Pergamon

Tetrahedron Letters 42 (2001) 3933–3937

TETRAHEDRON LETTERS

Enantioselective dialkylation of 1,2-phthalicdicarboxaldehyde

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Received 19 March 2001; accepted 6 April 2001

Abstract—A new two-step, one-pot procedure is reported for the enantioselective synthesis of C_2-symmetric diols derived from 1,2-phthalicdicarboxaldehyde. The first step involves the enantioselective addition of a dialkylzinc compound to one of the aldehyde groups, affording a lactol organozinc derivative. In the second step this lactol derivative is converted to the appropriate diol with the aid of a Grignard reagent and subsequent hydrolysis. This methodology also allows the synthesis of unsymmetric diols.

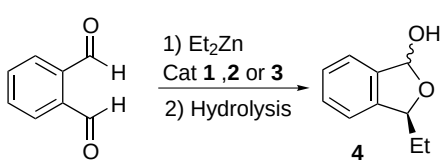
It has been recognized that enantiopure C_2-symmetrical bifunctional molecules are valuable starting materials in asymmetric synthesis.[1] In particular, enantiomerically pure diols are of importance, since these compounds can be easily transformed into other functionalized molecules, e.g. chiral bisphosphines,[2,3] which can be used as ligands in asymmetric catalysis.[4]

The zinc-mediated addition of alkylzinc compounds to aldehydes, using chiral amino alcohols[5] or amino thiols[6,7] as catalyst precursors, affords the corresponding alcohols in high enantiomeric purity and high chemical yield. Recently, this methodology has been applied to the synthesis of C_2-symmetric diols derived from terephthaldehyde and isophthaldehyde using (1*S*,2*R*)-DBNE **1** or (1*S*,2*R*)-PHONE as catalyst precursors.[8] When 1,2-phthalicdicarboxaldehyde is used as the substrate, lactol **4** (see Scheme 1) is the major product, as a result of the in situ cyclization of the monoethylated alcohol.[8,9] Under more forcing conditions, using the (1*S*,2*R*)-PHONE catalyst in the presence of Ti(O-*i*Pr)$_4$, the corresponding diol was formed, but although the enantiomeric purity of the C_2-symmetric isomer was high (e.e. 92%) the *meso* diastereoisomer was the one formed in excess[8] (*dl*/*meso* ratio 9/91). This makes this route very unattractive from a synthetic point of view because the minor *dl*-isomer is the chiral target molecule.

It should be noted that the enantioselective reduction of 1,3- and 1,4-diacetylbenzene with (+)-DiPCl affords the corresponding chiral diols with high e.e.s, whereas the same reaction with 1,2-diacetylbenzene affords a complex mixture of products.[10] However, the enantioselective allylboration of 1,2-phthalicdicarboxaldehyde using *B*-allyldiisocampheylborane with excellent e.e. and d.e.[11] has been reported. Both reactions require the use of stoichiometric amounts of expensive enantiopure chiral reagents, which can be a severe disadvantage.

It is surprising that, to our knowledge, lactol **4**, which can be prepared with high enantiopurity, has never been used as starting material for a further derivatization to chiral diols.[9] Herein, we report the synthesis of C_2-symmetric diols in high yield and excellent enantiopurity, starting from either pure lactol **4** or its in situ prepared alkoxyzinc derivative. The latter zinc intermediate was prepared via the enantioselective addition of Et_2Zn to 1,2-phthalicdicarboxaldehyde. This methodology also allows the synthesis of unsymmetrically substituted diols, i.e. diols having two different organic groups at the benzylic positions.

During our recent investigations of the synthesis of racemic and enantiomerically enriched 1,2- and 1,3-bis[1-(dimethylamino)ethyl]benzenes[12] from the corresponding diols, it appeared that the reaction of 1,2-phthalicdicarboxaldehyde with 2 equiv. of EtMgBr in THF gives diol **5** as the major product (entry 1 in



Scheme 1.

