

PII: S0040-4039(96)01236-1

Enantioselective Addition of Tris(TADDOL) Organocerium Reagents to Aldehydes

Nicholas Greeves* and J. Elizabeth Pease

Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, P.O. Box 147, Liverpool, L69 3BX, UK.

Abstract: A significant improvement in enantioselectivity (up to 92% ee) was achieved in butyl additions to a range of aldehydes with a novel tris(TADDOL) organocerium reagent. Copyright © 1996 Elsevier Science Ltd

TADDOLs ($\alpha, \alpha, \alpha', \alpha'$,-tetraaryl-1,3-dioxolan-4,5-dimethanols) have been successfully employed as chiral auxiliaries for a variety of synthetic organic transformations including stoichiometric^{1,2} and catalytic³⁻⁵ nucleophilic additions to carbonyls. Titanium⁵⁻⁷ and zinc⁸⁻¹² derived organometallic reagents with a variety of chiral auxiliaries have been used to carry out asymmetric additions to carbonyls with high enantioselectivity. However, these methods can be restricted by the range of alkyl groups that can be transferred and by reagent substrate specificity.

Organocerium reagents have found wide spread application in organic synthesis,¹³ their reduced basicity and high Lewis acidity often promoting clean addition to carbonyl compounds.¹⁴⁻¹⁶ We have recently reported the use of ligand modified organocerium reagents in the enantioselective addition of alkyl and aryl groups to aldehydes (Scheme 1).^{17,18} In this communication we wish to report the use of a tris(TADDOL) organocerium reagent to improve the enantioselectivities to greater than 90 % ee in one case.



Shibasaki *et al* have investigated the use of lanthanum binaphthol (binol) complexes for carboncarbon bond forming reactions and have observed some high enantioselectivities.^{19,20} During this work the structure of the catalyst was established as a tris(binaphthoxy) mixed-metal complex of lanthanum and lithium.²¹

Having established in earlier work¹⁸ that the dimethyl tetraphenyl TADDOL 1 in general produced the highest enantioselectivities for additions to aldehydes we examined the effect of changing the ratio of TADDOL:cerium on the enantioselectivity of butyl addition.

As before, the reagents were prepared by reaction of the optically pure dimethyl tetraphenyl TADDOL 1 with tributylcerium at -78 °C in diethyl ether together with additional equivalents of butyllithium to ensure the additional TADDOL hydroxyls were deprotonated. The dimethyl tetraphenyl TADDOL butylcerium species formed *in situ* then reacted at -98 °C with 0.5 equivalents of aldehyde added

over one hour to produce optically active secondary alcohol with quantitative recovery of dimethyl tetraphenyl TADDOL 1.

As can be seen from Table 1 for butyl addition to benzaldehyde and cyclohexanecarboxaldehyde the ratio of TADDOL:cerium had a marked effect on the enantioselectivity of the reaction.



Table 1. Reaction of Dimethyl Tetraphenyl TADDOL Butyl Cerium Reagent with Benzaldehyde (R=Ph) and Cyclohexanecarboxaldehyde (R=C₆H₁₁).

Entry	R	No of TADDOLs	Yield %	ee ^a %
		Z		
1	Ph	1	66	66
2	Ph	2	67	72
3	Ph	3	66	83
4	Ph	4	64	70
5	C ₆ H ₁₁	1	65	70
6	C ₆ H ₁₁	2	46	87
7	C ₆ H ₁₁	3	42	92
8	C ₆ H ₁₁	4	63	85

^a (R)-enantiomer, ee determined by g.c. analysis of Mosher's ester.

Increasing the number of equivalents of TADDOL per cerium improved the selectivity of the reaction with a ratio of 3:1 TADDOL:cerium being optimum (Entries 3 & 7). Unfortunately, increasing the quantity of TADDOL in the reaction further was detrimental to the selectivity (Entries 4 & 8), possibly due to the formation of a reagent which is so hindered that it prevents coordination of the aldehyde.

While the precise composition and structure of the reagent remain elusive, the results suggest the formation of a tris(TADDOL) cerium complex similar to Shibasaki's tris(binaphthoxy) mixed metal complex. The coordination of three TADDOLs per cerium appears optimal possibly due to the production of a more bulky monomeric reagent with a filled coordination sphere. However, it may also be possible that due to the presence of the extra TADDOL the aggregation state of the reagent is changed. The cerium may now achieve a saturated coordination sphere without forming complicated aggregates, thus preventing a reduction in the selectivity of the reaction that may result from additions *via* various different TADDOL organocerium species.

