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Enantioselective Addition of Organocerium Reagents to Aldehydes - Effects of TADDOL Ligand Structure

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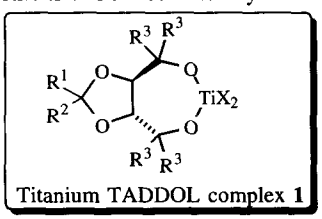
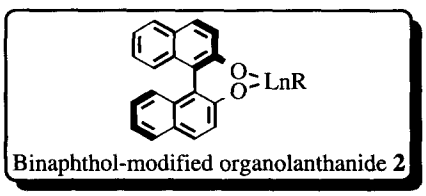
Abstract: A range of TADDOL organocerium reagents have been prepared and the effect of TADDOL structure on their enantioselective addition to aldehydes has been studied.

TADDOLs (α,α,α',α',-tetraaryl-1,3-dioxolan-4,5-dimethanols) have been successfully used as chiral auxiliaries for a variety of synthetic organic transformations. Titanium complexes (**1**) have been used for stoichiometric[1-4] and catalytic[5,6] nucleophilic additions to carbonyls, for Lewis acid facilitated [2+2][7] and [4+2][8-11] cycloadditions, for asymmetric hydrocyanation of aldehydes,[12] and recently for conjugate additions.[13,14] TADDOLs have also been shown to form clathrates with a wide variety of organic compounds. They have also been used as chiral solvating agents in NMR spectroscopy[15] and for the resolution of racemates.[16] Their solid state structure[17] and mechanism of enantioselective reaction of other organometallic reagents with aldehydes have also been studied.[18]

Organometallic reagents derived from titanium[2] and zinc[19,20] with a variety of chiral auxiliaries have been utilised to carry out asymmetric additions to carbonyl compounds with high enantioselectivity. However these methods can be restricted by the range of alkyl groups that can be transferred.

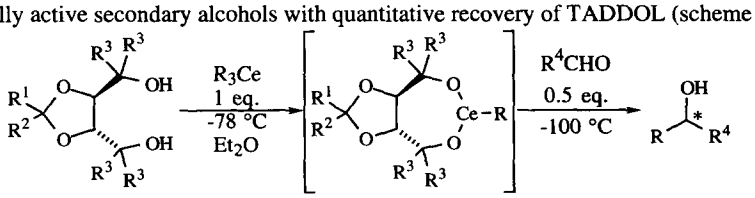


Titanium TADDOL complex **1**



Binaphthol-modified organolanthanide **2**

Cerium reagents have found widespread application in organic synthesis,[21] their reduced basicity and high Lewis acidity often promoting clean addition to carbonyl compounds.[22] We have recently reported the first use of homochiral binaphthol-modified organolanthanide (Ln = Ce, Yb) reagents (**2**) in the enantioselective addition of alkyl groups to aldehydes.[23] In this letter we wish to report the use of TADDOL organocerium reagents in enantioselective additions to aldehydes and the effect of varying the TADDOL structure. The reagents were prepared by reaction of the TADDOL with trialkylcerium at -78 °C in ether. The TADDOL organocerium species formed *in situ* then reacted at -100 °C with 0.5 equiv. of aldehyde added over one hour, to produce optically active secondary alcohols with quantitative recovery of TADDOL (scheme 1).



Scheme 1. Formation and Reaction of TADDOL Organocerium Reagent.

We selected benzaldehyde and cyclohexanecarboxaldehyde to study as these are representative examples of aromatic and aliphatic aldehydes and the results for *n*-butyl group addition are shown in Table 1.

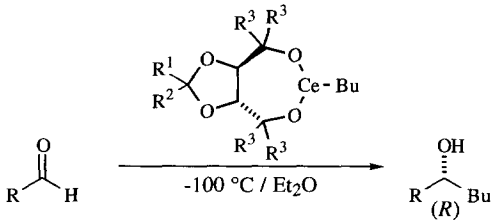


Table 1. Reaction of TADDOL Butylcerium Reagent with Benzaldehyde (R = Ph) and Cyclohexanecarboxaldehyde (R = C_6H_{11}).

