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Assembly of 4-Aminoquinolines via Palladium Catalysis: A Mild and Convenient Alternative to S_NAr Methodology

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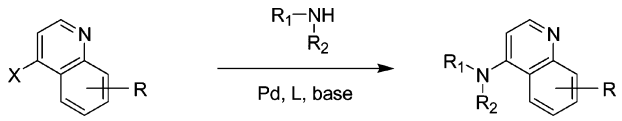


4-Aminoquinolines, classically prepared via S_NAr chemistry from an amine and 4-haloquinoline, are important scaffolds in medicinal chemistry. Interest in these compounds prompted us to explore palladium catalysis as an alternative to the existing methods for their preparation. Initial results followed by an iterative screening paradigm confirmed $Pd(OAc)_2$/DPEphos/K_3PO_4 as a mild and convenient alternative for the formation of the C−N bond in 4-aminoquinolines. A description of the screen and the scope of this methodology are discussed herein.

There are numerous therapeutic agents which highlight the significance of 4-aminoquinolines (4-AQ's) as important scaffolds in medicinal chemistry, including: those able to treat malaria,[1] cancer,[2] gastric disorders,[3] and those able to activate targets in the central nervous system (Figure 1).[4]

Historically, the assembly of 4-AQ's involves a S_NAr reaction between the requisite amine and a 4-haloquinoline (usually chloro). The S_NAr reaction is often carried out neat, or in the presence of phenol, at elevated temperatures (∼100−160 °C).[5] Isolating the desired product can be difficult since the reaction mixtures tend to solidify upon cooling and require an acid/base extraction to remove the excess phenol. Interest in these structures prompted us to explore palladium-catalyzed amination chemistry[6] as a mild and convenient alternative to classical methodologies for the synthesis of 4-AQ's. In these cases, one can simply adsorb the crude reaction mixture onto silica gel and purify directly, thus avoiding a formal aqueous workup and making this attractive for small scale or parallel reactions.

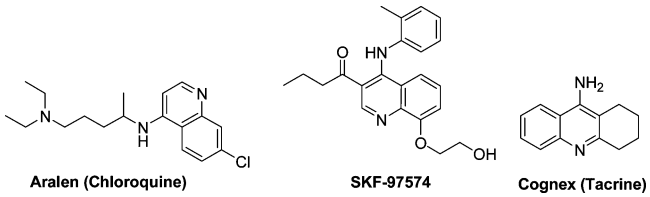
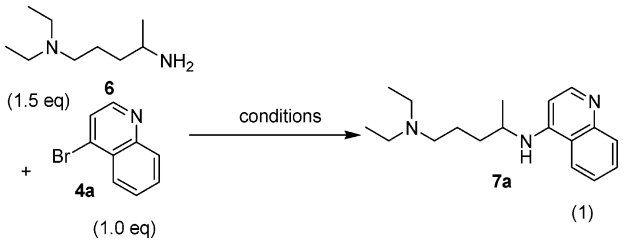


FIGURE 1. Marketed drugs/drug candidates containing a 4-AQ core.

Encouraged by an initial result with $Pd(OAc)_2$/DPEphos/K_3PO_4 in toluene to couple 4-bromoquinoline (**4a**) with a primary alkylamine, a series of iterative screens to optimize this catalyst system were undertaken in a controlled fashion selecting the α-methyl amine (**6**) present in chloroquine as a representative amine in these studies (eq 1).



Recognizing that an exhaustive matrix evaluation was impractical given the number of possible permutations, we took a three-step approach in the following order: (1) solvents, (2) bases, and (3) phosphine ligands. The decision was made to use only one palladium source [precatalyst $Pd(II)(OAc)_2$] for this work. In addition, for convenience, an artificial end point of 18 h was imposed for the reactions. For the base and phosphine screens, reactions were analyzed by analytical HPLC, and yields were calculated relative to an internal standard (IS).[7]

Using the $Pd(OAc)_2$/DPEphos/K_3PO_4 system, several solvents including dioxane, PhMe, and DME were evaluated. Either dioxane or PhMe was found to be optimal (these results were not quantitated). Of these, dioxane was chosen for further study mainly for its relatively low boiling point and low UV cutoff. A small survey of bases commonly used in palladium-catalyzed aminations was preformed as the second iteration; K_3PO_4 was found to be optimal for this system (Table 1).

