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Utilization of Sequential Palladium-Catalyzed Cross-Coupling Reactions in the Stereospecific Synthesis of Trisubstituted Olefins

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Abstract:

A stereospecific synthesis of the drug-candidate 1 is described. The synthetic sequence, aimed at accomplishing modularity and cost savings, features a series of organometallic steps to afford stereospecifically the desired trisubstituded olefin active pharmaceutical ingredient. Key developments consist of a mild Sonogashira reaction of aryl bromide 7a with the polymerization prone propargyl alcohol and a stereospecific hydroalumination, Zn/Al exchange, and Pd-catalyzed cross-coupling sequence facilitated by the commercially available PEPPSI catalyst.

Introduction

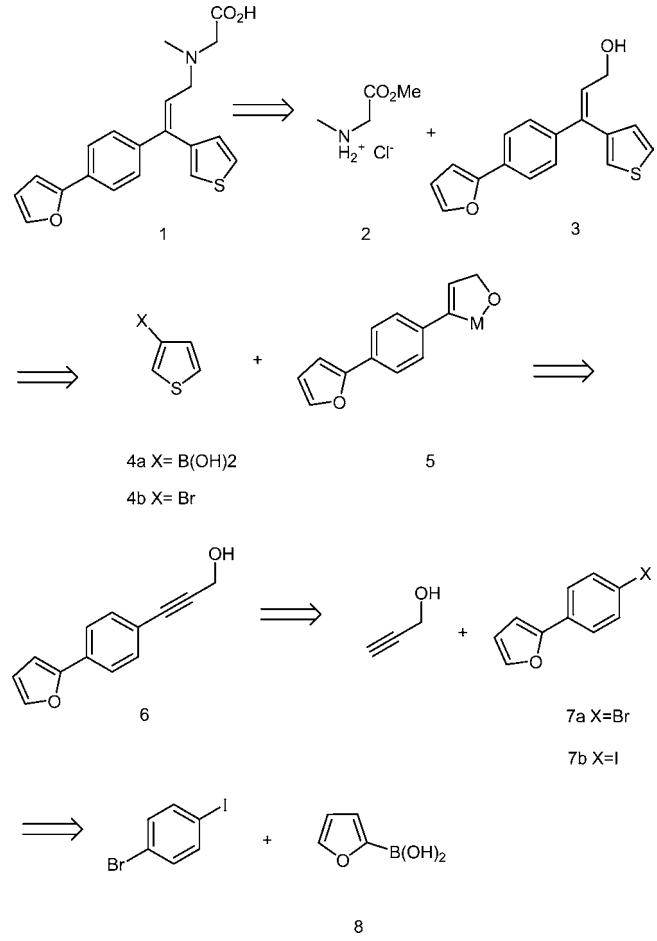
In the course of the last several decades, there has been an explosion of transition metal-catalyzed cross-coupling reactions of aromatic and aliphatic electrophiles starting with, literally, the entire gamut of organometallic reagents (B, Mg, Sn, In, Cu, Mn, etc.).[1]

These reactions have found particular use in heterocyclic chemistry and are applied vigorously in the pharmaceutical industry.[2]

One area where these reactions can be most useful is the stereospecific construction of trisubstituted olefins by combining hydro- or carbometalation with cross-coupling or alkylation protocols. The application of these methods still presents a challenge despite significant advances in the field.[3]

In this contribution we describe the development and optimization of an "all organometallic" synthetic sequence for the synthesis of **1** (Scheme 1) where several challenging catalytic steps had to be developed in order to accommodate the specific reactivity of our substrate. Although **1** does not possess significant structural complexity, this actually places an additional demand to develop a most efficient and economically advantageous synthetic sequence.

Scheme 1. **Retrosynthetic analysis**



Results and Discussion

Retrosynthetic Analysis. Our strategy focused on a sequence of cross-coupling reactions in the early steps of the synthesis leaving for the end the allylic amination reaction in order to avoid the use of transition metals in the final step, thus reducing the chances of transition metal contamination in the final product.

