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An Efficient Preparation of Optically Pure C_2-Symmetric Aromatic Diols by the Asymmetric Reduction of Diacylaromatic Compounds with *B*-Chlorodiisopinocampheylborane [1]

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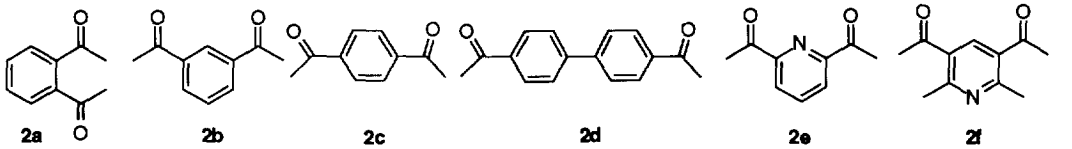
Abstract: Asymmetric reduction of diacylaromatic compounds with *B*-chlorodiisopinocampheylborane provides the product diols in excellent diastereomeric and enantiomeric purity. Copyright © 1996 Elsevier Science Ltd

The growing importance of asymmetric syntheses,[2] especially those involving C_2-symmetric molecules as chiral directors, provides an impetus for the preparation of such compounds.[3] Asymmetric reduction of symmetric diketones offers a promising synthetic route to C_2-symmetric diols. Asymmetric dihydroxylation of olefins[4] and catalytic asymmetric hydrogenation[5] are among several other alternate procedures used to achieve an efficient synthesis of such chiral diols.

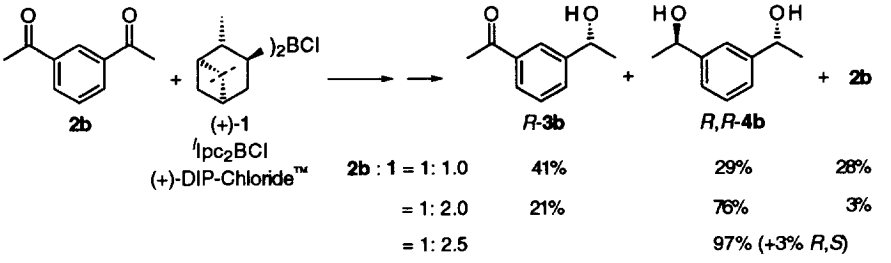
Recently Chong and co-workers utilized *B*-chlorodiisopinocampheylborane ($^{l}Ipc_2BCl$, Aldrich: DIP-Chloride™, **1**),[6] an excellent reagent for the asymmetric reduction of aralkyl ketones, for the asymmetric reduction of 1,4-diphenyl-1,4-butanedione and obtained the product diol in ≥98:≤2, dl:meso, with the dl component showing ≥99% ee.[7] They also reported that catalytic oxazaborolidine-BH_3 reductions[8] of the same ketone provided 1,4-diphenyl-1,4-butanediol in 3:1 to 14:1 dl:meso ratio, depending on the amino alcohol used. Quallich and co-workers reported the reduction of symmetric diketones using *erythro*-diphenyloxazaborolidine-BH_3, obtaining the diols in good to moderate dl:meso ratio.[9] The amount of the dl portion improved when the oxazaborolidine was used in stoichiometric quantity. However, Schwink and Knochel prepared C_2-symmetric 1,1'-ferrocenediols in high de and ee using a catalytic CBS reduction.[10]

The important potential applications of optically pure C_2-symmetric diols persuaded us to undertake a systematic study of the convenient synthesis of such compounds by the Ipc_2BCl reduction of representative diacetylaromatic compounds, **2a-f**. Following the initiation of this project, a report by Hoshino appeared for the reduction of 2,6-dipivaloylpyridine with **1** to prepare a catalyst for diethylzinc additions.[11] However, they utilized a 2.5 fold excess of the reagent (5 equiv), but obtained the desired diol in only 45% yield. The diastereomeric ratio was not discussed. In most of the cases that we tested, the products are obtained in good to excellent yield in essentially enantiomerically pure form.



The reduction of 1,2-diacetylbenzene (**2a**) produces a complex mixture of products. However, the reduction of 1,3-diacetylbenzene (**2b**) with one equiv of the reagent is complete in 2 h and the usual diethanolamine workup provides a mixture of the hydroxyketone, 1-[3-(1-hydroxyethyl)phenyl]ethanone (**3b**) (41%), the diol, α,α'-dimethyl-1,3-benzenedimethanol (**4b**) (29%) and 28% of the unreacted ketone (eq 1).

