N-Aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides: K_{ATP} Potassium Channel Openers. Modifications on the Western Region

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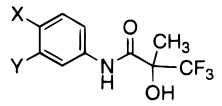
A subset of antiandrogen compounds, the *N*-aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides **1**, were found to activate ATP sensitive potassium channels (K_{ATP}) and represent a new class of potassium channel openers (PCOs). A structure−activity relationship was carried out on the western region of this series with the goal of obtaining an activator of the ATP sensitive potassium channel suitable for use in the treatment of urge urinary incontinence. In particular three large 4-(*N*-aryl) substituents, the (*N*-phenyl-*N*-methylamino)sulfonyl, benzoyl, and 4-pyridylsulfonyl moieties, yielded non-antiandrogen, K_{ATP} potassium channel openers (**39**, **41**, and **64**, respectively) that are bladder selective in an *in vivo* rat model that simultaneously measures bladder contractions, heart rate, and blood pressure. Substitutions of the aryl rings of **41** and **64** gave several derivatives that also display selectivity in the *in vivo* rat model; however, none appear to offer a substantial advantage over **41** and **64**. The PCO activity of **41** and **64** resides in the (*S*)-(−) enantiomers. ZD6169, **41(S)**, has been selected into development for the treatment of urge urinary incontinence.

Introduction

Some members of a series of potent antiandrogen[1,2] *N*-aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides **1** were found to possess undesirable hypotensive activity. It has recently been reported that the hypotensive activity of those compounds is most likely attributable to the opening of ATP sensitive potassium channels, and therefore these agents represent a novel class of potassium channel openers (PCOs).[3−5]

PCOs hyperpolarize smooth muscle cells by increasing membrane potassium ion permeability, thereby preventing the influx of Ca^{2+} through voltage-operated Ca^{2+} channels and thus relaxing smooth muscle. Several therapeutic areas where such a mechanism is of proven or potential utility include hypertension, male pattern baldness, asthma, and urinary incontinence.[6] Potassium channel openers currently used in the clinic as antihypertensive agents, such as pinacidil and minoxidil, and those compounds that have proven thus far to be the most useful pharmacological tools apparently act through a mechanism involving the activation of a specific channel, the ATP dependent potassium channel (K_{ATP}).[7]

The work reported in this and a forthcoming paper explores the K_{ATP} PCO structure−activity relationship (SAR) of the series **1** with the goal of obtaining derivatives suitable for use in urge urinary incontinence (UI).



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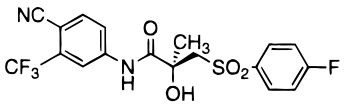

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The PCO cromakalim has been reported to show encouraging results in a small UI trial,[8,9] indicating that PCOs may be effective in urinary incontinence although the potent vasodilator properties seen with cromakalim may preclude its use for this disorder. Thus for a UI application both the potent hypotensive and antiandrogen activities of **1** are anticipated to be deleterious. Fortunately, the SAR for antiandrogen activity and the PCO SAR were found to diverge in two important apparently sterically regulated aspects. Firstly, the antiandrogen SAR has a less restrictive steric requirement in the "eastern" region of the molecule [i.e. the antiandrogen CASODEX (bicalutamide) **2** has neither PCO nor hypotensive activity]. Secondly, the PCO SAR has a less restrictive steric requirement in the "western" region of the molecule (i.e. the PCO **3** is not an antiandrogen as determined by measuring its effect on rat seminal vesicle weight in comparison with the standard antiandrogen flutamide). However, **3** displays no selectivity for the bladder over the cardiovascular system effects as determined in an *in vivo* rat model that simultaneously measures cardiovascular and bladder effects (normotensive conscious rat bladder model).[10,11] In this paper we present our work on the PCO SAR of the western region in a series of *N*-aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides related to **3** and our search for derivatives with *in vivo* selectiv-

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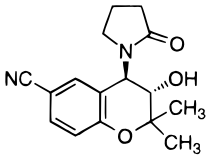
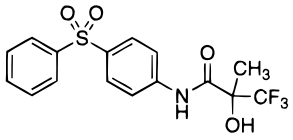
ity for the bladder versus the vasculature. A separate paper will present our work on the eastern region.



cromakalim



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Chemistry

The synthesis of most of the novel *N*-aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides described in this paper (see Table 1) was achieved through the coupling of the appropriate arylamine and 3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid using the thionyl chloride−dimethylacetamide method described by Morris et al.[2] (method A1, Scheme 1). Several other variants were employed where this standard method proved deficient (methods A2 and A4, see the Experimental Section). Several *N*-(4-(arylsulfonyl)aryl)-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides (Table 1) were prepared by the permanganate oxidation of the corresponding sulfide (method B, Scheme 1). Several hydroxy-substituted *N*-aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides were prepared by the action of boron tribromide on the corresponding methoxy derivative (method C, see the Experimental Section).

Most of the novel sulfide and sulfone aniline precursors were prepared using standard synthetic methods and following the routes described in Scheme 2. Several of the novel 4-aminobenzophenones were prepared essentially by a method described by Staskum[12] (method F, Scheme 2).

Resolutions of two compounds of particular interest, **41** and **64**, were carried out via flash column chromatographic separation and saponification of the camphanic and Mosher's esters, respectively. The PCO activity resides in the (−) enantiomers, which were shown to be of the (*S*) configuration by X-ray crystallography. Compounds **41(S)** and **64(S)** were also prepared by method A1 employing (*S*)-(−)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid. The required (*S*)-(−)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid was obtained with approximately 20% recovery by multiple recrystallization of racemic acid·(*S*)-(−)-α-methylbenzylamine salt from either 2.5% ethanol in toluene or 10% 1-butanol in toluene. The absolute stereochemistry of the obtained (−) acid was determined to be (*S*) by further conversion to **41(S)** and **64(S)**. As noted above, the stereochemistry of **41(S)** and **64(S)** was determined by X-ray crystallography. A resolution of 2-hydroxy-2-(trifluoromethyl)propionic acid using brucine as the amine was previously reported to give very low yields of the resolved acids.[13]

Pharmacological Results and Discussion

The pharmacological characterization of selected members of the series as K_{ATP} PCOs was carried out essentially as reported previously.[3] Compounds **3, 41**, and **64** relaxed bladder strips contracted with 15 mM KCl,[14] and the relaxation was antagonized in a surmountable manner by glibenclamide, a relatively selective blocker of K_{ATP}. Consistent with a PCO mechanism, **3, 41**, and **64** displayed only weak activity against guinea pig detrusor strip contracted with 80 mM KCl, a profile of action similar to that seen with cromakalim. Furthermore **3, 41**, and **64** were shown to increase the rate of $^{42}K^+$ efflux from detrusor smooth muscle. Glibenclamide was also shown to antagonize the drug-induced increase in $^{42}K^+$ efflux.

The *N*-aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides were initially tested in the 15 mM KCl depolarized isolated guinea pig detrusor strip model.[14] In this screen the PCOs cromakalim and **3** are essentially equipotent. Compounds that showed potency in the 15 mM KCl depolarized isolated guinea pig detrusor strip model at least in the order of 0.1−0.2 times cromakalim's potency were further evaluated in a rat blood pressure (bp) model in normotensive rats or directly into a normotensive conscious rat bladder model.[10,11] Compounds active in lowering bp in the rat bp model were not taken forward into the normotensive conscious rat bladder model.

The initial synthetic effort to obtain bladder selectivity concentrated on lowering the lipophilicity of **3** with the view that less lipophilic compounds would be more likely to be rapidly excreted via the urine and therefore have a greater chance of showing bladder selectivity. For that reason the saccharine analogs **72** and **73** were prepared; however **72** has an IC_{50} greater than 30 μM in the 15 mM KCl depolarized isolated guinea pig detrusor strip model and **73** has an IC_{50} of 26 μM (Table 2).

A series of heterocyclic derivatives of **3** (Ar^1 ring varied; Table 1, **62**−**69**) was also prepared from which **64** (Ar^1 ring = 4-pyridyl) proved to be selective in the normotensive conscious rat bladder model (Table 3). The reason for the bladder selectivity of **64** versus **3** cannot be explained by lowered lipophilicity as the positional isomer **63** (Ar^1 ring = 3-pyridyl; **64** Ar^1 ring = 4-pyridyl), which has a nearly identical IC_{50} in the 15 mM KCl depolarized isolated guinea pig detrusor strip model, has both cardiovascular and bladder effects in the normotensive conscious rat bladder model (Table 3). The mechanism behind the bladder selectivity of **64** is currently unknown, although we expect that pharmacokinetics are responsible for the selectivity. In support of this view is the observation that **64** has relatively potent activity in an isolated guinea pig portal vein model[14] (Table 2) and thus is not tissue selective *in vitro*.

The 3-phenylsulfonyl analog **4** has an $IC_{50} > 30$ μM in the 15 mM KCl depolarized isolated guinea pig detrusor strip model; however the addition of the small electron-withdrawing cyano group in the 4-position gave an active compound **10** ($IC_{50} = 2.6$ μM) while the larger 4-nitro derivative **34** was also $IC_{50} > 30$ μM. That the activity of **10** was largely due to the small 4-electron-withdrawing group (EWG) is illustrated by the fact that the 3-phenylsulfide 4-cyano derivative **11** and the 3-phenylsulfide 4-nitro derivative **35** have IC_{50}s of 8.3 and 16 μM, respectively, in the 15 mM KCl depolarized isolated guinea pig detrusor strip model. As it was anticipated that a large group in the western region is required to exclude antiandrogen activity and 3-large substituent 4-small EWG derivatives offered limited scope for synthetic manipulation, this line of exploration was not carried further.

