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Ligand Effects on Diastereoselective Addition of Organocerium Reagents to Aldehydes and Cyclic Ketones

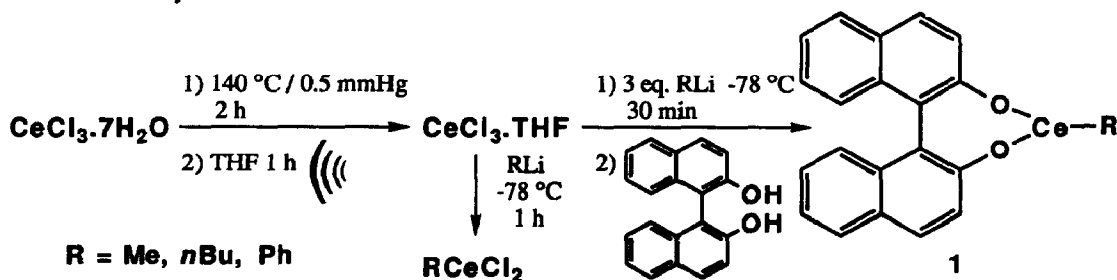
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Abstract: A new class of chiral dialkoxy- and diaryloxyorganocerium reagent has been prepared and the diastereoselectivity of carbonyl addition reactions has been compared with that of conventional organocerium reagents.

Diastereoselective addition of organometallic reagents to carbonyl compounds is a topic of immense current interest as the search for ever increasing generality and selectivity continues.¹ Recent contributions have included a study of the effect of changing the ligand in traditional Grignard reagents from halide to carboxylate,² the use of organomanganese reagents with similar ligands,³ and unprecedented stereoselectivity in cyclohexanone additions with organoiron (II) reagents.⁴ Organocerium reagents, prepared from organolithium or Grignard reagents and anhydrous cerium (III) chloride,⁵⁻⁷ are becoming increasingly important in organic synthesis. The reagents, derived from all classes of organolithium, undergo clean addition to a wide range of carbonyl compounds in very high yield but there has been no detailed study of the diastereoselectivity of these or related reagents.⁸ Organoytterbium reagents, produced from ytterbium (III) triflate and organolithiums, exhibited high levels of diastereoselectivity with aldehydes and ketones⁹ while the ate complexes formed from cerium (III) isopropoxide were less suitable for selective addition.³

We have recently reported a simple modification to the experimental procedure for the formation of organocerium reagents that uses ultrasound to accelerate the preparation of the suspension of anhydrous cerium chloride in dry THF and to ensure reproducible results in a substantially reduced reaction time.¹⁰ Conventional organocerium reagents (RCeCl_2) have an unknown structure but clearly are achiral if monomeric. Substitution of the halide ligands by a chiral bidentate ligand would create a new class of organocerium reagent which would be chiral and thus, with homochiral ligands, enantioselective. We would now like to report our efforts to modify the co-ordination sphere around cerium by incorporation of diol ligands and the effect of this on reagent activity and diastereoselectivity.



Scheme 1. Formation of organocerium reagents

We reasoned that treatment of a slurry of anhydrous cerium chloride in THF at $-78\text{ }^{\circ}\text{C}$, prepared by sonication for one hour or stirring overnight, with three equivalents of organolithium would produce a reagent which could be formulated as R_3Ce on the basis of stoichiometry. The nature of this species is unknown and has proved resistant to study.¹¹ Addition of a diol would then result in double deprotonation of the ligand (with formation of two equivalents of inert hydrocarbon) which could co-ordinate to the cerium ion to generate the new reagent **1**. The success of this approach is illustrated in scheme 1 with racemic binaphthol as the diol ligand. The reactivity of the reagents was essentially unchanged by the change of ligand which may be an indication of the predominantly ionic nature of organocerium chemistry. Additions of reagent **1** to a range of simple aldehydes, ketones, and esters occurred in high yield. Removal of the binaphthol ligand was readily achieved by washing with base after the cerium ions had first been removed by reaction with sodium fluoride. We decided to investigate the diastereoselectivity of carbonyl addition reactions with this new class of chiral dialkoxy- and diaryloxyorganocerium reagent and to compare the results with those of conventional organocerium reagents. We selected Cram's original aldehyde **2** as this has been widely used as a test system (*vide supra*) and the results are shown in Table 1.¹²

