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Nucleophilic Displacement at Benzhydryl Centers: Asymmetric Synthesis of 1,1-Diarylalkyl Derivatives

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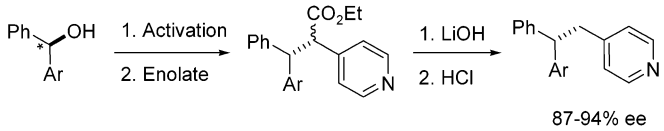
ABSTRACT

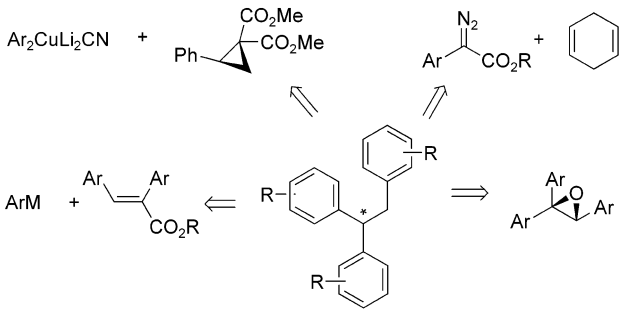


Activation of substituted 1,1-diarylmethanols as their corresponding toluenesulfonates and subsequent displacement with a range of carbon, nitrogen, oxygen, and sulfur nucleophiles proceeds in 81–96% yield. Enantiomerically enriched diarylmethanols 8a–c were activated and displaced with pyridine acetate enolate with complete stereochemical inversion at carbon to yield 1,1-diarylalkyl derivatives 10a–c without loss of optical purity.

Substituted 1,1-diarylalkyl derivatives form the core structure of a number of pharmacologically active compounds. For example, the 1,1-diarylalkyl structural element is found in compounds with reported activity as antimuscarinics,[1] antidepressants,[2] and endothelin antagonists.[3] As such, there is a need for practical synthetic methodologies for the preparation of a wide variety of compounds of this type, especially in optically pure form.

The asymmetric synthesis of the 1,1-diarylalkyl skeleton poses some interesting challenges. Reported syntheses include methods based on asymmetric epoxidation of a trisubstituted alkene or chiral sulfur-ylide,[4] catalytic asymmetric C−H insertion of rhodium carbenoids derived from aryl diazoacetates into cyclohexadienes,[5] aryl cuprate addition to chiral cyclopropane dicarboxylates,[6] and diastereoselective and enantioselective conjugate addition of organometallic reagents to cinnamate derivatives[7] (Scheme 1).

Scheme 1. Synthetic Approaches to 1,1-Diarylalkyl Derivatives



Our interest in this structural motif originated from the discovery of CDP-840[8] and compound **I**[9] as potent and

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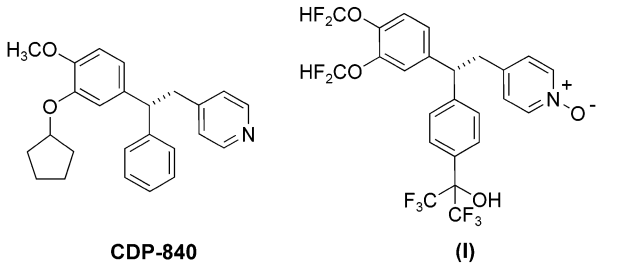
selective phosphodiesterase IV (PDE-IV) inhibitors (Figure 1). Selective PDE-IV inhibitors are currently under investigation as potential therapeutic agents for the treatment of asthma and chronic obstructive pulmonary disease (COPD), and a number of these compounds have entered clinical trials.[10]



CDP-840 (I)

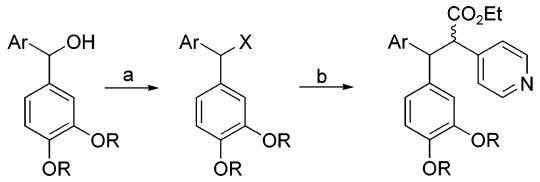
Figure 1. PDE-IV Inhibitors.

