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Development of a New Variant of the Migita Reaction for Carbon−Sulfur Bond Formation Used in the Manufacture of Tetrahydro-4-[3-[4-(2-methyl-1*H*-imidazol-1-yl)phenyl]thio]phenyl-2*H*-pyran-4-carboxamide

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Abstract:

Palladium-catalyzed carbon−sulfur bond formation using modified Migita reaction conditions was explored and applied to the synthesis of a former antiasthma drug candidate, tetrahydro-4-[3-[4-(2-methyl-1*H*-imidazol-1-yl)phenyl]thio]phenyl-2*H*-pyran-4-carboxamide (5). The reaction was developed into a general method for thioaryl halide cross-coupling, and a specific example of its use to synthesize a key intermediate, tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2*H*-pyran-4-carboxamide (6) was demonstrated at large scale to provide phase II clinical supplies of 5. Comparison of the multistep phase I process and the two-step phase II process showed an overall yield advantage over the bond-forming steps from common starting material (1) to API 5 of 40%. The ligand effect in the modified Migita reaction is described in detail. The second step of the scale-up process illustrated formation of carbon−nitrogen bonds without use of palladium catalysis, providing a contrast to the first reaction; both reactions were developed into efficient single-vessel direct isolation processes.

Introduction

Active pharmaceutical ingredient (API) **5** was a former antiasthma candidate that required scale-up for phase II operations in the drug development timeline. The early synthetic route for phase I is shown in Scheme 1 and consists of five bond-forming steps from **1** through **5** via intermediates **2**, **3**, and **4**.

The motivation for the improvement work was to reduce the cost of goods by reducing the number of steps and isolations by developing a streamlined process. A new[1] modification of the Migita reaction[2] was used to achieve the end result. The new process used for phase II clinical studies was reduced to two steps as shown in Scheme 2. The first reaction is a palladium-catalyzed coupling with an auxiliary ligand used to speed up the reaction kinetics to form a carbon−sulfur bond and concomitant hydrolysis of the nitrile functional group to amide. Both the carbon−sulfur bond formation and nitrile hydrolysis are promoted by use of potassium hydroxide which provides a neat tandem result. The second reaction is aromatic nucleophilic substitution of fluorine with 2-methylimidazole promoted by cesium carbonate.

Development of the Modified Migita Reaction. The original Migita reaction[3] provides a high-yielding route for the formation of diarylthioethers by reaction of aryl iodides with thiophenols in the presence of a strong alkoxide base, sodium *tert*-butoxide in an aprotic solvent such as DMSO, catalyzed by $Pd(PPh_3)_4$; see Scheme 3, part a. The reaction was carried out at ∼100 °C, with yields in the range 51−100%. The reaction also worked using alkylthiols. Solvents other than DMSO could be used, for example DMF, acetonitrile, *n*-butanol, or ethanol. These solvents with the exception of *n*-butanol usually gave lower yields. Aryl bromides also tended to give lower yields than corresponding iodides in this reaction, and aryl chloride examples showed little or no reaction with thiophenols.

In the synthesis of target molecule **5** there was an opportunity to carry out concomitant nitrile hydrolysis to amide as well as the desired formation of a diarylthioether by formation of a carbon−sulfur bond. Additionally it was decided to target the aryl bromide, **1** (rather than the iodide), as a cheaper more accessible intermediate. During the initial stage of the investigation into the phase II route design it was determined that a catalytic quantity of bidentate phosphorus ligands significantly accelerated the rate of reaction. This resulted in improved coupling yields at lower reaction temperatures in an environmentally friendly solvent, 2-propanol. It turned out that the reaction shown in Scheme 3, part b, using catalytic quantities of $Pd(PPh_3)_4$ and (*S*)-BINAP[4] [or (*R*)-BINAP] was quite generally applicable to aryl bromides and thiophenols. Experimental details are contained in the Supporting Information and Table 1 (see later). In addition to the work reported here it should be noted that other workers have investigated improvements to the Migita reaction, for example use of CyPF-*t*-Bu ligand which allowed aryl chlorides to partner in the coupling[5] and some other general methods which also allowed coupling of aryl chlorides and bromides.[6] Interestingly use of BINAP ligand was not useful in the methodology described by Buchwald, illustrating the subtlety of catalytic Pd and ligand combinations in these types of reactions.

Kinetics and Reaction Pathway. Initially using the original Migita conditions with only catalytic $Pd(PPh_3)_4$ and no additional ligand, but in refluxing 2-propanol with 2 moles KOH (relative to the limiting reagent **1**) it was possible to obtain the

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(1) This work was carried out in the timeframe 1997−1999. An oral presentation of the catalytic process was made at the XIXth International Symposium on Organic Chemistry of Sulfur (ISOCS) held in Sheffield UK, June 25, 2000.

(2) Migita, T; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385–1389.

(3) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, *1*, 3–14. See also table in ref 2 on p 1386 for full details.

(4) (*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl.

(5) Fernandez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181.

(6) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397–7403.

