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A STUDY OF METHYL AND TERT-BUTYL AS NON MIGRATING GROUPS IN THE REACTION OF ME(ORGANYL)ZINC AND t-BU(ORGANYL)ZINC WITH ALDEHYDES.

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Abstract: A series of mixed methyl (organyl) and tert-butyl(organyl)zincs were prepared by reaction of $ZnCl_2$ with Grignard reagents. In the presence of salts t-butyl migrates to a lessor extent than methyl in the reaction with aldehydes. In the absence of salts both groups are comparable. BuZnMe prepared under salt-free conditions adds to benzaldehyde in 82.4 % ee and in 85 % yield, comparable to the reaction with distilled dibutylzinc.

In 1984 Oguni and Omi reported that amino alcohols accelerate the addition of diorganylzincs to aldehydes.[1] With optically active amino alcohols, optically active secondary alcohols were obtained. The next few years saw a virtual explosion of activity in this reaction, with the emphasis on the design of improved optically active ligands.[2] The mechanism of the reaction was explored and elucidated and the nature of the actual catalyst was determined.[3] Thus it was found that only one organyl group transfers from the diorganylzinc to the aldehyde. In their work on conjugate addition of triorganylzincates to enones, Tüchmantel and coworkers found a considerable difference in the rate of transfer of organyl groups from zincates.[4] In particular it was shown that the methyl group on the one hand and the tert-butyl group on the other migrate from zinc much more slowly than other organyl groups. Nehl, in a study of mixed diorganyl zincs, R^1R^2Zn, prepared by mixing symmetrical $R^1{}_2Zn$ and $R^2{}_2Zn$, found that the equilibrium constants favored the mixed species in many cases.[5] It seems that a criterion for obtaining a favorable equilibrium is the size of the mixed species attached to the zinc. Thus at equilibrium, both t-BuZnPh and t-BuZnChx are present in 99%, while t-BuZnMenthyl is present at only 43%. It appeared to us that the methyl group, being the smallest of the organyl groups, would also be a particularly good candidate for preparing mixed diorganylzincs. Since the utility of the asymmetric diorganylzinc addition reaction would be greatly increased if a inexpensive non-migrating group were employed, we decided to investigate the preparation of mixed methylorganyl- and tert-butylorganylzincs and their reaction with aldehydes.[6] We also have demonstrated the usefulness of this approach by using our mixed diorganylzincs in the asymmetric synthesis.

The mixed diorganylzincs were prepared by mixing equal molar amounts of either MeMgCl or t-BuMgCl with $ZnCl_2$ followed by the addition of RMgX and an aldehyde at 0 °C. We initially evaluated the reactants with benzaldehyde (Table 1). All organyl groups in the mixed MeRZn and t-BuRZn migrated preferentially. In the presence of salts, tert-butyl gave superior results. In salt free solutions obtained by filtration of precipitates followed by addition of 1,4-dioxane,[6,7] filtration and addition of N-methylpiperidine[8] as catalyst, mixed MeRZn and t-BuRZn gave comparable results (Table 1, entries 2,5, 8). We also compared the migration of methyl and t-butyl in the mixed Me(t-Bu)Zn. Methyl transfers almost exclusively (Table 1, entry 14).

Table 1. Reaction of Methyl(Organyl)Zinc and tert-Butyl(Organyl)Zinc with Benzaldehyde[a]

Entry	R	Organometallic	Solvent, Conditions	Product Distribution[b]			Yield[c]
				% Me	% t-Butyl	% R	
1	Et	EtMgCl, MeMgCl	Et_2O, THF	7		93	64
2	Et	EtMgCl, MeMgCl	Et_2O, THF, A[d]	1		99	65
3	Et	EtMgCl, t-BuMgCl	Et_2O		4	96	83
4	n-Bu	n-BuMgCl, MeMgCl	Et_2O, THF	37		63	61
5	n-Bu	n-BuMgCl, MeMgCl	Et_2O, A[d]	5		95	75
6	n-Bu	n-BuMgCl, t-BuMgCl	Et_2O		<1	>99	56
7	Chx	ChxMgCl, MeMgCl	Et_2O, THF	38		62	52
8	Chx	ChxMgCl, MeMgCl	Et_2O, THF, A[d]	5		95	65
9	Chx	ChxMgCl, t-BuMgCl	Et_2O		10	90	67
10	Bz	BzMgCl, MeMgCl	THF	<1		>99	90
11	Bz	BzMgCl, t-BuMgCl	THF, Et_2O		<1	>99	91
12	Vinyl	VinylMgBr, MeMgCl	THF	<1		>99	65
13	Vinyl	VinylMgBr, t-BuMgCl	THF, Et_2O		10	90	64
14	t-Bu	t-BuMgCl, MeMgCl	Et_2O, THF	>99	<1		45
15	Pr	PrMgCl, t-BuMgCl	Et_2O		<1	>99	64

[a]The reactions were run on a three mmol scale with one equivalent each of MeMgCl, RMgX, $ZnCl_2$ and benzaldehyde at 0 °C for four hours. [b]Determined by GC. [c]GC yields determined in the presence of an internal standard. [d]The solids were filtered and 5 mol % 1,4-dioxane was added. After precipitation stopped, the mixture was again filtered and N-methylpiperidine, 10 mol % was added as a catalyst.