We sought to develop a practical methodology that would allow access to a large number of racemic analogues of **I** that also had the potential to be developed into an asymmetric synthesis. We reasoned that a protocol based on nucleophilic displacement of suitably activated benzhydryl alcohol derivatives could provide access to a wide variety of 1,1-diaryl substituted products in a minimal number of steps from readily available, simple starting materials. With the exception of bromides and chlorides, the synthetic utility of activated benzhydryl derivatives has received scant attention in the literature. This may be a consequence of the general expectation that diaryl-substituted electrophiles may be exceedingly prone to ionization, racemization, and decomposition and therefore not synthetically useful.

In this communication, we describe our efforts to identify a suitable leaving group and develop a synthetic methodology for the rapid synthesis of 1,1-diarylalkyl derivatives in both racemic and enantioenriched form.

We initially focused our efforts on developing a suitable electrophile for alkylation by the lithium enolate of ethyl 4-pyridyl acetate using 1,1-diarylmethanols such as **1** (Scheme 2). Although racemic chloride and bromide derivatives **2a** were previously demonstrated to be reasonably good substrates for nucleophilic displacement with pyridinyl enolates,[9,11] our attempts to prepare chlorides and bromides from the corresponding optically enriched alcohols were unsuccessful because of extensive racemization during their formation. Other activating groups were thus screened. Phosphate leaving groups **2b** (R= Et, *i*-Pr) could be readily prepared but were unreactive toward lithium enolates. Attempted preparation of methanesulfonate **2c** using methanesulfonyl chloride led exclusively to the corresponding chloride, while use of methanesulfonic anhydride led to decomposition of the starting benzhydrol. Similarly, attempts

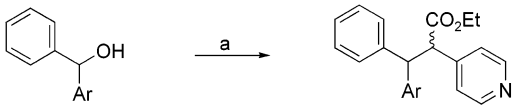
Scheme 2 [a]



1: R = CF_2H **2a**: X=Br, Cl **2b**: X=OP(O)(OR)$_2$ **2c**: X=OMs **2d**: X=OTs **3**

[a] Conditions: (a) Activation. (b) Ethyl 4-pyridylacetate, LiN(SiMe$_3$)$_2$, THF, DMPU, −40 °C.

Table 1. Displacement of Benzhydrol Toluenesulfonates with Lithium Enolate of Ethyl 4-Pyridyl Acetate[a]



4a-k **5a-k**

entry	Ar	product	yield (%)
1	4-MeOC$_6$H$_4$	**5a**	68
2	3-MeOC$_6$H$_4$	**5b**	73
3	2-MeOC$_6$H$_4$	**5c**	15
4	3,5-MeOC$_6$H$_3$	**5d**	28
5	C$_6$H$_5$	**5e**	76
6	4-CF$_3$C$_6$H$_4$	**5f**	74
7	3-CF$_3$C$_6$H$_4$	**5g**	68
8	2-CF$_3$C$_6$H$_4$	**5h**	<5
9	3,5-CF$_3$C$_6$H$_3$	**5i**	94
10	3,4-MeOC$_6$H$_3$	**5j**	<5
11	3,4-HCF$_2$OC$_6$H$_3$	**5k**	73

[a] Conditions: (a) *n*-BuLi or LiN(SiMe$_3$)$_2$, THF, −78 °C; Ts$_2$O, THF; ethyl 4-pyridyl acetate, LiN(SiMe$_3$)$_2$, THF, DMPU, −40 °C.

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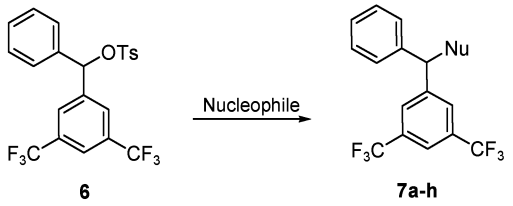
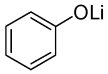
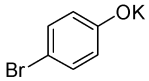
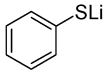
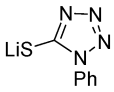
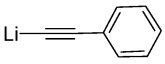
Table 2. Displacement of Benzhydrol Toluenesulfonate **6** with Various Nucleophiles



6 **7a-h**

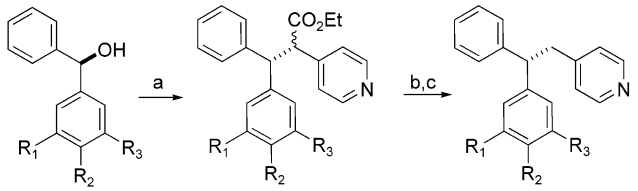
entry	nucleophile[13]	7	yield (%)
1		**7a**	81[a]
2		**7b**	88[a]
3		**7c**	95
4	NaSCN	**7d**	87[b]
5		**7e**	98
6	$LiCH_2CN$	**7f**	82
7		**7g**	95
8	NaN_3	**7h**	96[b]