We envisioned that **1** could be derived by alkylation of an activated derivative of **3** with sarcosine hydrochloride **2**. In turn, the allylic alcohol **3** could be prepared via a stereospecific cross-coupling reaction of a nucleophilic (**4a**)[4] or electrophilic (**4b**) thiophene derivative with an appropriately functionalized

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(1) (a) Anctil, E. J.-G.; Snieckus, V., *Metal-Catalyzed Cross Couping Reactions*, 2nd ed.; Wiley: New York, 2004; pp 761−814. (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (c) Suzuki, A. *Metal-Catalyzed Cross Couping Reactions*; Wiley-VCH: New York, 1998; p 49.
(2) King, A. O.; Yasuda, N. *Organometallics in Process Chemistry*; Springer-Verlag: Berlin, 2004; pp 205−245.
(3) (a) Huang, Z.; Negishi, E. *J. Am. Chem. Soc.* **2007**, *129*, 14788. (b) Langille, N. F.; Jamison, T. F. *Org. Lett.* **2006**, *8*, 3761. Yin, N.; Wang, G.; Qian, M.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2916. Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(4) The reaction of the commercially available boronic acid **4a** with the vinyl iodide **9** has been carried out and is successful. It is described in the Experimental Section but will not be discussed in detail here.

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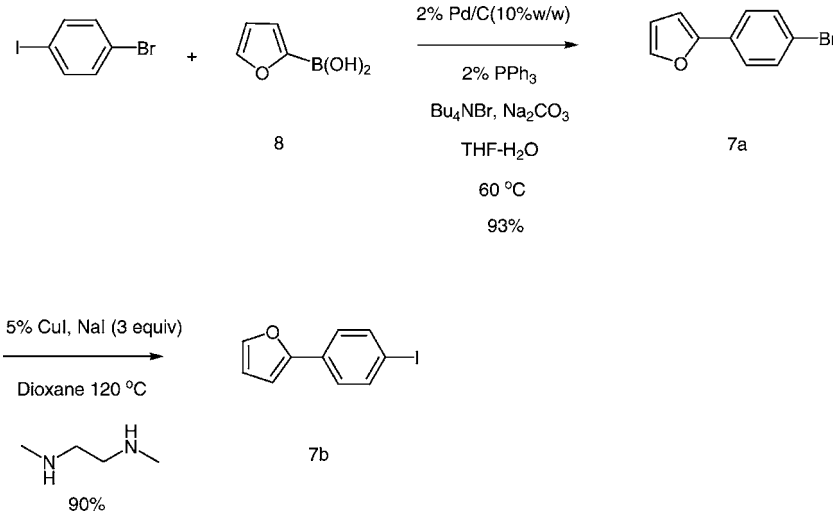
Scheme 2. **Synthesis of bis-aryl halides 7a and 7b**



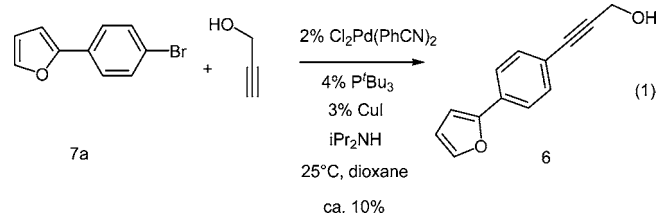
compound **5** (M = I, Zn/Al, respectively). We anticipated that the well-known stereocontrolling element of the coordination of the alkoxide to an appropriate metal (M in **5**) could be exploited in the subsequent cross-coupling reaction in order to define the stereochemistry of the double bond.[5] Such coordination could be engineered by a hydro-alumination reaction of unprotected propargyl alcohols, such as **6**, the latter being a product of a Sonogashira reaction of the commercially available **7a** or **7b** and propargyl alcohol.

Preparation of Propargyl Alcohol 6. For commercial-scale production, both **7a** and **7b** are available at relatively low cost. However, for research purposes they were conveniently synthesized as shown in Scheme 2.