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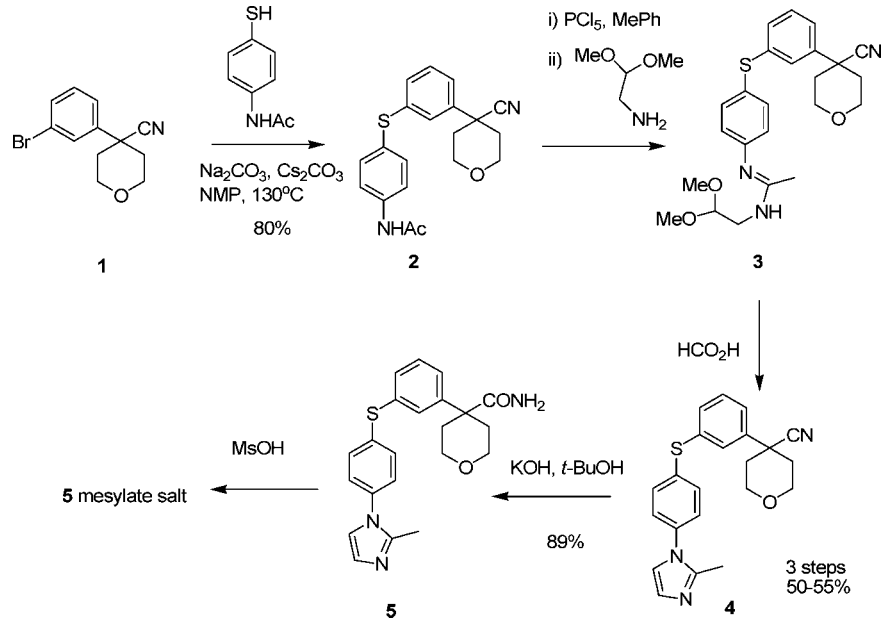
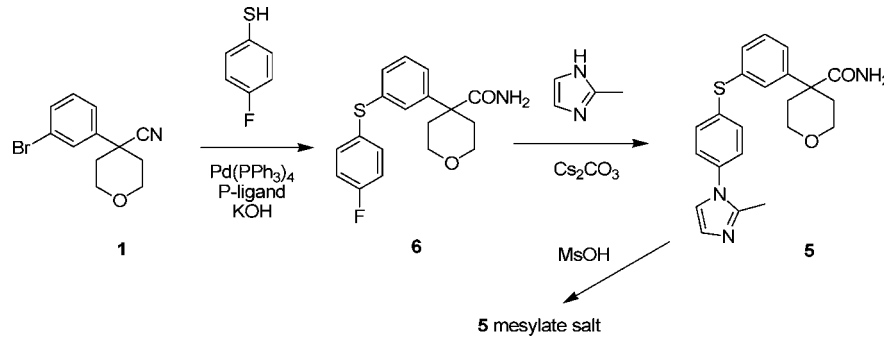
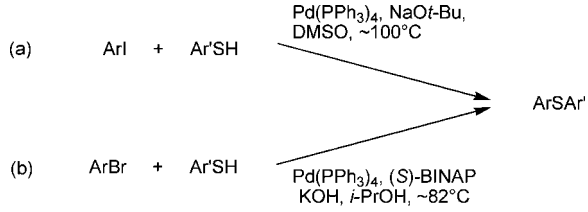
Scheme 1. **Synthesis of 5 used for phase I clinical studies**



Scheme 2. **Synthesis of 5 used for phase II clinical studies**



Scheme 3. **(a) Original Migita reaction; (b) modified Migita reaction**



key intermediate **6** (Scheme 2). These reaction conditions successfully formed the desired carbon−sulfur bond and hydrolyzed the nitrile to amide at the same time. The yield obtained was 62%. When a catalytic quantity of monodentate phosphorus ligand PPh_3 was added, the yield was improved to 74%, and when a catalytic quantity of (*S*)-BINAP was added, the yield improved to 82%. These reactions are detailed in the Experimental Section. A large-scale manufacturing procedure for the (*S*)-BINAP reaction is also noted in the Experimental Section and is based on a 45-kg input for the limiting reactant, **1**.

Focusing on the successful BINAP result led to the careful examination of the reaction kinetics under different conditions, such as when catalytic BINAP was used in various forms and when it was absent form the reaction. This demonstrated that pure enantiomeric (*S*)- or (*R*)- BINAP gave the best results and, somewhat surprisingly, racemic BINAP gave slower kinetic results which were intermediate between enantiomeric BINAP and absence of BINAP (Figure 1). Water had a small impact on the reaction kinetics. The reactions were carried out under nitrogen but did not require rigorous exclusion of oxygen, which some catalytic palladium processes require.

So that the reaction pathway could be studied, the transient intermediates and residual trace intermediates observed by HPLC were identified and independently synthesized to confirm their structure (see Experimental Section for description of details). The amide **7** and the nitrile **8** are transient, but stable, intermediates observed in the modified Migita reaction. The ultimate hydrolysis product, carboxylic acid **9** (see Experimental Section) derived from amide **6** was usually observed as a trace impurity at the end of reaction. Compound **9** never grew to a significant impurity when the reaction was run for modestly extended reaction times, confirming the reaction's robustness making it suitable for scale-up. The Migita reaction was monitored by HPLC until the reaction was complete. The conditions outlined in Scheme 3, part b, were used; *p*-fluorothiophenol and nitrile **1** were reacted in equimolar proportions in 2-propanol (5 mL g^{-1}) at ~82 °C with potassium hydroxide (2 equiv) and catalytic $Pd(PPh_3)_4$ (0.01 equiv). BINAP, if used, was added catalytically at 0.02 equiv. The results obtained are plotted

Table 1. **Formation of diarylsulfides from aryl bromides and thiophenols using catalytic quantities of phosphorus ligand (*S*)-BINAP and $Pd(PPh_3)_4$ complex**

ArBr	Ar′SH	ArSAr′	yield (%)	$Pd(PPh_3)_4$ (rel mol)	(*S*)-BINAP (rel mol)	reaction time (h)
3-bromotoluene	thiophenol	phenyl-3-tolylsulfide	96	0.005	0.01	21
3-bromoanisole	thiophenol	phenyl-3-methoxyphenylsulfide	97	0.005	0.01	21
4-bromoanisole	thiophenol	phenyl-4-methoxyphenylsulfide	93	0.005	0.01	23
3-bromoanisole	4-methylbenzenethiol	3-methoxyphenyl-4′-tolylsulfide[a]	38	0.01	0.02	4
3-bromotoluene	4-thiocresol	3-tolyl-4′-tolylsulfide	83	0.01	0.02	4
3-bromotoluene	4-methoxybenzenethiol	4-methoxy phenyl-3′-tolylsulfide	88	0.01	0.02	4
3-bromotoluene	4-fluoro benzenethiol	4-fluoro phenyl-3′-tolylsulfide	93	0.01	0.01	6
4-bromotoluene	4-methoxy benzenethiol	bis (4-methoxyphenyl)sulfide	88	0.005	0.01	23
4-bromoanisole	4-fluoro benzenethiol	4-fluoro phenyl-4′-methoxyphenylsulfide	93	0.005	0.01	23
1-bromo-3-fluorobenzene	4-fluoro benzenethiol	3-fluorophenyl-4′-fluorophenylsulfide[a]	87	0.005	0.01	4
3-bromoanisole	4-fluorobenzenethiol	4-fluorophenyl-3′-methoxyphenylsulfide[a]	80	0.01	0.02	4
3-bromoanisole	4-methoxybenzenethiol	3-methoxyphenyl-4′-methoxyphenylsulfide	57	0.01	0.02	6

[a] New compound.