[a] Additives: 15-crown-5 (6.5 equiv) and CH_3CN (0.06 M). [b] Additive: 15-crown-5 (6.5 equiv).

to prepare toluenesulfonate **2d** using *p*-toluenesulfonyl chloride were unsuccessful.[12] We were thus delighted to find that treatment of a lithium alkoxide of **1** in THF at −78 °C with *p*-toluenesulfonic anhydride (Ts_2O) followed by addition of the lithium enolate of ethyl 4-pyridyl acetate gave the desired displacement product **3** in ∼90% yield.

To further explore this chemistry, a series of benzhydrols **4a**−**k** containing both electron-donating and electron-withdrawing substituents were prepared. Activation as toluenesulfonates and nucleophilic displacement with the lithium enolate of ethyl 4-pyridyl acetate gave adducts **5a**−**k** (Table 1).

Table 3. Nucleophilic Displacement of Optically Enriched Benzhydryl Toluenesulfonates[a]



8a: R_1,R_3 = CF_3, R_2 = H **9a-c** **10a-c**
8b: R_1 = H, R_2, R_3 = OCF_2H
8c: R_1, R_2 = Cl, R_3 = H

entry	8	ee (%)	10	ee (%)	yield (%)
1	**8a**	87	**10a**	87	93
2	**8b**	91	**10b**	91	81
3	**8c**	94	**10c**	94	94

[a] Conditions: (a) $LiN(SiMe_3)_2$, THF, −78 °C; Ts_2O, THF, −20 °C; ethyl 4-pyridyl acetate, $LiN(SiMe_3)_2$, THF, DMPU, −20 °C. (b) LiOH, MeOH, THF, H_2O, 60 °C. (c) 6 N HCl, rt.

In general, electron-donating and withdrawing substituents are well tolerated. However, substituents in the ortho position (entries 3, 8) gave lower yields, presumably due to steric hindrance. The reaction proved to be more difficult on substrates with electron-donating groups in both the 3,5-positions (entry 4), suggesting a problem with the stability of the tosylate intermediate. By comparison, substrates with electron-withdrawing groups in the same positions gave the desired product in 94% yield (entry 9). Interestingly, replacing electron-donating 3,4-methoxy groups with 3,4-difluoromethoxy groups increased the yield from <5% to 73% (entries 10, 11).

In an effort to determine the scope and limitations of the reaction, we investigated the displacement of 3,5-bis(trifluoromethyl)phenylmethyltoluenesulfonate with a range of nucleophiles (Table 2).

Thus, treatment of toluenesulfonate **6** with phenoxide, thiolate, lithiated acetonitrile, and acetylide nucleophiles gave the expected products **7a**−**h** in uniformly excellent yields. By comparison, a number of nitrogen nucleophiles were screened and only azide ion gave the desired product (Table 2, entry 8). No reaction was observed when primary or secondary amines were used as nucleophiles.[14]

Finally, we investigated the activation and displacement of optically enriched substituted benzhydrols. Diarylmethanols **8a**−**c** were conveniently prepared by the catalyzed addition of diphenylzinc to the corresponding aldehydes in the presence of a chiral ferrocene ligand as described by Bolm et al.[15] The treatment of secondary lithium alkoxides

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(13) In the cases of heteroatom nucleophiles, the reaction mixture was heterogeneous after their addition. Addition of 15-crown-5 (in conjunction with CH_3CN for phenoxides) improved the solubility and in all cases significantly increased the yield of the reaction.

(14) When tosylate **6** was treated with the lithium anion of either aniline, *n*-butylamine, or indole, the corresponding ketone product was obtained, presumably via abstraction of the benzylic proton and elimination of toluenesulfinate anion. The use of less basic phthalimide anions resulted in recovery of starting materials.

of **8a**−**c** with *p*-toluenesulfonic anhydride followed by addition of the lithium enolate of ethyl 4-pyridyl acetate led to the expected ester products **9a**−**c** in excellent yields. Ester hydrolysis with lithium hydroxide and decarboxylation upon treatment with aqueous 6 N HCl gave the corresponding 1,1-diarylalkylpyridines **10a**−**c** in excellent overall yield with no loss of optical purity across the entire sequence as verified by chiral HPLC (Table 3).[16] The stereochemical outcome of the nucleophilic displacement was confirmed by single-crystal X-ray crystallographic analysis of alcohol **8c** and pyridine **10c** as its bisulfate salt.

