Pergamon

Tetrahedron Letters, Vol. 38, No. 38, pp. 6647-6650, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01580-3

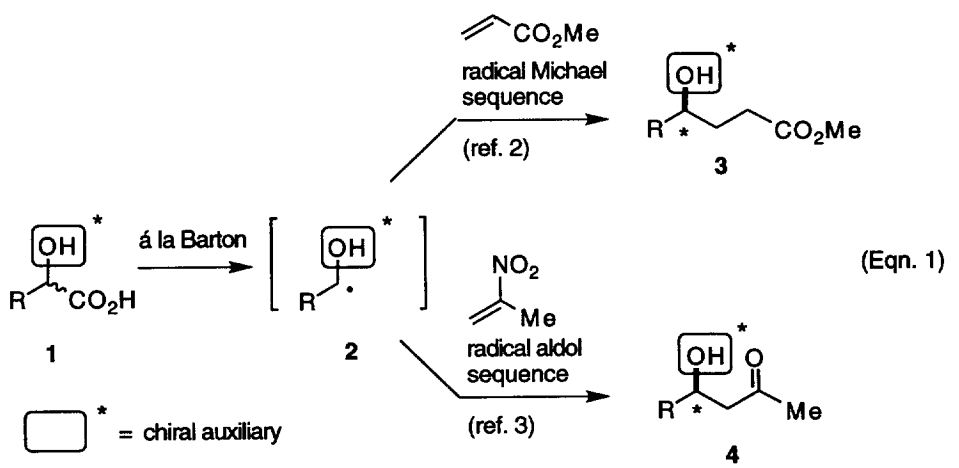
A Rationally Designed Chiral Auxiliary for Hydroxyalkyl Radicals Leads to Exceptional ρ-Stereocontrol

Philip Garner* and James T. Anderson

Department of Chemistry
Case Western Reserve University
Cleveland, Ohio 44106-7078

Abstract: *Substitution of a t-butyl group at C-6 of the THP ring results in a chiral auxiliary that exerts exceptional stereocontrol in radical addition reactions. For example, radical 2c adds to 2-nitropropene at -78 °C to give, after reductive hydrolysis, the protected aldol 4c with a diastereoselectivity of 35/1. Good selectivity (ds = 8/1) is even observed when the reaction is conducted at ambient temperature.* © 1997 Elsevier Science Ltd.

The development of new methods for asymmetric synthesis using radical reactions continues to be an active area of research.[1] We now wish to report an extraordinarily effective and practical chiral auxiliary for hydroxyalkyl radicals such as **2** (equation 1). In our original communication on this subject,[2] we reported good ρ-selectivities for the radical Michael reaction at -78 °C with both 3,4,6-tri-O-benzyl-2-deoxy-α-glucosyl (Glu, series "a") and tetrahydropyranyl (THP, series "b") auxiliaries (Figure 1 & Table 1, entries 1 & 3). *Ab initio* TS modeling studies provided us with a working hypothesis to explain the sense (and degree) of asymmetric induction. According to this model, auxiliary substituents at C-6 (THP numbering) restrict the number of alkene orientations available for *re*-attack, resulting in the observed *si*-selectivity. However, when we turned to the more reactive 2-nitropropene trap for our radical aldol studies,[3] the ρ-selectivities were found to be modest at best - even at low reaction temperatures (entries 2 & 4). We reasoned that this drop-off in ρ-selectivity was a consequence of an earlier TS, with commitment to bond formation occuring beyond the effect of the Glu and THP C-6 substituents (see Figure 1).



(Eqn. 1)

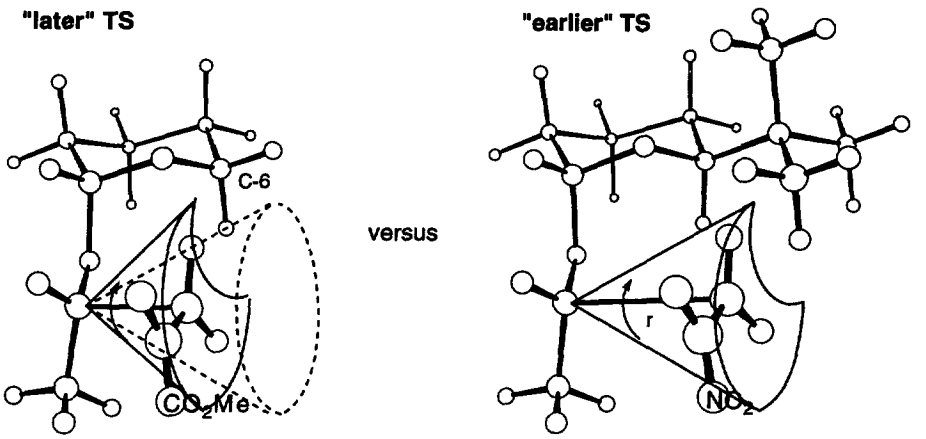


Figure 1. Postulated effect of C-6 substitution on the transition states for *re*-approach of radical traps with differing reactivities. (Note that approach from the *si*-face would be less hindered in either case.)