The effect of the substitution of alternate large EWGs for the 4-phenylsulfonyl group of **3** was also examined. The benzoyl group appeared to be an appropriate replacement both electronically and sterically, and

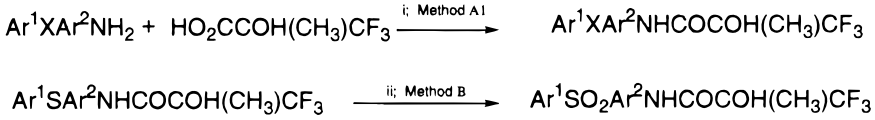
Table 1. Structures, Physical Properties, and Activities of *N*-Aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides in 15 mM KCl Depolarized Isolated Guinea Pig Detrusor Strip Model

Ar^1-X-Ar^2-NHCOCOH(CH_3)CF_3

compd	Ar^1	X	Ar^2	% yield (method)	precursor	mp (°C)	formula	anal.[a]	IC_{50} GP bladder strip[14]
3	C_6H_5	SO_2	4-C_6H_4	93 (A1)	ref 15	164−6	$C_{16}H_{14}F_3NO_4S$	C,H,N	0.47 ± 0.12
4	C_6H_5	SO_2	3-C_6H_4	60 (A1)	purchased	145−7	$C_{16}H_{14}F_3NO_4S$	C,H,N	>30
5	C_6H_5	SO_2	4-(3-FC_6H_3)	68 (A1)	**113**[b]	147−9	$C_{16}H_{13}F_4NO_4S$	C,H,N	1.8 ± 0.5
6	2-FC_6H_4	SO_2	4-C_6H_4	82 (A1)	ref 16	133−35	$C_{16}H_{13}F_4NO_4S$	C,H,N	1.3 ± 0.3
7	3-FC_6H_4	SO_2	4-C_6H_4	73 (A1)	ref 16	147−8	$C_{16}H_{13}F_4NO_4S$	C,H,N	3.4 ± 0.9
8	4-FC_6H_4	SO_2	4-C_6H_4	71 (A1)	ref 16	168−70	$C_{16}H_{13}F_4NO_4S$	C,H,N	8.6 ± 2.0
9	C_6H_5	SO_2	4-(3-CNC_6H_3)	75 (B)	**78**[c]	163−5	$C_{17}H_{13}F_3N_2O_4S$	C,H,N	3.8 ± 1.9
10	C_6H_5	SO_2	3-(4-CNC_6H_3)	85 (B)	**11**	185−7	$C_{17}H_{13}F_3N_2O_4S$	C,H,N	2.6 ± 0.6
11	C_6H_5	S	3-(4-CNC_6H_3)	91 (A1)	**115**[b], expt	111−3	$C_{17}H_{13}F_3N_2O_2S$	C[d],H,N	8.3 ± 1.5
12	2-CNC_6H_4	SO_2	4-C_6H_4	72 (A1)	**116**[b], expt	156−8	$C_{17}H_{13}F_3N_2O_4S$[e]	C,H,N	1.1 ± 0.1
13	4-CNC_6H_4	SO_2	4-C_6H_4	63 (A1)	ref 17	194−6	$C_{17}H_{13}F_3N_2O_4S$	C,H,N	>30
14	C_6H_5	SO_2	4-(3-HOC_6H_3)	46 (C)	**18**	155−6	$C_{16}H_{14}F_3NO_5S$	C,H,N	0.43 ± 0.12
15	2-HOC_6H_4	SO_2	4-C_6H_4	77 (C)	**19**	184−6	$C_{16}H_{14}F_3NO_5S$	C,H,N	3.09 ± 0.57
16	3-HOC_6H_4	SO_2	4-C_6H_4	78 (C)	**20**	164−7	$C_{16}H_{14}F_3NO_5S$[e]	C,H,N	18 ± 4.8
17	4-HOC_6H_4	SO_2	4-C_6H_4	81 (C)	**21**	207−10	$C_{16}H_{14}F_3NO_5S$[e]	C,H,N	>30
18	C_6H_5	SO_2	4-(3-$CH_3OC_6H_3$)	82 (A1)	**117**[b]	202−4	$C_{17}H_{16}F_3NO_5S$	C,H,N	5.9 ± 0.8
19	2-$CH_3OC_6H_4$	SO_2	4-C_6H_4	69 (A1)	**118**[b]	209−11	$C_{17}H_{16}F_3NO_5S$	C,H,N	1.6 ± 0.3
20	3-$CH_3OC_6H_4$	SO_2	4-C_6H_4	90 (A1)	**119**[b]	147−8	$C_{17}H_{16}F_3NO_5S$	C[f],H,N	16 ± 3.0
21	4-$CH_3OC_6H_4$	SO_2	4-C_6H_4	82 (A1)	ref 18	162−4	$C_{17}H_{16}F_3NO_5S$	C,H,N	>30
22	C_6H_5	SO_2	4-(3-ClC_6H_3)	94 (A1)	ref 19	141−3	$C_{16}H_{13}ClF_3NO_4S$	C[g],H,N	2.2 ± 0.5
23	2-ClC_6H_4	SO_2	4-C_6H_4	94 (A1)	ref 20	136−8	$C_{16}H_{13}ClF_3NO_4S$	C,H,N	2.3 ± 0.7
24	3-ClC_6H_4	SO_2	4-C_6H_4	58 (A1)	purchased	154−6	$C_{16}H_{13}ClF_3NO_4S$	C[h],H,N	10 ± 3.5
25	C_6H_5	SO_2	4-(3-$CH_3C_6H_3$)	82 (A1)	**120**[b], expt	141−3	$C_{17}H_{16}F_3NO_4S$	C,H,N	1.6 ± 0.4
26	2-$CH_3C_6H_4$	SO_2	4-C_6H_4	77 (A1)	ref 20	126−8	$C_{17}H_{16}F_3NO_4S$	C,H,N	5.1 ± 1.9
27	3-$CH_3C_6H_4$	SO_2	4-C_6H_4	74 (A1)	**121**[b]	164−6	$C_{17}H_{16}F_3NO_4S$	C,H,N	2.2 ± 0.5
28	4-$CH_3C_6H_4$	SO_2	4-C_6H_4	42 (A1)	purchased	155−8	$C_{17}H_{16}F_3NO_4S$	C,H,N	>30
29	4-BrC_6H_4	SO_2	4-C_6H_4	71 (A1)	purchased	193−5	$C_{16}H_{13}BrF_3NO_4S$	C,H,N	>30
30	C_6H_5	SO_2	4-(3-$CF_3C_6H_3$)	69 (A1)	**122**[b]	175−6	$C_{17}H_{13}F_6NO_4S$	C[i],H,N	>30
31	3-$CF_3C_6H_4$	SO_2	4-C_6H_4	85 (A1)	**123**[b]	149−50	$C_{17}H_{13}F_6NO_4S$	C,H,N	>30
32	C_6H_5	SO_2	4-(2-$NO_2C_6H_3$)	17 (A2)	ref 21	191−2.5	$C_{16}H_{13}F_3N_2O_6S$	C,H,N	7.9 ± 2.0
33	C_6H_5	SO_2	4-(3-$NO_2C_6H_3$)	84 (B)	**79**[c]	135−8	$C_{16}H_{13}F_3N_2O_6S$	C[j],H,N	>30
34	C_6H_5	SO_2	3-(4-$NO_2C_6H_3$)	81 (B)	**35**	170−2	$C_{16}H_{13}F_3N_2O_6S$	C,H,N	>30
35	C_6H_5	S	3-(4-$NO_2C_6H_3$)	43 (A1)	ref 22	165.5−7.5	$C_{16}H_{13}F_3N_2O_4S$	C,H,N	16 ± 2
36	4-$NO_2C_6H_4$	SO_2	4-C_6H_4	39 (A3)	purchased	213−5	$C_{16}H_{13}F_3N_2O_6S$	C,H,N	>30
37	C_6H_5	SO_2	4-(2-$HO_2CC_6H_3$)	10	**125**[b]	218−20	$C_{17}H_{14}F_3NO_6S$	C,H,N	>30
38	C_6H_5	SO_2	4-(3-$HO_2CC_6H_3$)	56 (B)	**80**[c]	197−9	$C_{17}H_{14}F_3NO_6S$[k]	C,H,N	>30
39	$C_6H_5CH_3N$	SO_2	4-C_6H_4	59 (A1)	ref 23	147−9	$C_{17}H_{17}F_3N_2O_4S$	C,H,N	2.0 ± 0.5
40	$(C_6H_5)_2N$	SO_2	4-C_6H_4	50 (A4)	see expt	217−20	$C_{22}H_{19}F_3N_2O_4S$	C,H,N	>30
41	C_6H_5	C=O	4-C_6H_4	86 (A1)	purchased	151−3	$C_{17}H_{14}F_3NO_3$	C,H,N	3.8 ± 1.6
41(S)	C_6H_5	C=O	4-C_6H_4	see expt.		171−3	$C_{17}H_{14}F_3NO_3$	C,H,N	1.6 ± 0.2
41(R)	C_6H_5	C=O	4-C_6H_4	see expt.		172−3	$C_{17}H_{14}F_3NO_3$	C,H,N	>30
42	C_6H_5	C=$NOCH_3$	4-C_6H_4	58	**41**	119−30	$C_{18}H_{17}F_3N_2O_3$[e]	C,H,N	>30
43	C_6H_5	C=O	4-(2-FC_6H_3)	63 (A1)	**133**[b]	138−9	$C_{17}H_{13}F_NO_3$	C,H,N	11 ± 1
44	C_6H_5	C=O	4-(3-FC_6H_3)	80 (A1)	**134**[b]	132−4	$C_{17}H_{13}F_4NO_3$	C,H,N	2.7 ± 0.7
45	2-FC_6H_4	C=O	4-C_6H_4	75 (A1)	**135**[b]	141−2	$C_{17}H_{13}F_4NO_3$	C,H,N	2.3 ± 0.5
46	3-FC_6H_4	C=O	4-C_6H_4	63 (A1)	**136**[b], expt	121−3	$C_{17}H_{13}F_4NO_3$	C,H,N	2.6 ± 1.0
47	4-FC_6H_4	C=O	4-C_6H_4	58 (A1)	ref 12	131−3	$C_{17}H_{13}F_4NO_3$	C,H,N	14 ± 2
48	C_6H_5	C=O	4-(2-CNC_6H_3)	35 (A5)	**139**[b]	202−4	$C_{18}H_{13}F_3N_2O_3$[e]	C,H,N	3.8 ± 0.9
49	C_6H_5	C=O	4-(2-HOC_6H_3)	52 (A1)	ref 24	119−21	$C_{17}H_{14}F_3NO_4$		15 ± 5
50	C_6H_5	C=O	4-(3-HOC_6H_3)	71 (A1)	ref 25	173−5	$C_{17}H_{14}F_3NO_4$	C,H,N	4.2 ± 0.6
51	C_6H_5	C=O	4-(2-$CH_3OC_6H_3$)	46 (A1)	ref 26	126−8	$C_{18}H_{16}F_3NO_4$[l]	C,H,N	6.1 ± 1.4
52	C_6H_5	C=O	4-(2-ClC_6H_3)	43 (A1)	ref 26	142−4	$C_{17}H_{13}F_3ClNO_3$	C,H,N	>30
53	3-ClC_6H_4	C=O	4-C_6H_4	78 (A1)	ref 12	52−4	$C_{17}H_{13}ClF_3NO_3$	C,H,N	>30
54	C_6H_5	C=O	4-(2-$CH_3C_6H_3$)	63 (A1)	ref 27	123−4	$C_{18}H_{16}F_3NO_3$	C,H,N	5.0 ± 1.3
54(S)	C_6H_5	C=O	4-(2-$CH_3C_6H_3$)	36 (A1)	ref 27	60−2	$C_{18}H_{16}F_3NO_3$[l]	C,H,N	2.6 ± 0.8
55	3-$CH_3C_6H_4$	C=O	4-C_6H_4	76 (A1)	**140**[b]	51−3	$C_{18}H_{16}F_3NO_3$[m]	C,H,N	>30
56	C_6H_5	C=O	4-(2,6-$(CH_3)_2C_6H_2$)	62 (A4)	ref 28	156−9	$C_{19}H_{18}F_3NO_3$		>30
57	C_6H_5	C=O	4-(2-BrC_6H_3)	38 (A1)	**141**[b]	138−40	$C_{17}H_{13}BrF_3NO_3$	C,H,N	>30
58	C_6H_5	CHOH	4-C_6H_4	75[n]	**41**	144.5−6.5	$C_{17}H_{16}F_3NO_3$	C,H,N	>30
59	10,10-dioxy-9-oxo-9*H*-thioxanthen-3-yl			43 (A1)	**142**[b]	246−48	$C_{17}H_{12}F_3NO_5S$	C,H,N	>30
60	5,5-dioxydibenzothiophen-2-yl			37 (A1)	purchased	269−70	$C_{16}H_{12}F_3NO_4S$	C,H,N	24 ± 6
61	anthraquinon-2-yl			41 (A1)	purchased	195−7	$C_{18}H_{12}F_3NO_4$[o]	C,H,N	>30
62	2-C_5H_4N	SO_2	4-C_6H_4	79 (A1)	**143**[b]	162−3	$C_{15}H_{13}F_3N_2O_4S$	C,H,N	0.60 ± 0.08
63	3-C_5H_4N	SO_2	4-C_6H_4	74 (A1)	**144**[b]	207−9	$C_{15}H_{13}F_3N_2O_4S$	C,H,N	3.5 ± 0.6
64	4-C_5H_4N	SO_2	4-C_6H_4	60 (A1)	ref 29	255−7	$C_{15}H_{13}F_3N_2O_4S$	C,H,N	2.7 ± 1.2
64(S)	4-C_5H_4N	SO_2	4-C_6H_4	see expt		216−7	$C_{15}H_{13}F_3N_2O_4S$	C,H,N	1.6 ± 0.4
64(R)	4-C_5H_4N	SO_2	4-C_6H_4	see expt		216−8	$C_{15}H_{13}F_3N_2O_4S$	C,H,N	>30
65	4-C_5H_4N	SO_2	4-(3-HOC_6H_3)	18 (C)	**106**[c]	188−9	$C_{15}H_{13}F_3N_2O_5S$[l]	C,H,N	1.3 ± 0.1
66	5-(1,3-$C_4H_3N_2$)	SO_2	4-C_6H_4	40 (A1)	**148**[b]	205−7	$C_{14}H_{12}F_3N_3O_4S$	C,H,N	>30
67	2-(1,4-$C_4H_3N_2$)	SO_2	4-C_6H_4	81 (A1)	**149**[b]	181−3	$C_{14}H_{12}F_3N_3O_4S$	C,H,N	12 ± 2
68	2-(1,3-C_3H_2NS)	SO_2	4-C_6H_4	63 (A1)	**150**[b]	161−3	$C_{13}H_{11}F_3N_2O_4S_2$	C,H,N	1.4 ± 0.3
69	5-(1,3-C_3H_2NS)	SO_2	4-C_6H_4	74 (A1)	**151**[b]	191−3	$C_{13}H_{11}F_3N_2O_4S_2$	C,H,N	7.7 ± 1.6
70	C_6H_5	SO_2	2,5-C_5H_3N	79 (B)	**112**[c]	175−7	$C_{15}H_{13}F_3N_2O_4S$	C,H,N	6.2 ± 1.2
71	C_6H_5	C=O	2,5-C_4H_3S	59 (A1)	ref 30	167−9	$C_{15}H_{12}F_3NO_3S$	C,H,N	>30
72	−CONHSO$_2$−		3,4-C_6H_3	41 (A1)	ref 31	294−5[d]	$C_{11}H_9F_3N_2O_5S$	C,H,N	>30
73	−CON(CH_3)SO$_2$−		3,4-C_6H_3	57 (A1)	**154**[b], expt	224−6	$C_{12}H_{11}F_3N_2O_5S$	C,H,N	26 ± 5
74	$(C_6H_5)_2PO$		4-C_6H_4	76 (A1)	**155**[b], expt	139.5−41.5	$C_{22}H_9F_3NO_3P$	C,H,N	>30