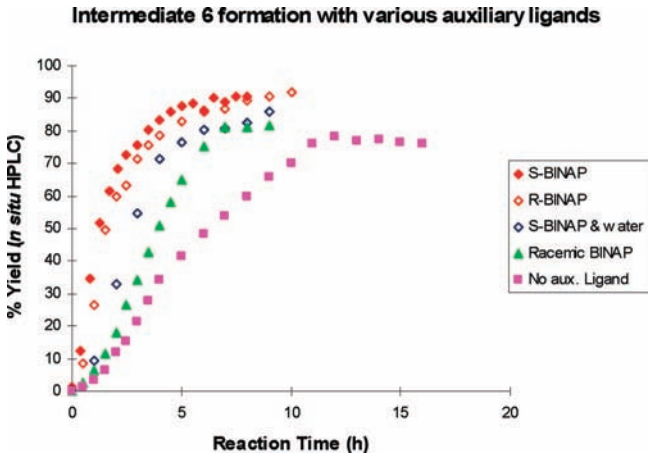


Figure 1. **Kinetics of formation of intermediate 6 under various conditions. (HPLC).**

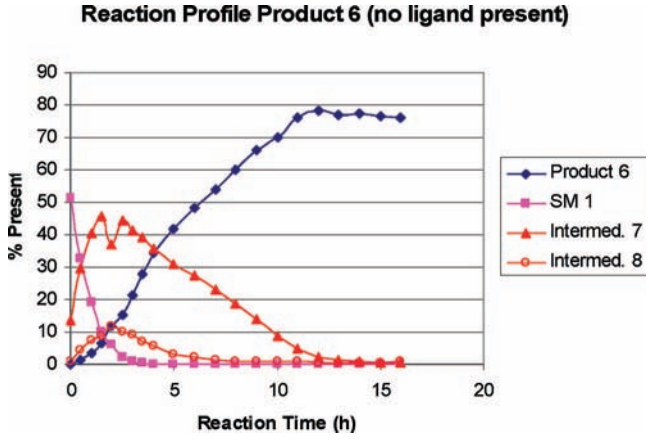


Figure 2. **Formation of 6, decay of starting material 1, intermediates 7, and 8 with no auxiliary ligand.**

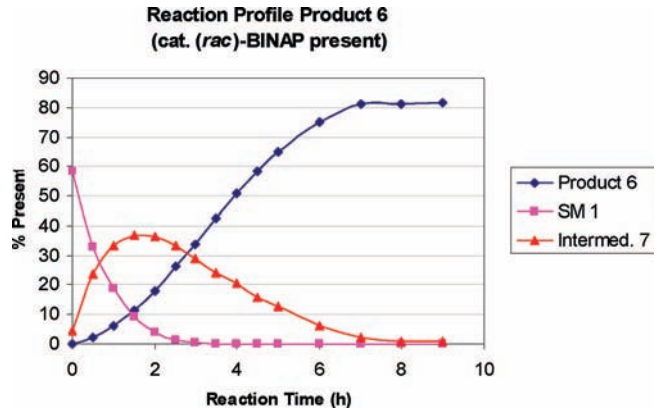


Figure 3. **Formation of 6, decay of starting material 1 and predominant intermediate 7 with catalytic (*rac*)-BINAP.**

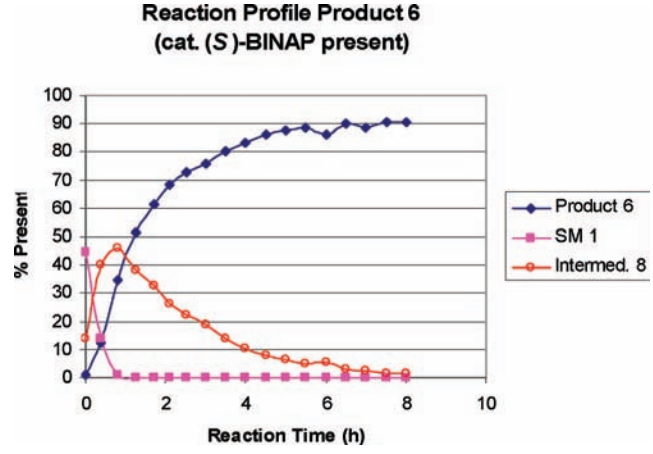
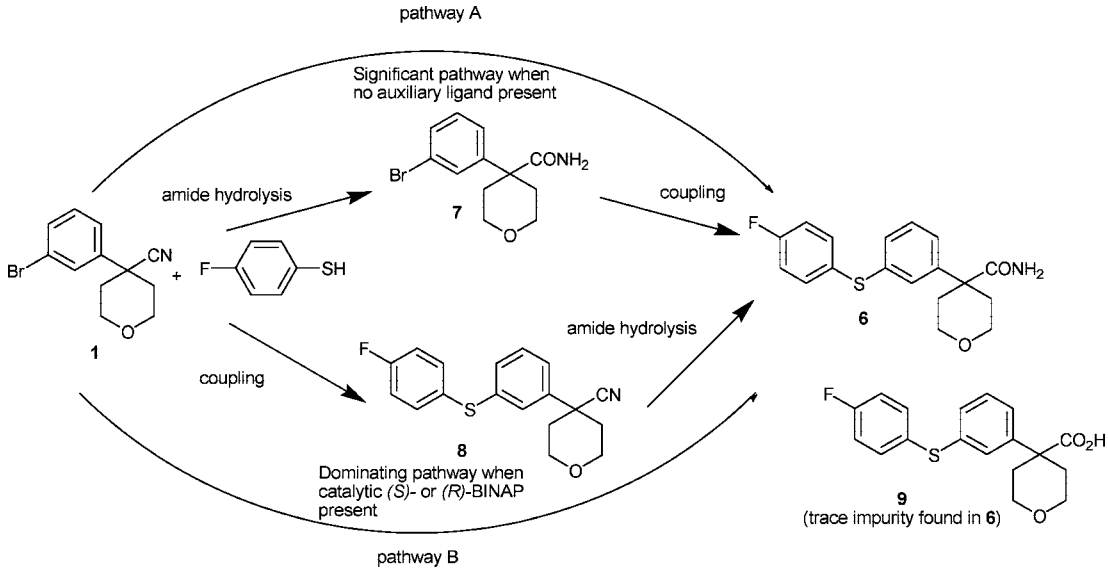


