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New Enantioselective Syntheses of Acetylenic Alcohols Using Functionalized Diorganozincs.

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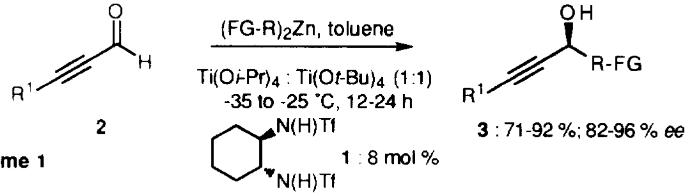
Abstract: *Two new enantioselective preparations of polyfunctional propargylic alcohols (82 to >96 % ee) have been developed. They were obtained by using the addition of functionalized dialkylzincs to acetylenic aldehydes in the presence of a 1:1 mixture of* $Ti(Oi\text{-}Pr)_4$ *and* $Ti(Ot\text{-}Bu)_4$ *and* ***1*** *as a catalyst. In a second method, dialkylzincs were added to α-bromo-α,β-unsaturated aldehydes leading to allylic bromo-alcohols (84 to > 96 % ee) which were smoothly converted to propargylic alcohols by treatment with NaH in DMF (25 °C, 10 min).*

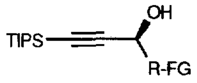
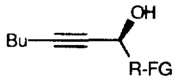
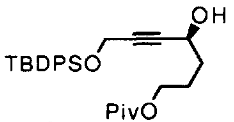
Chiral acetylenic alcohols in enantiomerically pure form are important building blocks for the synthesis of chiral molecules.[1] They can be prepared in good enantiomeric purity by the enantioselective reduction of acetylenic ketones.[2] The addition of Et_2Zn[3] and *bis*(3-butenyl)zinc[4] to acetylenic aldehydes using a titanium TADDOL[5] catalyst provides acetylenic alcohols with excellent enantioselectivity. In contrast, the addition of dialkynylzinc reagents to various aldehydes in the presence of an amino-alcohol as catalyst affords alkynyl alcohols in moderate enantioselectivity.[6] Recently, we have reported that various functionalized dialkylzincs can be added to aromatic, unsaturated and aliphatic aldehydes in the presence of (1R,2R)-catalyst[7] **1** (5-8 mol %) leading topolyfunctional secondary alcohols with excellent enantioselectivity.[8]



Scheme 1

Herein, we wish to report our first results showing that polyfunctional propargylic alcohols can also be prepared in high enantioselectivity using functionlized dialkylzincs. Our first attempt to add ($Zn((CH_2)_3OPiv)_2$) to the acetylenic aldehyde **2a** (R^1 = TIPS) under standard reaction conditions ($Ti(Oi\text{-}Pr)_4$ (1.4 equiv), **1** (8 mol %), toluene, -35 °C, 12 h) was quite disappointing affording the propargylic alcohol **3a** in 75 % yield and 8 % *ee* (Scheme 1 and Table 1). The replacement of $Ti(Oi\text{-}Pr)_4$ by $Ti(Ot\text{-}Bu)_4$ which had been used with great success for the addition of small non-functionalized dialkylzincs,[8] was not satisfactory due to the lower reactivity of functionalized dialkylzincs like ($Zn((CH_2)_3OPiv)_2$). Sluggish reactions and moderate chemical yields were observed. However, an impressive enhancement of the enantioselectivity (92 % *ee* instead of 8 % *ee*) was obtained by using 15 mol % of the catalyst **1**, ***equimolar mixtures*** of $Ti(Oi\text{-}Pr)_4$ ***and*** $Ti(Ot\text{-}Bu)_4$ and by performing a slow and simultaneous addition of these alkoxides and the aldehyde. This behavior proved to be general and various dialkylzincs could be added under these conditions to acetylenic aldehydes (Table 1). In the case of unfunctionalized dialkylzincs (entries 3, 6 and 8 of Table 1), satisfactory enantioselectivities are obtained with $Ti(Ot\text{-}Bu)_4$ alone at 0 °C. Although, this direct asymmetric preparation of propargylic alcohols was satisfactory in many cases, an alternative method allowing the use of commercially available $Ti(Oi\text{-}Pr)_4$ was developed. It has been shown previously[10] that the addition of $(FG\text{-}R)_2Zn$ to α-substituted aldehydes furnishes allylic alcohols with high enantioselectivity. Thus the treatment of unsaturated aldehydes **4** with bromine (0 °C, CH_2Cl_2) followed by Et_3N furnishes (Z)-α-bromo-α,β-unsaturated aldehydes **5**[11] in good yields (67-89 %). As expected excellent enantioselectivities (84 to >96 % *ee*) are obtained by the addition of various dialkylzincs to **5** (Table 2). The resulting allylic bromo-alcohols **6** eliminate readily HBr (NaH (2-3 equiv), DMF, 25 °C, 10 min) affording the propargylic alcohols **3** in 76-96 % yield (Scheme 2 and Table 2). No loss of stereochemistry occurs during the elimination step as verified by preparing the corresponding O-acetylmandelates.[12]

