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Efficient General Asymmetric Syntheses of 3-Substituted 1(3*H*)-Isobenzofuranones in Very High Enantiomeric Excess

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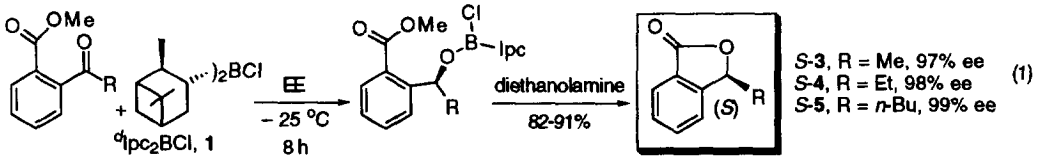
Abstract: The intermolecular asymmetric reduction of methyl *o*-(1-oxoalkyl)benzoates with *B*-chlorodiisopinocampheylborane provides, after workup, 3-alkylphthalides in ≥97% ee. Unfortunately, this procedure is not as efficient for the preparation of 3-arylphthalides. However, an intramolecular reduction of *B*-(*o*-benzoylbenzoyloxy)diisopinocampheylborane, readily prepared by the treatment of *o*-benzoyl benzoic acid with diisopinocampheylborane, provides 3-phenylphthalide in ≥96% ee.

1(3*H*)-Isobenzofuranones (phthalides) possess a wide range of medicinal properties. For example, 3-*n*-butylphthalide, a constituent of celery seed oil,[2] used for seasoning and flavoring purposes, exhibits anti-asthmatic,[3] anti-convulsant,[4] anti-tumor,[5] and anasthesia prolongation[6] properties. Subtituted 3-*n*-butylphthalides have been shown to be $PGF_{2\alpha}$ inhibitors.[7] 3-Alkylphthalides have been utilized in hair growth[8] and shower bath preparations.[9] Since phthalides form part of several alkaloids[10] (eg: the convulsant alkaloid biculline[10b]), they serve as intermediates for their synthesis.

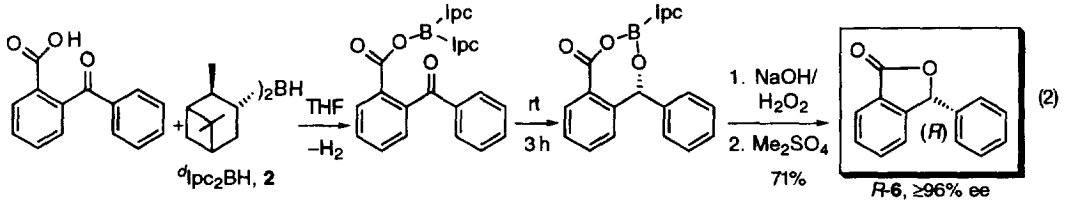
The impressive list of applications of phthalides has encouraged organic chemists to develop improved methods for their synthesis.[11] The crusades by medicinal chemists[12] and new regulations by the U.S. Food and Drug Administration mandating the synthesis and clinical studies of optically pure pharmaceuticals[13] have led to an increased interest in asymmetric syntheses during the last decade. Accordingly, several methodologies have become available for the asymmetric syntheses of phthalides as well. Asami and Mukaiyama's reaction of a chiral aryllithium with aldehydes[14] has been adapted by Ogawa,[15] Alexakis,[16] Takahashi[17] and their coworkers. Meyers' chiral lithiated oxazolines,[18] Soai's[19a] and Butsugan's[19b] dialkylzinc addition in the presence of chiral amino alcohols, Seebach's chiral organotitanium alkylation,[20] and Noyori's Binap-Ru(II) catalyzed hydrogenation[21] have all been applied to prepare optically active 3-alkylphthalides.

Herein we report convenient and general syntheses of chiral 3-substituted phthalides in very high enantiomeric excess (ee) via asymmetric reduction. The treatment of methyl *o*-acetylbenzoate with (–)-*B*-chlorodiisopinocampheylborane (^{d}Ipc$_2$BCl, Aldrich: (–)-DIP-Chloride, **1**),[22] in ethyl ether (EE) at –25 °C for 8 h, followed by the usual diethanolamine workup provides an 87% yield of 3-methylphthalide (**3**). The analysis of this lactone using a Chiraldex-GTA capillary column, shows an ee of 97% (eq 1). The optical rotation, $[\alpha]_D^{22} = -27.85$ (*c* 1.3, MeOH), reveals it to be the expected *S*-isomer.[17] The reduction of methyl *o*-propionyl- and *o*-valerylbenzoates provides *S*-3-ethyl- (*S*-**4**) and *S*-3-*n*-butylphthalides (*S*-**5**) in 98% ee and 99% ee, respectively.