The hydroxyketone, analyzed as the menthylchloroformate (MCF) derivative[12a] using a gas chromatograph on a SPB-5 column, is of 97% ee. With two equiv of the reagent, 21% of **3b** along with 76% of **4b** and 3% of the starting ketone are obtained. The formation of **3b** and recovery of the starting ketone is avoided by conducting the reduction with 2.5 equiv of the reagent providing a 95% isolated yield of **4b** as a pale yellow semi-solid which forms colorless crystals upon cooling. The bis-MTPA ester[12b] of this material, on analysis using ^{1}H NMR spectroscopy as reported in the literature[13] reveals a ≥97:≤3 mixture of dl and meso compounds. The dl component is enantiomerically pure.



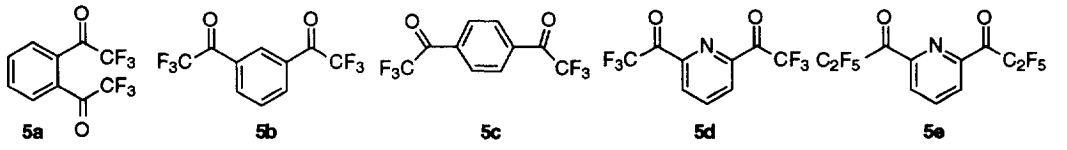
(1)

Similar results are realized in the reduction of 1,4-diacetylbenzene (**2c**). Because of the poor solubility of **2c** in ether solvents, its reduction was carried out in CH_2Cl_2. Having standardized the conditions for the exclusive formation of the diol, we used 2.5 equiv of **1** in subsequent reductions. The diol, α,α'-dimethyl-1,4-benzenedimethanol (**4c**) is obtained as a solid in 92% yield. Analysis of the bis-MTPA ester shows it to be ≥99% *R,R*-isomer. Since we realized excellent yields of the enantiomerically pure diol, we did not attempt the quantification of the minor amount of the meso product that might be produced in the reaction.[14] The reduction of 4,4'-diacetylbiphenyl (**2d**) in EE, at –25 °C, is complete within 6 h and the diol is obtained in 92-94% isolated yield in ≥99% ee. Again, the solid nature of the product aided in the isolation of the *R,R*-**4d**, easily separated from the minor amount of the meso product possibly formed in the reduction.[14]

The success achieved encouraged us to extend the study to the reduction of diacetylpyridines in the hope of achieving the syntheses of tridentate chiral ligands. However, 2,6-diacetylpyridine (**2e**) could not be completely reduced even by using 2.5 equiv of the reagent. Since the nitrogen atom of the pyridine complexes with the boron atom of the reagent[6] (^{11}B: δ 11 ppm), we added one equiv of BF_3•EE before the addition of 2.5 equiv of the reagent. Yet, we could not avoid the formation of the hydroxyketone (**3e**). Since the workup is complicated and the yields are poor using the above procedure, we utilized 3.3 equiv of the reagent for the reduction (one equiv of the reagent was expected to coordinate with the ketone). Treatment with acetaldehyde to quench the excess reagent, followed by an acidic workup, provides 36% of 1-[6-(1-hydroxyethyl)-2-pyridyl]-ethanone (**3e**) and 59% of the required diol, α,α'-dimethyl-2,6-pyridinedimethanol (**4e**). We repeated the reaction with 2.5 equiv of **1** and carried out the usual acidic workup[6] to separate the products in a combined yield of 94%. We are studying this reaction more carefully in the hope of realizing conditions that will provide a quantitative conversion to the diol.

Earlier, we had observed that the nitrogen atom of 2,6-lutidine does not coordinate with **1**.[6] Accordingly, the reduction of 3,5-diacetyl-2,6-lutidine (**2f**) was carried out with 2.5 equiv of (+)-**1**. The reaction was complete in 5h. An acidic workup provides the diol, α,α',2,6-tetramethylpyridine-3,5-dimethanol (**4f**) in 97% yield and in ≥99% ee.

The difficulties in obtaining pure diols from **2a** and **2e** prompted us to study the reaction of the corresponding diperfluoroacyl analogs with **1**. We have earlier shown that **1** is an excellent reagent for the reduction of perfluoroalkyl ketones providing the product alcohols of opposite stereochemistry.[15] Accordingly, we prepared diperfluoroacyl ketones **5a-d** from the corresponding dibromo ketones following literature procedures,[16] and carried out the reductions with 2.5 equiv of **1**.