This hypothesis suggested that the incorporation of a t-butyl group at C-6 of the THP auxiliary would hinder *re*-approach for even the reactive 2-nitropropene trap, leading to enhanced ρ-selectivity. Although one might expect the benzyloxymethyl substituent of the sugar-derived auxiliary to be large enough to hinder the *re*-approach of any trap, this is true for only one of the three available staggered rotamers about the exocyclic C–C bond. No such ambiguity exists with the t-butyl substituent, which necessarily places a methyl group in the path of the incoming trap irrespective of exocyclic C–C bond rotation. An efficient asymmetric synthesis of the t-butyl substituted lactol **9**, which serves as an effective auxiliary precursor, is shown in Scheme 1.[4] The synthetic sequence, which is based on the work of Crimmins,[5] begins with the chiral epoxyalcohol **5**. This compound, in turn, was obtained in >98% ee by Sharpless asymmetric epoxidation of the corresponding allylic alcohol.[6] Regioselective opening of the epoxide with Red-Al afforded the 1,3-diol **6**,[7] which was sequentially tosylated (1° alcohol) then acetylated (2° alcohol) to give compound **7**. After Finkelstein iodination, ring closure was effected by enolate displacement of the tosylate to give the δ-lactone **8**. DIBAL reduction of this compound then produced the desired lactol **9** as a mixture of anomers in 44% overall yield from **7**. This mixture of anomers **9** reacted cleanly with an excess of ethyl lactate in the presence of PPTS to give the α-anomer **10** in good yield. The lactate ester could then be processed (saponification/Barton ester formation[8]/photolysis) and the resulting chiral radical **2c** trapped with either methyl acrylate or 2-nitropropene to give **3c** or **4c** (ca. 50% overall yield in each case) after reductive desulfurization or hydrolysis.

As the results in Table 1 indicate, use of the t-butyl substituted auxiliary leads to a dramatic enhancement of ρ-selectivity during addition of the lactate derived radical to 2-nitropropene. Significantly, the ratio of diastereomeric protected aldols **4c** was 35/1 at -78 °C (entry 6), which corresponds to a diastereomeric excess (de) of 94%. This represents a seven-fold increase in ρ-selectivity over that observed with the glucose-derived

auxiliary at the same reaction temperature. In fact, considerable stereodifferentiation is still observed at higher reactions temperatures with this auxiliary (entries 7 and 8). Even when the addition was performed at ambient temperatures, the diastereoselectivity was higher than that observed with the glucose-derived auxiliary at -78 °C! The radical Michael reaction also benefits from the use of this new auxiliary, with a ρ-selectivity of 9/1 being obtained for addition to methyl acrylate at RT (entry 5). The configuration of the major product was correlated with (*S*)-4-methylbutyrolactone (as described in reference 2),[4] confirming that the absolute sense of stereocontrol with this auxiliary conforms with our TS model. These results open the door for the practical development of our radical methodology and its application to asymmetric synthesis. Further refinement of this promising chiral auxiliary system is currently being pursued and will be reported on in due course.

