A Highly Efficient Asymmetric Synthesis of a 4,4-Disubstituted Butan-4-olide by the 1,7-Asymmetric Inductive Addition of Grignard Reagents to γ-Keto Esters

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An efficient asymmetric synthesis of a butan-4-olide having a quaternary asymmetric carbon centre was achieved with up to 97% enantiomeric excess (e.e.) by the 1,7-asymmetric inductive addition of Grignard reagents to the γ-keto esters **4–7**, the e.e. of which was highly dependent on the structure of the chelating group of the chiral auxiliaries **1–3**.

Optically active 4,4-disubstituted butan-4-olides are not only substances present in natural products such as tobacco flavour components[1] and a norbisabolide,[2] but also important intermediates for the synthesis of chiral functional compounds.[3] While the asymmetric nucleophilic addition of an organometallic reagent to the keto carbonyl group of γ-keto acid derivatives is a promising method for the synthesis of such lactones, no efficient method has been reported in either an enantioselective or a diastereoselective fashion.[4,5] Recently, we reported a new chiral podand type auxiliary 2′-[2-(2-methoxyethoxy)ethoxy]-1,1′-binaphthalen-2-ol **1** which enables the efficient 1,7-asymmetric inductive reduction of γ-keto esters to be carried out.[6] In this communication, we report the results of the nucleophilic addition of Grignard reagents to the γ-keto esters of the chiral auxiliary **1** and its analogues **2** and **3**.

The podand type chiral auxiliaries (*R*)-**1**, -**2** and -**3**, and their γ-keto esters (*R*)-**4**, -**5**, -**6** and -**7** were prepared by previously reported methods.[6]† The nucleophilic addition was performed

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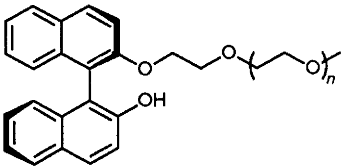
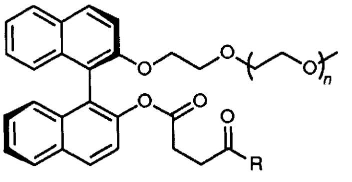
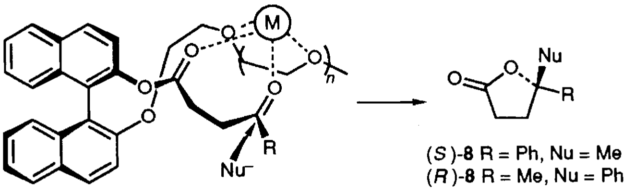
† All new compounds gave satisfactory spectral data and elemental analyses.



(*R*)-**1** *n* = 1
(*R*)-**2** *n* = 2
(*R*)-**3** *n* = 0



(*R*)-**4** *n* = 1, R = Ph
(*R*)-**5** *n* = 2, R = Ph
(*R*)-**6** *n* = 0, R = Ph
(*R*)-**7** *n* = 0, R = Me



(*S*)-**8** R = Ph, Nu = Me
(*R*)-**8** R = Me, Nu = Ph

A, (*R*)-**4–7**

by adding an ethereal solution of a Grignard reagent dropwise to a dichloromethane solution of the γ-keto ester in the presence or absence of a Lewis acid until the γ-keto ester was almost completely consumed. The resulting γ-hydroxy ester spontaneously cyclized under the reaction conditions to afford the optically active 4-methyl-4-phenylbutan-4-olide[7] **8**. The enantiomeric excess (e.e.) of **8**, and thus the diastereoselectivity of the reaction, was determined by GLC.[‡]

Table 1 shows the results of the addition reactions. It should be noted that the addition of MeMgBr to **4** resulted in poor diastereoselectivity (14% e.e., Table 1, run 1), while the diisobutylaluminium hydride reduction of **4** gave rather high diastereoselectivity (82% e.e.).[6] On the other hand, highly diastereoselective additions were achieved with up to 95% e.e. in the reaction of **5** (run 2) and **6** (run 4). The halogen atom of the Grignard reagent did not affect the stereoselectivity (run 6).

In runs 1, 2 and 4, the lactone **8** with the (*S*) configuration was obtained, this configuration being the result of the addition of the Grignard reagent to the same face of the keto carbonyl π-bond as that observed in the hydride addition (structure **A**).[6] Furthermore, the addition of PhMgBr to the laevulinic acid ester **7** (run 8) yielded **8** with very high diastereoselectivity (97% e.e.) and an absolute configuration opposite to that observed in the addition of MeMgBr to **6**, as expected from structure **A**. Although no simple explanation for the dramatic effect of the podand structure on the stereoselectivity can be offered at present, the asymmetric induction mechanism may be similar to that of the hydride addition; the cooperative chelation of the oxygen atoms of the oxyethylene chain and the carbonyl groups to the Lewis acid play an important role in the efficient remote asymmetric induction.[6]

Table 1 Nucleophilic addition of Grignard reagents to the γ-keto esters **4**, **5**, **6** and **7**[a]

Run	Sub-strate	Reagent	Lewis acid	Yield[b] (%)	E.e. (%) (Abs. confign.)
1	**4**	MeMgBr	$MgBr_2\cdot OEt_2$	75	14 (*S*)
2	**5**	MeMgBr	$MgBr_2\cdot OEt_2$	78	88 (*S*)
3	**5**	MeMgBr	None	60	57 (*S*)
4	**6**	MeMgBr	$MgBr_2\cdot OEt_2$	72	95 (*S*)
5	**6**	MeMgBr	None	53	79 (*S*)
6	**6**	MeMgI	$MgBr_2\cdot OEt_2$	67	92 (*S*)
7	**6**	MeZnCl[c]	$ZnCl_2$	No reaction	
8	**7**	PhMgBr	$MgBr_2\cdot OEt_2$	74	97 (*R*)

[a] Unless otherwise noted, reactions were performed using the Grignard reagent (diethyl ether; 1.0 mol dm^{-3}) in CH_2Cl_2 ([substrate] = 0.02 mol dm^{-3}) in the presence of 3.0 equiv. of Lewis acid at −78 °C. [b] Yields are for the isolated pure products. [c] MeZnCl was prepared by adding an ethereal solution of MeMgBr (1.0 mol dm^{-3}) to $ZnCl_2$ in diethyl ether (1.0 mol dm^{-3}) at 0 °C.

In contrast to the reduction of **6**,[§] the reaction of **5** (run 3) and **6** (run 5) without adding $MgBr_2\cdot OEt_2$ before the MeMgBr addition resulted in (*S*)-**8** with relatively high diastereoselectivity. It seems that the $MgBr_2$ present in the MeMgBr solution could undergo cooperative chelation to some extent before the MeMgBr attacked the non-chelated keto carbonyl group; it should be noted that the reaction rates of all runs are so slow as to require about 12 h for completion. Furthermore, the addition of MeZnCl to **6** resulted in no reaction (run 7).

In conclusion, the present method gives an easy and highly diastereoselective (>95% e.e.) entry to the asymmetric synthesis of 4,4-disubstituted butan-4-olides having a quaternary asymmetric carbon centre.

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[‡] The GLC analyses were performed using an ASTEC Chiraldex G-TA column (25 m × 0.25 mm i.d.) at 120 °C. Carrier gas: He.

[§] The Bu^i_2AlH reduction of **6** without the Lewis acid resulted in poor diastereoselectivity (<10% d.e.).