† Participant in the 2006 Lilly Corporate Summer Intern Program.

(1) Chloroquine exemplifies a class of 4-AQ antimalarial agents. Also see: (a) O'Neill, P. M.; Ward, S. A.; Berry, N. G.; Jeyadevan, J. P.; Biagini, G. A.; Asadollaly, E.; Park, K. B.; Bray, P. G. *Curr. Top. Med. Chem.* **2006**, *6* (5), 479−507. (b) Madrid, P. B.; Sherrill, J.; Liou, A. P.; Weisman, J. L.; DeRisi, J. L.; Guy, R. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1015−1018. (c) Pradines, B.; Tall, F.; Ramiandrasoa, A.; Spiegel, C.; Sokhna, C.; Fusai, J.; Mosnier, J.; Daries, W.; Trape, J. F.; Kunesch, G.; Parzy, D.; Rogier, C. *J. Antimicrob. Chemother.* **2006**, *57* (6), 1093−1099. (d) Biot, C.; Daher, W.; Chavain, N.; Fandeur, T.; Khalife, J.; Dive, D.; De Clercq, E. *J. Med. Chem.* **2006**, *49* (9), 2845−2849.

(2) Ruchelman, A. L.; Singh, S. K.; Abhijit, R.; Wu, X. H.; Yang, J.; Li, T.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2061−2073.

(3) SKF-97574 was in Phase III clinical trials for the treatment of upper gastrointestinal ulcers. (a) Leach, C. A.; Brown, T. H.; Ife, R. J.; Keeling, D. J.; Parsons, M. E.; Theobald, C. J.; Wiggall, K. J. *J. Med. Chem.* **1995**, *38* (14), 2748−2762. (b) Atkins, R. J.; Breen, G. F.; Crawford, L. P.; Grinter, T. J.; Harris, M. A.; Hayes, J. F; Moores, C. J.; Saunders, R. N.; Share, A. C.; Walsgrove, T. C.; Wicks, C. *Org. Process Res. Dev.* **1997**, *1*, 185−197.

(4) Tacrine is approved to treat the symptoms of Alzheimer's disease. For a series of 4-aminoquinoline-based H_3 antagonists, see: Turner, S. C.; Esbenshade, T. A.; Bennani, Y. L.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2131−2135.

(5) (a) Surrey, A. R.; Hammer, H. F. *J. Am. Chem. Soc.* **1946**, *68*, 113−116. (b) Surrey, A. R.; Cutler, R. *A. J. Am. Chem. Soc.* **1951**, *73*, 2623−2626.

(6) (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negiahi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1051. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209.

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TABLE 1. Survey of Common Bases

entry[a]	base[b]	% yield **7a**[c]
1	K_3PO_4	89
2	NaO*t*-Bu	78
3	K_2CO_3	39

[a] Reactions were run in dioxane, using 4 mol % $Pd(OAc)_2$/8 mol % DPEphos, then analyzed after 18 h at 85 °C. [b] Molar ratio of base to bromide was 2.5. [c] Yield as detected by quantitative HPLC using 4,4′-dimethoxybiphenyl as IS.

TABLE 2. Screen of Phosphine Ligands

entry[a]	ligand[b]	% yield **7a**[c]	entry[a]	ligand[b]	% yield **7a**[c]
1	DPEphos	**95**	10[g]	dtbf	50
2	(*R*)-BINAP	**94**	11[h]	PCy_2 biphenyl	50
3[d]	P(*t*-Bu)$_3$	**92**	12	CTC-Q-Phos	49
4	S-Phos	85	13[i]	PPh_2 NMe_2 biphenyl	44
5	DPPF	84	14[8,j]	PEPPSI	40
6	DavePhos	73	15[9,j]	(IPr)Pd(acac)Cl	37
7[e]	PCy_2 Me biphenyl	71	16	X-Phos	18
8	Xantphos	64	17[k]	P(*t*-Bu)$_2$ Me biphenyl	11
9[f]	dippf	58	18	PPh_3	5