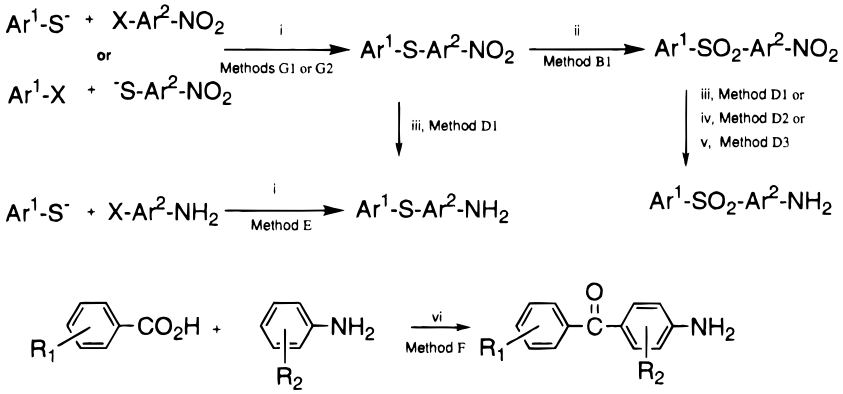
[a] Analytical results were within ± 0.4% of the theoretical value; nd = not determined. [b] Melting point, method of preparation and yield of this novel precursor aniline is available in Supporting Information. [c] The novel sulfide or methoxy propanamide precursor is described in Supporting Information. [d] C: calcd, 55.73; found 55.27. [e] 0.5 Hydrate. [f] C: calcd 50.62; found 50.13. [g] C: calcd 47.13; found 46.72. [h] C: calcd 47.13; found 46.81. [i] C: calcd 46.26; found 45.75. [j] C: calcd 45.94; found 45.46. [k] 0.35 Hydrate. [l] 0.25 Hydrate. [m] 0.2 Hydrate. [n] Prepared by the reaction of $NaBH_4$ with the corresponding ketone. [o] 0.3 Hydrate.

Scheme 1[a]



[a] Reagents: (i) $SOCl_2$/dimethylacetamide, −15 °C to room temperature; (ii) $KMnO_4$, HOAc−H_2O, room temperature.

Scheme 2[a]



[a] See Supporting Information for specific values for Ar^1, X, Ar^2, R_1, and R_2; [b] reagents: (i) K^+ salt, DMF; (ii) $KMnO_4$, HOAc−H_2O, room temperature; (iii) $SnCl_2 \cdot 2H_2O$, EtOH, reflux; (iv) Fe, HCl, EtOH, reflux; (v) H_2/Pd−C; (vi) PPA, 180−190 °C.

Table 2. ClogP and Guinea Pig Bladder Strip and Portal Vein Data for Selected Compounds

		IC_{50}	
compd	CLogP[a]	GP bladder strip[14]	GP portal vein[14]
cromakalim	1.11	0.57 ± 0.07	0.020 ± 0.004
3	2.86	0.47 ± 0.12	0.044 ± 0.019
41	3.49	3.8 ± 1.6	0.082 ± 0.02
63	1.46	3.5 ± 0.6	0.13 ± 0.03
64	1.46	2.7 ± 1.2	0.54 ± 0.02
72	0.87	>30	ND

[a] MedChem software version 3.1 supplied by Pamona College.

indeed **41** proved to be active as a PCO and selective in the conscious rat model (Table 3). Reduction of the carbonyl group of **41** yielded the (±) alcohol **58**, which has an IC_{50} greater than 30 μM in the 15 mM KCl depolarized isolated guinea pig detrusor strip model, providing further evidence for the requirement of an electron-withdrawing 4-substituent to maintain meaningful PCO activity. Also conversion of the carbonyl group of **41** to a lesser electron-withdrawing moiety in **42** (the *O*-methyloxime of **41**) also yielded a derivative with an IC_{50} greater than 30 μM.

