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New Homochiral Binaphthol-Modified Organolanthanide Reagents for the Enantioselective Addition to Aldehydes

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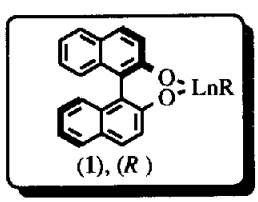
Abstract: Optically active secondary alcohols were obtained in high chemical yield and optical purity (up to 85% ee) from the lanthanide-mediated enantioselective addition of alkyl nucleophiles to aromatic aldehydes.

Metals such as titanium[1,2] and zinc[3-5] have been used widely and successfully to achieve high stereoselectivity in enantioselective carbonyl addition reactions. However, there are some limitations and problems in the use of these metals. In particular the range of alkyl groups that can be transferred with high enantioselectivity is restricted. With certain titanium reagents, β-hydride elimination is a major drawback, and with these and other metals (e.g. lithium and magnesium)[3] clean carbonyl addition is not effected in some systems. Either there is a lack of reaction or enolisation/reduction processes compete with the desired 1,2-carbonyl addition. All these limitations and problems are almost completely suppressed in achiral lanthanide-mediated transformations.

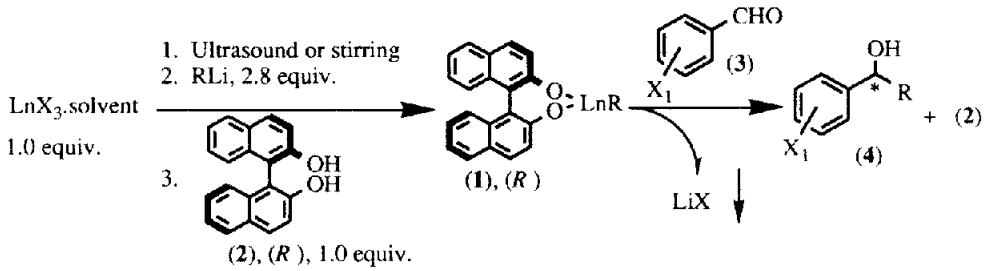
Since the discovery and utilisation by Imamoto[6,7] of the diminished basicity and high Lewis acidity of organocerium reagents, the application of these reagents to organic synthesis has been widespread and the literature contains an increasing number of reports on this subject.[8,9] As yet there are no examples of enantioselective organolanthanide reagents for use in carbonyl addition reactions.[10] We have recently described the preparation and diastereoselective carbonyl addition reactions of a new class of chiral racemic organocerium reagent.[11]



(1), (*R*)

In this communication we wish to report the first use of homochiral organolanthanide (Ln = Ce, Yb) reagents (**1**) in enantioselective additions of alkyl groups to aldehydes to produce secondary alcohols in moderate to high optical purity, scheme 1. The reagents were prepared by reaction of the optically pure ligand, (*R*)-(+)-binaphthol (**2**),[12,13] with the trialkyllanthanide species[14] that was generated from 2.8 equivalents of alkyllithium and one equivalent of anhydrous lanthanide (III) chloride or triflate suspended[15] in the appropriate solvent at -78 °C. This stoichiometry was essential to ensure that no unreacted organolithium precursor, which would be detrimental to the enantiomeric excess, was present. Two equivalents of the alkyllanthanide are

required to doubly deprotonate binaphthol and 0.8 equivalents remains to form the active modified organolanthanide reagent. The reagents (**1**) react *in situ* with various aromatic aldehydes (**3**) to produce optically active secondary alcohols (**4**) in high chemical yield and optical purity, under suitable conditions, with quantitative recovery of optically pure binaphthol which is reusable, scheme 1 and table 1.