[a] Each reaction ran for 18 h at 85 °C with 5 mol % $Pd(OAc)_2$. [b] The per-atom ratio of P:Pd for this screen was held constant at 4:1. Therefore, 20 mol % of L was used for monodentate ligands, and 10 mol % for bidentate ligands. Except where indicated by reference or CAS number, names are as listed on www.strem.com. [c] Yield as detected by quantitative HPLC using 4,4′-dimethoxybiphenyl as IS. [d] Also used was the [(*t*-$Bu_3PH)BF_4$] salt which gave an identical yield.[10] [e] CAS [251320−86-2]. [f] CAS [97239-80-0]. [g] CAS [84680-95-5]. [h] CAS [247940-06-3]. [i] CAS [240417-00-9]. [j] KO*t*-Bu was used as the base in DME. [k] CAS [255837-19-5].

TABLE 3. Varying the Ratio of P:Pd

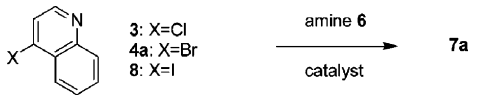
entry[a]	% yield **7a**[b]	P:Pd ratio[c]
1	95	4:1
2	89	2:1
3	35	1:1

[a] Reactions were run in dioxane, using 4 mol % of $Pd(OAc)_2$, then analyzed after 18 h at 85 °C. [b] Yield as detected by quantitative HPLC using 4,4-dimethoxybiphenyl as IS. [c] Expressed on a per-atom basis.

A diverse sampling of phosphine ligands was selected to build upon the DPEphos result. Several of these gave high HPLC yields (identical, within experimental error) of coupled product **7a** (Table 2, entries 1−3).

Cost was selected as a filter criterion, and DPEphos was chosen for further study.[11] Since our initial experiments used a per-atom ratio of P:Pd of 4:1, we wondered if a lower phosphine loading would work equally as well in the chosen 18 h time window. We found that a ratio of 4:1 was superior to a lower phosphine loading; however, good conversion was also obtained with a 2:1 ratio (Table 3, entries 1 and 2).

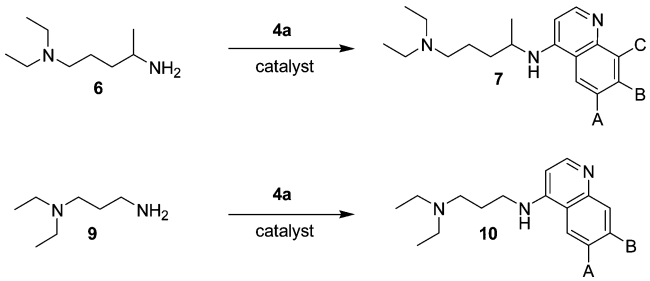
TABLE 4. Quinoline Substrate Scope (1)



entry[a]	X	HPLC yield, %[b]	isolated yield, % **7a**[c]
1	Cl	93	92
2	Br	95	88
3	I	52	N/A

[a] Reactions were run in dioxane, using 4 mol % $Pd(OAc)_2$/8 mol % DPEphos, then analyzed after 18 h at 85 °C. [b] Yield relative to IS 4,4′-dimethoxybiphenyl. [c] Isolated yield averaged from 2 runs which were adsorbed onto silica and purified after 18 h at 85 °C

TABLE 5. Quinoline Substrate Scope (2)



A	B	C	isolated yield, % **7**[a]	isolated yield, % **10**[a]
H			88 (**7a**)	
SMe			63 (**7b**)	
OMe			78 (**7c**)	
	Cl		74 (**7d**)	
Br			58[b,c] (**7e**)	65[b] (**10e**)
	NO_2		32[c] (**7f**)	74 (**10f**)
CN			51[d] (**7h**)	85 (**10h**)
CO_2Me			75 (**7i**)	
F		F	74 (**7j**)	
OMe	OMe		79 (**7k**)	

[a] Average of 2 runs; reactions were cooled and adsorbed onto silica gel, then purified after 18 h at 85 °C; when appropriate, yields have been adjusted down to account for any trace solvents present as detected by ^{1}H NMR. [b] Isolated as a mixture of 4-amino-6-bromo/4-bromo-6-amino with a ratio of 15:1 by ^{1}H NMR. [c] Reaction did not go to completion after 18 h. [d] Reduced quinoline was detected in crude reaction by ESMS but never isolated.