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PII: S0040-4039(01)00586-X

Table 1). Surprisingly, this reaction is fairly diastereoselective, the *dl*/*meso* ratio being 81/19. This is in contrast to the reactions of terephthaldehyde and isophthaldehyde with EtMgBr, which give the corresponding diols without diastereoselection (*dl*/*meso* 1/1). These observations suggest that the formation of the second chiral center is mainly controlled by the stereochemistry of the initially formed chiral center and that high enantioselectivities might be expected when chiral lactol **4** is converted to a diol using a Grignard reagent.

Indeed, reaction of lactol **4** (with an enantiopurity of approximately 85%, vide infra) with EtMgBr in THF afforded the C_2-symmetric diol **5** with an e.e. of 80% (entry 3 in Table 1). Attempts to prepare **5** directly from 1,2-phthalicdicarboxaldehyde and excess Et_2Zn in the presence of one of the chiral catalyst precursors shown in Fig. 1 failed, even under forcing conditions. The only product isolated after acidic work-up of these reaction mixtures was lactol **4**, a phenomenon also observed by other authors.[8]

Based on the above-mentioned observations, a two-step, one-pot procedure for the synthesis of diol **5** was developed (see Scheme 2). The first step involves the enantioselective addition of Et_2Zn to 1,2-phthalicdicarboxaldehyde to give the EtZn-alkoxy derivative **4b**. After the formation of **4b** is complete, EtMgBr in THF is added to give the free diol **5** after hydrolysis of the reaction mixture. The formation of minor amounts of monoalkylated **6** is notable and is most probably a result of the reducing properties of Grignard reagents.

In order to investigate the influence of the nature of the catalyst on the enantio- and diastereoselectivity of the products, both the aminoalcohol-based (**1a**[5] and **1b**[13]) and the aminoarenethiolate-based catalyst precursors (**2**–**3b**[6,7]) (see Fig. 1) were applied in this reaction.

Table 1. The influence of the nature of the catalyst on product distribution (Scheme 2)[a,b]

Entry	Cat.	(*S*,*S*)-**5**	(*R*,*R*)-**5**	(*S*,*R*)-**5**	**6**	e.e. (%)[e]	*dl*/*meso*
1	–	33.5	33.5	15.5	17.5	0	81/19
2	**2**[c]	15.0	73.0	4.0	8.0	66	95/5
3	**3a**[c]	80.3	8.8	6.2	4.7	80	93/7
4	**3a**[d]	75.0	8.9	15.7	5.6	78	84/16
5	**3b**[c]	77.5	6.5	8.0	8.0	84	91/9
6	**3b**[d]	70.0	6.0	16.0	8.0	83	83/17
7	**1a**[c]	55.8	19.7	12.4	12.1	48	86/14
8	**1a**[d]	50.0	24.0	14.0	11.0	36	84/16
9	**1b**[c]	65.8	13.3	11.4	9.5	66	87/13
10	**1b**[d]	60.0	14.0	18.0	8.0	62	80/20

[a] All Et_2Zn additions were carried out in toluene at rt, followed by the addition of 1.1 equiv. of EtMgBr in THF at 40°C, reaction time 18 h.
[b] Product distributions were determined by HPLC analysis using a Daicel Chiracel OD column (25 cm×4.6 mm); eluent: 2-propanol/*n*-hexane 1/99; flow: 1 mL/min.
[c] 5 mol% catalyst.
[d] 0.5 mol% catalyst.
[e] With respect to the amount of *dl* isomers formed.

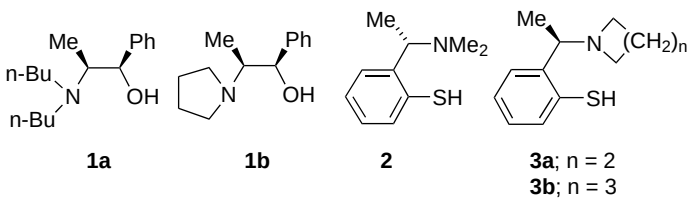
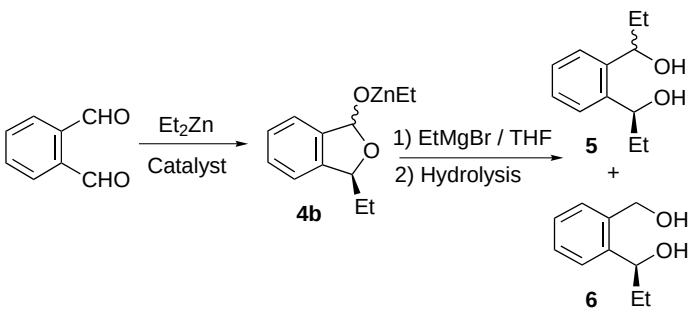


Figure 1.