Scheme 1. Formation and Reactions of Modified Organocerium Reagents

Table 1. Generation of Reagents (**1**) and their Reaction with Aromatic Aldehydes (**3**)

Entry	LnX_3	Solvent	R	X_1	Temp.	Addition time[a]	Yield / % (**4**)	ee[b] / % (**4**)[16]
1.	$Yb(OTf)_3$[17]	THF	*n*-Bu	H	-78 °C	20 min	79	7
2.	$Yb(OTf)_3$	Et_2O	*n*-Bu	H	-78 °C	6 min	87	33
3.	$CeCl_3$	THF	*n*-Bu	H	-78 °C	2 min	47	12
4.	$CeCl_3$	Et_2O	*n*-Bu	H	-78 °C	23 min	86	33
5.	$Ce(OTf)_3$[18,19]	Et_2O	*n*-Bu	H	-78 °C	25 min	84	26
6.	$CeCl_3$	Et_2O	*n*-Bu	H	-100 °C	25 min	85	52
7.	$CeCl_3$	Et_2O	*n*-Bu	H	-100 °C	1.5 h	86	**77**
8.	$CeCl_3$	THF	Me	H	-78 °C	2 min	81	2
9.	$CeCl_3$	Et_2O	Me	H	-78 °C	20 min	58[c]	48[d]
10.	$CeCl_3$	Et_2O	Me	H	-100 °C	20 min	63[c]	48[d]
11.	$CeCl_3$	Et_2O	Me	H	-100 °C	1.5 h	64[c]	50[d]
12.	$CeCl_3$	Et_2O	*n*-Bu	2-OMe	-100 °C	20 min	78	53[e]
13.	$CeCl_3$	Et_2O	*n*-Bu	4-OMe	-100 °C	30 min	87	52[e]
14.	$CeCl_3$	Et_2O	Me	4-OMe	-100 °C	20 min	75	68[f]
15.	$CeCl_3$	Et_2O	*n*-Bu	4-Cl	-100 °C	1.5 h	69	51
16.	$CeCl_3$	Et_2O	Me	4-Cl	-100 °C	1.5 h	53	75
17.	$CeCl_3$	Et_2O	*n*-Bu	4-Me	-100 °C	1.5 h	71	**85**
18.	$CeCl_3$	Et_2O	Me	4-Me	-100 °C	1.5 h	69	**77**
19.	$Ce(OTf)_3$	Et_2O	Me	4-Me	-100 °C	1.5 h	62	57
20.	$Yb(OTf)_3$	Et_2O	Me	4-Me	-100 °C	1.0 h	56	65

[a]Period over which the aldehyde in the appropriate solvent was added. The reactions were stirred for a further 1-3 h after complete addition of the aldehyde; [b]Determined by ^1H NMR and GC analysis of Mosher's esters and by comparison with the corresponding racemic compounds; [c]Lower yields may be due to the volatile nature of the alcohols; [d]Different bottles of MeLi gave varying results; [e]Determined by ^{19}F NMR analysis of Mosher's esters; [f]Determined by ^1H NMR analysis of Mosher's esters.

The LnX_3.solvent slurry [except for $Yb(OTf)_3$.THF which is a solution] was prepared by sonication[15] or stirring and, whichever method was used, reproducible results were obtained. It became clear very quickly that diethyl ether (Et_2O) was the best of the readily available ethereal solvents (THF, DME, *t*-BuOMe) and was significantly superior to THF for these additions (entries 1-4, 8-9). Slow addition of the aldehydes, in the appropriate solvent, to the reagent at lower temperature gave higher enantiomeric excess (entries 4-7). The effect of counterion was studied briefly and, for cerium, chloride was better than triflate (entries 4-5, 18-19). Any "complexing salt effect", from the salts formed *in situ* (LiCl or LiOTf), may be unimportant with these lanthanide reagents as LiCl is insoluble in Et_2O and LiOTf has been shown not to be a complexing salt in THF.[20]

The improvement in enantiomeric excess observed with ytterbium triflate over the cerium triflate (entries 2, 4, 19-20) suggested ytterbium metal might prove superior but as yet we have been unable to compare the performance of cerium with ytterbium as chlorides directly. In Et_2O, reactions involving $YbCl_3$ do not occur at -78 °C requiring the use of higher temperatures (-63 °C) at the price of low enantiomeric excess (R = Me, 34% ee; R = *n*-Bu, 24% ee). The corresponding reactions in THF are facile and are complete within 2 h at -78 °C but the enantiomeric excesses are poorer than those from the corresponding reactions in Et_2O.