Table 1. Propargylic alcohols **3a-i** obtained by the addition of $(FG\text{-}R)_2Zn$ to the acetylenic aldehydes **2** in the presence of $Ti(Oi\text{-}Pr)_4$: $Ti(Ot\text{-}Bu)_4$ (1:1) and 15 mol % of **1**.

Entry	R^1	FG-R	Product 3	Yield (%)[a]	% *ee*[b]
					
1	TIPS	$PivO(CH_2)_3$	**3a**: R-FG = $PivO(CH_2)_3$	71(76)[c]	92 (8)[c]
2	TIPS	$PivO(CH_2)_4$	**3b**: R-FG = $PivO(CH_2)_4$	86	86
3	TIPS	Pent	**3c**: R-FG = Pent	92	96[d]
					
4	Bu	$PivO(CH_2)_3$	**3d**: R-FG = $PivO(CH_2)_3$	83	90
5	Bu	$PivO(CH_2)_4$	**3e**: R-FG = $PivO(CH_2)_4$	73	82
6	Bu	Pent	**3f**: R-FG = Pent	81	91[d]
7	Ph	$PivO(CH_2)_3$	**3g**: R-FG = $PivO(CH_2)_3$	85	88
8	Ph	Pent	**3h**: R-FG = Pent	87	92[d]
9	$TBDPSOCH_2$	$PivO(CH_2)_3$	 **3i**	76	94

[a] Isolated yields of analytically pure products [b] Determined by preparing the corresponding O-acetylmandelates using (S)-(+)-O-acetylmandelic acid. In each case, a calibration sample using (±)-O-acetylmandelate was prepared [c] Only $Ti(Oi\text{-}Pr)_4$ was used [d] The reaction was performed at 0 °C using only $Ti(O\text{-}t\text{-}Bu)_4$ and 8 mol % of **1**

Scheme 2

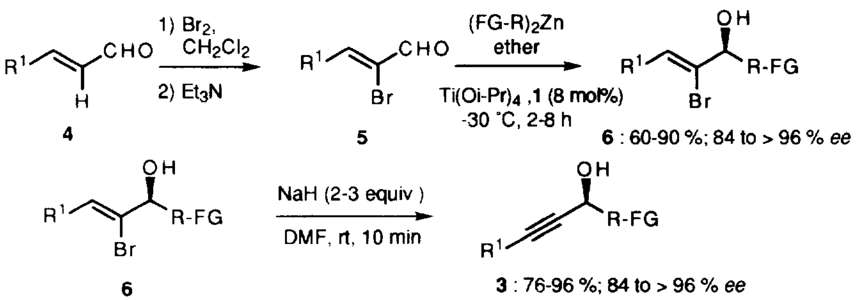
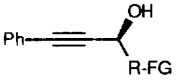
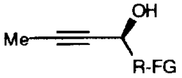
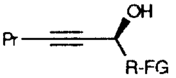


Table 2. Propargylic alcohols of type **3** obtained by the addition of $(FG\text{-}R)_2Zn$ to α-bromo-α,β-unsaturated aldehydes **5**, followed by NaH elimination.