Cyclized derivatives **59**−**61** of the lead compounds **3** and **41** that hold the Ar^1 ring in the same plane as the Ar^2 ring all had IC_{50} values greater than 24 μM in the 15 mM KCl depolarized isolated guinea pig detrusor strip model. Whether this lack of meaningful activity is due to a unfavorable spatial relationship of the Ar^1 and Ar^2 rings or is a reflection of the presence of deleterious large substituents at both the 3- and 4-positions is not known.

The Ar^1 rings of **41** and **64** in low-energy conformations (and in the X-ray conformations of the PCO active (*S*)-(−) enantiomers) are in different areas of space when the rest of the molecules are overlaid (Figure 1), suggesting that a compound that can take advantage of both ring binding sites might show increased activity. A diphenylphosphinyl group offers an opportunity to test such a hypothesis. X-ray structures of triphenylphosphine oxide, diphenyl sulfone, and benzophenone from the Cambridge X-ray database were overlaid on a common ring, and it was found that the other phosphine oxide rings overlap relatively well with each of the remaining rings of diphenyl sulfone and benzophenone. The diphenyphosphinyl derivative **74** was, however, only weakly active, suggesting that perhaps the binding site could not accommodate both phenyl rings at the same time. The diphenylsulfonamide **40** was prepared for the same overlay reasoning although the molecular-modeling overlay is not as efficient with **40**. Compound **40** had an IC_{50} value greater than 30 μM in the 15 mM KCl depolarized isolated guinea pig detrusor strip model, but the sulfonamide **39** showed selectivity in the normotensive conscious rat bladder model (Table 3).

Table 3. *In Vivo* Activity of Selected Compounds in the Normotensive Conscious Rat Bladder Model

			time post dosing								
			1 h			3 h			5 h		
compd	dose (mg/kg)	N	%ΔIC[a]	%ΔMAP[b]	%ΔHR[c]	%ΔIC	%ΔMAP	%ΔHR	%ΔIC	%ΔMAP	%ΔHR
crom	1.0	4	54 ± 5	−18 ± 4	20 ± 5	104 ± 5	−14 ± 5	13 ± 2	114 ± 25	−12 ± 3	9 ± 4
3	3.0	4	24 ± 7	−25 ± 4	32 ± 2	79 ± 6	−24 ± 2	27 ± 4	97 ± 14	23 ± 3	−22 ± 3
39	3.0	4	30 ± 12	−1 ± 2	−1 ± 1	33 ± 10	−3 ± 2	4 ± 4	56 ± 15	−4 ± 2	1 ± 6
41	3.0	5	35 ± 11	−1 ± 1	2 ± 5	73 ± 11	1 ± 1	−3 ± 3	128 ± 21	2 ± 1	−4 ± 2
46	3.0	4	25 ± 10	4 ± 2	9 ± 3	56 ± 17	2 ± 1	4 ± 2	61 ± 11	1 ± 2	6 ± 2
54	3.0	7	26 ± 7	−3 ± 1	0 ± 1	50 ± 8	−4 ± 2	−1 ± 2	71 ± 6	−4 ± 2	1 ± 2
63	3.0	4	64 ± 6	−16 ± 2	19 ± 7	83 ± 7	−14 ± 1	3 ± 2	125 ± 16	−11 ± 2	−2 ± 2
64	3.0	4	20 ± 4	4 ± 3	5 ± 3	76 ± 5	5 ± 1	1 ± 4	76 ± 9	1 ± 1	0 ± 3
65	3.0	4	25 ± 15	1 ± 2	2 ± 2	42 ± 12	1 ± 3	2 ± 2	95 ± 19	−4 ± 4	6 ± 4

[a] IC = interval between bladder contractions. [b] MAP = mean arterial pressure. [c] HR = heart rate.

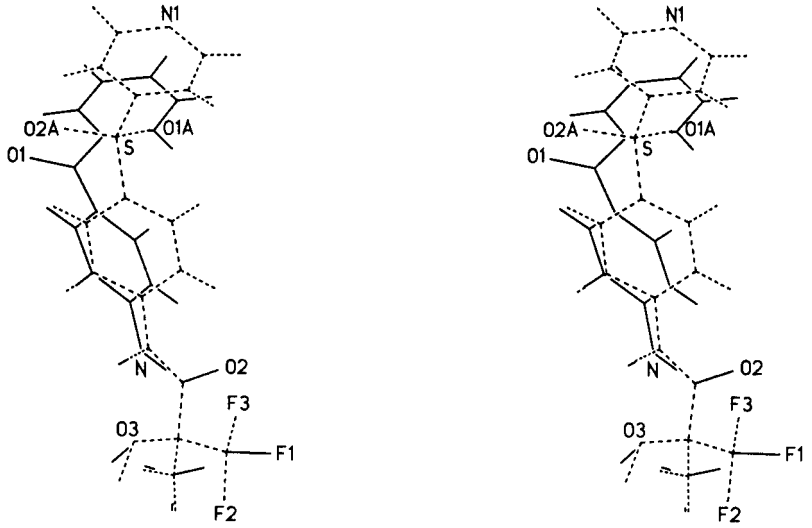
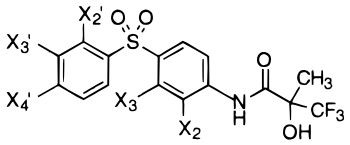


Figure 1. Stereoview of **41(S)** (solid lines) and **64(S)** (dashed lines) with COH, CH_3, and CF_3 groups superimposed by least-squares fit (non-hydrogen atoms only). RMS deviation is 0.029 Å. Heteroatom labels for both molecules are given except for those atoms shared in common (i.e. N, O2, O3, Fl, F2, F3), in which the atom labeling scheme for **41(S)** prevails as shown.

Table 4. Activity of Monosubstituted Aryl Derivatives of **3** in the 15 mM KCl Depolarized Isolated Guinea Pig Detrusor Strip Model



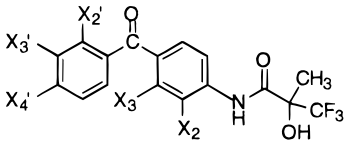
substituent	X_2	X_3	X_2'	X_3'	X_4'
F		1.8 ± 0.5	1.3 ± 0.3	3.4 ± 0.9	8.6 ± 2.0
CN		3.8 ± 1.9	1.1 ± 0.1		>30
OH		0.43 ± 0.12	3.1 ± 0.6	18 ± 5	>30
CH_3O		5.9 ± 0.8	1.6 ± 0.3	16 ± 3	>30
Cl		2.2 ± 0.5	2.3 ± 0.7	10 ± 3.5	
CH_3		1.6 ± 0.4	5.1 ± 1.9	2.2 ± 0.5	>30
Br					>30
CF_3		>30		>30	
NO_2	7.9 ± 2.0	>30			>30
CO_2H	>30	>30			

Substitution of the aromatic rings of **3** did not give compounds that were more active than **3** in the 15 mM KCl depolarized isolated guinea pig detrusor strip model. In fact, of those derivatives prepared, only the 3-hydroxy derivative **14** retained the activity of **3** in the guinea pig detrusor strip model. Several of the positions examined appear sterically regulated in their SAR. In the X_3 position (Table 4), small groups are most active and substituents larger than CF_3 had IC_{50}s greater than 30 μM in the 15 mM KCl depolarized isolated guinea pig detrusor strip model. In a plot of MR versus log $1/C$ for the actives $n = 7$ (H, F, CN, HO, CH_3O, Cl, CH_3) $r^2 = 0.58$, $p > 0.046$ or for $n = 6$ (F omitted) $r^2 = 0.90$, $p > 0.0035$. In the X_2' position a plot of Es versus log $1/C$ for $n = 6$ (H, F, HO, CH_3O, Cl, CH_3) $r^2 = 0.79$, $p > 0.018$ or for $n = 5$ (HO omitted) $r^2 = 0.95$, $p > 0.0045$. In the X_4' position only the sterically small F has any activity among those derivatives prepared. In the X_3' position there is generally a loss of activity upon substitution, with CH_3 being the most active of those prepared. Although only a limited number of analogs of **3** substituted in the X_2 position were prepared, the NO_2 compound displays modest activity.

From an analysis of the SAR of the heterocyclic Ar^1 ring analogs of **3** (Table 1, **62**−**69**) it appears that the 3′-position plays an important role in determining the activity of these derivatives. In the simplest analysis a 3′-H must be available for activity as a PCO (15 mM KCl depolarized isolated guinea pig detrusor strip model). Thus the 5-pyrimidyl derivative **66**, which has a nitrogen in both meta positions, has an IC_{50} greater than 30 μM, and those derivatives with a single nitrogen in the meta position are 5−20 times less active than a derivative with both meta positions (or psuedometa in the case of thiazole) substituted with H. Compare for example the 2-pyrazinyl **67** ($IC_{50} = 12$ μM) and 3-pyridyl **63** ($IC_{50} = 3.5$ μM) derivatives with the 2-pyridyl derivative **62** ($IC_{50} = 0.60$ μM) and the 5-thiazolyl derivative **69** ($IC_{50} = 7.7$ μM) with the 2-thiazolyl derivative **68** ($IC_{50} = 1.4$ μM). The nature of this interaction is not known, although one can visualize an edge to face π HAr interaction of this ring with the receptor. The extent to which a mono meta substituent would allow favorable conditions (sterically and electronically) for such an interaction might then account for the SAR of the 3′-substituents seen in Table 4.