Entry	R	R^1	R^2	R^3	TADDOL	C_1/C_2	Yield/%	ee[a]/%	*ref.*
1	Ph	Me	Me	Ph	1	C_2	66	**66**	*1*
2	Ph	Me	Me	3,5-dimethylPh	2	C_2	60	21	
3	Ph	Et	Et	Ph	3	C_2	51	36	
4	Ph	Et	Et	3,5-dimethylPh	4	C_2	80	18	*25*
5	Ph	^{t}Bu	H	Ph	5	C_1	81	39	*17*
6	Ph	-$(CH_2)_5$-		Ph	6	C_2	55	37	*17*
7	Ph	Me	Me	Me	7	C_2	57	21	*1*
8	Ph	Ph	H	Ph	8	C_1	67	20	*15*
9	C_6H_{11}	Me	Me	Ph	1	C_2	65	**70**	*1*
10	C_6H_{11}	Me	Me	3,5-dimethylPh	2	C_2	59	20	
11	C_6H_{11}	Et	Et	Ph	3	C_2	35[b]	47	
12	C_6H_{11}	Et	Et	3,5-dimethylPh	4	C_2	16[b]	19	*25*
13	C_6H_{11}	-$(CH_2)_5$-		Ph	6	C_2	52	52	*17*
14	C_6H_{11}	Ph	H	Ph	8	C_1	71	35	*15*
15	C_6H_{11}	^{t}Bu	H	Ph	5	C_1	71	32	*17*
16	C_6H_{11}	Me	Me	Me	7	C_2	66	18	*1*

[a] (*R*)- enantiomer, ee determined by g.c. analysis of Mosher's ester. [b] Lower yields may be due to volatile nature of alcohols.

As expected, the structure of the TADDOL had a significant effect on the enantioselectivity of the reaction. This is exemplified by a comparison of TADDOLs 1 and 4. TADDOL 1 produced the alcohols in 66% ee and 70% ee for benzaldehyde and cyclohexanecarboxaldehyde respectively (entries 1 & 9), whereas TADDOL 4 only produced 18% ee and 19% ee for the aromatic and aliphatic aldehydes respectively (entries 4 & 12). Although the relationship between structure and enantioselectivity is not clear, certain features of the TADDOL ligand seem to be responsible for the extent of enantioselection. In general, C_2 symmetric TADDOLs produced higher enantioselectivities than those with no symmetry (C_1); TADDOL 1, a C_2 symmetric TADDOL produced the highest ee with both aldehydes (entries 1 & 9), whereas TADDOL 8, a C_1 TADDOL which is otherwise very similar in structure, produced low enantioselectivities in both cases (entries 8 & 14).

The acetal backbone is extremely important even though it is remote from the metal in the reagent. Non-aromatic substituents induced higher selectivity for example TADDOL 5 (R^1 = ^{t}butyl) produced 39% ee with benzaldehyde (entry 5), whereas TADDOL 8 (R^1 = Ph) produced only 20% ee (entry 8). The size of the aliphatic substituent was also crucial. With both R^3 = phenyl and R^3 = 3,5-dimethylphenyl, the dimethyl acetal

backbone, TADDOLs 1 & 2, respectively produced higher enantioselectivities than the diethyl acetal backbone, TADDOLs 3 & 4, respectively for both aldehydes.

The steric size of R^3 affected the outcome of the reactions and there appears to be an optimum size which is neither too large nor too small. Although TADDOL 7 (R^3 = Me) is both C_2 symmetric and has a non-aromatic acetal backbone it produced low selectivity 21% ee for benzaldehyde (entry 7) and 18% ee for cyclohexanecarboxaldehyde (entry 16), probably due to the lack of steric crowding about the hydroxyl groups. However, increasing the steric demands by substituting R^3= 3,5-dimethylphenyl instead of phenyl also reduced the selectivity of the reaction with the dimethyl acetal. This was evident for benzaldehyde TADDOL 1 66% ee versus TADDOL 2 21% ee for benzaldehyde (entries 1 & 2), and for cyclohexanecarboxaldehyde, 70% ee versus 20% ee respectively (entries 9 & 10).

We also chose to study phenyl addition to cyclohexanecarboxaldehyde as this nucleophile had shown interesting results in our previous diastereoselective additions to cyclohexanones.[24] The results are shown in Table 2.