The best results were obtained with cerium chloride in Et_2O and the substituent X_1 on the aromatic ring was observed to have an interesting effect (entries 12-18). The 4-methyl group gave higher ee than the corresponding 4-chloro group with both methyl and butyl addition which may be due to an electronic effect. Very similar results have been reported recently in the asymmetric hydrophosphonylation of aromatic aldehydes catalysed by lanthanum-binaphthol complexes.[21] On the basis of this work, we are inclined to suppose that cerium, an early lanthanide, gives better enantiomeric excess than ytterbium, a late lanthanide. This is in accord with observations made by others in the lanthanide-mediated catalytic asymmetric nitroaldol reaction.[22] It is noteworthy that the analogous reagents (**1**) derived from Grignard precursors[7] and the lanthanide chloride or triflate generally showed poor enantioselectivity compared to their alkyllithium-derived counterparts.

The observed enantioselectivity in the reactions of reagents (**1**) presumably results from the high oxophilicity and unusually large coordination sphere of the lanthanide (III) centre that permits coordination to the carbonyl group of the aldehyde and possibly to solvent molecules to introduce asymmetry *via* a tightly bound transition state in which steric interactions with the ligand, binaphthol, are significant.

In summary, we have shown for the first time that lanthanides can mediate the transfer of alkyl groups to carbonyl substrates in an enantioselective manner. The wide range of carbon nucleophiles which can be delivered successfully with simple organolanthanide reagents suggests that our method should be an attractive one. Studies aimed at improving the enantioselectivity, extending the scope, and understanding the nature of these reagents are underway.

General Procedure: Cerium (III) chloride ($CeCl_3.7H_2O$) (0.27 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 2 hours. While the flask was still hot, argon was introduced. The flask was cooled in an ice bath and dry solvent (7 ml / mmol of hydrate) was introduced *via* 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 then cooled to -78 °C, the organolithium (2.8 equiv.) was added dropwise *via* syringe. After 1 hour, (*R*)-(+)-binaphthol (1.0 equiv.) in dry solvent (7 ml / mmol, dissolved by sonication) was added dropwise *via* syringe and the suspension was stirred for a further 1 hour at -78 °C before being cooled, if appropriate, to the

required temperature. The aldehyde (0.8 equiv.) in dry solvent (1.0 ml / mmol of aldehyde) was added slowly (see table 1) *via* syringe and, after a further 1-3 hours, the reaction was quenched with saturated ammonium chloride solution (4 ml / mmol of hydrate) 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 (150 °C / 0.5 mmHg) to free the product alcohols from binaphthol.

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REFERENCES AND NOTES

1. Bussche-Hünnefeld, J. L. v. d.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719-5730.
2. Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807-832.
3. Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597-1606.
4. Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Eng.* **1991**, *30*, 49-69.
5. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833-856.
6. Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904-3912.
7. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392-4398.
8. Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747-752.
9. Bunnelle, W. H.; Narayanan, B. A. *Org. Synth.* **1990**, *69*, 89-95.
10. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29-68.
11. Greeves, N.; Lyford, L.; Pease, J. E., submitted for publication.
12. Kazlauskas, R. J. *Org. Synth.* **1991**, *70*, 60-67.
13. For applications of binaphthol in enantioselective synthesis see: Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503-517.
14. Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569-578.
15. Greeves, N.; Lyford, L. *Tetrahedron Lett.* **1992**, *33*, 4759-4760.
16. The major enantiomer of the alcohols (**4**) has the (*R*)-configuration based upon NMR and GC correlation with the Mosher's ester of a commercial sample of (*R*)-(+)-α-methylbenzyl alcohol.
17. Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017-1021.
18. Kreh, R. P.; Spotnitz, R. M.; Lundquist, J. T. *J. Org. Chem.* **1989**, *54*, 1526-1531.
19. Vincentini, G.; Zinner, L. B. *Inorg. Nucl. Chem.* **1980**, *42*, 1510-1514.
20. Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990-4991.
21. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783-1784.
22. Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657-2660.