The SAR of aryl-substituted **3** was generated with two purposes in mind. First, there was the possibility that the substituted derivatives of **3** might show bladder selectivity in the normotensive conscious rat bladder model, although none that were tested did. Secondly the SAR generated with derivatives of **3** could then be transferred to the *in vivo* rat model bladder selective 4-pyridyl derivative **64** as it was felt that the conforma-

Table 5. Activity of Monosubstituted Aryl Derivatives of **41** in the 15 mM KCl Depolarized Isolated Guinea Pig Detrusor Strip Model



substituent	X_2	X_3	X_2'	X_3'	X_4'
F	11 ± 1	2.7 ± 0.7	2.3 ± 0.5	2.6 ± 1.0	14 ± 2
CN	3.9 ± 0.9				
OH	15 ± 5	4.2 ± 0.6			
CH_3O	6.1 ± 1.4				
Cl	>30			>30	
CH_3	5.0 ± 1.3			>30	
	2.6 ± 0.8 (*S*)				
Br	>30				

tions should be close if not identical. In support of that assumption, **64** and its 3-hydroxy derivative **65** are about equipotent in the *in vitro* gp detrusor strip model as expected by extrapolation from the **3**, **14** pair. As with **64**, **65** was also shown to be bladder selective in the normotensive conscious rat bladder model at a dose of 3 mg/kg (Table 3).

The conformation of the Ar[1] ring of the selective benzoyl derivative **41**, as discussed earlier, is different than that of **3**, and thus extrapolation of the SAR of **3** to **41** was not *a priori* expected to be valid. The SAR of **41** was explored primarily by looking at the monosubstitution of F in all the available aryl positions (Table 5). The underlying thought was to determine if steric factors, as with the SAR of **3**, would again play a role in a large portion of this SAR. Preparation of **50**, X_3 = OH, **55**, $X_3' = CH_3$, and the monofluorinated derivatives **43**−**47** gave an SAR picture of the benzoyl derivative much like that of **3**. The $X_3' = F$ derivative **46** is about equal in potency to **41** and also demonstrated selectivity in the normotensive conscious rat bladder model, whereas **44** and **45** were weakly active in that screen, both on the bladder and on bp. The X_2 position was examined in more detail in this SAR, and the 2-methyl derivative **54** was discovered to retain the profile of **41** both in the 15 mM KCl depolarized isolated guinea pig detrusor strip model and the normotensive conscious rat bladder model; however most other 2 substituents and the 2,6-dimethyl derivative **56** were of lower activity.

Two hetero Ar[2] ring substitutions were prepared. Compound **70**, a pyridine for phenyl substitution, was 12-fold less active than **3**, while **71**, a thiophene analog of **41**, had an IC_{50} greater than 30 μM in the 15 mM KCl depolarized isolated guinea pig detrusor strip model.

In summary, the results of our SAR studies on the western region of a novel series anilide tertiary carbinol K_{ATP} potassium channel openers has been described. The goal of the work was achieved in that several derivatives of the series were discovered that demonstrate bladder selectivity in an *in vivo* rat model that simultaneously measures bladder contractions, heart rate, and blood pressure. Based on the herein described and additional biological evaluation, **41(S)**, ZD6169, has been selected into development for the treatment of urge urinary incontinence.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker WM 250 (250 MHz) or a Brucker AM 300 (300 MHz) instrument, and chemical shifts are reported in δ units with tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS-80 instrument. Combustion analysis were performed on a Perkin-Elmer 241 instrument. Flash chromatography was conducted on Keiselgel 60 (230-400 mesh) supplied by E. Merck.

Methods for the Synthesis of *N*-Aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides. General Method A1: *N*-[4-[[(2-Fluorophenyl)sulfonyl]phenyl]-3,3,3,-trifluoro-2-hydroxy-2-methylpropanamide (6). To a stirred, cooled (−20 °C) solution of 3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (1.42 g 9.0 mmol) in *N*,*N*-dimethylacetamide (13 mL) was rapidly added thionyl chloride (1.13 g, 9.5 mmol), and the mixture (a precipitate formed after a few minutes) was stirred at −15 to −5 °C for 1 h. 4-[(2-Fluorophenyl)sulfonyl]-aniline (1.51 g, 6.0 mmol) was then added in one portion and the mixture allowed to stir at room temperature overnight. The solution was poured into water, and the cloudy solution was decanted from the resulting gum and filtered through a thin pad of Celite. The Celite pad was washed with methylene chloride and the solution added to a solution of the gum in methylene chloride. The combined methylene chloride solution was dried ($MgSO_4$) and filtered and the solvent removed *in vacuo*. The resulting gum was treated with hexane (100 mL) and enough methylene chloride (ca. 100 mL) to effect a solution. Methylene chloride was then boiled off on a steam bath at atmospheric pressure until cloudiness developed. The solution was cooled and scratched with a spatula until crystal growth began, returned to the steam bath, and concentrated with swirling until the final volume was 100 mL. After cooling the solid was filtered off to yield **6** (1.92 g, 82%) as a light tan solid: mp 133−135 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) 1.59 (s, 3H, CH_3), 7.41 (t, 1H, aromatic), 7.51 (t, 1H, aromatic), 7.59 (s, 1H, OH), 7.77 (m, 1H, aromatic), 7.85 (d, J = 8.7 Hz, 2H, aromatic), 7.98−8.06 (m, 3H, aromatic), 10.48 (s, 1H, NH); MS (CI, CH_4) 392 (M + 1). Anal. ($C_{16}H_{13}F_4NO_4S$) C, H, N.

Alternately, the oil obtained on pouring the reaction mixture onto water was extracted with an organic solvent such as CH_2Cl_2. However, this method of isolation yielded product containing DMA which hindered further purification efforts. When the product solidified upon pouring the crude reaction mixture onto water the resulting solid was collected by suction filtration. Purification by flash chromatography (5−20% EtOAc in CH_2Cl_2 or 10−20% Et_2O in CH_2Cl_2) was employed where appropriate. Compounds of this class dissolved normally in a number of hot organic solvents but frequently did not precipitate when cooled, hence the use of the unique crystallization technique described in method A1. Some compounds of this class, however, did crystallize by conventional procedures; for example **9**, **41**, **62**, **63**, and **69** were crystallized from EtOAc−hexane.

Method A2: *N*-[4-(Phenylsulfonyl)-2-nitrophenyl]-3,3,3,-trifluoro-2-hydroxy-2-methylpropanamide (32). A mixture of 3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (1.00 g 6.3 mmol), 1,1′-carbonyldiimidazole (1.03 g, 6.3 mmol), and 25 mL of dry THF was heated, under N_2, at 45 °C in an ultrasound bath for 0.5 h. 2-Nitro-4-(phenylsulfonyl)aniline[21] (1.75 g, 6.3 mmol) was added, and the reaction mixture was

heated at 45 °C for 18 h, poured onto water (350 mL), and extracted with Et_2O. The combined extracts were washed with saturated brine, dried ($MgSO_4$), evaporated to an orange solid (3.01 g), and chromatographed ($CHCl_3$) to yield **32** as a pale yellow solid (0.46 g, 17%): mp 191−2.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.58 (s, 3H, CH_3), 7.63−7.76 (m, 3H, aromatic), 8.02−8.07 (d, 3H, aromatic) 8.34 (dd, 1H, J = 2.2, 8.6 Hz, aromatic), 8.59 (s, 1H, NH), 8.61 (d, 1H, J = 2.3 Hz, aromatic); MS (CI, CH_4) 419 (M + 1). Anal. ($C_{16}H_{13}F_3N_2O_6S$) C, H, N.

Method A3: *N*-[4-[(4-Nitrophenyl)sulfonyl]phenyl]-3,3,3,-trifluoro-2-hydroxy-2-methylpropanamide (36). To a stirred solution of 3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (1.00 g, 6.3 mmol) in toluene (10 mL) was added thionyl chloride (0.75 g, 6.3 mmol) and the mixture heated at reflux for 3 h. The reaction mixture was cooled to room temperature and added to a mixture of 4-[(4-nitrophenyl)-sulfonyl]aniline (1.75 g, 6.3 mmol) in toluene (20 mL) and the reaction mixture heated at reflux overnight. The toluene was removed *in vacuo*, and the resulting solid was recrystallized from ethyl acetate. Unreacted 4-[(4-nitrophenyl)sulfonyl]-aniline was recovered by filtration as the desired product remained in the filtrate. The filtrate was concentrated and the product purified by flash chromatography (0−10% v/v ethyl ether in methylene chloride) to yield **36** (1.02 g, 39%): mp 213−215 °C; ^{1}H-NMR (250 MHz, DMSO-d_6) 1.58 (s, 3H, CH_3) 7.58 (s, 1H, OH), 8.00−8.06 (m, 4H, aromatic), 8.20 (dd, 2H, J = 7.0, 1.9 Hz, aromatic), 8.40 (dd, 2H, J = 7.0, 1.8 Hz, aromatic), 10.48 (s, 1H, NH); MS (CI, CH_4) 419 (M + 1). Anal. ($C_{16}H_{13}F_3N_2O_6S$) C, H, N.

Method A4: *N*-[4-[(*N*′,*N*′-Diphenylamino)sulfonyl]-phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (40). To a stirred, cooled (−20 °C) solution of 4-(dimethylamino)pyridine (0.125 g, 1.02 mmol) in methylene chloride (10 mL) was added thionyl chloride (0.12 g, 0.83 mmol) and the mixture stirred for 10 min. 3,3,3-Trifluoro-2-hydroxy-2-methylpropanoic acid (0.13 g, 0.83 mmol) was added and the mixture stirred at −20 °C for 30 min. A solution of 4-(dimethylamino)pyridine (0.125 g, 1.02 mmol) and *N*,*N*-diphenyl-4-aminobenzenesulfonamide (0.27 g, 0.83 mmol) in methylene chloride (4 mL) was added and the reaction mixture stirred at −20 °C for 10 min and at room temperature for 2 h and heated at reflux for 48 h. The cooled solution was treated with water (50 mL) and extracted with methylene chloride. The crude material was chromatographed (methylene chloride/ethyl ether, 12:1) to yield **40** as a colorless solid (0.19 g, 50%): mp 217−20 °C; ^{1}H NMR (250 MHz, DMSO-d_6) 1.60 (s, 3H, CH_3), 3.32 (br s, 1H, OH), 7.28−7.42 (m, 9H, aromatic), 7.58−7.65 (m, 3H, aromatic), 8.00−8.03 (m, 2H, aromatic); MS (CI, CH_4) 465 (M + 1). Anal. ($C_{22}H_{19}F_3N_2O_4S$) C, H, N.