This process most likely proceeds by a Pd-catalyzed mechanism as demonstrated by a control experiment lacking the Pd-$(OAc)_2$. Under these conditions, no **7a** was detected even after one week at 85 °C. To summarize the results of the screen iterations, an optimized set of conditions for this reaction follow: 1.0 equiv of halide, 8 mol % DPEphos/4 mol % Pd-$(OAc)_2$, 1.5 equiv of amine, 2.5 equiv of K_3PO_4 in dioxane at 85 °C.[12]

In an attempt to demonstrate the generality of these reaction conditions, additional quinolines were prepared and/or purchased. Scheme 1 depicts the synthetic route used to generate

(7) Yields are reported with a 95% measurement error prediction interval. The prediction interval reflects both the uncertainty in the measure for each reaction condition as well as the two-point calibration used within each batch. The interval was derived assuming normally distributed errors for the AUC measurements, scaling of the reaction product AUC values to the spiked internal standard AUC value within each injection, a correlation coefficient of 0.7 between the AUC of the product of interest and the internal standard across repeated injections, and a constant AUC total coefficient of variation estimated from the between and within batch variance from the spiked internal standard AUC values.

(8) *Aldrich Chem. Files* **2006**, *6* (3).

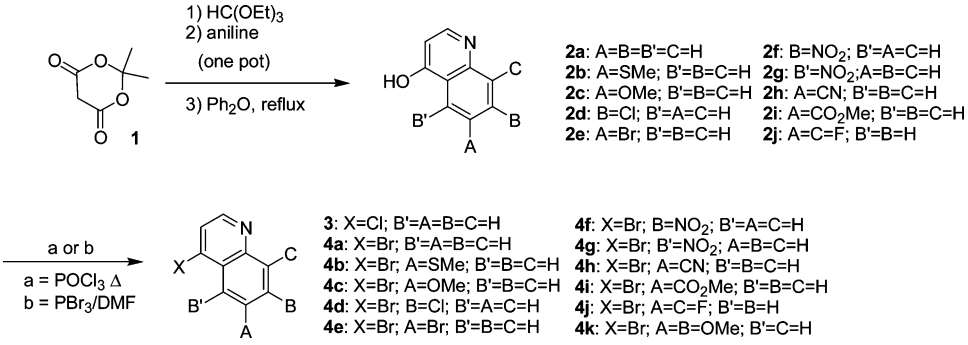
(9) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816−3821.

(10) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

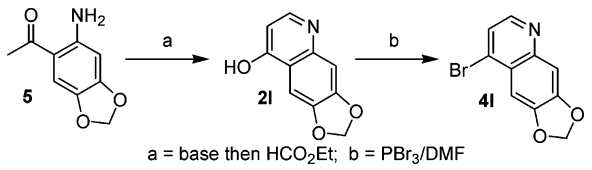
(11) Strem Catalog No. 20 (2004−2006).

(12) During the course of our investigation, Beletskaya and co-workers reported the amination of 4-chloroquinoline derivatives under the influence of palladium catalysis employing either BINAP or DPPF derivatives as ligands, see: Beletskaya, I. P.; Tsvetkob, A. V.; Latyshev, G. V.; Lukashev, N. V. *Russ. Chem. Bull. Int. Ed.* **2005**, *54* (1), 215−219.

SCHEME 1. Preparation of 4-Haloquinolines



SCHEME 2. Alternative Preparation of Substituted 4-Haloquinolines



the 4-haloquinolines from their respective anilines.[13] Noteworthy is the possibility of regioisomers in the instances when the desired quinoline is derived from a meta-substituted aniline (for example, **2f** and **2g**). In our hands, these isomers were separated by silica gel chromatography after the bromination step to give pure **4f** and **4g**, respectively.