In summary we have developed a practical methodology for the preparation of a variety of 1,1-diaryl-substituted products in racemic or enantioenriched form via nucleophilic displacement of activated benzhydryl derivatives. We are currently investigating the mechanism of the nucleophilic displacement and the displacement of optically enriched benzhydryls with heteroatom-based nucleophiles.

Acknowledgment. The authors wish to thank Mr. Philippe Dagneau and Dr. Xin Wang for preliminary experiments.

Supporting Information Available: Experimental procedures and characterization data for compounds **5a**,**b**,**d**−**g**,**i**,**k**, **7a**−**k**, **8a**−**c**, and **10a**,**b** and X-ray crystallographic data for compounds **8c** and **10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **Typical Procedure.** To a solution of alcohol **8c** (331 mg, 1.31 mmol, 94% ee) and (4-phenylazo)diphenylamine indicator (4 mg, 0.0131 mmol) in THF (3.3 mL) at −78 °C under N_2 was added dropwise $LiN(SiMe_3)_2$ (1.4 mL, 1.4 mmol, 1M in THF) until the solution turned deep pink. The solution was aged at −78 °C for 10 min, and a solution of Ts_2O (513 mg, 1.57 mmol) in THF (3.6 mL) was added dropwise. The reaction mixture was warmed to −20 °C and aged for 1.5 h. In a separate flask, a solution of ethyl 4-pyridyl acetate (1.08 g, 6.55 mmol) in THF (6.6 mL) and DMPU (2.2 mL) was cooled to −50 °C, and $LiN(SiMe_3)_2$ (6.4 mL, 6.4 mmol, 1 M in THF) was added dropwise. The enolate mixture was warmed to −30 °C and aged for 1 h prior to its transfer via cannula to the flask containing the toluenesulfonate. The reaction mixture was aged at −25 °C for 16 h, quenched with 1 N HCl (10.5 mL, 10.5 mmol), and extracted with toluene (30 mL). The organic layer was washed with water (5 × 10 mL) and concentrated. The residue was diluted with THF/MeOH/H_2O (24 mL:8 mL:8 mL), and 2 N LiOH (6 mL, 11.79 mmol) was added. The green reaction mixture was heated to 60 °C under N_2 for 2.5 h. After cooling to room temperature, the solution was acidified to pH 1.5 with 6 N HCl (∼5 mL). The volatiles were removed under reduced pressure, and the residue was basified with 5 N NaOH (∼ 5 mL) and extracted with MTBE (30 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:1) to afford pyridine **10c** as a clear oil (403 mg, 94% yield, 94% ee): $[\alpha]^{20}_D$ −18.9 (*c* 8.9, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, 2H, J = 1.5, 4.5 Hz), 7.33−7.27 (m, 4H), 7.24−7.20 (tm, 1H, J = 7.3 Hz), 7.15 (m, 2H), 7.01 (dd, 1H, J = 2.1, 8.3 Hz), 6.92 (m, 2H), 4.19 (t, 1H, J = 7.9 Hz), 3.34 (dd, 1H, J = 13.7, 7.9 Hz), 3.29 (dd, 1H, J = 13.7, 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 148.1, 143.7, 142.0, 132.2, 130.2, 129.5, 128.5, 127.5, 127.1, 126.8, 124.1, 50.9, 40.7; IR (neat, cm^{-1}) 3065, 3030, 2945, 1602, 1471, 1135, 1031, 803; LRMS calcd for $C_{19}H_{15}Cl_2N$ 327.06, found 328.0 [M + 1]; chiral SFC−HPLC Chiralpak OD 250 × 4.6 mm column, gradient 5−15% MeOH at 1%/min, 2.0 mL/min, 300 bar, λ = 215 nm, 35 °C; $t_{r\ minor}$ = 14.5 min, $t_{r\ major}$ = 15.1 min (94% ee).