Entry	R^1	FG-R	Yield of **6** (%)	% *ee*	Product **3**	Yield (%)[a]	% *ee*[b]
1	Ph	$PivO(CH_2)_3$	73	90	**3g**	86	90
2	Ph	Pent	73	92	**3h**	93	92
							
3	Ph	$PivO(CH_2)_4$	78	84	**3j**: R-FG = $PivO(CH_2)_3$	78	84
4	Ph	$PivO(CH_2)_5$	72	86	**3k**: R-FG = $PivO(CH_2)_5$	89	86
							
5	Me	Pent	66	96	**3l**: R-FG = Pent	96	96
6	Me	$PivO(CH_2)_3$	63	95	**3m**: R-FG = $PivO(CH_2)_3$	78	95
7	Me	$PivO(CH_2)_4$	85	92	**3n**: R-FG = $PivO(CH_2)_4$	77	92
8	Me	$PivO(CH_2)_5$	76	84	**3o** R-FG = $PivO(CH_2)_5$	84	84
							
9	Pr	Pent	69	>96	**3p** R-FG = Pent	89	>96
10	Pr	$PivO(CH_2)_3$	76	>96	**3q**: R-FG = $PivO(CH_2)_3$	85	>96
11	Pr	$PivO(CH_2)_4$	88	>96	**3r**: R-FG = $PivO(CH_2)_4$	88	>96
12	*c*-Hex	Et	89	94	**3s**: R-FG = Et	88	94

[a,b] See previous Table.

In summary, we have reported two new complementary preparations of polyfunctional propargylic alcohols in good to excellent enantioselectivity by using the addition of functionalized dialkylzincs to acetylenic or α-bromo unsaturated aldehydes.

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13. **Typical procedures:** (a) Preparation of **3i** (entry 9 of Table 1). A 20 mL three-necked flask equipped with an argon inlet, a thermometer and a septum cap was charged with the catalyst **1** (0.25 g, 0.66 mmol), Ti(O*t*-Bu)$_4$ (0.28 g, 0.82 mmol) and toluene (1 mL). This mixture was heated to 75 °C for 0.5 h and cooled back to -35 °C. A solution of (PivO(CH$_2$)$_3$)$_2$Zn[8] (11.4 mmol, 2.7 equiv) in toluene was added and after 0.5 h, the aldehyde **2** (R=TBDPSOCH$_2$; 1.35 g, 4.19 mmol) and a solution of Ti(O*i*-Pr)$_2$(O*t*-Bu)$_2$ (2.42 g, 7.75 mmol prepared by mixing equimolar amounts of Ti(O*i*-Pr)$_4$ and Ti(O*t*-Bu)$_4$ and destilling the resulting mixture (bp 46 °C/ 0.6 mmHg)). The addition of Ti(O*i*-Pr)$_2$(O*t*-Bu)$_2$ was complete after 0.5 h and GC analysis of a reaction aliquot indicates the completion of the reaction after 12 h. The reaction mixture was worked up as usual and the resulting oil was purified by flash-chromatography (hexanes:ether 4:1) affording the propargylic alcohol **3i** (1.49 g, 3.19 mmol, 76 % yield) as a colorless oil (94 % *ee*; $[\alpha]^{24}_D = -2.33$ (c = 4.37, chloroform)). (b) Preparation of **3q** (entry 10 of Table 2): *Bis*(3-pivaloxypropyl)zinc prepared[8] from 3-iodopropyl pivalate (13.6 g, 50 mmol) and Et$_2$Zn (8.0 mL, 80 mmol, 1.6 equiv) was dissolved in ether and added at -40 °C via syringe to an ether solution (10 mL) of the catalyst **1** (300 mg, 0.8 mmol) and Ti(Oi-Pr)$_4$ (6.0 mL, 20 mmol). After 15 min of stirring, 2-bromo-2-hexenal (1.90 g, 10.7 mmol) was added and the reaction mixture was warmed up to -20 °C and stirred for 2 h. After the usual work-up, the crude residue was purified by flash-chromatography (hexanes:ether 4:1) affording the desired allylic alcohol (2.61 g, 8.12 mmol, 76 % yield >96 % *ee*). $[\alpha]^{24}_D = + 2.04$ (c = 2.45, CHCl$_3$). To a DMF solution (5 mL) of this alcohol (800 mg, 2.49 mmol) was added NaH (80 % suspension in oil, 150 mg, 5 mmol). An exothermic reaction occured and the reaction mixture was poured after 5 min into a dilute solution HCl and was extracted with ether. Purification by flash-chromatography (hexanes:ether 4:1) affords the propargylic alcohol **3q** (509 mg, 2.12 mmol, 85 %). The enantiomeric purity of **3q** was determined to be >96 % *ee*; $[\alpha]^{24}_D = -2.96$ (c = 1.69, CHCl$_3$).

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