Thus, Suzuki coupling of *p*-bromo-iodobenzene with 2-furyl boronic acid **8** was readily accomplished using Pd/C in THF−water mixtures although a small amount of PPh_3 was needed for the reaction to proceed at a reasonable rate.[6] The product **7a**, can be isolated in ~93% yield with >99% purity by crystallization from ethanol−water. Although the Pd-content in solution was not measured at this juncture, the isolated product contained <10 ppm of Pd. It is worth noting that this purification is crucial as crude **7a** (97% purity) performed erratically in the subsequent Sonogashira reaction. The iodide **7b** was obtained in high yield by following the Buchwald protocol.[7]

Since its discovery, the Songashira reaction has been a valuable tool for the functionalization of aromatic and heteroaromatic halides with the versatile acetylene function.[8] Apart from the normal acetylene manipulations, these derivatives can undergo cyclization reactions to prepare indoles, benzo- and heteroarylfurans, and other useful pharmacophores.[2] One of the difficulties of the reaction is the propensity of acetylenes to dimerize under the reaction conditions particularly when the cross-coupling reaction is slow as in the case of aromatic bromides and chlorides which normally require elevated temperatures. In our case the need to employ propargyl alcohol as the acetylene complicates the problem further as this reagent polymerizes rather easily at higher temperatures.[9]

In order to avoid these higher temperatures we started our investigation by utilizing the protocol developed by Buchwald and Fu (eq 1) for performing the Sonogashira reaction of acetylenes with aryl bromides and chlorides at ambient temperature.[10] Unfortunately, these conditions[11] afforded only 50% conversion along with visible polymerization products. Examination of alternative methods to effect this coupling, for example employing the corresponding silyl protected acetylene, were also not successful.[12]



To find a catalyst system that would allow complete conversion while minimizing polymerization of propargyl alcohol, we undertook an extensive screening of catalysts and reaction conditions. Initial experiments showed that polar aprotic solvents such as DMF and NMP (but not DMSO) were much more effective than THF, toluene, or dioxane. In addition, it was established that inorganic bases were not useful for this transformation.

These initial observations allowed for a more focused screening of ~60 experiments with the most pertinent "hits" shown in Table 1.

The trends observed for this reaction can be summarized as follows: PPh_3 was the best ligand (Table 1, entries 1−7), while $BuNH_2$ or DMPU were the preferred solvents for this reaction (Table 1, entries 1, 8, and 10). We have confirmed earlier observations that primary amine bases were preferred to

(5) (a) Sato, F.; Kodama, H.; Sato, M. *J. Organomet. Chem.* **1978**, *157*, C30. (b) Baba, S.; Van Horn, D. E.; Negishi, E. *Tetrahedron Lett.* **1976**, *17*, 1927. (c) Ziegler, F. E.; Mikami, K. *Tetrahedron Lett.* **1984**, *25*, 131. (d) Review: Hudrlik, P. F.; Hudrlik, A. M. *The Chemistry of the Carbon-Carbon Triple Bond*; John Wiley and Sons: New York, 1978; pp 199−273.

(6) (a) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819. (b) Eichen, K.; Gebhart, J.; Rack, M.; Schafer, P. Int. Patent WO 97/733846, 1997.

(7) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.

(8) Sonogashira, K. *Metal-Catalyzed Reactions*; Wiley-VCH: New York, 1998; pp 203−229.

Table 1. **Initial screening of the Sonogashira coupling of 7a with propargyl alcohol[a]**