5a **5b** **5c** **5d** **5e**

Table. Asymmetric Reduction of Diacylaromatics with DIP-Chloride

ketone	reagent	reaction condition				hydroxy ketone			diol[a]						
		ketone: reagent	solvent	temp °C	time h	yield[b] %	ee[c] %	config.[d]	yield[b] %	dl	meso	ee[e] %	config.[d]	$[\alpha]^{25}_D$[f]	
2b	(+)-**1**	1:1.0	EE	–25	2	41	≥97	*R*	29			≥99	(*R*,*R*)		
2b	(+)-**1**	1:2.0	EE	–25	2	21	≥97	*R*	76			≥99	(*R*,*R*)	+69.4 (*c* 1.25)	
2b	(+)-**1**	1:2.5	EE	–25	5	0			95	97	3	≥99	(*R*,*R*)	+69.4 (*c* 1.25)	
2b	(–)-**1**	1:2.5	EE	–25	5	0			98	97	3	≥99	(*S*,*S*)	–69.4 (*c* 2.1)	
2c	(+)-**1**	1:1.1	CH_2Cl_2	0	2	51	91.4	*R*	25			≥99	(*R*,*R*)	+84.7 (*c* 1.58)	
2c	(+)-**1**	1:2.1	CH_2Cl_2	0	3	8	90.0	*R*	81			≥99	(*R*,*R*)	+86.1 (*c* 1.3)	
2c	(+)-**1**	1:2.5	CH_2Cl_2	–25	4	0			92[g]	≥99[h]		≥99	(*R*,*R*)	+86.3 (*c* 1.76)	
2c	(–)-**1**	1:2.5	CH_2Cl_2	–25	4	0			92[g]	≥99[h]		≥99	(*S*,*S*)	–86.3 (*c* 1.7)	
2d	(+)-**1**	1:2.5	EE	+25	3	0			94[g]	≥99[h]		≥99	(*R*,*R*)	+79.1 (*c* 1.3)	
2d	(+)-**1**	1:2.5	CH_2Cl_2	–25	6	0			92[g]	≥99[h]		≥99	(*R*,*R*)	+79.2 (*c* 0.7)	
2d	(–)-**1**	1:2.5	CH_2Cl_2	–25	3	0			90[g]	≥99[h]		≥99	(*S*,*S*)	–79.0 (*c* 1.5)	
2e	(+)-**1**	1:2.5	EE	–25	12	44	≥95	*R*[i,j]	50	91	9	≥99	(*R*,*R*)	+ 44.6 (*c* 2.3)	
2e	(–)-**1**	1:3.5	EE	–25	17	36	≥95	*S*[i,k]	59	91	9	≥99	(*S*,*S*)	–45.99 (*c* 1.9)	
2f	(+)-**1**	1:2.5	EE	–25	5	0			97[g]	≥99[h]		≥99	(*R*,*R*)[i]	+138.1 (*c* 2.2)	
2f	(–)-**1**	1:2.5	EE	–25	5	0			94[g]	≥99[h]		≥99	(*S*,*S*)[i]	–138.0 (*c* 2.32)	
5a	(–)-**1**	1:2.5	EE	+25	No reduction										
5b	(–)-**1**	1:2.5	EE	+25	3d	0			81	85[l]	15	81[l]	(*S*,*S*)[i,m]	+38.1 (*c* 7.7)[n,o]	
5c	(–)-**1**	1:2.5	EE	+25	6d	0			95	93[l]	7	≥99[l]	(*S*,*S*)[p,m]	+47.9 (*c* 6.9)[n]	
5d	(–)-**1**	1:2.5	EE	+25	3d	0			71	98[l]	2	≥99[l]	(*S*,*S*)[m,q]	+36.1 (*c* 6.9)[n]	
5e	(–)-**1**	1:2.5	THF	+25	7d	0			72	97[l]	3	≥99[l]	(*S*,*S*)[i,m]	+34.5 (*c* 5.3)[n]	