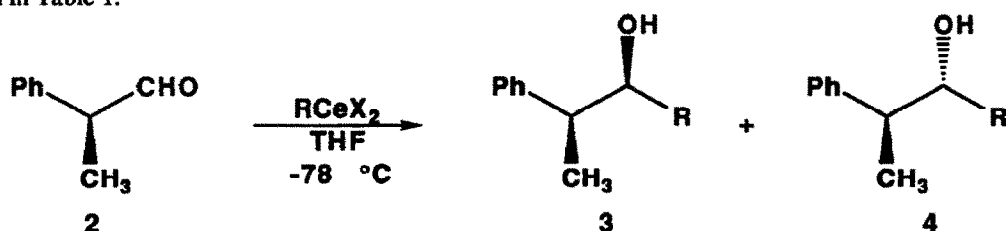


Table 1. Stereoselective Additions of Organocerium Reagents to Aldehyde **2**

Entry	Reagent (RCeX_2)	Ratio		Yield/%	% enolisation ^b
		3 ^a	4		
1	MeCeCl_2	88.2	: 11.8	87	<1
2	MeCeBinaphthol	87	: 13	62	6
3	$n\text{-BuCeCl}_2$	88	: 12	88	<1
4	$n\text{-BuCeCl}_2^c$	90	: 10	85	<1
5	$n\text{-BuCeBinaphthol}$	87	: 13	47	<1
6	$n\text{-BuCePinacol}$	90	: 10	46	3
7	PhCeCl_2	87	: 13	94	<1
8	PhCeBinaphthol	85.5	: 14.5	75	<1

^aRatio of diastereoisomers by gc/ms. ^bRatio by gc/ms. ^cAldehyde addition over 30 min at $-98\text{ }^{\circ}\text{C}$.

The additions of RCeCl_2 were high yielding and proceeded with good diastereoselectivity in every case.¹² Slow addition of the aldehyde at $-98\text{ }^{\circ}\text{C}$ gave a slight improvement (entry 4) but we found it more convenient to carry out the additions at $-78\text{ }^{\circ}\text{C}$. The reagents derived from racemic binaphthol gave slightly lower diastereoselectivity than their achiral counterparts in every case (entries 1-2, 3-5, 7-8) while the use of 2,3-dimethylbutan-2,3-diol (pinacol) as a ligand had no effect on the diastereoselectivity. These results are highly significant as they indicate that the addition may be occurring under partial "reagent control"¹³ so that the facial selectivity of the *racemic* reagent (which would produce 50:50 if reagent control were overwhelming) is opposing the intrinsic Cram selectivity of the substrate. The conclusion that the use of optically pure binaphthol would produce an enantioselective reagent is currently under investigation.¹⁴

We then examined the diastereoselectivity of both classes of reagents with a range of substituted cyclohexanones. We selected two standard test ketones, 4-*tert*-butylcyclohexanone **5a** and 2-methylcyclohexanone **5b** together with 2-phenylcyclohexanone **5c**, which is not normally used due to problems with enolisation, and the 4-phenyl regioisomer **5d**. The results of the additions are shown in Table 2.¹²

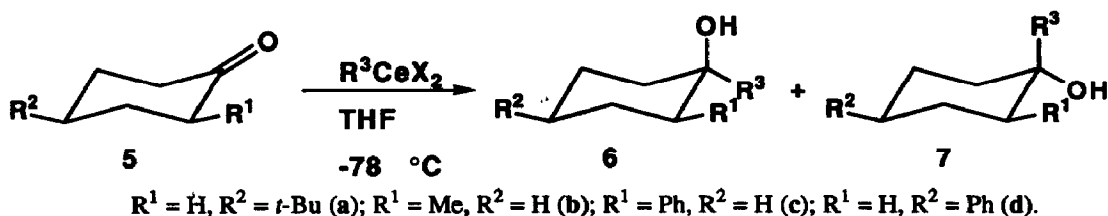


Table 2. Stereoselective Additions of Organocerium Reagents to Cyclohexanones 5

Entry	Ketone	Reagent (RCeX ₂)	Ratio		Yield/%	% enolisation ^b
			6 ^a	7		
1	5a	MeCeCl ₂	67	: 33	62	<1
2	5a	MeCeBinaphthol	58	: 42	55	<1
3	5a	<i>n</i> -BuCeCl ₂	74	: 26	95	<1
4	5a	<i>n</i> -BuCeCl ₂ ^c	84	: 16	64	4
5	5a	<i>n</i> -BuCeBinaphthol	87	: 13	52	6
6	5a	PhCeCl ₂	60	: 40	84	<1
7	5a	PhCeBinaphthol	50	: 50	81	<1
8	5b	MeCeCl ₂	93	: 7	97	6
9	5b	MeCeBinaphthol	88	: 12	68	20
10	5b	<i>n</i> -BuCeCl ₂	97	: 3	70	<1
11	5b	<i>n</i> -BuCeBinaphthol	98	: 2	71	<1
12	5b	PhCeCl ₂	99	: 1	80	<1
13	5b	PhCeBinaphthol	97	: 3	38	<1
14	5c	<i>n</i> -BuCeCl ₂	>95 ^d	: <5	86	<1
15	5c	<i>n</i> -BuCeBinaphthol	95 ^d	: 5	87	<1
16	5d	<i>n</i> -BuCeBinaphthol	80 ^d	: 20	57	<1

^aRatio of diastereoisomers by gc/ms. ^bRatio by gc/ms. ^cEt₂O as solvent. ^dRatio of diastereoisomers by nmr.