entry	base (equiv)	Pd/L (additive)	Pd/L (mol %)	solvent	time [h]	**7a**[b]	**6**[b]	Σ rest[c]	in situ yield[d]
1	*n*-$BuNH_2$	$Pd(OAc)_2/PPh_3$	2/8	NMP	16	35	51	13	–
2	Cy_2NMe	$Pd(OAc)_2/PPh_3$	2/8	NMP	16	90	<10	–	–
3	*n*-$BuNH_2$	$Pd(OAc)_2$/P(furyl)$_3$	2/8	NMP	4	>80			
4	*n*-$BuNH_2$	$Pd(OAc)_2$/P(*t*-Bu)$_2$-norbornylxHBF_4	2/8	NMP	18	>80			22
5	*n*-$BuNH_2$	$Pd(OAc)_2$/P(*t*-Bu)$_2$-norbornylxHBF_4	2/8[e]	NMP	18	>80			23
6	*n*-$BuNH_2$	$Pd(OAc)_2$/P(*t*-Bu)$_2$-biphenyl	2/8	NMP	4	>80			19
7	*n*-$BuNH_2$	$Pd(OAc)_2/PCy_3$	2/8	NMP	4	>80			16
8	*n*-$BuNH_2$	$Pd(OAc)_2/PPh_3$	2/8	*n*-$BuNH_2$	4				80
	(excess)				18	**12**	**76**	**12**	**86**
9	*n*-$BuNH_2$	$Pd(OAc)_2/PPh_3$	2/8	*n*-$BuNH_2$	18	>30	75	~15	71
	(excess)	1,2-diaminobenzene (8%)							
10	*n*-$BuNH_2$	$Pd(OAc)_2/PPh_3$	2/8	DMPU	1	29	59	12	68
					4	7	83	10	96
					18	**3**	**90**	**7**	**95**
11	*n*-$BuNH_2$	Pd/C (5%)/PPh_3	2/8[f]	DMPU	16	11	82	7	74
12	*n*-$BuNH_2$	$(TPPTS)_2PdCl_2$	1/2	DMPU	22	92	8	–	–
	(2.0 equiv)								
13	*n*-$BuNH_2$	Na_2PdCl_4/PPh_3	1/2.5[f]	DMPU	22			>15	65
	(1.5 equiv)								
14	*n*-$BuNH_2$	Na_2PdCl_4/PPh_3	1/3[f]	DMPU	21	1	97	>10	74
	(2.0 equiv)								
15	*n*-$BuNH_2$	Na_2PdCl_4/PPh_3	1/4[f]	DMPU	22	0	>95	–	93
	(5.0 equiv)								
16	*n*-$BuNH_2$	$Pd_2(dba)_3/PPh_3$	1/3[f]	DMPU	16	–	–	–	61
17	*n*-$BuNH_2$	$Pd_2(dba)_3/PPh_3$	1/3[f]	DMPU	4	29	68	3	73
		2 vol % H_2O			16	2	94	3	100

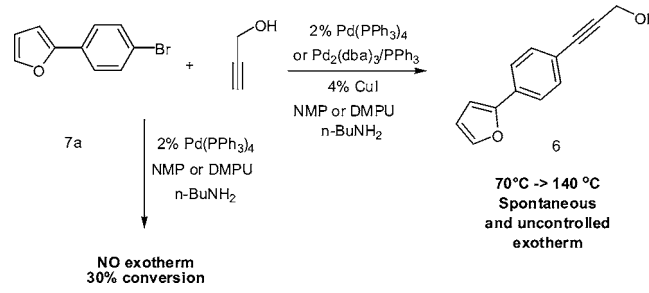
[a] These experiments were performed by dissolving 1 mmol of **7a** in 5 mL of the appropriate solvent, followed by 1.1−1.3 equiv of amine (unless otherwise mentioned), 4 mol % CuI (unless otherwise mentioned) 2−8 mol % of phosphine ligand, 1−2 mol % of Pd-precursor and using 1.1−1.3 equiv of propargylic alcohol added in one portion). Finally the blue-green homogeneous mixture was heated 70 °C. [b] Determined by GLC analysis (area %). [c] Sum of the total remaining impurities determined by GLC analysis (area %). [d] Yield of **6** determined by GLC analysis using biphenyl as the internal standard. [e] CuBr was used instead of CuI. [f] 2 mol % CuI was used.

secondary or tertiary,[13] while bulky alkyl phosphines were surprisingly ineffective ligands (Table 1, entries 3−7 and eq 1). The first success with PPh_3 (Table 1, entry 8) provided 86% *in situ* yield of **6**; however, the reaction did not proceed to completion, and a number of impurities were observed as well as obvious polymerization products. The Pd/L ratio and the amount of *n*-$BuNH_2$ also seems crucial (entries 13−15), whereas the Pd-precursor does not seem to have an important influence on the reaction.