Scheme 2 shows a complementary methodology particularly useful for accessing quinolines in a regiospecific fashion, starting from the requisite substituted *o*-aminoacetophenone.[14]

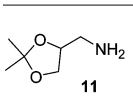
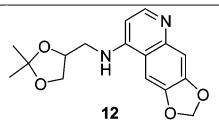
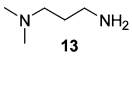
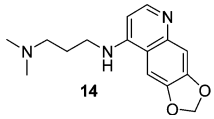
As alluded to in Scheme 1, one can easily convert a quinolin-4-ol to its corresponding 4-haloquinoline (chloro or bromo) via treatment with either $POCl_3$ at reflux[5] or PBr_3/DMF, respectively.[15] Operationally, we feel that preparation of the bromide over the chloride is advantageous for two reasons: (1) the reaction conditions are mild and rapid (ambient temperature versus refluxing $POCl_3$) and (2) products are easily isolated from the reaction mixture (via a precipitation from water or sodium bicarbonate (aq) then filtration versus *in vacuo* removal of $POCl_3$ followed by careful neutralization and a formal aqueous workup).

In general, the coupling reaction with 8 mol % DPEphos/4 mol % $Pd(OAc)_2$, 1.5 equiv of amine, and 2.5 equiv of K_3PO_4 in dioxane at 85 °C tolerates both 4-chloroquinoline (**3**) and 4-bromoquinoline (**4a**) (Table 4). Interestingly, this catalyst system did not work well with an iodo group (Table 4, entry 3). After the 18 h time period, unreacted iodo starting material (**8**) was detected along with coupled product (**7a**) and a small amount of dehalogenated quinoline (amount not quantitated).

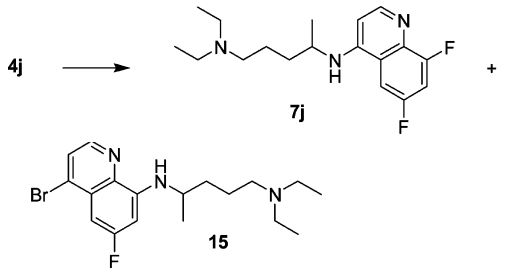
In general, the coupling reaction tolerates a range of electronic effects on the quinoline as shown in Table 5. Several examples did give a low yield when the coupling partner was α-methylamine **6** (compounds **7e**,**f**,**h**). These bromoquinolines were evaluated with another amine lacking the α-substitution (**9**). As shown by the notable increase in yield (Table 5, **10e**,**f**,**h**), the α-methylamine is a more challenging substrate for this reaction.

Direct comparison to a literature example with 4-chloro-6,7-methylenedioxyquinoline and two different amines demonstrates the advantages of the Pd-catalyzed amination route to 4-AQ's (Table 6).

TABLE 6. Direct Comparison to Literature Examples

amine	product	isolated yield Pd catalysis[a]	isolated yield S_NAr[2]
 11	 12	85 %	34 %
 13	 14	85 %	25 %

[a] Average of 2 runs; reactions were cooled and adsorbed onto silica gel, then purified after 18 h at 85 °C.



An additional advantage is realized with polyhaloquinolines (eq 2). In our hands, the S_NAr conditions reported by Surrey and Cutler[5b] with 4-bromo-6,8-difluoroquinoline (**4j**) generated a mixture of 4-substituted **7j** and 8-substituted **15** in a ratio of approximately 1:2 after chromatography with the desired 4-substituted **7j** being the minor component. The Pd-catalyzed conditions are specific for the formation of **7j** (74 % isolated yield with no detectable **15** present).

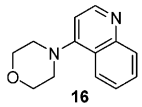
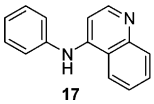
Amine substrate scope was expanded to include a secondary amine and an aniline, both of which ran in moderate to good yield (Table 7).

(13) (a) Davies, D. T.; Elder, J. S.; Forrest, A. K.; Jarvest, R. L.; Pearson, N. D.; Sheppard, R. J. WO 2004/014361A1 (PCT Int. Appl.), Feb 19, 2004. (b) Walz, A. J.; Sundberg, R. J. *J. Org. Chem.* **2000**, *65* (23), 8001−2010. (c) Gordon, H. J.; Martin, J. C.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1983**, 957−958.

