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Sparteine-Mediated Asymmetric Nucleophilic Substitution at Prochiral, sp^3-Hybridized Carbon

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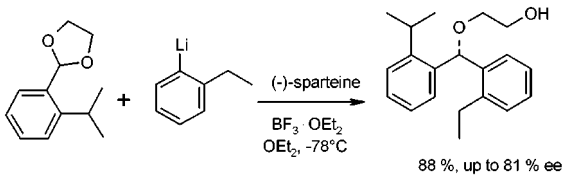
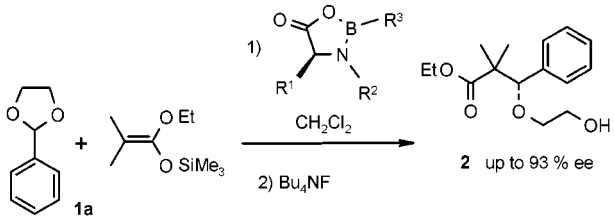
ABSTRACT



2-Phenyl-1,3-dioxolanes (1) react with organolithium reagents (2), associated with (−)-sparteine, in the presence of $BF_3 \cdot OEt_2$ to afford chiral monosubstitution products 3. Enantioselectivity is highest if both 1 and 2 carry alkyl substituents in the *ortho* position. However, the enantioselectivity decreases in the case of very bulky substituents such as *tert*-butyl or phenyl.

Efficient protocols for catalytic and, at the same time, enantioselective nucleophilic substitutions have been developed for opening of epoxides[1] and aziridines.[2] In these reactions, nucleophilic attack occurs preferentially at one of two enantiotopic centers of *meso* compounds. In principle, enantioselective nucleophilic substitution at a single prochiral carbon atom carrying two enantiotopic leaving groups is also possible but has been much less investigated. To our knowledge, the only reported reaction of this type consists of opening of 2-aryl-1,3-dioxolanes **1** by enol silyl ethers in the presence of a chiral, nonracemic boron complex. Enantioselectivities of up to 93% have been achieved in the substitution product **2**[3] (Scheme 1). In these reactions enantioselectivity originates from differential activation of the enantiotopic centers by the chiral Lewis acid or via enantioselective association of the Lewis acid with one of the enantiotopic leaving groups, respectively.

Scheme 1



Recently we reported the enantioselective desymmetrization of *meso*-*N*-sulfonylaziridines with organolithium or Grignard reagents in the presence of CuOTf and chiral ligands. In these latter reactions, enantioselectivity results probably from association of the organometallic reagent with the ligand to generate a chiral nucleophile, but not from electrophilic catalysis.[2a] In this account we report the

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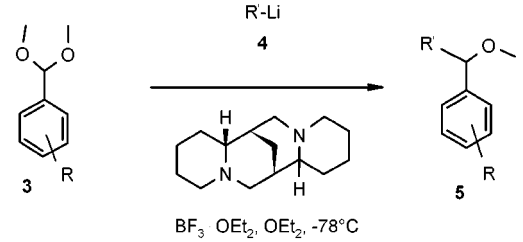
extension of the approach to acetals. Exploratory experiments with benzaldehyde dimethyl acetal **3** and reagents such as $TMSN_3$ and Et_2Zn in conjunction with electrophilic catalysts were not successful. However, we found that the combination of organolithium reagent **4** with sparteine and BF_3, under conditions similar to those used previously by Alexakis[4] for epoxide opening, was capable of effecting the desired transformation. Sparteine is the most efficient chiral ligand for organolithium compounds[5] with which it forms tight ion pairs upon association.

Reactions of benzaldehyde dimethyl acetal (**3a**) with a series of organolithium reagents **4** confirmed the feasibility of the approach, although the enantioselectivities were marginal to modest (Scheme 2 and Table 1). The highest

Scheme 2



induction occurred upon exposure of the acetal **3m** to *o*-ethylphenyllithium (**4m**). However, more encouraging

Table 1. Reaction of Benzaldehyde Dimethyl Acetals (**3**) with Organolithium Reagents (**4**) in the Presence of Sparteine

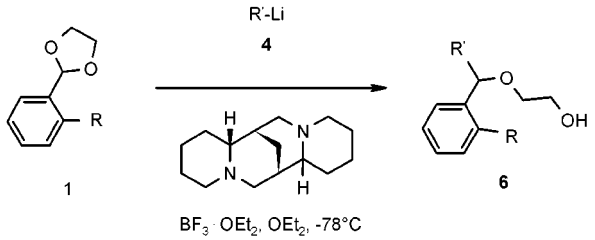
run	**3**, R =	**4**, R′ =	yield of **5**, %	ee, %	$[\alpha]_D$[b]
a	H	Me	50	11	
b	H	Bu	90	25	+10.3
c	H	*p*-Me-phenyl	85	23	+07.5
d	H	*o*-Me-phenyl	89	9	
e	H	*p*-MeO-phenyl	76	16	
f	H	*o*-MeO-phenyl	90	5	
g	*p*-Me	phenyl	95	7	
h	*p*-Me	*o*-Me-phenyl	93	12	
i	*p*-Me	*o*-MeO-phenyl	92	12	
k	*p*-MeO	*o*-Me-phenyl	95	7	
l	*p*-MeO	*o*-MeO-phenyl	81	13	
m	*o*-*i*-Pr[a]	*o*-Et-phenyl	92	40	+06.5