Scheme 2.

The reactions were carried out under standard conditions, using either 5 mol% (total t.o.n. 20) or 0.5 mol% (total t.o.n. 200) of catalyst precursor. The results are given in Table 1.

Table 1 shows especially that the enantioselectivity of the reaction is controlled by the nature of the catalyst precursor. Using catalyst precursor **3b** (entry 5), the C_2-symmetric diol (*R*,*R*)-**5** is formed with high enantioselectivity (84%) and diastereoselectivity (*dl*/*meso* 91/9). When the e.e. values of the diol obtained from the aminoalcohol-based catalyzed reactions (entries 7–10) are compared with those of the aminoarenethiol-based catalyzed reactions (entries 2–6), it is clear that the latter catalyst precursors are superior. Furthermore, the use of piperidine or pyrrolidine arene thiol derivatives instead of normal dialkylamine-substituted ones gives rise to considerably enhanced enantioselectivities (cf. entry 2 versus 3–6, and entries 7, 8 versus 9, 10). This observation can be explained by: (i) an enhancement of the differences in relative thermodynamic stabilities of the intermediates that are formed during this reaction, and (ii) an enhanced rate of the transfer of the alkyl group from zinc to the substrate (for a discussion see Ref. 7). The importance of the latter factor appears from the observation that the uncatalyzed reaction of Et_2Zn with 1,2-phthalicdicarboxaldehyde to lactol **4** needs about 18 h for completion.

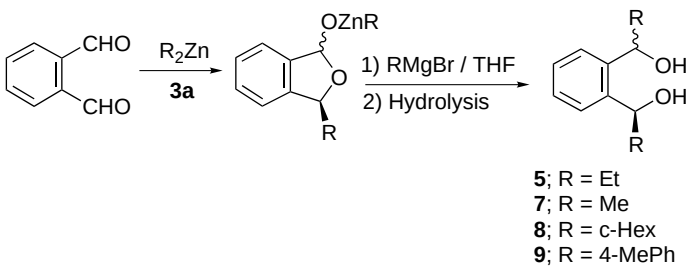
These observations suggest that enantioselection occurs during the first step, i.e. during the formation of the alkoxy-EtZn derivative of **4b** (see Scheme 2). In the second step, the stereochemistry of the second stereocenter is controlled by the initially formed stereocenter to the effect that the C_2-symmetric isomer becomes the predominant product.

To determine the enantioselectivity of the first reaction step, lactol **4**, prepared using the reaction conditions given in entry 5 in Table 1, was reduced with $NaBH_4$ to the corresponding 1-[(2-hydroxymethyl)phenyl]propanol.[9] The measured optical rotation of $[\alpha]_D^{22} = -24°$ (*c* 1.3, $CHCl_3$) contrasts[14] with the value of $[\alpha]_D^{22} = +18.4°$ (*c* 0.87, $CHCl_3$), reported by other authors for a 98% e.e. pure sample of this alcohol.[9] The opposite sign of the optical rotation of the 1-[(2-hydroxymethyl)phenyl]propanol is evidence for the fact that the absolute stereochemistry of the initially formed stereocenter using the (*R*)-catalyst is indeed (*S*).

The fact that the catalyst has no significant influence indeed on the formation of the second stereocenter was confirmed by the outcome of a separate experiment in which pure lactol **4** (e.e. 90%) was treated with EtMgBr. The e.e. of the resulting C_2-symmetric diastereoisomer **5** was 80%, a value which is very close to those found for diols formed in reaction mixtures in which the catalyst is still present (see Table 1). It should be noted, however, that a slight decrease of the diastereoselectivity was also observed (*dl*/*meso* 83/17).