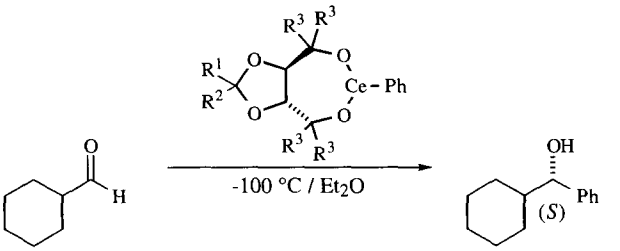


Table 2. Reaction of TADDOL Phenylcerium Reagent with Cyclohexanecarboxaldehyde.

Entry	R^1	R^2	R^3	TADDOL	C_1/C_2	Yield/%	ee[a]/%	*ref.*
1	Me	Me	Ph	1	C_2	88	32	*1*
2	Me	Me	3,5-dimethylPh	2	C_2	92	33	
3	Et	Et	Ph	3	C_2	61	25	
4	Et	Et	3,5-dimethylPh	4	C_2	91	**40**	*25*
5	^{t}Bu	H	Ph	5	C_1	90	11	*17*
6	-$(CH_2)_5$-		Ph	6	C_2	94	19	*17*
7	Me	Me	Me	7	C_2	36	16	*1*
8	Ph	H	Ph	8	C_1	96	14	*15*

[a] (*S*)- enantiomer, ee determined by g.c. analysis of Mosher's ester.

The effect of the TADDOL structure on enantioselectivity for butyl addition to both aldehydes was different to that for phenyl addition. TADDOL 4 produced the highest enantioselectivity at 40% ee (entry 4) whereas for butyl addition, TADDOL 1 produced the highest ee. The highest enantioselectivity for phenyl addition is lower than that for the corresponding butyl addition to cyclohexanecarboxaldehyde 40% ee (Table 2 entry 4) versus 70% ee (Table 1 entry 9) respectively, even though phenyl is a larger nucleophile and hence might be expected to produce a larger ee. This may be due to the flat board like structure of phenyl allowing attack along a less hindered trajectory.[24] For phenyl addition the TADDOL with R^3 = 3,5-dimethylphenyl produced higher selectivity than when R^3 = Ph, with the diethyl acetal TADDOLs 4 & 3 producing enantioselectivities of 40% ee versus 25% ee respectively (entry 4 versus 3). This may be due to the ability of the TADDOL to form a transition state with the phenyl nucleophile in which π-stacking occurs or may be due to steric interactions. Corey has used this TADDOL for Diels-Alder reactions proposing a favoured transition state where a stacking arrangement occurs *via* π–interactions, and hence inducing high selectivity.[25]

In summary, we have shown that the TADDOL structure has a large effect on enantioselectivity. In general it appears that C_2 symmetric TADDOLs ($R^1 = R^2$) produce higher selectivity than C_1 and that a non-aromatic acetal backbone (R^1, $R^2 \neq$ Ph) is advantageous. The steric crowding around the hydroxyl groups (R^3) plays an important part and for phenyl addition the electronic nature of the group may also be important. As yet, no detailed explanation for the effect the different TADDOL structures have on enantioselectivity has been found but further investigations with different TADDOLs are underway to advance our understanding.

General Procedure: Cerium (III) chloride ($CeCl_3.7H_2O$) (2 mmol) was placed in a 50 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 2 hours. While the flask was still hot, argon was introduced. The flask was cooled in an ice bath and dry diethyl ether (10 ml) was introduced *via* a syringe. The flask was then placed in an ultrasonic bath (Camlab transonic T460/H) for 1 hour or the suspension was stirred overnight at room temperature. The resulting white slurry was cooled to -78 °C, the organolithium (5.6 mmol) was added dropwise *via* syringe. After 1 hour, TADDOL (2 mmol) in dry diethyl ether (10-15 ml, dissolved by sonication) was added dropwise *via* syringe and the suspension was stirred for a further hour at -78 °C before being cooled to -100 °C. The aldehyde (0.8 mmol) in dry diethyl ether (3 ml) was added over 1 hour using a syringe pump. The mixture was stirred at -100 °C for a further 2 hours and was quenched with saturated ammonium chloride solution (10 ml) and extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and concentrated to yield an oil which was distilled under reduced pressure (Kugelrohr) to isolate the alcohols from the TADDOL (which was recovered unchanged and reused after recrystallisation).

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