[a]The dl/meso ratios are determined by the ^1H NMR spectroscopy of the bis-MTPA esters unless otherwise stated. [b]Isolated yield. [c]The %ee was determined by GC ananlysis of the MCF derivative on a SPB-5 column. [d]Determined by comparing the rotation with known product. Ref. 13. [e]The % ee was determined by ^{19}F NMR of the bis-MTPA ester of the diol. [f]Rotations are for optically pure material unless otherwise stated. Rotations are measured in acetone unless otherwise stated. [g]Isolated yield of ≥99% ee diol after chromatography. [h]Determined by ^{19}F NMR of the bis-MTPA ester of the diol. [i]The configuration is based on analogy. [j]$[\alpha]_D^{25}$ = +40.53 (*c* 3.8, acetone). [k]$[\alpha]_D^{25}$ = –40.16 (*c* 4.4, acetone). [l]dl/meso and % ee determined by GC analyses of the bis-TFA derivative on a Chiraldex-GTA capillary column. [m]Opposite stereochemistry. *S,S*-configuration is an artifact of Cahn-Ingold-Prelog rules. [n]Rotations measured in methanol. [o] Rotation of the material of 70% de and 81% ee. [p]Ref. 17. [q]The configuration is determined based on X-ray analysis.

While the reduction of **2a** produces a complex mixture of products, **5a** undergoes negligible reduction, if any, even after 15 d. 1,3-Di-(trifluoroacetyl)benzene is completely reduced within 2 d. The GC analysis of the ditrifluoroacetate of the diol on a Chiraldex-GTA column reveals only 70% de and 81% ee. 1,4-Di-(trifluoroacetyl)benzene is reduced in 93:7 dl:meso ratio, with the dl portion revealing ≥99% ee. Unlike **2e**, the pyridyl ketones **5d** and **5e** are completely reduced to the diol in a ratio of 97-98% dl : 3-2% meso, and the dl portion is optically pure. On the basis of the reduction of aryl and alkyl perfluoroalkyl ketones with **1**, the stereochemistry of the di-(trifluoromethyl)-diols are expected to be opposite as compared to the methyl analogs. The comparison of the optical rotation of the diol produced from **5c** with that reported in the literature[17] confirmed this. Furthermore, analysis of the diol obtained from the reduction of **5d** with (–)-**1** by X-ray crystallography reveals the configuration to be, as expected, *S,S*. Thus, in all of the cases studied, the (+)-

reagent provides the *R,R*-diols and the *S,S*-isomers are prepared by using the antipode of the reagent. All of the results are summarized in the Table.

In conclusion, we have demonstrated the utility of **1** in reducing diacyl aromatic compounds to the corresponding optically pure diols. The reduction of 2,6-diacylpyridyl ketones provides an efficient preparation of tridentate ligands for use in catalytic asymmetric reactions. The possibility of obtaining such diols of differing electronic and steric environments has made possible[18] a study of the electronic and steric effects of ligands in catalytic asymmetric reactions.[19] The compatibility of the reagent **1** with the great majority of functional groups on the aromatic ring provides the possibility for further change in the steric and electronic environments. The applications of several of these and other pyridinediols for various transition-metal catalyzed asymmetric reactions are in progress.[20,21]

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21. The reduction of **2b** is representative. All operations were carried out under an inert atmosphere. DIP-Chloride (4.95 g, 15.43 mmol) was transferred to the flask in a glove bag and dissolved in EE (15 mL), followed by the addition of 1.0 g (6.17 mmol) of the ketone at –25 °C. Upon completion of the reaction (2h, ^{11}B NMR spectrum of a methanolyzed aliquot: singlets at δ 52 and 32 ppm in an approximate ratio of 1:4), diethanolamine workup provided the crude product which was chromatographed through silica (*n*-pentane:ethylacetate = 2:1 as eluent) to obtain 0.96 g (93.7%) of a pale yellow solid. $[\alpha]^{25}_D = -69.4$ (*c* 1.2, acetone), corresponds to ≥99% ee on the basis of the rotation of $[\alpha]^{25}_D = -65.9$ (*c* 1.2, acetone) for ≥94% ee material reported in the literature.[13] The structure was confirmed by ^1H and ^{13}C NMR. In the case of the acetylpyridines **2e** and **2f**, once the reaction was complete, 3*N* dilute HCl (3 equiv) was added to the reaction mixture and stirred for 30 min. The organic layer was removed by extracting with EE and the aqueous layer was treated with aqueous 3*N* NaOH to pH 9. The product was extracted with ethyl acetate after saturating the aqueous layer with sodium chloride. The crude product was further purified by chromatography over silica.

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