[a] With 2 equiv of sparteine and 3 equiv of BF_3·OEt_2. [b] In EtOH, 21 °C.

results were obtained with 2-phenyl-1,3-dioxolanes (**1**) (Scheme 3 and Table 2).

The reactions were carried out routinely at −78 °C by adding BF_3·OEt_2 (3.0 equiv) dropwise to a solution of the acetal (1.0 equiv), the organometallic reagent (4.0 equiv), and sparteine (4.0 equiv) in ether. Yields of **5** and **6**,

Scheme 3



respectively, are given in Tables 1 and 2 and refer to isolated products.

Table 2. Reaction of 2-Phenyl-1,3-dioxolanes **1** with Organolithium Reagents **4** in the Presence of Sparteine

run	**1**, R =	**4**, R′ =	yield of **6**, %	ee, %	$[\alpha]_D$[a]
a	H	Me	61	3	
b	H	*n*-Bu	94	15	
c	H	*p*-Me-phenyl	89	12	
d	H	*o*-Me-phenyl	91	34	+03.6
e	H	*p*-MeO-phenyl	81	13	
f	H	*o*-MeO-phenyl	88	10	
g	H	1-naphthyl	77	33	−03.2
h	H	*o*-Et-phenyl	90	30	−05.9
i	H	*o*-*i*-Pr-phenyl	94	46	+01.5
k	H	*o*−*t*-Bu-phenyl	92	4	
l	H	*o*-Phe-phenyl	91	2	
m	Me	*o*-Et-phenyl	76	52	+02.5
n	*i*-Pr	*o*-Et-phenyl	85	75	+10.0
o	*n*-Bu	*o*-Et-phenyl	58	58	+01.9
p	*t*-Bu	*o*-Et-phenyl	87	60	−15.3
q	Phenyl	*o*-Et-phenyl	77	69	+28.4

[a] In EtOH, 21 °C.

Simple alkyllithium reagents produced only low selectivities, but aryllithiums were more appropriate. After extensive optimizations we found that moderately bulky substituents had a beneficial effect on the enantioselectivity, but very bulky substituents were detrimental. The most favorable combination was that of *o*-isopropyl-2-phenyl-1,3-dioxolane with *o*-ethylphenyllithium to afford **6n** with 75% ee.[6,7]

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(5) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316.

(6) Sample run: To 2-bromoethylbenzene (296 mg, 1.6 mmol, 4 equiv) and (−)-sparteine (187 mg, 0.8 mmol, 2.0 equiv) in Et_2O (2.0 mL) was added BuLi (1.0 mL, 1.6 M in hexane) at −30 °C. After stirring during 1 h, the mixture was cooled to −78 °C and 2-(2-isopropylphenyl)-1,3-dioxolane (**1n**) (77 mg, 0.40 mmol, 1 equiv.) was added, followed by slow addition of BF_3·OEt (0.16 mL, 1.2 mmol). Stirring was continued at −78 °C during 1 h. The mixture was then hydrolyzed with saturated NH_4Cl (5 mL). After usual workup, the crude product was purified by flash chromatography (pentane/AcOEt 4:1) to afford **6n** (105 mg, 88%) as colorless oil.

(7) Data of **6n**: colorless oil; $[\alpha]^{21}_D = +10.6$ ($c = 1.1$, $EtOH_3$) for 81% ee (by HPLC, OD, H column with hexane/2-propanol 25:1, $T_1 = 14.0$ min; $T_2 = 14.9$ min); IR ($CHCl_3$) 3623 m, 2956 m, 2892 w, 1447 w, 1394 w, 1245 w, 1052 s, 877 m; ^1H NMR (500 MHz, $CDCl_3$) 1.11 (d, $J = 7$, 3H), 1.15 (t, $J = 7.6$, 3H), 1.31 (d, $J = 7$, 3H), 1.89 (s, broad), 2.57−2.72 (m, 2H), 3.15 (sept, $J = 7$, 1H), 3.63−3.67 (m, 2H), 5.95 (s, 1H), 7.12−7.39 (m, 8H); ^{13}C NMR (125 MHz) 14.9 (q), 23.7 (q), 24.3 (q), 25.2 (d), 28.5 (d), 62.2 (t), 71.1 (t), 77.2 (d), 125.65 (d), 125.7 (d), 125.9 (d), 126.6 (d),

The enantioselectivity of the reaction depended upon the sparteine concentration. When the excess of sparteine was decreased from 4 to 1.5 equiv over the substrate while that of **4n** was maintained at 4 equiv, the ee fluctuated insignificantly between 75 and 81% (Table 3), but it dropped to 68 and 23%, respectively, when 1.0 or 0.5 equiv of sparteine was used. In these latter experiments, the concentration of ArLi reagent **4n** exceeded that of sparteine, but nevertheless some induction occurred. However, the reaction could so far not be realized under conditions catalytic with respect to sparteine.