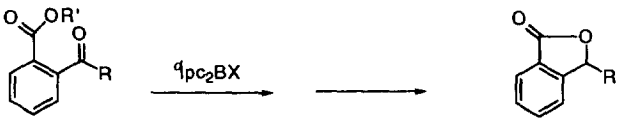
On the basis of the intramolecular reduction of *o*-hydroxyacetophenones (*o*-acetylphenols) with **1** to *o*-hydroxyphenethanols of opposite configuration in very high ee,[23] we envisaged a similar reduction of *o*-acylbenzoic acids with **1** to prepare the corresponding phthalides. The treatment of *o*-acetylbenzoic acid with one equiv of **1** at –25 °C, provides an intermediate whose ^{11}B NMR spectrum shows a singlet at δ 53, probably corresponding to the borinate ester. There is little reaction at this temperature. Upon warming to room temperature (rt), the reaction proceeds to completion in 24 h (^{11}B: δ 32). Aqueous NaOH workup, followed by acidification, furnishes **3** in 68% yield. The analysis of this material reveals 34% ee in the opposite (*R*) isomer, as expected on the basis of the intramolecular reduction of *o*-hydroxyacetophenone.[23] However, the low ee remained a puzzle. During an unrelated study, we have observed an equilibrium between *B*-benzoyloxydiisopinocampheylborane and **1**. That such an equilibrium exists in this case is established by repeating the above reduction in the presence of one equiv of triethylamine and obtaining *R*-**3** in 80% ee. Probably, the decrease in ee is caused by the simultaneous inter- and intramolecular reductions. The presence of free HCl may also have some deleterious effect. This led to an examination of diisopinocampheylborane (Ipc_2BH, **2**) to produce the reducing intermediate.

Although **2** is not an excellent chiral reducing agent itself,[24] it serves well in situations involving intramolecular reductions.[23] The reagent forms the benzoylborinate with *o*-acetylbenzoic acid in tetrahydrofuran (THF) within 1 h (complete evolution of hydrogen) and the reduction, at rt, is complete in 12 h (^{11}B: δ 32). Workup as above provides *R*-**3** in 80% ee. At 0 °C, the reaction is complete in 7 d and workup provides **3** in 84% ee. Since there is no significant difference in asymmetric induction, subsequent reductions were carried out at rt. The intramolecular reduction of *B*-(*o*-propionyl)- and *B*-(*o*-valerylbenzoyloxy)diisopinocampheylboranes are somewhat slower, requiring 48 h for completion, and workup provides *R*-**4** and *R*-**5** in 68% ee and 67% ee, respectively. However, the reaction of *B*-(*o*-benzoylbenzoyloxy)diisopinocampheylborane is complete in 3 h (eq 2). The yield of 3-phenylphthalide (**6**) is low, probably, due to the incomplete lactonization. Hence an oxidative ($NaOH/H_2O_2$) workup, followed by the treatment with Me_2SO_4 was adopted which affords 71% of **6**.[25] Comparison of the rotation with that reported in the literature[18] reveals an optical purity of 90% in the *R*-isomer. However, the ^{19}F NMR analysis of the bis-MTPA ester[26] of the diol, produced by the $LiAlH_4$ reduction of the lactone, reveals an ee of ≥96% ee.[27,28]



The reduction of the methyl ester of *ortho*-benzoylbenzoic acid with **1** is slow, even at rt, complete within 10 d, and workup furnishes 72% yield of *R*-**6** in 30% ee. The results are summarized in Table 1.

Table 1. Synthesis of chiral 3-substituted phthalides



ketone R	ketone R'	reagent ^{d}Ipc$_2$BX X	reaction condn. solvent	temp °C	time h	yield isol.	% ee[a]	phthalide config.[b]	$[\alpha]_D^{22}$
Me	Me	Cl	EE	–25	8	87	97	*S*	–27.85 (*c* 1.3, MeOH)[17]
Me	H	Cl	EE	25	24	68	34	*R*	
Me	H	Cl	EE	25	6d	60	80[c]	*R*	
Me	H	H	EE	25	12	82	81	*R*	
Me	H	H	THF	25	12	67	80	*R*	
Me	H	H	THF	0	7d	62	84	*R*	
Et	Me	Cl	EE	–25	8	82	98	*S*	–76.0 (*c* 5.5, $CHCl_3$)[19b]
Et	H	H	THF	25	48	62	68	*R*	
Bu	Me	Cl	EE	–25	8	91	99	*S*	–62.0 (*c* 4.2, $CHCl_3$)[19b]
Bu	H	H	THF	25	48	66	67	*R*	
Ph	Me	Cl	THF	25	10d	72	30[d]	*R*	
Ph	H	H	THF	25	3	71	≥96[d]	*R*	–48.6 (*c* 2.1, $CHCl_3$)[18]

[a]Determined directly on a GC using a Chiraldex-GTA capillary column. [b]Based on the rotation reported in the literature. [c]For a reaction in the presence of triethylamine. [d]Determined by ^{19}F NMR of the di-MTPA ester of the reduced product (diol).