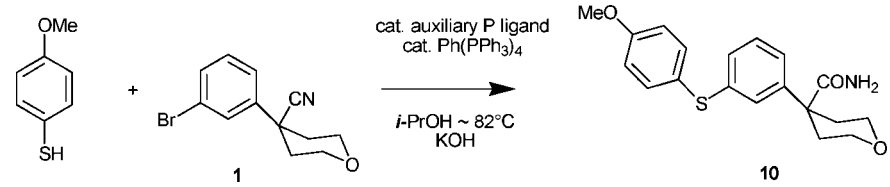
Figure 4. **Formation of 6, decay of starting material 1 and predominant intermediate 8 with catalytic (*S*)-BINAP.**

in Figures 2, 3, and 4. Figure 2 shows that when no additional auxiliary ligand was present the time to reaction completion was approximately double that when some form of bidentate ligand such as BINAP was present. In this case it appears that the amide **7** was the initially formed intermediate, indicating that hydrolysis of the nitrile function occurs prior to carbon−sulfur bond formation (pathway A in Scheme 4). Some product was formed by pathway B as intermediate **8** was observed to form and decay also but at a much lower concentration than intermediate **7**. Pathway A was observed as predominant, when racemic BINAP was introduced at catalytic levels, although the reaction time to final product **6** was faster than when no ligand was used (Figure 3). However, when catalytic quantities of (*S*)-BINAP were introduced, Figure 4 shows that carbon−sulfur bond formation occurs first, forming nitrile intermediate **8** followed by hydrolysis to yield **6**, thus indicating pathway B, Scheme 4, predominated for this example. It should be pointed out that in

Scheme 4. **Reaction pathways observed during formation of intermediate 6**



Scheme 5. **Formation of amide 10 in model system**



these cases the predominating pathway was not exclusive. The minor intermediate in each case and residual trace intermediate **9** were omitted from Figures 3 and 4 for clarity.

We also examined briefly a related model system in which fluorine was replaced with methoxide in the thiophenol moiety to see if there was any possibility of some generality of the ligand effect. Thus, *p*-methoxythiophenol reacted with **1** to form **10** (Scheme 5). It was demonstrated using HPLC reaction monitoring that in this system the rate of formation of **10** depended on the presence of a bidentate ligand and was in the order (*S*)-BINAP > (*rac*)-BINAP > no auxiliary ligand, similar to the API synthesis case (Figure 5).

Mechanism Discussion. Palladium-catalyzed carbon−sulfur bond formation, first reported by Migita, led to other carbon−heteroatom bond formations catalyzed by palladium salts or complexes. The use of auxiliary ligands to improve the catalytic efficiency has been reported by Hartwig[7] and Buchwald.[8] Hartwig has studied carbon−sulfur bond formation and has isolated a series of palladium complexes of general formula [(L)Pd(R)(SR′)] containing sulfur[9] that are almost certainly intermediates in the catalytic cycle of the carbon− sulfur bond-forming process. A reaction related to the one we developed using aryl triflates in place of aryl bromides has been reported.[10] See also Hartwig's mechanistic study on carbon−nitrogen bond formation using palladium catalyst and BINAP.[11]

The data collected in the current study cannot explain in a rigorous way the differences observed between racemic BINAP and optically pure BINAP because the overall reaction rates to **6** are complicated by the simultaneous nitrile hydrolysis reaction, which results in different pathways being observed. It should be pointed out that the Pd cross-coupling reaction is affected by the type of ligand present, but the concomitant hydrolysis

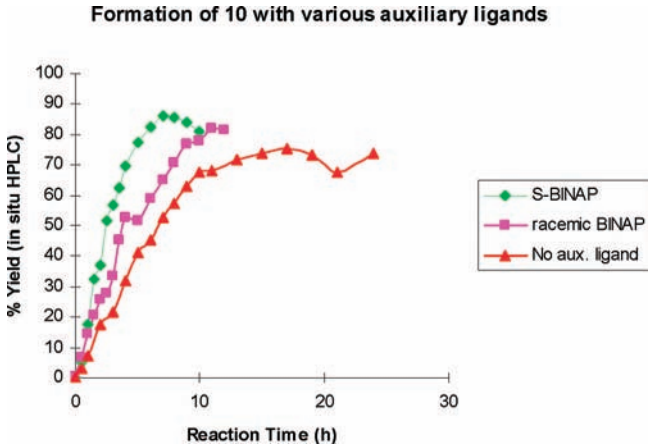


Figure 5. **Kinetics of formation of intermediate 10 under various conditions.**

(7) (a) Hartwig, J. F *Acc. Chem. Res.* **1998**, *31* (12), 852–860. (b) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618–4630. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370. (e) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005–8008. (f) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245.

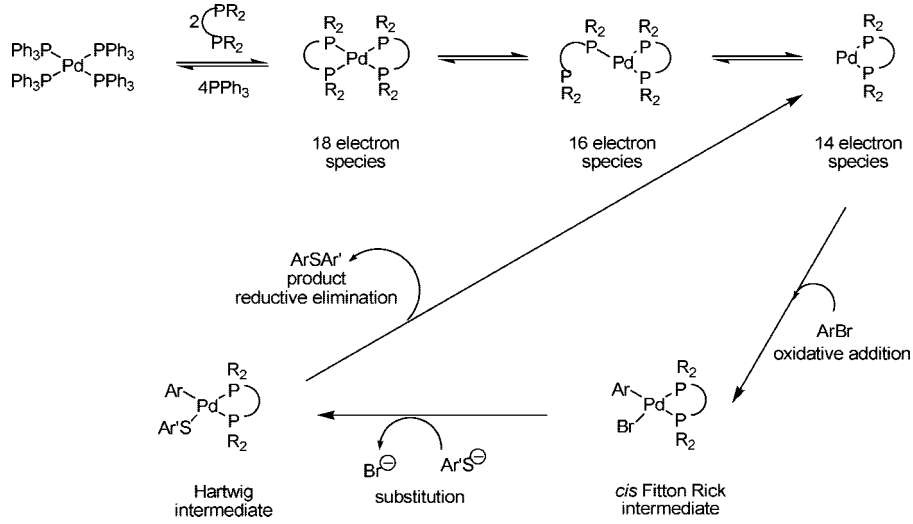
(8) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174. (c) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359–6362.

(9) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219.

(10) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D., III; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606–9607.