Having established that the reagent derived from three equivalents of TADDOL per cerium produced high enantioselectivities we decided to investigate briefly the scope of the reaction by testing a variety of aldehydes.

We carried out the enantioselective additions using the tris(dimethyl tetraphenyl TADDOL) butyl cerium reagent generated as before (Table 2).



 Table 2. Reaction of Tris(dimethyl tetraphenyl TADDOL) Butyl Cerium Reagent with a Range of

 Aldehydes

Entry	Aldehyde	Yield %	ee ^a %
1	o ⊢∕_́́́́ _н	42	92
2		66	83
3	CI-CI-C	54	76
4		38	75
5	Н	56	64
6	PhH	36	33
7	C H	43	32

^a ee determined by g.c. analysis of Mosher's ester.

Cyclohexanecarboxaldehyde produced the highest selectivity at 92 % ee (Entry 1) which is the highest enantioselectivity observed in aldehyde additions with an organocerium reagent to date. The range of aldehydes tested did not all produce good enantioselectivities. As we observed in additions of the binol alkyl cerium reagents to aromatic aldehydes,¹⁷ substituents on the phenyl ring of benzaldehyde produced changes in enantioselectivity. The tris(TADDOL) reagent gave slightly lower selectivity irrespective of whether the substituent was an electron withdrawing chlorine atom or an electron donating methyl group (Entries 2, 3 & 4). Cinnamaldehyde, the only non-aromatic example examined, was disappointing at 33 % ee and 2-furaldehyde also produced a low enantioselectivity of 32 % ee (Entry 6 and 7). This may be due to the ability of the oxygen atom of furan to chelate to the cerium and therefore alter the transition state.

In summary we have demonstrated that significant increases in enantioselectivity result from incorporation of additional equivalents of TADDOL ligand into organocerium reagents. The tris(dimethyl tetraphenyl TADDOL) butyl cerium reagent appears optimal and has the potential to produce secondary alcohols with high enantiomeric purity with certain substrates. The success of these reactions seems inconsistent with a very recent report that "anhydrous" cerium chloride contains a bound water molecule,²² further investigation is underway.

General Procedure: Cerium (III) chloride heptahydrate (2 mmol) was placed in a 100 ml Schlenk flask with a stirrer bar. The flask was placed in an oil bath and heated to 135-140 °C *in vacuo* with stirring for 2 hours. While the flask was still hot, argon was introduced and the flask was then cooled in an ice bath, dry diethyl ether (10 ml) was added and the mixture was either sonicated for one hour or left to stir overnight. The resulting white suspension generated was then cooled to -78 °C and butyllithium (13.6 mmol) was added. The reaction was then stirred for one hour and dimethyl tetraphenyl TADDOL 1 (6 mmol) was added in dry diethyl ether having previously been sonicated to assist dissolution. The white suspension produced was then stirred for a further hour at -78 °C and then cooled to -98 °C. The aldehyde (0.8 mmol) was added in dry diethyl ether (3 ml) over one hour using a syringe pump. The white suspension was stirred for a further two hours and then quenched with saturated sodium fluoride solution. The off white cerium fluoride precipitate formed was removed by suction filtration and the organics were extracted with diethyl ether, dried over MgSO4 and concentrated. The resulting mixture was distilled under reduced pressure (Kugelrohr) to isolate the alcohols from the TADDOL (which was recovered unchanged and reused after recrystallisation).

Acknowledgements. We would like to thank Dr. S. Brown and Dr. M. Bowden for many helpful discussions and are grateful to EPSRC and Zeneca FCMO, Huddersfield for financial support (CASE award to JEP).