Scheme 1

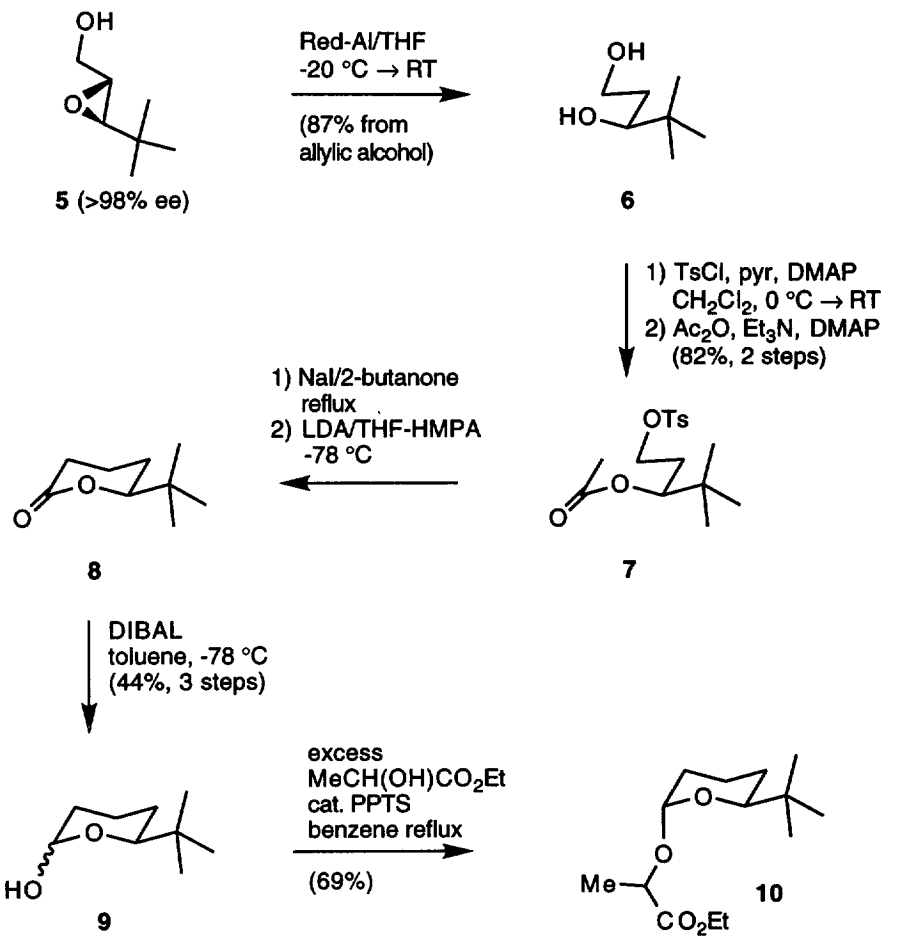
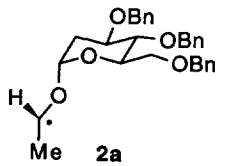
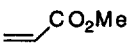
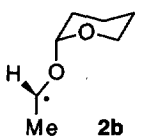
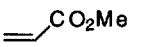
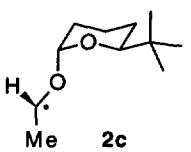
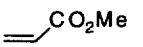


Table 1 Comparative Radical Trapping Experiments

entry	chiral radical	trap	T (°C)	product (% yield)	p-ds[a]
1	 **2a**		-78	**3a** (54)[b]	12/1
2			-78	**4a** (77)	5/1
3	 **2b**		-78	**3b** (43)[b]	19/1
4			-78	**4b** (67)	3/1
5	 **2c**		RT	**3c** (48)	9/1
6			-78	**4c** (43)	35/1
7			0	**4c** (52)	15/1
8			RT	**4c** (38)	8/1

[a] Determined by NMR integration on crude reaction mixtures of products **3** (methyl acrylate trap) and **4** (2-nitropropene trap). [b]From reference 2.

Acknowledgement. This work was supported in part by the National Institutes of General Medical Sciences.

References and Notes

1 Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**.

2 Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183-4184.

3 Garner, P.; Leslie, R.; Anderson, J. T. *J. Org. Chem.* **1996**, *61*, 6754-6755.

4 Our work on t-butyl substituted auxiliaries actually involved the antipodes of the structures shown in this paper. However, the D-series has been depicted to facilitate comparison with the structures from our previous publications.

5 Crimmins, M. T.; Al-awar, R. S.; Vallin, I. M.; Hollis, W. G.; O'Mahony, R.; Lever, J. G.; Bankaitis-Davis, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 7513-7528.

6 (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922-1925; (b) The enantiomeric excess (ee) of **5** was determined via its Mosher ester derivative: Dale, J. A.; Dull, D. A.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

7 Compounds **5** and **6** are known. See: Konoike, T.; Hayashi, T.; Araki, Y. *Tetrahedron Asymmetry* **1994**, *5*, 1559-1566, and reference 17 cited therein.

8 The thiohydroxamate (Barton) ester was conveniently prepared by treating the carboxylic acid with O-(pyridine-2-thione-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and Et_3N. Details of this method for Barton ester formation will be reported separately.

(*Received in USA* 2 *July* 1997; *revised* 17 *July* 1997; *accepted* 18 *July* 1997)