DMPU appears to be the best solvent, and it is worth noting that thorough degassing of the solvent is essential. Finally, the presence of water does not adversely affect the outcome of the reaction and may indeed be helpful (Table 1, entry 17).

However, we were surprised to find that when the reaction was attempted on larger scale (~100 g) a significant exotherm was observed when applying the protocol used in the screening reactions. Specifically, mixing the components at room temperature in a 2 L vessel followed by slow heating over 45 min to 70 °C caused an abrupt temperature rise to 145 °C along with the visible formation of dark polymeric material. This highly exothermic polymerization of the acetylene was determined not surprisingly to be due to CuI.[8] Control experiments established that the copper cocatalyst is needed in this transformation (Scheme 3).

Scheme 3. **Observation of exothermic behavior in the reaction of 7a with propargyl alcohol**



The optimal reaction conditions were established by limiting the concentration of propargyl alcohol in the medium. Thus, heating a dark-green solution of a mixture of **7a**, $Pd_2(dba)_3 \cdot CHCl_3$ (0.5 mol %),[14] PPh_3 (4 mol %), and CuI (2 mol %) in DMPU or DMI, followed by slow addition of propargyl alcohol, afforded **6** in >90% assay yield with little polymerization (eq 2). The isolation of **6** from the reaction mixture was problematic and could be accomplished in one of two ways: (a) filtration through a pad of silica gel (silica:**6** = 3:1, elution with toluene; Pd level <50 ppm) or (b) treatment

(9) Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* **2005**, *70*, 2832, and reference 4d therein.

(10) Hundermark, T.; Litke, A. F.; Buchwald, S. L.; Fu, C. G. *Org. Lett.* **2000**, *2*, 1729.

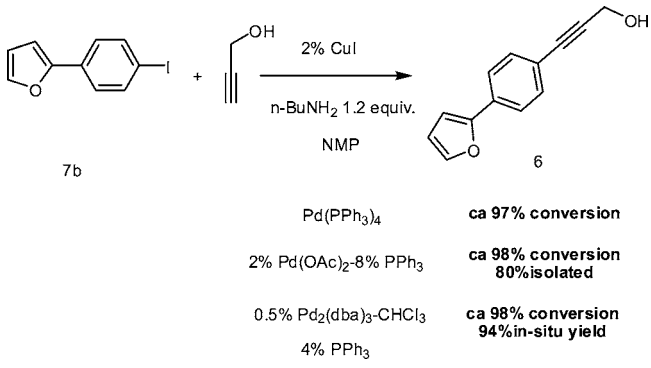
(11) Reasonable variations of the prescribed conditions were attempted, such as temperature, Pd:ligand ratio, base and catalyst loading, without significant success.

(12) Use of the silyl protected acetylene in the presence of *N*-heterocyclic carbenes was also not successful in this transformation: Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.

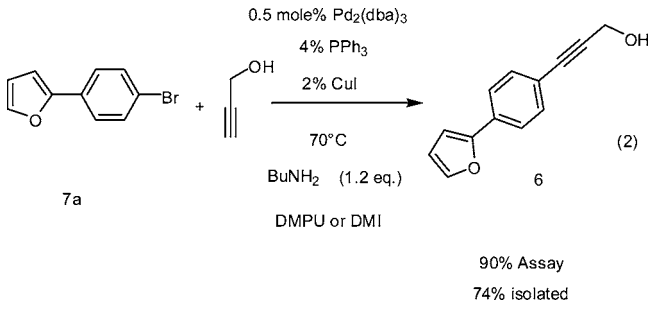
(13) Repeating the xperiment in Table 1, entry 10, with Et_3N or *i*-Pr_2NH afforded no conversion to the desired product. Houpis, I. N.; Choi, W.-B.; Reider, P. J.; Molina, Churchill, A. H.; Lynch, J.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 9355.