***N*,*N*-Diphenyl-4-aminobenzenesulfonamide.** A stirred suspension of 4-acetamidobenzenesulfonyl chloride (2.0 g, 8.56 mmol), diphenylamine (2.9 g, 17.1 mmol), 4-pyrrolidinopyridine (0.064g, 0.43 mmol), and triethylamine (1.73 g, 17.1 mmol) in acetonitrile (5 mL) was refluxed for 72 h. The cooled mixture was diluted with water (50 mL) and extracted with ethyl acetate, and the dark oil thus obtained was purified by column chromatography (methylene chloride/ethyl ether, 8:1) to give 0.46 g (15%) of tan solid. The solid was dissolved in hot ethanol (35 mL), 6 N HCl (10 mL) was added, and the mixture was stirred at 75−80 °C for 3 h. The cooled mixture was treated with concentrated NH_4Cl to pH = 9 and the solid filtered off and washed well with water to yield 0.24 g (68%, 10% overall) of *N*,*N*-diphenyl-4-aminobenzenesulfonamide: mp 151−3 °C; MS (CI, CH_4) 325 (M + 1).

General Method A5: *N*-[2-Cyano-4-(phenylcarbonyl)-phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (48). A stirred solution of 3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (0.15 g, 1.0 mmol) and thionyl chloride (0.12 g, 1.0 mmol) in methylene chloride (15 mL) was heated at reflux for 3 h. Triethylamine (0.11 g, 1.1 mmol) was added to the cooled reaction mixture and the solution heated at reflux for 30 min. A solution of 4-amino-3-cyanobenzophenone (0.19 g, 0.9 mmol) in tetrahydrofuran (2.5 mL) was added to the cooled mixture, and the reaction mixture was heated at reflux for 20 h. The solvents were removed *in vacuo*, and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$) and concentrated to a clear oil. Purification by flash chromatography (2% v/v ethyl ether/methylene chloride) yielded **48** as a white solid (0.11 g, 35%): mp 202−4 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) 1.64 (s, 3H, CH_3), 7.57−7.62 (m, 2H, aromatic), 7.70−7.76 (m, 3H, aromatic + OH), 7.89 (d, 1H, J = 4.0 Hz, aromatic), 7.96−8.07 (m, 2H, aromatic), 8.17 (s, 1H, aromatic), 10.46 (s, 1H, NH); MS (CI, CH_4) 363 (M + 1). Anal. ($C_{18}H_{13}F_3N_2O_3 \cdot 0.5H_2O$) C, H, N.

General Method B: *N*-(4-(Phenylsulfonyl)-3-cyanophenyl)-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (9). To a stirred solution of 1.91 g (5.2 mmol) of *N*-(4-(phenylthio)-3-cyanophenyl)-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide and 150 mL of glacial acetic acid was added a solution of 0.99 g (6.3 mmol) of potassium permanganate and 100 mL of water in one portion. The mixture was stirred at ambient temperature for 45 min, poured into 400 mL of water, clarified with a little solid sodium bisulfite, and extracted with three 250 mL portions of chloroform. The extracts were dried ($MgSO_4$) and filtered, and the solvent was removed to yield an oil which was chromatographed on 300 g of silica gel using a ethyl ether (0%, 10%, 15%, and 20%) in methylene chloride gradient. The material was further recrystallized from hexane containing a small amount of ethyl acetate to yield 1.57 g (75%) of the title propanamide as a white solid: mp 163−165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.59 (s, 3H, CH_3), 7.66−7.77 (m, 4H, aromatic, OH), 7.99 (d, 2H, J = 7.3 Hz, aromatic), 8.32 (d, 1H, J = 8.6 Hz, aromatic), 8.40−8.43 (m, 2H, aromatic), 10.77 (s, 1H, NH); MS (CI, CH_4) 399 (M + 1). Anal. ($C_{17}H_{13}F_3N_2O_4S$) C, H, N.

General Method C: *N*-[3-Hydroxy-4-(phenylsulfonyl)-phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (14). To a stirred suspension of **18** (0.75 g, 1.9 mmol) in dry methylene chloride (22 mL) was added boron tribromide (3.8 mL of a 1.0 M solution of boron tribromide in methylene chloride, 3.8 mmol). The resulting solution was stirred at room temperature for 3 h, diluted with methylene chloride (50 mL), and washed with water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield an off-white foam. Purification by flash column chromatography (10−30% v/v ethyl acetate in methylene chloride) yielded **14** as a white solid (0.34 g, 46%): mp 155−156 °C; ^{1}H-NMR (250 MHz, DMSO-d_6) 1.58 (s, 3H, CH_3), 7.30 (dd, 1H, J = 8.8, 1.8 Hz, aromatic), 7.48 (s, 1H, OH), 7.51−1.66 (m, 4H, aromatic), 7.80−7.86 (m, 3H, aromatic), 10.19 (s, 1H, NH), 10.60 (s, 1H, OH); MS (CI, CH_4) 390 (M + 1). Anal. ($C_{16}H_{14}F_3NO_5S$) C, H, N.

Resolution of 41. (*S*)-(−)-*N*-[4-(Phenylcarbonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide [41(S)]. To a cooled (0 °C), stirred solution of **41** (6.87 g, 20.4 mmol) and triethylamine (3.2 mL, 23 mmol) in methylene chloride (70 mL) was added 4-(dimethylamino)pyridine (catalytic) followed by the dropwise addition of (1*S*)-(−)-camphanic acid chloride (5.00 g. 23.1 mmol). The mixture was stirred at room temperature for 2 h, diluted with methylene chloride (70 mL), and washed with water, 3 N HCl (200 mL), and water. The dried ($MgSO_4$) organics were filtered, and the solvent was removed *in vacuo* to yield a white foam. The diastereomers were separated by repeated flash column chromatography (0−3% v/v ethyl ether gradient in methylene chloride). The camphanic ester which eluted first was isolated as a white foam (3.20 g, 30%). Optical purity of >98% de was determined by chiral HPLC (Chiralcel OD column, 15% v/v ethanol in hexane, flow rate: 1 mL/min): ^{1}H-NMR (300 MHz, DMSO-d_6) 0.97 (s, 3H, CH_3), 1.037 (s, 3H, CH_3), 1.044 (s, 3H, CH_3), 1.58−1.61 (m, 1H, aliphatic), 2.00−2.10 (m, 5H, CH_3, aliphatic), 2.43−2.47 (m, 1H, aliphatic), 7.54−7.59 (m, 2H, aromatic), 7.66−7.82 (m, 7H, aromatic), 10.34 (s, 1H, NH). To a suspension of the first eluting camphanic ester (3.20 g, 6.2 mmol) in methanol (40 mL) was added 2 N NaOH (3 mL) and the yellow solution stirred at room temperature for 1 h. The methanol was removed *in vacuo*, the residue treated with water, and the mixture extracted with methylene chloride (2 × 50 mL). The dried ($MgSO_4$) organics were filtered, the solvent was removed *in vacuo*, and the white solid was recrystallized from methylene chloride/hexane to yield 1.80 g (86%) of **41(S)**: mp 171−3 °C; $[\alpha]^{27}_D$ = −18.8°, c = 1.01 in methanol; optical purity >98% ee by chiral HPLC (Chiralcel OD column, 15% v/v ethanol in hexane, flow rate 1 mL/min). The compound was determined to have the (*S*) configuration

by X-ray crystallography: ^{1}H-NMR (250 MHz, DMSO-d_6) 1.60 (s, 3H, CH_3), 7.53−7.59 (m, 3H, aromatic, OH), 7.64−7.76 (m, 5H, aromatic), 7.96 (d, 2H, J = 8.7 Hz, aromatic), 10.33 (s, 1H, NH); MS (CI, CH_4) 338 (M + 1). Anal. ($C_{17}H_{14}F_3NO_3$) C, H, N.

(*R*)-(+)-*N*-[4-(Phenylcarbonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide [41(R)]. The second eluting camphanic ester (3.50 g, 6.8 mmol) was worked up as described above to yield 1.99 g (87%) of **41(R)**: mp 172−3 °C; $[\alpha]^{27}_D$ = +18.8°, c = 1.04 in methanol; optical purity >98% ee by chiral HPLC (Chiralcel OD column, 15% v/v ethanol in hexane, flow rate 1 mL/min). The compound was determined to have the (*R*) configuration by X-ray crystallography.