Several classes of aldehydes were then reacted with either MeRZn under salt-free conditions or with t-BuRZn (Table 2). These results indicate that a variety of aliphatic and aromatic aldehydes react similarly to benzaldehyde and are suitable substrates for either of the mixed organylzincs. In all cases examined the R groups in the mixed diorganylzincs migrated almost exclusively.

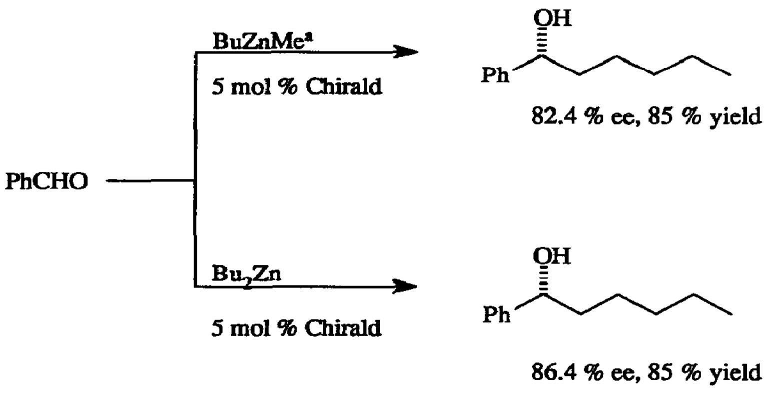
Chirald, a commercially available 1,3-amino alcohol[9], has been used in the asymmetric addition of dibutylzinc to benzaldehyde.[10] We decided to test our system using this ligand with our mixed diorganylzincs. As a control, we reacted distilled dibutylzinc with benzaldehyde in the presence of 5 mol % chirald. The enantiomeric excess (% ee) of the product was then determined by capillary GC analysis of the (+)-MTPA esters.[11] The product, 1-phenyl-1-pentanol, was obtained in 86 % ee and in 66 % isolated yield.[12] Our mixed Me(Bu)Zn under salt free conditions gave the product in 82.4 % ee and in 85 % chemical yield (Scheme 1).[13]

Table 2. Reaction of Mixed MeRZn and t-BuRZn with Various Aldehydes[a]

Entry	Diorganylzinc	Aldehyde[b]	Product Distribution[c]			Yield[d]
			% Me	% t-Bu	% R	
1	Bz, t-Bu	Valeraldehyde		<1	>99	46
2	Vinyl, t-Bu	Valeraldehyde		<1	>99	51
3	Et, t-Bu	Valeraldehyde		<1	>99	48
4	Et, t-Bu	Hydrocinnamaldehyde		<1	>99	87
5	Vinyl, t-Bu	Hydrocinnamaldehyde		<1	>99	57
6	Bz, t-Bu	Furaldehyde		<1	>99	64
7	Et, t-Bu	Furaldehyde		8	92	40
8	Et, t-Bu	Tolualdehyde		<1	>99	76
9	Vinyl, t-Bu	Tolualdehyde		<1	>99	53
10	Me, Cyclopentyl[e]	Propionaldehyde	<1		>99	65
11	Me, n-Bu	Cyclohexylaldehyde	<1		>99	85

[a] The reactions were run on a three mmol scale with one equivalent each of MeMgCl, RMgX, $ZnCl_2$ and benzaldehyde at O °C. [b] Freshly distilled prior to use. [c] GC determination. [d] GC determination in the presence of an internal standard. [e] Prepared under salt free conditions. See footnote under Table 1.

Scheme 1



[a] Prepared from $ZnCl_2$, BuMgCl and MeMgCl, filtered, 5 mol % 1,4-dioxane added and again filtered.

In conclusion we have demonstrated that it is possible to utilize either the methyl group or the tert-butyl group as non-migrating ligands in the preparation of mixed MeZnR and t-BuZnR. Further, under salt-free and asymmetric conditions, BuZnMe exclusively transfers the butyl group to benzaldehyde to provide the product with %ee comparable to that obtained from distilled dibutylzinc.

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(13) Preparation of Butyl(Methyl)Zinc and its reaction with benzaldehyde. All operations were done with oven dried glassware cooled under an inert atmosphere. A thick glass centrifuge tube was charged with 3 mL of 1 N $ZnCl_2$ in ether. 1 mL of 3 N MeMgCl in THF was added slowly followed by the slow addition of 1.5 mL of 2 N BuMgCl in ether. After stirring for 15 min the solution was centrifuged at 4000 rpm for five min. The supernatant was then transferred with a double ended needle through a filter into a 50 mL round-bottom flask. The remaining salts in the centrifuge tube were washed with 10 mL of distilled hexanes and the washings which were also centrifuged transferred to the round bottom flask. 12.8 µL of 1,4-dioxane was added to the clear solution and stirred for 15 min. It was then filtered and transferred to another 50 mL flask containing 0.0425 g of Chirald. The salt-free solution was then cooled to 0 °C and reacted with 0.3 mL of benzaldehyde for 8 hr. The reaction mixture was finally quenched with saturated NH_4Cl, dried and volatiles removed in vacuo. After chromatography on silica gel pure (R)-(+)-1-phenyl-1-pentanol was obtained Yield: 0.42 g; $[\alpha]_D$ (c= 1.02, $CHCl_3$) = +32.48°.[12]

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