(11) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618–4630.

Scheme 6. **Proposed catalytic cycle for bidentate ligands in modified Migita reactions**



reaction is likely not. Thus, when the overall reaction progress is tracked by monitoring the rate of formation of the amide **6** or **10**, the ligand effect observed for the cross-coupling reaction is confounded by the rate of the hydrolysis reaction. In fact the rate of formation of **6** or **10** is composed of two cross-coupling reactions and two hydrolysis reactions as reflected in Scheme 4, which shows the specific situation for amide **6**. Additionally, note that in Scheme 4 although one pathway can dominate, depending on the ligand used, the less dominant pathway is still progressing in the background and contributing to the formation of final product **6**. This is also true for compound **10** in the model example. The rate of formation of either **6** or **10** cannot be used to derive anything other than a composite reaction rate as there are four reactions contributing to the overall reaction observed.

It is not unreasonable, however, to postulate a possible catalytic cycle and associated equilibria of the C−S bond-forming process when bidentate ligands are present, as shown in Scheme 6. The initial step in the catalytic cycle has long been believed to be similar to the reaction of ArBr with $Pd(PPh_3)_4$ to form *cis*-[$(PPh_3)_2$Pd(Ar)(Br)] complex which rapidly converts into the *trans* complex characterized by Fitton and Rick.[12] The oxidative addition would be similar for palladium bidentate phosphine ligand complexes except the *cis*/*trans* isomerization would likely not occur, although it cannot be ruled out completely. The actual reaction of ArBr is probably with a 14-electron palladium species $(R_3P)_2Pd$ or [R_2P-$(CH_m)_nPR_2$]Pd with two vacant coordination sites, which is in equilibrium with the fully saturated 18-electron palladium species in which all the available coordination sites are filled with a phosphorus atom via an intermediate 16-electron palladium species. The architecture of BINAP does not allow all four phosphorus atoms to have a have equal P−Pd bond lengths and the 18-electron palladium species $(BINAP)_2Pd$ probably has a distorted tetrahedral environment by analogy with the X-ray structure recently reported for [(*R*)-Tol-BINAP]$_2$Pd.[13] Thus, in solution the equilibrium is pushed towards the 16-electron species with a vacant coordination site. The next step is attack by arylsulfide ion displacing bromide ion to yield the Hartwig complex, which then reductively eliminates product ArSAr′ to regenerate the active catalytic species that is believed to be a 14-electron palladium species with vacant coordination sites.

General Application of Modified Migita Reaction. The conditions used to develop the phase II synthesis of API **5** were found to be generally useful in the synthesis of diarylthiols from aryl bromides and thiophenols. The results obtained are summarized in Table 1, and the experimental details are included in the Supporting Information. The reactions were carried out in 2-propanol (6 mL g^{-1} of aryl bromide) at ∼83 °C under house nitrogen. The base was potassium hydroxide (2 mol/mol aryl bromide). The aryl bromide and thiophenol were introduced in equal molar proportions. Individual reaction times are noted in Table 1.

Formation of Carbon−Nitrogen Bond. The final bond-forming step of the phase II process requires formation of a carbon−nitrogen bond by aromatic nucleophilic displacement of fluorine with an imidazole nitrogen atom. It is not necessary to use a palladium catalytic process for this transformation. A convenient single-reactor direct product precipitation process can be used to accomplish the desired result. One mole of the amide **6** was reacted directly with 2 moles of 2-methylimidazole in DMSO with cesium carbonate (2 mol) at ∼130 °C for 24 h. The product was isolated by addition of water to precipitate crystals of API base **5** in 95% yield. The manufacturing scale description is provided in the Experimental Section and was carried out using 37.7 kg of the limiting reactant **6** in the example reported. Several batches at approximately this scale were run. This particular drug candidate did not move past phase II; however, in preparation for the next phase of development, the cesium carbonate process was replaced with a sodium hydroxide process which used catalytic quantities of cesium carbonate (process yield 99%) or a phase transfer catalyst (process yield 93%). It was also demonstrated that a 90% yield could be achieved with sodium hydroxide alone. These pro-

(12) Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287–291.
(13) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618–4630; see ORTEP drawing on p 4620.

cesses were never scaled but are noted in the Experimental Section since they represent useful inexpensive protocols that are scalable.

Conclusions

The use of palladium catalysis in the phase II process enabled a penultimate intermediate to be accessed in a single step (81%) followed by a high-yielding final bond-forming step (95%). Both processes were essentially single-vessel operations with minimal workup purification required. Thus, the multistep phase I process overall yield of 37% from **1** to **5** was improved to 77% for the same starting material and final API base, **5**. Finally, a useful, scalable general method for formation of diarylthiols using palladium catalysis was developed.

Experimental Section

Synthesis of Tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2H-pyran-4-carboxamide (6). *Using No Catalytic Auxiliary Ligand.* 2-Propanol (311 mL), tetrahydro-4-(3-bromophenyl)-2H-pyran-4-nitrile 1 (51.91 g, 0.195 mol, 1 equiv), potassium hydroxide (25.16 g, 0.39 mol, 2 equiv), water (4 mL, 0.39 mol, 2 equiv), tetrakis(triphenylphosphine)palladium(0) (2.26 g, 0.00195 mol, 0.01 equiv), and 4-fluorothiophenol (25 g, 0.195 mol, 1 equiv) were added to a reaction flask set for reflux under a nitrogen atmosphere. The resultant reaction mixture was refluxed[14] for 20−24 h. The reaction mixture was cooled to 20−25 °C, and water (315 mL) was added to obtain a slurry. The crude product was isolated by filtration, washed with 1:1 water/2-propanol (125 mL), and pulled dry. Crude dry product was dissolved in methanol (1900 mL), treated with activated charcoal (Darco KB-B (2.5 g)), and Celite filter aid (10 g) at reflux temperature (∼60 °C) for 20 min, and then was filtered free of charcoal and filter aid. The filter cake was washed with hot methanol (200 mL) and the wash combined with the main filtrate. The methanol was concentrated by distillation to a volume of ∼700 mL. The concentrate was cooled to 10−0 °C and granulated at this temperature range for 1−3 h to establish crystal formation. The product crystals were isolated by filtration, washed with cold methanol (125 mL) and dried under vacuum at 40−45 °C. Yield 40.2 g (62.2%): mp 175−178 °C; *m/z* 332 (M + 1); $C_{18}H_{18}FNO_2S$ requires: C, 65.2; H, 5.47; N, 4.23; S, 9.68. Found: C, 65.2; H, 5.38; N, 3.99, S, 9.29%; ^{1}H NMR (300 MHz, DMSO- d_6) δ 7.37 (m, 8H), 7.11 (m, 2H), 3.60 (m, 2H), 2.30 (m, 2H), 2.40 (m, 2H), 1.77 (m, 2H); IR (cm^{-1}) ν_{max}; 3394, 3198, 3078, 3014, 2970, 2931, 2880, 2824, 1681, 1664, 1664, 1623, 1588, 1569.

