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Enantioselective Preparation of Polyfunctional Secondary Allylic Alcohols Using Functionalized Dialkylzincs Prepared by a Copper(I) Catalyzed Iodine-Zinc Exchange Reaction.

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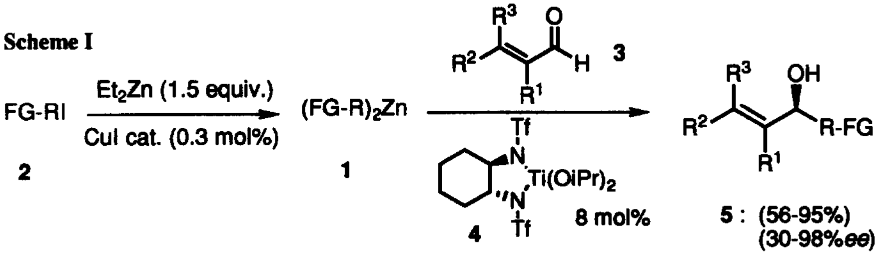
Summary

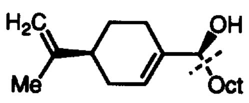
Catalytic amounts of Cu(I) salts considerably facilitate the iodine-zinc exchange reaction leading to polyfunctional dialkylzincs. The catalytic asymmetric addition of these zinc reagents to a wide range of α,β -unsaturated aldehydes provides polyfunctional allylic alcohols with a high enantioselectivity.

Recently, we reported a novel preparation of polyfunctionalized dialkylzincs $(FG\text{-}R)_2Zn$ **1** prepared from the corresponding alkyl iodides (FG-RI) **2** using an iodine-zinc exchange reaction. These organometallics are very useful reagents in asymmetric synthesis and add with high enantioselectivity to various aldehydes affording polyfunctional secondary alcohols.[2] Unfortunately, our original reaction conditions required the use of a large excess of Et_2Zn (5 equiv.) and we observed that the scale-up of this reaction led to lower conversions. We now report an improved procedure involving a copper(I) catalysis as well as our preliminary results concerning the catalytic asymmetric addition of **1** to unsaturated aldehydes **3** in the presence of the chiral catalyst **4** (8 mol%) allowing a unique preparation of polyfunctional secondary allylic alcohols **5** with a high level of enantioselectivity (Scheme I).

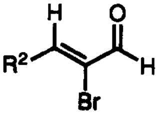
Scheme I



The performance of the iodine-zinc exchange in the presence of CuI or CuCN (0.3 mol%) considerably facilitates the reaction. A two-fold rate increase is observed and more importantly *an excess of only 1.5 equiv. of Et_2Zn is sufficient* to achieve over 95% conversion. Furthermore, the scale-up of the iodine-zinc



6 : 82%; 92%*ee*



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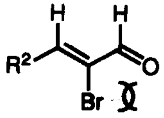

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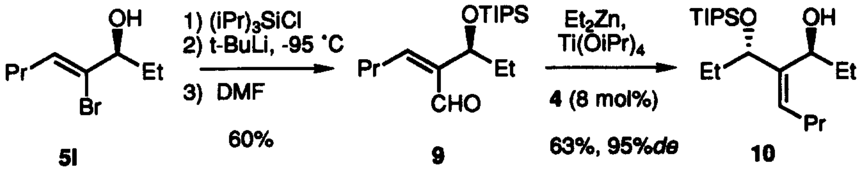
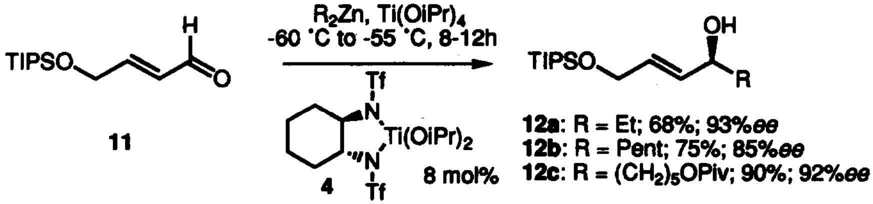
reaction is now possible. For example, 3-iodopropyl pivalate (50 mmol) has been converted to di(3-pivaloxypropyl)zinc within 8 h at 50-55°C (neat, Et_2Zn (75 mmol), CuI (0.15 mmol)) in over 90% yield. In the absence of Cu(I) salts and using 5 equiv. of Et_2Zn (250 mmol !) this reaction stops at a conversion of only 33%. We have verified that the presence of small amounts of ZnI_2 formed during the iodine-zinc exchange reaction has no detrimental effect on the enantioselectivity of the addition reaction. Thus the addition of Oct_2Zn (2 equiv.) prepared using this improved method to (*S*)-(-)-perillaldehyde (1 equiv.) in the presence of **4** (8 mol%) and $Ti(OiPr)_4$ (2 equiv.) provides the expected alcohol **6** in 85% yield (toluene, -20°C, 12 h) and 92%*ee*.[3,4]

