetric addition to aldehydes proceeds with excellent enantioselectivity affording the unsaturated hydroxyesters **3i** and **3j** (95 and 80 % *ee* respectively, entries 9 and 10). It is interesting to notice that although it was known that the presence of a cyano group disturbs the asymmetric addition (low *ee*),[6] our new reaction conditions allow to obtain a satisfactory enantioselectivity by using *p*-cyanobenzaldehyde (80 % *ee*, entry 10). Whereas a pivaloxy group is well tolerated (91 % *ee*; entries 5 and 8), it was found that a bulky triisopropylsilyl (TIPS) substituent leads to a lower enantioselectivity (50 % *ee*; entry 6). Its replacement with the less sterically hindered *t*-butyldimethylsilyl (TBDMS) group and the introduction of an additional carbon into the chain provides again 92 % *ee* (entry 7). The addition of the intermediate dialkylzincs to an α-nonsubstituted α,β-unsaturated aldehyde is improved by replacing the cocatalyst $Ti(Oi\text{-}Pr)_4$ (78 % *ee*) by the more bulky alkoxide[7] $Ti(Ot\text{-}Bu)_4$ (> 96 % *ee*; entries 4 and 8). Bromine- (and iodine-) containing zinc reagents which are not available using previous methods can be prepared readily and added to aldehydes (86-90 % *ee*; entries 11 and 12). These new reagents have been used to prepare (*S*)-10-nonacosanol (ginnol) in 3 steps and 61 % overall yield with 92 % *ee*. This compound is found in several plants and possess the interesting property to crystallize as pure enantiomer in double layers forming small lipophilic tubes.[8] Thus, the oxidation of commercially available eicosanol **7** (PCC on SiO_2, CH_2Cl_2, 0 ° to 25 °C) provides the aldehyde **8** in 94 % yield. First a direct addition of dinonylzinc to **8** (2 step synthesis of ginnol) was performed (78 % yield), however it was not possible to determine the optical purity of **6** obtained in this way. All attempted optical purity determination methods failed due to the very similar structure of the alkyl substituents at the chiral center.[8] To circumvent this problem the bromoalcohol **9** was prepared in 69 % yield and 92 % *ee* (determined by simple conversion to the (S)-*O*-acetylmandelate) by the one-pot hydroboration, boron-zinc exchange of 5-bromo-1-pentene[9] and its asymmetric addition to **8** under our standard conditions in ether. The coupling of **9** with $Bu_2Cu(CN)Li_2$ (5 equiv; -60 °C to 0 °C, 1 h)[10] affords ginnol **6** in 95 % yield (Scheme 2). This reaction sequence represents a considerable improvement compared to a synthesis reported previously (6 steps; ca. 1-2 % overall yield; 78 % ee).[8]



Scheme 2

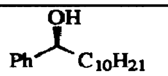
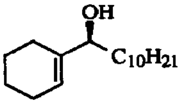
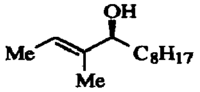
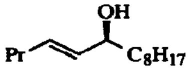
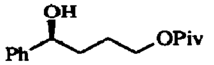
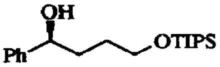
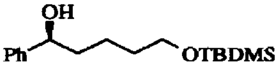
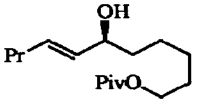
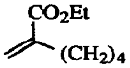
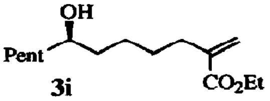
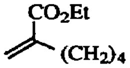
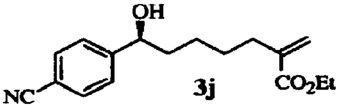
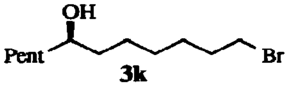
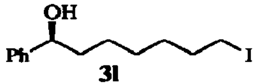
Secondary dialkylzincs are difficult to prepare by most methods. However, our approach allows an efficient synthesis of these reagents as long as the starting disubstituted olefin is not sterically hindered. Thus, the hydroboration of cyclohexene with Et_2BH followed by a treatment with Et_2Zn (2 equiv, 25 °C, 1.5 h) furnishes $(c\text{-}Hex)_2Zn$ which adds to benzaldehyde leading to the alcohol **10** in 67 % yield and 80 % *ee* (Scheme 3).