The ready syntheses of *o*-acylbenzoic acids, from phthalic anhydride via the corresponding alkylmetal[29] or the Friedel-Crafts reaction,[30] coupled with this simple inter- or intramolecular reduction, provides convenient general syntheses of chiral 3-alkyl- and 3-arylphthalides, respectively, in ≥96% ee. Substitutions in the aromatic rings on either side of the carbonyl moiety should not affect the chiral outcome. The ready availability of both isomers of α-pinene and the commercial availability of the reagent makes this procedure one of the more convenient general syntheses of the antipodes of 3-substituted isobenzofuranones. We are currently studying the intramolecular reductions of α- and β-keto acids with **1** and **2**.

Reduction of methyl o-acylbenzoates with ^{d}Ipc$_2$BCl. All operations were carried out under a nitrogen atmosphere.[31] The preparation of *S*-**5** is representative. An oven-dried, 50 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. ^{d}Ipc$_2$BCl (7.1 g, 22 mmol) was transferred to the flask in a glove bag, dissolved in EE (25 mL) and cooled to –25 °C. Methyl *o*-valerylbenzoate[29] (4.4 g, 20 mmol) was added, dropwise, to this solution and the reaction was followed by ^{11}B NMR spectroscopy (δ 74 corresponding to the reagent and δ 42 corresponding to the intermediate). Upon completion of the reaction (8 h), the usual diethanolamine workup[22] provided the crude product which was purfied by column chromatography (silica, EE:hexane 2:8) to provide 3.5 g (91%) of a colorless liquid, $[\alpha]_D^{21}$ –62.0 (*c* 4.2, $CHCl_3$) (lit.[19b] $[\alpha]_D^{24}$ +62.7 (*c* 1.2, $CHCl_3$) for 94% ee, (*S*)) . GC analysis of this lactone on a Chiraldex-GTA capillary column revealed an ee of 99%. The structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

Reduction of o-acyl benzoic acids with ^{d}Ipc$_2$BH. The preparation of *R*-**6** is as follows. A solution of *o*-benzoylbenzoic acid (2.3 g, 10.0 mmol) in 10 mL THF was added dropwise to ^{d}Ipc$_2$BH (3.1 g, 11 mmol) in 10 mL THF at 0 °C, and warmed to rt. Hydrogen evolution (one equiv) ceased after one h and the ^{11}B NMR spectrum of the solution showed two singlets at δ 52 and 32, the latter corresponding to the product. After the completion of the reaction (3 h), 10 mL of 3N NaOH was added, followed by 5 mL of 30% H_2O_2 and

stirred for 3 h. The organics were removed with EE (2x15 mL). The aqueous portion was layered with CH_2Cl_2 (20 mL) and 0.3 g (1mmol) of benzyltriethylamine chloride was added, followed by the dropwise addition of excess dimethylsulfate and stirred for 2 h. The organic layer was then washed with water (2x10 mL) and brine (2x10 mL), dried over $MgSO_4$ and chromatographed over silica (1:1 CH_2Cl_2:hexane) to obtain 1.5 g (71%) of the lactone. mp. 152 °C; $[\alpha]_D^{22}$ –48.6 (*c* 2.1, $CHCl_3$) (lit.[18] $[\alpha]_D^{22}$ + 37.9 (*c* 4.3, $CHCl_3$) for 70% ee in the *S*-isomer). The above phthalide was reduced with $LiAlH_4$ and the bis-MTPA ester was prepared using a literature procedure,[26] and analyzed using ^{19}F NMR to reveal an ee of ≥96% in the (*R*)-isomer.[28]

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28. The ^{19}F NMR spectum of the bis-MTPA ester of the racemic diol shows 4 peaks at δ 72.61, 72.75, 72.90 and 73.02. The di-ester of the reduction product shows only two peaks at δ 72.61 and 72.90, corresponding to the *R*-isomer as determined by comparing the rotation with that reported in the literature. To be within the margin of error allowed in analyses using NMR spectroscopy, we report ≥96% ee.
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