(14) Lower catalyst loads seemed to afford "cleaner" (less colored) reaction mixtures; however, reducing the pre-catalyst load below the 0.5 mol % level led to incomplete reactions.

Scheme 4. **Reaction of the iodide 7b with propargyl alcohol**



with Silica-*Bond*-thiol[15] and activated carbon (Norit A supra, 10 weight %) followed by with toluene−heptane crystallization to afford 74% yield of the desired compound (Pd content 120−150 ppm). Both of these treatments were needed to remove Pd contaminants and "gummy" byproduct that interfere with the crystallization. Fortunately Cu was much less of an issue with two ammonia treatments, during workup, effectively reducing the Cu levels to <20 ppm.



Finally it is worth noting that in some cases,[16] evaporation of *n*-$BuNH_2$ or propargyl alcohol were observed which necessitated further addition of these reagents to effect complete conversion.

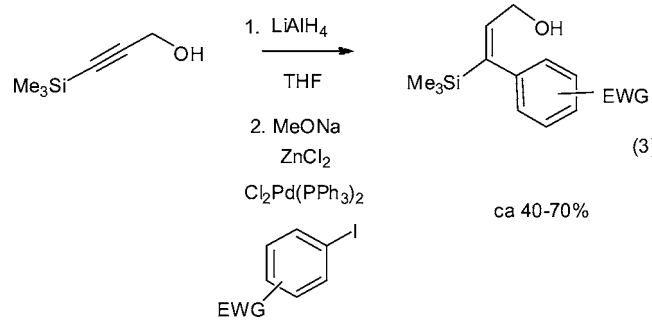
Predictably, using the iodide **7b** (Scheme 4) allowed the reaction to proceed smoothly at 40 °C with no polymerization and thus a more facile workup. It is worth noting, however, that the iodide is not commercially available and would have to be prepared from the bromide. Thus, the bromide was selected as our starting material for further processing.

Stereospecific Synthesis of the Trisubstituted Allylic Alcohol 3. Our strategy for effecting stereoselective formation of **3** is based on the selective formation of a reactive aluminate intermediate **5** which would have the dual role of defining the geometry of the double bond, via the internal chelation, while providing the appropriate reactivity for further reaction (Scheme 1).

The hydroxyl-directed hydroalumination[17] reaction provides an excellent vehicle to accomplish both goals as it affords almost complete stereocontrol due to the formation of the stable intermediate **5** which directs both the regio- and diastereoselectivity of the addition to the triple bond.[18] Stereocomplementary results can be obtained if the alcohol function is protected.

In the original reports of the hydroalumination reaction, pyrophoric DiBALH or $LiAlH_4$ was used; however, this problem has recently been overcome by the introduction of a safer reagent, Red-Al [$NaH_2Al(OCH_2CH_2OMe)_2$],[3b] which is readily available on large scale under the trade name Vitride™.

As our plan was to use **5** for further elaboration via a Pd- or Ni-catalyzed cross-coupling reaction (e.g., with bromo-thiophene **4b**) we decided to study the hydroalumination reaction and the stability of the vinyl aluminate species **5**. We were quite hopeful that this strategy would succeed since earlier work by the Dvořák group indicated convenient access to the desired coupled product (eq 3).[19]



Thus, purified **6** was dissolved in THF in a MultiMax equipped with a calorimeter and an IR probe and cooled to −20 °C followed by addition of Red-Al in toluene (Scheme 5). During addition of the first 0.5 mol equiv of the reagent, there was vigorous gas evolution and significant exothermic behavior due to reaction of the aluminum hydride with the free hydroxyl group. The acetylene signals were still present in the IR, whereas no olefinic resonance could be observed. From these observations, we are postulating the formation of the tetraalkoxy intermediate **5a**. Upon further addition of Red-Al, a second large and rapid exotherm occurred, followed by the appearance of the olefinic bands of **5**, albeit at a slower rate. From the magnitude and rate of the observed exotherm and the slower appearance of **5** we postulate initial rapid formation of **5b**, followed by a somewhat slower intramolecular hydroalumination. An intermolecular delivery of the hydride cannot be conclusively ruled out but does appear inconsistent with the thermal and IR data and further studies are needed to establish the course of this reaction.