To study the influence of the nature of the diorganozinc and Grignard reagents, similar reactions were carried out under optimized reaction conditions, using Me_2Zn, *c*-Hex_2Zn, 4-$MePh_2Zn$ and the corresponding Grignard reagents (see Scheme 3 and Table 2).

Reactions of Me_2Zn and MeMgCl (Table 2, entry 2) under standard conditions afforded diols **7** in high chemical yield. Although the enantioselective induction with respect to the *dl* diastereoisomers was high (83%) and comparable to the values obtained for Et_2Zn (cf. entry 1 in Table 2), the diastereoselectivity was disappointingly low (*dl*/*meso* 66/34), whereas the reactions of



Scheme 3.

Table 2. The influence of the nature of the diorganozinc compound on product distribution (Scheme 3)[a,b]

Entry	R	(*S*,*S*)	(*R*,*R*)	*meso*	e.e.	*dl*/*meso*
1	Et	80.3	8.8	6.2	80	93/7
2	Me	60.8	5.3	33.9	83	66/34
3	*c*-Hex	60.0	37.0	3.0	25	97/3
4	4-MePh	74.6	6.3	19.1	84	81/19

[a] All R_2Zn additions were carried out in toluene at rt, followed by the addition of 1.1 equiv. of RMgBr in THF at 40°C, reaction time 18 h, 1 mol% catalyst **3a**.

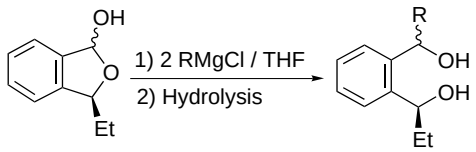
[b] Product distributions were determined by HPLC analysis using a Daicel Chiracel OD column (25 cm×4.6 mm); eluent: 2-propanol/*n*-hexane 1/99; flow: 1 mL/min.

c-Hex_2Zn and *c*-Hex_2MgCl (entry 3 in Table 2) occurred with excellent diastereoselectivity (*dl*/*meso* 97/3). Obviously, the formation of the second stereocenter is mainly controlled by steric factors and depends on both the steric bulk of the organic group first introduced at a benzylic position and the steric bulk of the Grignard reagent itself. The observed low enantioselectivity (25%) in reactions using *c*-Hex_2Zn is not unprecedented. It has been reported before that the aminoalcoholate- or aminoarenethiolate-catalyzed addition of secondary dialkylzinc compounds to aldehydes proceeds with a considerably lower enantioselectivity as compared to the e.e.s realized for primary dialkylzinc compounds.[5–7]

The methodology described here also opens a new pathway to the synthesis of unsymmetrically substituted diols derived from 1,2-phthalicdicarboxaldehyde. In a preliminary experiment in which the in situ prepared alkoxy-EtZn derivative **4b** was treated with *c*-HexMgCl, considerable amounts of diol **5** were formed in addition to the unsymmetric diol **11**. This observation indicates that scrambling of organic groups between zinc and magnesium occurs. Therefore, further experiments were carried out using the purified lactol **4** as starting material.

The results of the reactions of pure **4** with MeMgCl, *c*-HexMgCl and PhMgCl (see Scheme 4) are presented in Table 3.[15]

Reaction of MeMgCl with (*S*)-**4** gave **10** as two stereoisomers (as well as the corresponding diastereoisomers of the (*R*)-**4** impurity; see Scheme 4 and Table 3, entry 1), (*S*,*S*)-**10** being the major product. The ratio of the (*S*,*S*)/(*S*,*R*) diastereoisomers (74/26) has a value close to that obtained for the symmetrically dimethyl-substituted diol **7**, vide supra.



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10; R = Me
11; R = c-Hex
12; R = Ph

Scheme 4.

Table 3. Reaction of lactol **4** with Grignard reagents RMgCl[a]

Entry	R	(*S*,*S*)	(*R*,*R*)	(*S*,*R*)	(*R*,*S*)
1	Me	68.3	5.5	24.5	1.7
2	*c*-Hex	76.0	6.6		17.4[b]
3	Ph	69.8	7.2		23.0[b]

[a] Product distributions were determined by HPLC analysis using a Daicel Chiracel OD column (25 cm×4.6 mm); eluent: 2-propanol/*n*-hexane 1/99; flow: 1 mL/min.