Resolution of 64. (*S*)-(−)-*N*-[4-(4-Pyridylsulfonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide [64-(S)]. To a stirred cooled (0 °C) solution of **64** (30.86 g, 82 mmol) and triethylamine (13.8 mL, 99 mmol) in dry methylene chloride (500 mL), cooled to 0 °C, was added 4-(dimethylamino)pyridine (0.20 g, 1.64 mmol) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (24.90 g, 99 mmol); the mixture was allowed to stir in the ice bath for 30 min and then at room temperature for 7 h. The reaction was diluted with methylene chloride to a total volume of about 900 mL, treated with water, and filtered through a pad of Celite. The organic layer was separated, and the aqueous phase was extracted with methylene chloride (2 × 700 mL). The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed to yield a tan foam. The diastereomers were separated by repeated flash chromatography (10 v/v ethyl ether in methylene chloride). The ester which eluted second was isolated as a white solid (7.04 g, 15%), mp 159−160 °C. Optical purity of >99% ee was determined by chiral HPLC (Ultron ES OVM column, 12% v/v acetonitrile/KH_2PO_4 (0.013 M, pH 5.5), flow rate 1 mL/min): ^{1}H-NMR (250 MHz, DMSO-d_6) 2.12 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 7.51−7.60 (m, 5H, aromatic), 7.89 (d, 2H, J = 2.1 Hz, aromatic), 7.95 (d, 2H, J = 8.9 Hz, aromatic), 8.09 (d, 2H, J = 3.8 Hz, aromatic), 8.88 (d, 2H, J = 5.8 Hz, aromatic), 10.51 (s, 1H, NH); MS (CI CH_4) 591 (M + 1). To a stirred, cooled (ice bath) suspension of the second eluting Mosher's ester (7.04 g, 11.9 mmol) in methanol (100 mL) was added a solution of sodium hydroxide (0.52 g, 13.1 mmol) in water (10 mL). After the addition of the hydroxide solution the mixture was stirred for 15 min in the ice bath and an additional 15 min with the bath removed. The reaction mixture was then diluted with water to a final volume of 250 mL, the methanol removed *in vacuo*, and the white solid collected by filtration and dried. Acidification of the filtrate gave additional material. The combined yield was 4.25 g (96%): mp 216 −217 °C; $[\alpha]^{27}_D$ = −5.9°, c = 1.02 in DMF. Optical purity was established to be >99% ee by chiral HPLC (Ultron ES OVM column, 12% v/v acetonitrile/KH_2PO_4 (0.013 M, pH 5.5)). Compound from an analogous prior separation was determined to be of the (*S*) configuration by X-ray crystallography: ^{1}H-NMR (250 MHz, DMSO-d_6) 1.58 (s, 3H, CH_3), 7.61 (s, 1H, OH), 7.89 (dd, 2H, J = 4.4, 1.5 Hz, aromatic), 8.00 (d, 2H, J = 9.0 Hz, aromatic), 8.07 (d, 2H, J = 9.0 Hz, aromatic), 8.88 (dd, 2H, J = 4.5, 1.7 Hz, aromatic), 10.51 (s, 1H, NH); MS (CI CH_4) 375 (M + 1). Anal. ($C_{15}H_{13}F_3N_2O_4S$) C, H, N.

(*R*)-(+)-*N*-[4-(4-Pyridylsulfonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide [64(R)]. The Mosher's ester which eluted first (white solid, 13.0 g, 27%) was hydrolyzed as above to yield 5.81 g (71%) of **64(R)** which was not characterized further but from an analogous prior separation was determined to have mp 216−218 °C, $[\alpha]^{27}_D$ = +5.9°, c = 1.02 in DMF, and to be of the (*R*) configuration by X-ray crystallography.

Preparation of (*S*)-(−)-3,3,3-Trifluoro-2-hydroxy-2-methylpropanoic Acid. The solvent was removed *in vacuo* from a solution of (*R*,*S*)-(±)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (316.2 g, 3.0 mol) and (*S*)-(−)-α-methylbenzylamine (363.5 g, 3.0 mol) in ethanol (1.5 L), the residue was triturated with toluene, and the solid was collected, washed with toluene, and dried *in vacuo*. Recrystallization from 10% 1-butanol in toluene returned 126.0 g of 97% enantiomerically pure (by ^{19}F NMR) *S*,*S* salt, mp 161−4 °C. The solvent was removed from the recrystallization liquors, and the residue was recrystallized three times from 10% 1-butanol in toluene to yield an additional 24.0 g of 97% enantiomerically pure (by ^{19}F NMR) *S*,*S* salt, mp 162−5 °C. The 150.0 g of 97% enantiomerically pure salt was recrystallized twice from 10% 1-butanol in toluene to yield 85 g of > 99.5% enantiomerically pure (by ^{19}F NMR) *S*,*S* salt: mp 162.5−164 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) 1.25 (s, 3H, CH_3), 1.52 (d, 3H, J = 6.8 Hz, CH_3), 4.16 (m, 1H, aliphatic CH), 7.25−7.35 (m, 5H, aromatic) [the *R*,*S* salt displays the acid CH_3 peak at 1.18 ppm and was not evident in this proton spectra]; ^{19}F-NMR (376.5 MHz, $CDCl_3$) −79.83 [the *R*,*S* salt is shifted downfield by 13 Hz and was evident in this spectra at a level below the ^{13}C satellite peak (0.5%)]. The liquors from the recrystallization of the 97% enantiomerically pure salt were stripped *in vacuo* and the residue recrystallized three times from 10% 1-butanol in toluene to yield an additional 31.5 g of > 99% enantiomerically pure (by ^{19}F NMR) *S*,*S* salt. The 85 g of >99.5% pure *S*,*S* salt was partioned between aqueous HCl (105 mL of concentrated HCl and 700 mL of water) and ethyl ether (400 mL). The phases were separated, and the aqueous phase was further extracted with ethyl ether (5 × 400 mL). The dried extracts ($MgSO_4$) were filtered, and the solvent was removed to yield 47.0 g of (*S*)-(−)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid: mp 105−8 °C; $[\alpha]^{23}_D$ = −18.9°, c = 9.04 in methanol; ^{1}H-NMR (300 MHz, $CDCl_3$) 1.67 (s, CH_3); MS (CI CH_4) 159 (M + 1). Anal. ($C_4H_5F_3O_3$) C, H, N. The 31.5 g of >99% pure *S*,*S* salt was likewise partioned between aqueous HCl and ethyl ether to yield 17.4 g of (*S*)-(−)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid: mp 107−9 °C; $[\alpha]^{23}_D$ = −18.7°, c = 4.27 in methanol.

X-ray Diffraction. Clear, colorless prismatic crystals of **41(S)** were grown from slow evaporation of a methanol solution. Clear, colorless prismatic crystals of **64(S)** were grown from acetone/hexane. A complete summary of crystal data as well as of data collection and solution and refinement parameters is given in the Supporting Information. All measurements were made on a Siemens P4/RA diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.541 78 Å), 2q−q scan mode at ambient temperature (294 K). Intensities were corrected for Lorentz and polarization effects, as well as for extinction according to the equation in the Supporting Information. An absorption correction was applied to the data set of **64(S)** using the semiempirical correction for an ellipsoid derived from y-scan data. The structures were solved by direct methods and refined by full-matrix least-squares analysis on a MicroVAX using the SHELXTL PLUS system of programs.[32] All non-hydrogen atoms were refined anisotropically. Difference Fourier maps subsequently identified electron density peaks at the approximate positions of all hydrogen atoms. All hydrogens bonded to carbon atoms were assigned with idealized geometries relative to neighboring non-hydrogen atoms and refined according to the riding model, in which the shift vectors for hydrogen and its parent atom are equal. Hydrogens bonded to heteroatoms were located in difference Fourier maps and then refined according to the riding model after bond lengths were idealized. Hydrogen temperature factors were allowed to refine isotropically, either individually or in the case of methyl group hydrogens sharing a common temperature factor as a free variable. In the final stages of refinement, a least-squares variable introduced by Rogers for determining absolute configuration, h, was included and refined.[33] The convention for interpreting h is that if it converges on a value approaching +1, then absolute configuration is correctly assigned; whereas if h approaches −1 then the chirality should be reversed. The magnitude of the esd [$s(h)$] associated with the parameter serves an index of the degree of confidence that can be placed on the correctness of the assignment. For **41-(S)** h = 0.8(5) with (*S*)-chirality, while for **64(S)** h = 1.09(5), also with (*S*)-chirality; thus the significance ratio $(1 + |h|)/s(h)$, which describes the gap between the observed value for h and its value for the enantiomeric structure in terms of $s(h)$, was 3.6 for **41(S)** and 41.8 for **64(S)**. One would have to conclude that the absolute configuration assigned to **41(S)** was of marginal significance and not as definitive as the assignment for **64(S)**. However, both **41(S)** and **64(S)** can be prepared from the same (−) enantiomer of 3,3,3-trifluoro-2-

hydroxy-2-methylpropanoic acid and must have the same absolute configuration.

Preparation of Arylamines. General Method D1: 3-Methyl-4-(phenylsulfonyl)aniline. A stirred solution of 2-methyl-4-nitrodiphenyl sulfone[34] (2.72 g, 9.8 mmol) and stannous chloride dihydrate (11.06 g, 49.0 mmol) in absolute ethanol (30 mL) was heated at reflux for 1 h. The reaction mixture was poured into ice water, and the aqueous solution was basified with 15% NaOH and extracted with ethyl acetate (2 × 100 mL). The combined organic portions were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to yield an off-white solid. Recrystallization from ethyl acetate yielded 3-methyl-4-(phenylsulfonyl)aniline (2.12 g, 88%) as a white solid: mp 163−165° C; ^{1}H-NMR (300 MHz, DMSO-d_6) 2.17 (s, 3H, $ArCH_3$), 6.10 (s, 2H, NH_2), 6.38 (d, 1H, J = 2.1 Hz, aromatic), 6.53 (dd, 1H, J = 8.7, 2.2 Hz, aromatic), 7.54−7.62 (m, 4H, aromatic), 7.73−7.77 (m, 2H, aromatic); MS (CI, CH_4) 248 (M + 1). Anal. ($C_{13}H_{13}NO_2S$) C, H, N.