As expected, increasing steric hindrance in either the reagent ($R = \text{Me} \rightarrow \text{Bu}$) or the ketone ($5\text{a} \rightarrow 5\text{b} \rightarrow 5\text{c}$) led to increased preference for equatorial attack to produce the axial alcohol 6. The substitution of racemic binaphthol for the chloride ligands led to a slightly less selective reagent in reactions with chiral ketones 5b, 5c consistent with the analysis described above (except for entry 11). Butyl addition to achiral ketones 5a, 5d occurred with good selectivity for such a remote stereocentre with the binaphthol ligand, possibly as a result of the bulk of reagent.

The exception to the trend of increased equatorial attack with increased steric bulk of the reagent¹⁵ is shown in the additions of methyl and phenyl reagents to ketone 5a (entries 1-2, 6-7) compared with ketone 5b (entries 8-9, 12-13). In the former case, both phenyl reagents were less selective while in the additions to 2-methylcyclohexanone 5b higher selectivity was observed.

This anomalous behaviour may be explained by consideration of the possible orientations of the phenyl group on entry as shown in figure 1. The phenyl cerium reagent can attack ketone 5a from an axial direction, parallel to the 3,5-axial protons, with little steric hindrance, due to the flat board-like structure of the phenyl ring, so reducing the preference for equatorial attack. In ketone 5b the pseudo-axial proton from the 2-methyl group prevents attack *via* the same axial path as a result of severe interactions with the *ortho*-protons on the aromatic ring (figure 2). The alternative axial orientation, with the face of the phenyl ring perpendicular to the 3,5-axial protons, suffers from considerable steric interference. This anomalous stereoselectivity in the additions of planar nucleophiles has been described recently as "stealth stereocontrol".¹⁶

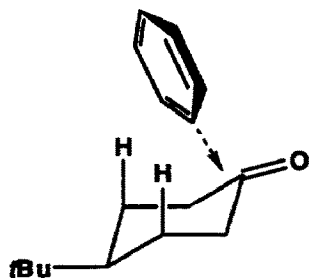


Figure 1. Axial Attack on Ketone 5a.

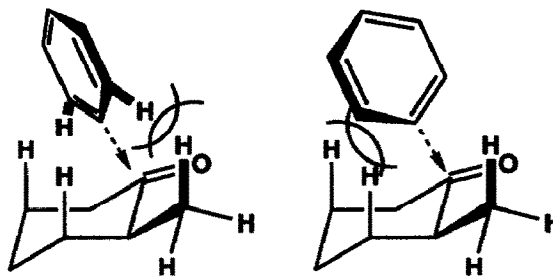


Figure 2. Axial Attack on Ketone 5b.

In summary, we have prepared a new class of chiral dialkoxy- and diaryloxyorganocerium reagents and have demonstrated that they react with carbonyl compounds diastereoselectively and in high yield. The wide range of carbon nucleophiles which can be delivered successfully with simple organolanthanide reagents suggests that our method should be an attractive one. In addition, the dependence on ligand implies that such reagents with homochiral ligands would be enantioselective reagents. Studies aimed at improving the diastereoselectivities, extending the scope, and understanding the nature of these reagents are underway.

General Procedure. (Binaphthol) Cerium (III) chloride ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) (560 mg, 1.5 mmol) was placed in a 25 ml Schlenk flask with a stirrer bar. The flask was placed in an oil bath and heated *in vacuo* to 135–140 °C /0.5 mmHg for 3 hours. While the flask was still hot, argon was introduced. The flask was cooled in an ice bath and dry THF (5 ml) was introduced *via* syringe. The flask was then placed in an ultrasonic bath (Camlab transonic T460/H) at room temperature for 1 hour or stirred overnight. The resulting white slurry was then cooled to -78 °C, the organolithium (4.5 mmol) was added dropwise *via* syringe. After stirring for 30 min, binaphthol (430 mg, 1.5 mmol) in dry THF (3 ml, dissolved by sonication for 30 min) was added dropwise *via* syringe and stirred for a further 30 min. The carbonyl compound (1 mmol) in THF (0.5 ml) was added dropwise *via* syringe. After stirring for a further 2.5 hours at -78 °C, the reaction was quenched with saturated sodium fluoride solution (5 ml) and filtered to remove cerium fluoride. The layers were separated and the aqueous layer was extracted with diethyl ether (4 x 20 ml) and washed with sodium hydroxide solution (2M, 4 x 20 ml). The combined organic extracts were dried over MgSO_4 and concentrated to yield an oil.

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- All products were identified by comparison of spectral properties, particularly gc/ms, with those of authentic compounds. Yields in the tables refer to isolated material.
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