[b] Under the analytical conditions applied, no well-resolved peaks were obtained for these diastereoisomers.

For the phenyl-substituted diol **12**, almost the same isomer distribution has been found (see entry 3 in Table 3). A considerable increase of the relative amount of the (*S*,*S*)(*R*,*R*) diastereoisomer was found for the cyclohexyl-substituted diol **11** (entry 2 in Table 3), which most likely is a consequence of the introduction of the sterically more crowded cyclohexyl group.

All the new diols were fully characterized by ^1H and ^{13}C NMR and elemental analysis; some of these, i.e. (*S*,*S*)-**9**, (*S*,*S*)-**11** and (*S*,*R*)-**12**, were obtained enantiomerically pure after recrystallization and were fully characterized.[16]

We have shown, making use of a newly developed one-pot, two-step synthesis, that C_2-symmetric diols derived from 1,2-phthalicdicarboxaldehyde are readily available in high yield, and high enantiomeric and diastereoisomeric purities. Moreover, this methodology allows the introduction of two different organic groups at two adjacent benzylic positions. Since both enantiomers of the applied chiral amino-arene thiolate catalyst are available,[7] there is complete control over the absolute stereochemistry of the chiral target molecule.

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14. Based on the observed isomer distributions in entry 5 in Table 1, the enantiomeric purity of lactol **4** and, thus, the enantiomeric purity of the 1-[(2-hydroxymethyl)phenyl]-propanol obtained from it cannot exceed 90%.
15. It should be noted that the formation of the unsymmetrically substituted diols causes a complicated analytical

situation due to the formation of a mixture of enantiomeric pairs of two diastereoisomers (no *meso* compound is formed).

16. (*S*,*S*)-**9**: Enantiomeric purity >99%; $[\alpha]_D^{22} = -102°$ (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37–7.08 (m, 12H, aromatic *H*); 5.92 (s, 2H, C*H*-OH); 2.86 (br s, 2H, O*H*); 2.35 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 141.2, 139.8, 137.0, 129.0, 128.6, 127.9 and 126.4 (aromatic *C*); 73.1 (*C*HOH); 21.0 (*C*H_3). Anal. calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.83; H, 7.11.
(*S*,*S*)-**11**: Enantiomeric purity >99%; $[\alpha]_D^{22} = -45.4°$ (*c* 1.0, $CHCl_3$); mp 116–117°C; ^{13}C NMR ($CDCl_3$): δ 141.8, 140.3, 127.6, 127.4, 127.0 and 125.8 (aromatic *C*); 76.0 (*C*HC_6H_{11}); 71.7 (*C*HC_2H_5); 44.6, 29.7, 29.2, 26.3, 26.1 and 25.9 (cyclohexyl *C*); 31.3 (*C*H_2CH$_3$); 10.5 (CH$_2$*C*H$_3$). Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.19; H, 9.81.
(*S*,*R*)-**12**: Enantiomeric purity >99%; $[\alpha]_D^{22} = 6.1°$ (*c* 1.02, $CHCl_3$); mp 125–126°C; ^1H NMR (C_6D_6): δ 7.41–6.98 (m, 9H, aromatic *H*); 5.92 (br s, 1H, C*H*C_6H_5); 4.72 (m, 1H, C*H*C_2H_5); 2.68 (br s, 1H, O*H*); 2.09 (br s, 1H, O*H*); 1.70–1.40 (m, 2H, CH_2CH$_3$); 0.80 (t, $J = 7.4$ Hz, 3H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$): δ 142.8, 141.8, 140.8, 128.3, 128.0, 127.6, 127.5, 127.4, 126.8 and 126.0 (aromatic *C*); 71.9 (*C*HC_6H_5); 70.7 (*C*HC_2H_5); 30.0 (*C*H_2CH$_3$); 10.6 (CH$_2$*C*H$_3$). Anal. calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.24; H, 7.54.