General Method D2: 4-[(2-Cyanophenyl)sulfonyl]-aniline. A stirred solution of 2-cyano-4′-nitrodiphenyl sulfone (2.54 g, 8.8 mmol) and iron powder (5.39 g, 96.5 mmol) in absolute ethanol (70 mL) was heated to reflux. Ethanolic HCl (0.53 mL of concentrated HCl in 20 mL of EtOH) was added dropwise over 30 min. The reaction mixture was heated at reflux for 4 h, diluted with absolute ethanol (100 mL), and filtered while hot through Celite. The Celite was washed with additional hot ethanol (100 mL). The combined ethanol portions were reduced to a volume of 75 mL and placed in a freezer overnight. The aniline was collected by filtration as a white solid (1.81 g, 80%): mp 177−179° C; ^{1}H-NMR (300 MHz, DMSO-d_6) 6.37 (s, 2H, NH_2), 6.65 (d, 2H, J = 8.8 Hz, aromatic), 7.61 (d, 2H, J = 8.8 Hz, aromatic), 7.81 (dd, 1H, J = 7.5, 1.0 Hz, aromatic), 7.93 (dt, 1H, J = 7.6, 1.1 Hz, aromatic), 8.06 (dd, 1H, J = 7.5, 1.0 Hz, aromatic), 8.17 (d, 1H, J = 7.4 Hz, aromatic); MS (CI, CH_4) 259 (M + 1). Anal. ($C_{13}H_{10}N_2O_2S \cdot 0.25H_2O$) C, H, N.

General Method D3: 5-Amino-1,1-dioxo-2-methyl-1,2-benzisothiazol-3(2*H*)-one. A mixture of 5-nitro-1,1-dioxo-2-methyl-1,2-benzisothiazol-3(2*H*)-one[35] (4.40g, 18 mmol) in *N*,*N*-dimethylformamide (50 mL)/ethanol (125 mL) and 10% Pd−C (0.5 g) was hydrogenated at 40 psi in a Parr apparatus for 18 h. The catalyst was removed by filtration through Celite and the solvent removed *in vacuo*. The residue was partioned between ethyl acetate and water and filtered to remove an orange solid, and the layers were separated. The aqueous phase was extracted twice more with ethyl acetate, the combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. The resulting oil was chromatographed using a 0−15% ethyl acetate in methylene chloride gradient to yield 5-amino-1,1-dioxo-2-methyl-1,2-benzisothiazol-3(2*H*)-one (1.18 g, 31%): mp 240−3 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) 3.08 (s, 3H, CH_3), 6.62 (s, 2H, NH_2), 6.97 (dd, 1H, J = 8.5, 2.1 Hz, aromatic), 7.06 (d, 1H, J = 2.1 Hz, aromatic), 7.81 (d, 1H, J = 8.5 Hz, aromatic); MS (CI, CH_4) 213 (M + 1). Anal. ($C_8H_8N_2O_3S$) C, H, N.

Also obtained was the corresponding hydroxylamine (1.26 g, 30%): mp 154−6 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) 3.12 (s, 3H, CH_3), 7.19 (dd, 1H, J = 8.6, 2.1 Hz, aromatic), 7.25 (d, 1H, J = 2.1 Hz, aromatic), 7.98 (d, 1H, J = 8.6 Hz, aromatic), 9.13 (s, 1H, NH), 9.58 (s, 1H, OH); MS (CI, CH_4) 229 (M + 1). Anal. ($C_8H_8N_2O_4S$) C, H, N.

General Method E: 4-Cyano-3-(phenylthio)aniline. 3-Chloro-4-cyanoaniline (20.0 g, 0.131 mol) was added to a *N*,*N*-dimethylformamide (115 mL) solution of thiophenol potassium salt [prepared by adding thiophenol (13.5 mL, 0.131 mol) to a solution of potassium hydroxide (7.35 g, 0.131 mol) in methanol followed by removal of the methanol *in vacuo*] and washed in with an additional 15 mL of *N*,*N*-dimethylformamide. After being stirred at 140 °C for 16 h, the mixture was poured into water and extracted with ethyl ether (3 × 150 mL) and the solvent removed *in vacuo* to yield a red oil. The oil was chromatographed on silica gel using methylene chloride as elutent. The fractions containing product (TLC: silica gel, 2% methanol/chloroform) were combined, the solvent was removed, and the material was rechromatographed using 2:1 methylene chloride/hexane as elutent. The proper fractions were combined, concentrated to a low volume, treated with hexane, and cooled (dry ice) and scratched as crystals formed. The white solid weighed 8.29 g (30%): mp 69 −71 °C; ^{1}H-NMR (250 MHz, $CDCl_3$) 4.07 (s, 2H, NH_2), 6.29 (d, 1H, J = 2.2 Hz, aromatic), 6.46 (dd 1H, J = 8.3, 2.2 Hz, aromatic), 7.36−7.50 (m, 6H, aromatic); MS (CI, CH_4) 227 (M + 1). Anal. ($C_{13}H_{10}N_2S$) C, H, N.

General Method F: 4-Amino-3′-fluorobenzophenone. To stirred 90 °C polyphosphoric acid (150 g) was added 10.72 g (7.65 mmol) of 3-fluorobenzoic acid and 6.98 g (7.5 mmol) of aniline, and the bath temperature was raised to 180−190 °C and held there for 1 h. A solution was obtained at about 130 °C. The heating bath was removed, and the stirred mixture (sublimate above the solution) was treated cautiously with 60 mL of water. The mixture was stirred at 140-155 °C for 1 h, the heating bath was removed, 50 mL of 3 N HCl was added, and the mixture was poured into 750 mL of water and filtered through a pad of Celite. The filtrate was basified with 15% sodium hydroxide and the resulting solid extracted with methylene chloride. The dried ($MgSO_4$) solution was filtered and the solvent removed to yield a brown solid. Recrystallization from ethanol−hexane (1:3) returned a greenish yellow solid that was chromatographed on silica gel (methylene chloride) to yield 4.83 g (30%) of yellow 4-amino-3′-fluorobenzophenone: mp 98−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 4.21 (s, 2H, NH_2), 6.66−6.70 (m, 2H, aromatic), 7.23−7.26 (m, 1H, aromatic), 7.39−7.51 (m, 3H, aromatic), 7.69−7.72 (m, 2H, aromatic); MS (CI, CH_4) 216 (M + 1). Anal. ($C_{13}H_{10}FNO$) C, H, N.

Methods for the Preparation of Nitro Aromatics. General Method G1: 4-Nitro-2-cyanophenyl Phenyl Sulfide. 4-Chloro-3-cyanonitrobenzene (12.5 g, 68.4 mmol) was added portionwise to a stirred *N*,*N*-dimethylformamide (50 mL) solution of thiophenol potassium salt [prepared by adding thiophenol (7.1 mL, 69 mmol) to a solution of potassium hydroxide (3.84 g, 68.4 mmol) in methanol followed by removal of the methanol *in vacuo*]. After being stirred at 105 °C for 2.5 h, the mixture was poured into ice water and filtered, and the collected solid was washed with water, dissolved in 300 mL of refluxing ethanol (charcoal), filtered, treated with 35 mL of water, and refrigerated. The resulting pale yellow solid weighed 13.3 g (76%): mp 82−84 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 6.93 (d, 1H, J = 9.0 Hz, aromatic), 7.51−7.62 (m, 5H, aromatic), 8.12(dd 1H, J = 9.2, 2.5 Hz, aromatic), 8.46 (d, 1H, J = 2.5 Hz, aromatic); MS (CI, CH_4) 257 (M + 1). Anal. ($C_{13}H_8N_2O_2S$) C, H, N.

General Method G2: 2-[(4-Nitrophenyl)thio]benzonitrile. A stirred solution of potassium 4-nitrophenylthiolate (10.61 g, 54.9 mmol) and 2-bromobenzonitrile (10.00 g, 54.9 mmol) in dimethylformamide (50 mL) was heated at 95 °C for 22 h. The reaction mixture was poured into ice water, and a yellow solid was collected by filtration. Purification by flash column chromatography (40% v/v methylene chloride−hexane) followed by recrystallization from 90% ethanol yielded 2-[(4-nitrophenyl)thio]benzonitrile (3.25 g, 23%) as a yellow solid: mp 151−153 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) 7.39 (dd, 2H, J = 6.9, 2.2 Hz, aromatic), 7.73−7.75 (m, 1H, aromatic), 7.81−7.84 (m, 2H, aromatic), 8.08 (dd, 1H, J = 7.7, 1.1 Hz, aromatic), 8.19 (dd, 2H, J = 6.9, 2.1 Hz, aromatic); MS (CI, CH_4) 257 (M + 1). Anal. ($C_{13}H_8N_2O_2S$) C, H, N.

(4-Aminophenyl)diphenylphosphine Oxide. To a stirred solution of the (4-acetamidophenyl)diphenylphosphine[36] (1.32g, 4.14 mmol) in ether (100 mL) at room temperature was added hydrogen peroxide (0.6 mL of 30% aqueous, 4.97 mmol). After 10 min the white precipitate which had formed was filtered off, washed with ether, and dried. The resulting phosphine oxide [0.94 g, 68%; ^{1}H-NMR (250 MHz, DMSO-d_6) 2.07 (s, 3H, CH_3), 7.05−7.75 (m, 14H, aromatic), 10.26 (s, 1H, NH); MS (CI, CH_4) 336 (M + 1)] was dissolved in ethanol (100 mL) containing 3 N HCl (50 mL). The solution was refluxed for 6 h, evaporated to low volume, and neutralized with $NaHCO_3$. The solution was then extracted three times with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated to give (4-aminophenyl)diphenylphosphine oxide (0.82 g, 100%) as a white solid. This material was essentially pure and was used in the coupling reaction without further purification: ^{1}H-NMR (250 MHz, DMSO-d_6) 5.82 (s, 2H, NH_2), 6.63 (dd, 2H, J = 8.5 and 2.3 Hz, aromatic), 7.19 (dd, 2H, J =

11.5 and 11.4 Hz, aromatic), 7.54 (m, 10H, aromatic); MS (CI, CH_4) 294 (M + 1).

Supporting Information Available: ORTEP diagrams and tables (with standard deviations) of atomic positional and thermal parameters, bond distances, bond angles, and torsion angles for **41(S)** and **64(S)**; tables listing the structures, method of synthesis, and physical properties of novel intermediate arylamines and nitro compounds as well as additional novel *N*-aryl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamides; and experimental procedures supporting additional methods employed in their synthesis (14 pages). Ordering information is given on any current masthead page.

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