Using Triphenylphosphine (TPP). 2-Propanol (150 mL), tetrahydro-4-(3-bromophenyl)-2*H*-pyran-4-nitrile, **1** (24.98 g, 93.9 mmol, 1 equiv), potassium hydroxide[15] (12.12 g, 188 mmol, 2 equiv), water (1.93 g, 188 mmol), tetrakis(triphenylphosphine)palladium(0) (1.085 g, 0.939 mmol, 0.01 equiv), TPP (187 mg, 0.301 mmol, 0.004 equiv), and 4-fluorothiophenol (12.03 g, 93.9 mmol, 1 equiv) were added to a reaction flask set for reflux under a nitrogen atmosphere. The resultant reaction mixture was refluxed for 20−24 h. The reaction mixture was cooled to 70 °C, and water (150 mL) was added to obtain a slurry, which was further cooled to room temperature. The crude product was isolated by filtration and washed with 1:1 water/2-propanol (60 mL) and pulled dry. Crude dry product was dissolved in acetic acid (200 mL) at 100 °C to obtain a yellow solution that was treated with activated charcoal (Darco KB-B, 1.25 g) and filter aid (Celite 2.5 g) for ∼30 min and was filtered free of insoluble material. The filter cake was washed with acetic acid (30 mL).The combined filtrate and wash was cooled to 75 °C, and water (150 mL) was added slowly over 15 min to precipitate white solids. This was cooled to room temperature and granulated in this temperature range for 1−3 h to establish crystal formation. The product crystals were isolated by filtration, washed with water (200 mL), and dried under vacuum at 40−45 °C. Yield 23.04 g (74%). Analytical data as reported above.

Using (S)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl or (S)-BINAP. 2-Propanol (120 mL), tetrahydro-4-(3-bromophenyl)-2H-pyran-4-nitrile (**1**) (20.0 g, 75.5 mmol, 1 equiv), potassium hydroxide[14] (9.76 g, 150.3 mmol, 2 equiv), tetrakis-(triphenylphosphine)palladium(0) (870 mg, 0.75 mmol, 0.01 equiv), (*S*)-BINAP (935 mg, 1.51 mmol, 0.02 equiv), and 4-fluorothiophenol (8.0 mL, 75.15 mmol, 1 equiv) were refluxed under a nitrogen atmosphere for 20−24 h. The reaction mixture was cooled to 20−25 °C, and water (120 mL) was added to obtain a slurry. The crude product was isolated by filtration, washed with 1:1 water/2-propanol (12 mL), and pulled dry. The crude dry product was dissolved in acetic acid (160 mL) at 100 °C to obtain a yellow solution and was filtered free of insoluble material. The filtrate was cooled to 75 °C, and water (120 mL) was added slowly over 15 min to precipitate white solids; this was cooled to room temperature and granulated in this temperature range for 1−3 h to establish crystal formation. The product crystals were isolated by filtration, washed with water (40 mL), and dried under vacuum at 40−45 °C. Yield 20.4 g (82%). Analytical data as reported above.

Synthesis of Starting Material Tetrahydro-4-(3-bromophenyl)-2H-pyran-4-nitrile (1). 3-Bromophenylacetonitrile (20.0 g, 102 mmol,1.0 equiv), tetrahydrofuran (120 mL), ∼66% w/w aqueous sodium hydroxide solution (180 mL), tetrabutylammonium hydrogen sulfate (3.46 g, 10.2 mmol, 0.1 equiv), and 2,2′-dichloroethyl ether (13.75 mL, 117.3 mmol, 1.15 equiv) were refluxed under a nitrogen atmosphere for 3 h. After the reaction was completed, it was cooled to room temperature and extracted with ethyl acetate (154 mL). The organic layer was concentrated to an oil, and 2-propanol (100 mL) and water (10 mL) were added. The resulting slurry was cooled to 5 °C and stirred overnight. The product was isolated by filtration, washed with 2-propanol (20 mL), and dried. Yield 18.57 g (68.4%); *m/z* 266; $C_{12}H_{12}BrNO$ requires: C, 54.2; H, 4.54; N, 5.26. Found: C, 54.1;H, 4.66;N, 5.16%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.50 (d, 1H), 7.42 (d, 1H), 7.30 (m, 1H), 4.10 (m, 2H), 3.88 (m, 2H), 2.05 (m, 4H), IR (cm^{-1}) ν_{max}; 2239, 1469, 1425, 1390, 1240, 1101, 1031, 718.

Independent Syntheses of Intermediates. *Tetrahydro-4-(3-bromophenyl)-2H-pyran-4-carboxamide (7).* Tetrahydro-4-(3-bromophenyl)-2*H*-pyran-4-nitrile **1** (20.0 g, 0.0752 mol, 1

(14) The reflux temperature of the modified Migita reaction mix when 2-propanol is used as solvent is ∼82−83 °C in all cases.

(15) The potassium hydroxide pellets that were used contained water. Assay 88% (w/w) as KOH.

equiv), 2-propanol (100 mL), and potassium hydroxide (13.8 g, 0.245 mol, 3.26 equiv) were boiled at reflux under a nitrogen atmosphere at ~83 °C for 5 h. After reaction was completed, it was cooled to room temperature. The resulting suspension was added to water (100 mL) with stirring. The product was isolated by filtration, washed with H_2O (30 mL), and vaccuum dried (40 °C). Yield 19.05 g (89%): mp 245−247 °C; *m/z* 284; $C_{12}H_{14}BrNO_2$ requires: C, 50.7; H, 4.97; N,4.93. Found: C, 50.5; H, 5.09; N, 4.92%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (s,1H), 7.50 (d, 1H), 7.38 (m, 2H), 3.77 (m, 2H), 3.50 (m, 2H), 2.43 (m, 2H), 1.80 (m, 2H); IR (cm^{-1}) ν_{max}; 3363, 3174, 1631, 1102, 943, 694.

Tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2H-pyran-4-carbonitrile (8). Tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2*H*-pyran-4-carboxamide **6** (2.10 g, 6.34 mmol, 1 equiv) and thionyl chloride (5 mL, 68.5 mmol, 10.8 equiv) were refluxed under a nitrogen atmosphere for 1 h (~80 °C). After the reaction was completed it was concentrated to form a yellow oil. The oil crystallized upon standing for 3 days at room temperature. The solids were triturated with hexanes (10 mL) and dichloromethane (1 mL). The solids dissolved and then reformed as the vessel was stirred, open to the atmosphere. The product was isolated, rinsed with hexanes, and vaccuum dried (~40 °C). Yield 1.42 g (72%); mp 56−58 °C; *m/z* 313; $C_{18}H_{16}FNOS$ requires: C, 69.0; H, 5.15; N, 4.47; S, 10.2. Found: C, 68.8; H, 5.20; N, 4.55; S, 10.3%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 (m, 5H), 7.38 (m, 2H), 7.20 (m, 1H), 4.00 (m, 2H), 3.65 (m, 2H), 2.07 (m, 4H), IR (cm^{-1}) ν_{max}; 1904, 1590, 1491, 1390, 1301, 1225, 1124, 835, 692.

Tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2H-pyran-4-carboxylic acid (9). Tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2*H*-pyran-4-carboxamide **6** (10.20 g, 30.8 mmol, 1 equiv), potassium hydroxide[14] (7.70 g, 119 mmol, 3.9 equiv), and *n*-butanol (75 mL) were added to a reaction flask set for reflux under a nitrogen atmosphere. The mixture was heated at 100 °C for 7 h. The resulting slurry was cooled to 20 °C and filtered. The retained solids were suspended in a mixture of dichloromethane (60 mL) and water (60 mL). The suspension was filtered, and the filtrate layers were settled and separated. Dichloromethane (60 mL) was added to the aqueous phase of the filtrate, and the pH of the stirred mixture was adjusted to 3.0 using concd HCl. The dichloromethane layer was concentrated to an oil (2.99 g). The oil was dissolved in isopropyl ether (12 mL) at ~55 °C. Upon cooling to 20 °C the product crystallized. The solids were collected by filtration and dried to give product, 1.33 g, (13.0%); *m/z* 332; $C_{18}H_{17}FO_3S$ requires C, 65.0; H, 5.16; S, 9.65. Found: C, 65.2; H, 5.19; S, 9.83%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.8 (s, 1H), 7.47 (m, 2H), 7.30 (m, 5H), 7.13 (m, 1H), 3.80 (m, 2H), 3.43 (m, 2H) 2.32 (m, 2H), 1.77 (m, 2H), IR (cm^{-1}) ν_{max}; 2882, 2596, 1716, 1490, 1304, 1208, 1132, 940, 828, 816.

Example of Synthesis of Model Compound. *Tetrahydro-4-[3-(4-methoxyphenyl)thio]phenyl-2H-pyran-4-carboxamide (10).* Tetrahydro-4-(3-bromophenyl)-2*H*-pyran-4-nitrile, **1** (4.33 g, 16.26 mmol, 1.0 equiv), 2-propanol (26 mL), potassium hydroxide (2.11 g, 32.52 mmol, 2.0 equiv), tetrakis(triphenylphosphine)palladium(0) (188 mg, 0.163 mmol, 0.01 equiv), (*S*)-BINAP (101 mg, 0.163 mmol, 0.01 equiv), and 4-methoxybenzenethiol (2.0 mL, 16.26 mmol, 1.0 equiv) were added to a reaction flask set for boiling at reflux under a nitrogen atmosphere. The mixture was refluxed for 16 h. After the reaction was completed, it was cooled (<30 °C) and quenched with water (30 mL) which resulted in formation of a precipitate. The resultant slurry was granulated for 1 h at room temperature (10−15 °C). The product was isolated by vacuum filtration and washed with a 1:1 mixture of 2-propanol and water (20 mL). The product was dried overnight in a vacuum oven at 40−45 °C. Yield 5.31 g, 95% Recrystallization from 2-propanol gave analytically pure material: *m/z* 343; $C_{19}H_{21}NO_3S$ requires: C, 66.45; H, 6.16; N, 4.08; S, 9.34. Found: C, 66.35; H, 5.84; N, 3.97; S, 9.65. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.44 (d, 2H), 7.22 (m, 2H), 7.08 (m, 2H), 6.92 (d, 2H), 3.8 (s, 3H), 3.72 (d, 2H), 3.45 (t, 2H), 2.51 (d, 2H), 1.7 (t, 2H); IR (cm^{-1}) ν_{max}; 3377, 3178, 2934, 1682.

This compound can also be made in the same way using tetrahydro-4-(3-bromophenyl)-2-*H*-pyran-4-carboxamide, **7**, in place of the nitrile **1**. Yield 88%.

Plant Procedures. *Manufacture of Tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2H-pyran-4-carboxamide (6).* 2-Propanol (270 L), potassium hydroxide (21.8 kg), tetrahydro-4-(3-bromophenyl)-2*H*-pyran-4-nitrile **1** (45.0 kg), tetrakis-(triphenylphosphine)palladium (1.0 kg), and (*S*)-BINAP (1.05 kg) were charged into a nitrogen-purged glass-lined jacketed reaction vessel fitted with a reflux condenser and agitator. Charged liquid 4-fluorothiophenol (21.7 kg) and 2-propanol (8 L) into a nitrogen purged ancillary jacketed glass lined vessel by using isolated vacuum application, when the charge was complete the nitrogen blanket was reestablished and agitation was commenced. Using isolated vacuum on the reactor slowly suck the contents of the ancillary vessel into the main reactor and reestablish the nitrogen blanket when the transfer process is complete. A 10 °C exotherm was observed during the addition process as the potassium thiolate salt was formed. Heated the reactor contents to 80−85 °C and established steady reflux under gentle agitation at ~83 °C and maintained for 18 h. The reactor contents were cooled to ~25 °C and reaction completion was confirmed on a representative sample of the reaction mixture. Added city water (270 L) to the agitated reactor over 1.5 h to precipitate product. The vessel contents were then warmed to 50−55 °C for 2 h. then cooled to ~20 °C. The resultant slurry was transferred onto a horizontal plate pressure filter and the crude product isolated. While on the pressure filter the isolate was washed with 50: 50 2-propanol/water mixture (220 L) via the reactor, and the isolate pulled as dry as practicable. The nitrogen purged reactor was charged with filter aid (3.0 kg), activated charcoal (2.25 kg), glacial acetic acid (360 L) and damp crude product isolate (~132 kg). The reactor contents were heated to 95−100 °C and held for 0.5 h and then cooled to ~65 °C. The carbon/filter aid residue was removed by filtration on a horizontal plate pressure filter at ~60 °C and the warm product solution transferred into a clean crystallizer ensuring the transfer was free of extraneous material. The crystallizer vessel was heated to 70−75 °C and city water (285 L) added over 0.75 h. to initiate product crystallization. The crystallizer contents were cooled to ~20 °C and granulated for 5 h.to form a solid−liquid slurry, this was filtered on a