Table 3. Effect of Sparteine Concentration on the Enantiomeric Excess of **6n**[a]

entry	[spart.][b]	solvent	yield of **6n**, %	ee, %
1	4.0	Et_2O	85	75
2	3.0	Et_2O	83	80
3	2.0	Et_2O	88	81
4	1.5	Et_2O	85	81
5	1.0	Et_2O	82	68
6	0.5	Et_2O	85	23

[a] 4 equiv of **4n** with respect to **1n**. [b] Equivalents of sparteine with respect to **1n**.

The reaction of **1n** proceeded with almost identical enantioselectivity in simple ethers, such as Et_2O and Bu_2O. With *tert*-butyl methyl ether, the ee decreased by ca. 10%, while in THF no enantioselectivity was obtained. This suggests efficient competition of THF with sparteine for complexation of Li. On the other hand, results in apolar solvents such as pentane or toluene were disappointing.

The reaction in trifluorotoluene was carried out at −50 °C owing to solidification of this solvent at lower temperature. Only a modest improvement in comparison with the unpolar solvents was observed (Table 4).

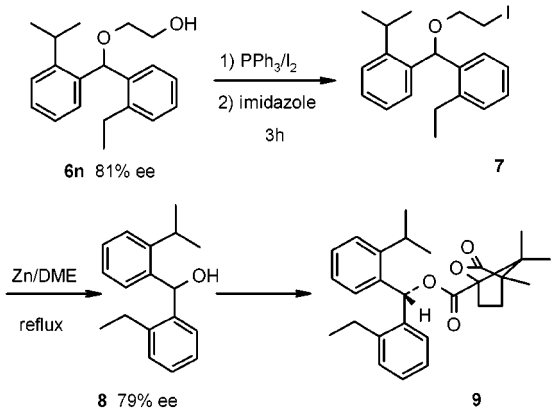
Table 4. Influence of Solvent on the Enantiomeric Excess of **6n**[a]

entry	solvent	yield of **6n**, %	ee, %
1	Bu_2O	86	77
2	*t*-Bu-O-Me	79	69
3	THF	68	0
4	pentane	72	41
5	toluene	82	24
6	$PhCF_3$[b]	65	32

[a] With 4.0 equiv of **4n** and 2.0 equiv of sparteine at −78 °C. [b] At −50 °C.

The ether cleavage of **6n** to **8** was readily achieved without loss of enantiopurity by conversion of the alcohol to the iodide **7** (89%)[8] followed by treatment with Zn in refluxing DME.[9] Reaction of the alcohol **8** with (−)-camphanoyl chloride produced a crystalline derivative **9** (>98% de), from which the absolute configuration at the new chiral center was determined to be *R* (Scheme 4).[10]

Scheme 4



To our knowledge, these are the first asymmetric nucleophilic substitution reactions occurring at a single prochiral center. The analogous carbonyl additions are known, however: Addition of EtMgBr to benzaldehyde in the presence of sparteine proceeds with 22% ee.[11] Other chiral bases, in particular, C_2-symmetric tertiary amines, produce enantioselectivities of up to 89% for addition of organometallic reagents to aldehydes,[12] and even better results are obtained with other chiral additives.[13] The mechanistic details of our asymmetric substitution are at present unknown. Nucleophilic attack by the chiral nucleophile may occur on the BF_3-complexed acetal or at an intermediate ion pair. At the present stage of development, the system is not catalytic, the enantioselectivity needs improvement, and synthetic applications appear to be limited. However, these problems may be overcome in the future. Replacement of BF_3 with a chiral electrophile could eventually allow additional control of enantioselectivity by intervention on the departing group.

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126.7 (d), 127.9 (d), 128.2 (d),; 136.9 (s), 137.9 (s), 142.4 (s), 147.5 (s); MS 237 (8), 236 (17), 221 (25), 208 (17), 207 (100), 194 (14), 193 (78), 192 (17), 179 (22), 135 (13), 133 (10), 132 (10), 131 (65), 117 (14), 91 (25), 79 (10), 45 (13). Anal. Calcd for $C_{20}H_{26}O_2$: C 80.49, H 8.78. Found: C 80.19, H 8.86.

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