References

- 1. a) Weber, B., Seebach, D. Angew. Chem. Int. Ed. Engl., 1992, 31, 84-86. b) Weber, B., Seebach, D. Tetrahedron, 1994, 50, 6117-6128.
- 2 a) Schmidt, B., Seebach, D. Angew. Chem. Int. Ed. Engl., 1991, 30, 99-101. b) Seebach, D., Behrendt, L., Felix, D. Angew. Chem. Int. Ed. Engl., 1991, 30, 1008-1009.
- 3. Schmidt, B., Seebach, D. Angew. Chem. Int. Ed. Engl., 1991, 30, 1321-1323.
- a) Seebach, D., Plattner, D. A., Beck, A. K., Wang, Y. M., Hunziker D., Petter, W. Helv. Chim. Acta, 1992, 75, 2171-2209.
 b) Seebach, D., Plattner, D. A., Beck, A. K., Schmidt, B., Wang, Y. M. Tetrahedron, 1994, 50, 4363-4384. c) Ito, Y. N., Ariza, X., Beck, A. K., Bohac, A., Ganter, C., Gawley, R. E., Kuhnle, F. N. M., Tuleja, J., Wang, Y. M., Seebach, D. Helv. Chim. Acta, 1994, 77, 2071-2110.
- 5. Weber, B., Seebach, D. Tetrahedron, 1994, 50, 7473-7484.
- 6. Duthaler, R., Hafner, A. Chem. Rev., 1992, 92, 807-832.
- 7. Reetz, M., Kukenhohner, T., Weinig, P. Tetrahedron Lett., 1986, 27, 5711-5714.
- a) Noyori, R., Kitamura, M. Angew. Chem. Int. Ed. Engl., 1991, 30, 49-69. b) Noyori, R., Suga, S., Kawai, K., Okada, S. Kitamura, M. Pure & Appl. Chem., 1988, 60, 1597-1606.
- a) Noyori, R., Suga, S., Kawai, K., Okada, S., Kitamura, M., Oguni, N., Hayashi, M., Kaneko, T., Matsuda, Y. J. Organomet. Chem., 1990, 382, 19-37. b) Kitamura, M., Okada, S., Suga, S., Noyori, R. J. Am. Chem. Soc., 1989, 111, 4028-4036.
- 10. Soai, K., Niwa, S. Chem. Rev., 1992, 92, 833-856.
- 11. Wallbaum, S., Martens, J. Tetrahedron : Asymmetry, 1993, 4, 637-640.
- a) Soai, K., Yokoyama, S., Hayasaka, T. J. Org. Chem., 1991, 56, 4264-4268. b) Soai, K., Hirose, Y., Ohno, Y. Tetrahedron : Asymmetry, 1993, 4, 1473-1474. c) Soai, K., Hayase, T., Takai K., Sugiyama, T. J. Org. Chem., 1994, 59, 7908-7909.
- 13. Molander, G. A. Chem. Rev., 1992, 92, 29-68.
- 14. Imamoto, T. Pure & Appl. Chem., 1990, 62, 747-752.
- 15. Imamoto, T., Kusumoto, T., Tawarayama, Y., Sugiura, Y., Mita, T., Hatanaka Y., Yokoyama, M. J. Org. Chem., 1984, 49, 3904-3912.
- 16 Kagan H. B., Namy, J. L. Tetrahedron, 1986, 42, 6573-6614.
- 17. Binaphthol: Chibale, K., Greeves, N., Lyford L., Pease, J. E. Tetrahedron : Asymmetry, 1993, 4, 2407-2410.
- 18. TADDOLs: Greeves, N., Pease, J. E., Bowden, M. C., Brown, S. M. Tetrahedron Lett., 1996, 37, 2675-2678.
- a) Sasai, H., Suzuki, T., Arai, S., Shibasaki, M. J. Am. Chem. Soc., 1992, 114, 4418-4420. b) Sasai, H., Suzuki, T., Itoh, N., Arai, S., Shibasaki, M. Tetrahedron Lett., 1993, 34, 2657-2660. c) Sasai, H., Arai T., Shibasaki, M. J. Am. Chem. Soc., 1994, 116, 1571-1572. d) Uotsu, K., Sasai H., Shibasaki, M. Tetrahedron: Asymmetry, 1995, 6, 71-74.
- a) Sasai, H., Suzuki, T., Itoh, N., Shibasaki, M. Tetrahedron Lett., 1993, 34, 851-854. b) Sasai, H., Suzuki, T., Itoh, N., Shibasaki, M. Tetrahedron Lett., 1993, 34, 855-858.
- 21. Sasai, H., Suzuki, T., Itoh, N., Tanaka, K., Date, T., Okamura K., Shibasaki, M. J. Am. Chem. Soc., 1993, 115, 10372-10373.
- 22. Evans, W. J., Feldman J. D. Ziller, J. W. J. Am. Chem. Soc., 1996, 118, 4581-4584.

(Received in UK 5 June 1996; revised 18 June 1996; accepted 21 June 1996)