We have applied this method to the enantioselective preparation of highly functionalized chiral allylic alcohols.[5,6] Our first experiment using (*E*)-2-methyl-2-butenal ($R^1 = R^2 = Me$) proceeds with very high enantioselectivity [2] (entries 1 and 2 of Table 1), however we noticed that in the case of the addition of di(5-acetoxypentyl)zinc to (*E*)-2-hexenal, the desired alcohol **5c** was only obtained in 83%*ee* (entry 3) showing the importance of the presence of a substituent in position 2 ($R^1 \neq H$). Furthermore we have observed that the introduction of a β-substituent (R^3) *cis* to the carbonyl group has a negative effect on the enantioselectivity . Thus the reaction of Oct_2Zn with 3-methyl-2-butenal ($R^2 = R^3 = Me$) furnishes the corresponding allylic alcohol **5f** with only 30%*ee* (95% yield, entry 6). Corey showed recently that the introduction of a bromine in position 2 of an unsaturated aldehyde leads to high enantioselectivities in catalytic asymmetric Diels-Alder reactions.[7] We have applied the same strategy and converted the α,β-unsaturated aldehydes to α-bromo-α,β-unsaturated aldehydes ((i) Br_2, CH_2Cl_2, 0 °C; (ii) Et_3N, 81% overall).[8] The bromine substituent will favor the *s*-cis conformer **7** over the *s*-trans conformer **8** and thus brings the double bond moiety closer to the chiral metal center allowing a better steric differenciation between the two carbonyl faces. A dramatic improvement of the enantioselectivity is observed. Thus (*Z*)-2-bromo-2-hexenal ($R^1 = Br$) reacts with $(AcO(CH_2)_5)_2Zn$ with 94%*ee* (compared to 83%*ee* ($R^1 = H$); see entries 3 and 8). Similar results are obtained with 2-bromo-3-methyl-2-butenal (68%*ee* compared to 30%*ee* when $R^1 = H$; entries 6 and 11).

Scheme II



Scheme III



12a: R = Et; 68%; 93%*ee*
12b: R = Pent; 75%; 85%*ee*
12c: R = $(CH_2)_5OPiv$; 90%; 92%*ee*

A wide range of functions are tolerated including a protected primary amino group and functionalized unsaturated 2-iodo-aldehydes can also be used (Table I).[9,10] The synthetic utility of unsaturated 2-bromoalcohols is shown in Scheme II. The alcohol **5l** (prepared with 95%*ee*) was silylated with TIPSCl (1.2 equiv., 20 °C, 10 h, 90% yield) and was treated with *t*BuLi (3 equiv., -95 °C, 1 h) followed by DMF (10 equiv., -95 °C to -20 °C, 2 h) affording the polyfunctional aldehyde **9** in 60% yield . The addition of Et_2Zn under the usual reaction conditions furnished the selectively protected unsaturated 1,3-diol **10** (63% yield, 95%*de*) which is a versatile chiral building block.[10] Finally, we found that some functionalized unsaturated aldehydes are excellent substrates and the readily available aldehyde **11**[11] reacts with excellent enantioselectivity with various dialkylzincs providing chiral selectively protected 1,4-diols **12 a-c** (85-93%*ee*; Scheme III) which are precursors to a wide range of poly-oxygenated molecules.[9,12]

Table 1. Polyfunctional alcohols **5** prepared by an enantioselective addition of dialkylzincs **1** to aldehydes **3**.

Entry	$(FG\text{-}R)_2Zn$ **1**	Unsaturated aldehyde **3**			Product of	Yield	Enantiomeric
	FG-R	R^1	R^2	R^3	type **5**	$(\%)^a$	excess $(\%ee)^b$
1	$AcO(CH_2)_5$	Me	Me	H	**5a**	70	98
2	Oct	Me	Me	H	**5b**	65	98
3	$AcO(CH_2)_5$	H	Pr	H	**5c**	75	83 $(88)^c$
4	Et	H	(E)- MeCH=CH	H	**5d**	85	80^d
5	$AcO(CH_2)_5$	Me	EtO_2C	H	**5e**	78	80
6	Oct	H	Me	Me	**5f**	95	30
7	$PhCH_2(Tf)N(CH_2)_3$	Br	Pr	H	**5g**	56	86^e
8	$AcO(CH_2)_5$	Br	Pr	H	**5h**	95	94
9	$Cl(CH_2)_4$	Br	Pr	H	**5i**	68	95
10	$PivO(CH_2)_3$	Br	Pr	H	**5j**	68	95
11	$AcO(CH_2)_5$	Br	Me	Me	**5k**	68	68
12	Et	Br	Pr	H	**5l**	94	95
13	$AcO(CH_2)_5$	Br	Me	H	**5m**	77	80
14	Et	I	Bu_3Sn	H	**5n**	75	94
15	$PhCH_2(Tf)N(CH_2)_3$	I	Bu_3Sn	H	**5o**	62	82