Scheme 3

10 : 67 %; 80 %*ee*

Table 1. Alcohols **3a-l** Obtained by a One-pot Hydroboration, Transmetalation and Asymmetric Addition of the Alkenes **1** to the Aldehydes **2**.

Entry	R^1	R^2	Product 3	Yield (%)[a]	*ee* (%)[b]
1	$C_{10}H_{21}$	Ph	 3a	57(88)[c]	64(>96)[c]
2	$C_{10}H_{21}$	1-cyclohexenyl	 3b	73	>96
3	C_8H_{17}	Z-1-methyl-1-propenyl	 3c	62	>96
4	C_8H_{17}	E-1-pentenyl	 3d	78(75)[d]	78(96)[d]
5	$PivO(CH_2)_3$	Ph	 3e	70	93
6	$TIPSO(CH_2)_3$	Ph	 3f	60	50
7	$TBDMSO(CH_2)_4$	Ph	 3g	82	92
8	$PivO(CH_2)_5$	E-1-pentenyl	 3h	41[d]	>95[d]
9		C_5H_{11}	 3i	72	95
10		*p*-NCC_6H_4	 3j	69	80
11	$Br(CH_2)_6$	C_5H_{11}	 3k	77	90
12	$I(CH_2)_6$	Ph	 3l	58	86

[a] Isolated yield of analytically pure products. [b] Determined by preparing the corresponding *O*-acetyl-mandelates using (S)-(+)-*O*-acetyl-mandelic acid. In each case, a calibration sample using (±)-*O*-acetyl-mandelic acid was prepared (Ref. 13). [c] Ether was used as solvent. [d] Ti(O*t*-Bu)$_4$ was used instead of Ti(O*i*-Pr)$_4$.

In summary, we have developed a one-pot procedure allowing a enantioselective addition of olefins to aldehydes via organo-boron and -zinc intermediates.[11] Extensions of the method are underway in our laboratories.

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(9) **Caution:** During the preparation of *bis*-(5-bromopentyl)zinc (removal of excess diethylzinc), the mixture should never been warmed over 10 °C, since several explosions have occured at temperatures between 30 and 50 °C. This behavior is exceptional. Other dialkylzincs can be heated to 50 °C without problems.

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(11) *Typical Procedure:* (R)-Ethyl 7-hydroxy-2-methylenedodecanoate (**3i**; entry 9 of Table 1).

(a) *Hydroboration:* A 50 mL two-neck flask equipped with an argon inlet and a rubber septum was charged under argon with ethyl 2-methylene-5-hexenoate (1.40 g, 9.1 mmol). Diethylborane (0.83 g, 9.0 mmol)[12] was added at -10 °C over 15 min. The reaction was allowed to warm slowly to 25 °C and was stirred 2 h at this temperature. The volatile by-products were evaporated under vacuum (0.3 mmHg) affording the crude hydroboration product (1.72 g).

(b) *Boron-zinc exchange:* To the organoborane prepared above was added Et_2Zn (2.0 mL, 19.5 mmol) at 0 °C. After 30 min, the excess diethylzinc and formed triethylborane were evaporated (0.3 mmHg, 50 °C, 4 h). The resulting dialkylzinc was diluted with toluene (4 mL) and was ready to use for the next step.

(c) *Asymmetric addition:* A suspension of (1R,2R)-1,2-*bis*-(trifluoromethanesulfonamido)cyclohexane **5** (42 mg, 0.112 mmol) and titanium(IV) isopropoxide (0.80 g, 2.81 mmol) in toluene (1 mL) was warmed to 50 °C for 0.5 h and cooled to -60 °C. The dialkylzinc prepared above was added *via* syringe and the resulting yellowish-green reaction mixture was warmed to -20 °C and was stirred for 20 min at this temperature. Hexanal (140 mg, 1.40 mmol) was added and the reaction mixture was stirred at this temperature for 12 h. The usual workup,[6] drying ($MgSO_4$) and evaporating of the solvents afforded a crude oil which was purified by chromatography (hexanes : ether 5 : 1) leading to analytically pure **3i** (257 mg, 1.0 mmol; 72 % yield; 95 % ee).[13] $[\alpha]_D = +0.3$ (c = 3.34, $CHCl_3$).

(12) A stock solution of diethylborane was prepared from triethylborane (30.34 g, 310 mmol) and borane dimethylsulfide complex (11.40 g, 150 mmol).

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