(14) (a) Kubo, K.; Shimizu, T.; Ohyama, S.; Murooka, H.; Iwai, A.; Nakamura, K.; Hasegawa, K.; Kobayashi, Y.; Takahashi, N.; Takahashi, K.; Kato, S.; Izawa, T.; Isoe, T. *J. Med. Chem.* **2005**, *48* (5), 1359−1366. (b) Ruchelman, A. L.; Houghton, P. J.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **2005**, *48* (3), 792−804. (c) Osawa, T.; Kubo, K.; Murooka, H.; Nakajima, T. WO 98/47873 (PCT Int. Appl.), Oct 29, 1998. (d) Nakajima, T.; Kamimasahara, M.; Matsunaga, N. JP 2002/030083A (Jpn. Kokai Tokkyo Koho), Jan 29, 2002.

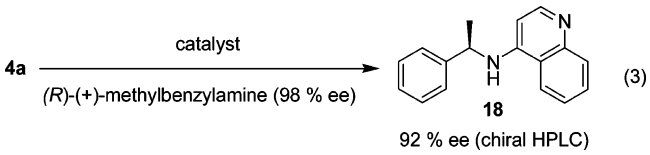
(15) Axten, J. M.; Daines, R. A.; Davies, D. T.; Gallagher, T. F.; Jones, G. E.; Miller, W. H.; Pearson, N. D.; Pendrak, I. (PCT Int. Appl) WO2004/002992 A1, Jan 8, 2004.

TABLE 7. Amine Substrate Scope

entry	amine	product	isolated yield[a]
1	**6**	**7a**	88 %
2	morpholine	 **16**	86 %
3	aniline	 **17**	77 %[b]

[a] Average of 2 runs; reactions were cooled and adsorbed onto silica gel, then purified after 18 h at 85 °C; when appropriate, yields have been adjusted down to account for any trace solvents present as detected by ^{1}H NMR. [b] This example gives a challenging mixture to purify; several mixed fractions were discarded in both cases.

Finally, the racemization of α-chiral amines has been observed in Pd-catalyzed reactions.[16] It was proposed that the coupling reaction of (*R*)-(+)-α-methylbenzylamine and **4a** would be a good measure of this effect with this catalyst system (eq 3). As expected with a bidentate phosphine ligand, the reaction proceeded with only a small erosion of enantiomeric excess (from 98 % ee to 92 % ee).



(3)

Herein we have demonstrated an alternative methodology for the synthesis of 4-aminoquinolines. The key step in this methodology exploits palladium catalysis to form the desired C−N bond under conditions that are milder and debatably more convenient than the existing S_NAr methodology. The described conditions were rapidly optimized by using an iterative screening technique, and the catalyst system was shown to be effective for a variety of quinoline/amine combinations.

(16) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.

Experimental Section

General Procedure for Palladium Catalyzed Amination of 4-Haloquinolines. An oven-dried 40-mL vial was charged with the 4-haloquinoline (1.0 mmol), $Pd(OAc)_2$ (4 mol %), DPEphos (8 mol %), K_3PO_4 (2.5 mmol), and the requisite amine (1.5 mmol). An upside-down 24/40 septum was placed over the vial and an 18 gauge needle inserted (as a vent) while the resulting mixture was purged with argon or nitrogen for several minutes through a second needle. Dioxane (4 mL) was introduced through the septum. The resulting suspension was sparged with argon or nitrogen for 3−5 min. The vial was quickly capped, then heated to 85 °C (block temp) for 18 h and cooled. The mixture was adsorbed onto silica gel and purified. Solvent systems for chromatography were based on either mixtures of EtOH (contains 10% NH_4OH)/CH_2Cl_2 or THF/hexanes (THF/hexanes mix contains 2% dimethylethylamine, and THF is inhibitor free).

Acknowledgment. We thank Michael Kalbfleisch for helpful discussions and guidance in the development of our quantitative HPLC assay and Robert D. Boyer for helpful discussions surrounding ^{1}H, ^{13}C, and ^{19}F NMR leading up to the characterization of several of the compounds reported herein. We also acknowledge the efforts of Richard E. Higgs for performing the statistical analysis on the data set generated from our screen. Finally, we thank James R. McCarthy for helpful discussions surrounding the preparation of this manuscript.

Supporting Information Available: Additional experimental procedures and spectral characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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