[a] Yield of analytically pure products. [b] Determined by ^1H NMR integration of the corresponding *O*-acetylmandelates (ref. 3). [c] 88%*ee* was obtained using 16 mol% of **4**. [d] The product **5d** was contamined with 13% of the *Z* isomer. [e] The reaction required 48 h and **5g** contained 13% of the *Z* isomer.

Acknowledgments

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References and Notes

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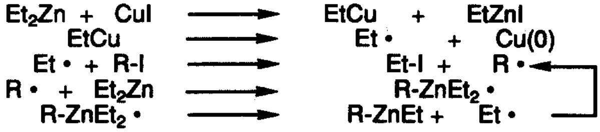
3. The enantiomeric excess was determined by the ^{1}H NMR analysis of the *O*-acetylmandelates of the corresponding secondary alcohols prepared by using (*S*)-*O*-acetylmandelic acid (Aldrich): Parker, D. *J. Chem. Soc., Perkin Trans. 2*, **1983**, 83.
4. The catalytic effect of Cu(I) salts may be rationalized by the following chain mechanism:



5. Allylic alcohols have been prepared by the enantioselective addition of di(alkenyl)zincs to aldehydes : (a) Oppolzer, W.; Radinov, R.N. *Tetrahedron Lett.* **1988**, *29*, 5645; (b) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777; (c) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170.
6. For the addition of dialkylzincs to some unsaturated aldehydes, see (a) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1321; (b) Schmidt, B.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*,1321; (c) Weber, B.; Seebach, D. *ibid.* **1991**, *31*, 84; v.d.Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719; (e) see also: Seebach, D.; Plattner, D.A.; Beck, A.K.; Wang, Y.M.; Hunziker, D.; Petter, W.; *Helv. Chim. Acta* **1992**, *75*, 2171; (f) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657; (g) Takahashi, H., Kawakita, T.;Yoshioka, M.; Ohno, M. . *ibid.* **1989**, *30*, 7095; (h) Takahashi, H., Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1989**, *48*, 5691.
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8. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
9. Further stereoselective transformations of these molecules are currently underway in our laboratories.
10. Marek, I., Alexakis, A., Normant, J. F. *Tetrahedron Lett.* **1991**, *32*, 6337.
11. Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *33*, 6227.
12. *Typical procedure* : a) Preparation of di(5-acetoxypentyl)zinc: A Schlenk-flask equipped with an argon inlet and a septum cap was charged with CuI (2 mg, ca. 0.01 mmol), 5-iodopentyl acetate (4.1 g, 16 mmol) and Et$_2$Zn (2.0 mL, 20 mmol). The reaction mixture was warmed to 50° C and stirred for 8 h at this temperature. The Schlenk flask was connected to the vacuum (0.1 mmHg) and the excess Et$_2$Zn and formed EtI was collected in a trap cooled with liquid N$_2$. This operation required ca. 2 h at 50°C. The resulting dialkylzinc was diluted in toluene (8 mL) and was ready to use.

b) Preparation of the allylic alcohol (*S*)-**5h**: A 100 ml three-neck flask equipped with an argon inlet, a thermometer and a septum cap was charged with dry toluene (3 ml), Ti(O*i*Pr)$_4$ (2.4 ml, 8.0 mmol) and (1*R*,2*R*)-1,2-bis-(trifluorosulfamido)cyclohexane (120 mg, 0.3 mmol). The reaction mixture was heated to 40-45°C for 0.5 h and cooled to -60 °C. Di(5-acetoxypentyl)zinc (8 mmol prepared as described above) in toluene and then (*Z*)-2-bromo-2-hexanal (710 mg, 4.0 mmol) were slowly added and stirred for 10 h at -20°C. After the usual work-up, the crude resulting oil was purified by flash-chromatography (hexanes-ether 9:1) affording the pure allylic alcohol **5h** (1.15 g, 95%, $[\alpha]^{25}_D = +2.71°$ (*c* = 3.32, C$_6$H$_6$), 94%*ee*) determined by the ^{1}H NMR analysis of its derivative with (*S*)-(-) *O*-acetylmandelic acid and comparaison with the spectrum of the racemic mixture.

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