horizontal plate pressure filter, washed with water (182 L) and the cake sucked as dry as practicable. The product cake was finally dried in a vacuum tray drier oven for 48 h at 50 °C. Yield product 45.2 kg (80.7%). HPLC main band assay 97.0%.

Manufacture of Tetrahydro-4-[3-[4-(2-methyl-1H-imidazol-1-yl)phenyl]thio]phenyl-2H-pyran-4-carboxamide (5). DMSO (380 L), tetrahydro-4-[3-(4-fluorophenyl)thio]phenyl-2H-pyran-4-carboxamide **6** (37.7 kg), 2-methylimidazole (18.7 kg) and cesium carbonate (74.1 kg) were charged into a clean dry nitrogen-purged glass-lined jacketed reaction vessel fitted with a reflux condenser and agitator. The vessel contents were heated to 127−133 °C with agitation for 24 h. The vessel contents were then cooled to ∼37 °C, and a reaction completion sample was removed. The vessel was further cooled to ∼25 °C; meanwhile HPLC confirmed the reaction had gone to completion. City water (380 L) was charged into the reactor over 1 h to precipitate product crystals. The reactor contents were reheated to 50−55 °C and stirred for 1 h (to dissolve cesium salts), cooled to 20−25 °C, and granulated for 2 h. The crystal slurry was isolated on a horizontal plate pressure filter and washed with water (213 L). The wet cake was recharged into the reactor vessel with water (418 L) and further reslurried under agitation for 2 h (20−25 °C). The product was reisolated and washed with city water (213 L). The product cake was finally dried in a vacuum tray drier oven for 48 h at 50 °C until the LOD was 0.31%. Yield product 42.9 kg (95.8%). HPLC main band assay 99.2%; mp 198−200 °C; *m/z* 396 (M + 1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41 (m, 10H), 7.12 (s, 1H), 6.93 (d, 1H), 3.75 (m, 2H), 3.48 (t, 2H), 2.48 (d, 2H), 2.3 (s, 3H), 1.75 (m, 2H); IR (cm^{-1}) υ_{max}; 3402, 3301, 3123, 3096, 2971, 2930, 2880, 1680, 1663, 1622, 1593, 1569, 1528.

Sodium Hydroxide-Based Laboratory Processes for 5. (a) Using a Catalytic Quantity of Cesium Carbonate with Solid Sodium Hydroxide. **6** (25.0 g, 75.4 mmol, 1.0 eqiv), DMSO (250 mL), 2-methylimidazole (12.39 g, 150.9 mmol, 2.0 equiv), sodium hydroxide (6.03 g, 150.9 mmol, 2.0 equiv), and cesium carbonate (1.23 g, 0.38 mmol, 0.005 equiv) were added to a reaction flask set for reflux under a nitrogen atmosphere, and the reaction mixture was heated at 125−130 °C for 17−24 h under nitrogen. After the reaction was completed it was cooled (<30 °C) and quenched with water (250 mL), which resulted in formation of a precipitate. An exothermic temperature increase (10−15 °C) was observed during the water addition. The reaction slurry formed, was cooled to room temperature (15−25 °C) and then granulated for 1 h. The product was isolated by vacuum filtration and washed with water (140 mL). The product was dried overnight in a vacuum oven at 40−45 °C. Yield 29.4 g, (99%).

(b) Using a Catalytic Quantity of a Phase Transfer Catalyst, Tetrabutylammonium Chloride with Solid Sodium Hydroxide. **6** (25.0 g, 75.4 mmol, 1 equiv), DMSO (250 mL), 2-methylimidazole (12.39 g, 150.9 mmol, 2.0 equiv), sodium hydroxide (6.03 g, 150.9 mmol, 2.0 equiv), and tetrabutylammonium chloride (0.210 g, 0.75 mmol, 0.05 equiv) were heated under a nitrogen atmosphere at 125−130 °C for 17−24 h. After the reaction was completed, it was cooled (<30 °C) and quenched with water (250 L), which resulted in formation of a precipitate. An exothermic temperature increase (10−15 °C) was observed during the water addition. The reaction slurry formed, was cooled to room temperature (15−25 °C) and then granulated for 1 h. The product was isolated by vacuum filtration and washed with water (140 mL). The product was dried overnight in a vacuum oven at 40−45 °C. Yield 27.6 g, (93.0%).

(c) Using Solid Sodium Hydroxide Alone with No Catalyst. **6** (6.5 g, 19.6 mmol, 1 equiv), DMSO (65 mL), 2-methylimidazole (3.22 g, 39.23 mmol, 2.0 equiv), and sodium hydroxide (1.57 g, 39.23 mmol, 2.0 equiv) were heated under a nitrogen atmosphere at 125−130 °C for 4 − 6 h. After the reaction was completed, it was cooled (<30 °C) and quenched with water (65 mL), which resulted in formation of a precipitate. An exothermic temperature increase (10−15 °C) was observed during the water addition. The reaction slurry formed, was cooled to room temperature (15−25 °C) and then granulated for 1 h. The product was isolated by vacuum filtration and washed with water (80 mL). The product was dried overnight in a vacuum oven at 40−45 °C. Yield 6.98 g, (90.4%).

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Supporting Information Available

Experimental procedures to prepare diarylthioethers and HPLC methodology.This material is available free of charge via the Internet at http://pubs.acs.org.

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