Next we investigated the reactivity and stability of **5** and in particular its thermal stability as the cross-coupling reactions were expected to take place above room temperature (Scheme 6). The effect of the equivalents of Red-Al was also examined

(15) Silica*Bond*-thiol is an efficient method for removing both Pd(II) and Pd(0) dissolved in reaction mixtures. It is marketed by Silicycle Corporation, and information and specification including efficiency of removal of Pd and other transition metal catalysts can be found at http://www.silicycle.com.

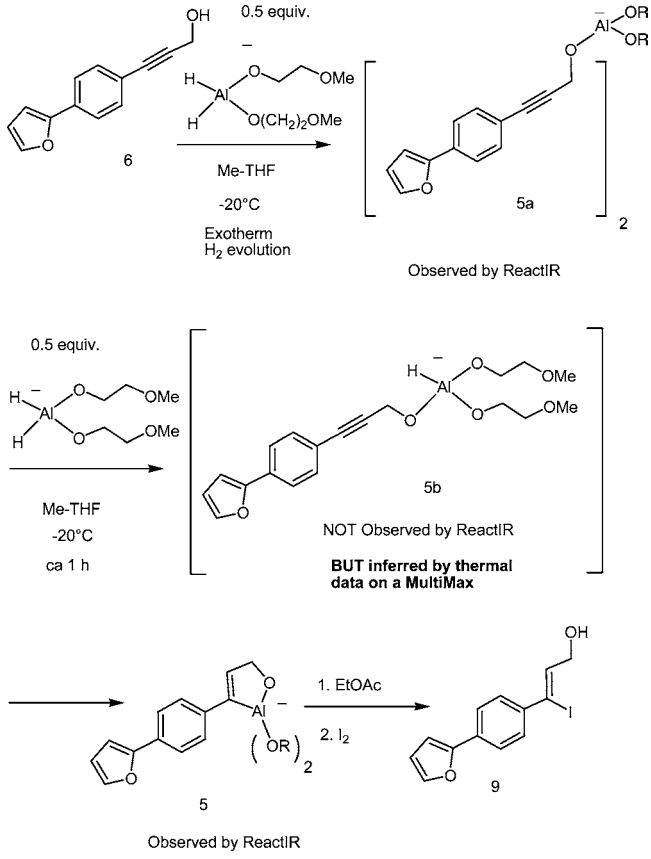
(16) The initial screening experiments were conducted in autoclave-type vessels where evaporation of the components was not an issue. However, when typical "bench-top" experimental setups were used, some evaporation was observed (despite the presence of a condenser) that necessitated further addition of amine and propargyl alcohol to drive the reaction to completion.

(17) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.

(18) The Jamison group (ref 3b) has elegantly demonstrated a complementary strategy where the resulting aluminate species is transmetallated to a Cu reagent and then functionalized via alkylation to afford stereodefined trisubstituted olefins.

(19) Havránek, M.; Dvořák, D. *J. Org. Chem.* **2002**, *67*, 2125.

Scheme 5. **Hydroalumination reaction: mechanism and iodine quench**



as excess reagent might interfere with the subsequent cross-coupling reaction. The stability of the aluminate was determined by quenching the mixture with I_2 and using the vinyl iodide **9** as a surrogate to the aluminate **5**.[20]

From these studies, we can draw the following conclusions: (a) the vinyl aluminum compound, **5**, is stable at −20 °C for several hours; (b) as described by Dvořák et al., it is also stable in the presence of EtOAc at −20 °C; (c) when the temperature rises above 0 °C, up to 16% of olefin **10** is observed particularly in the presence of excess (1.3 equiv) Red-Al; (d) a solvent screen showed that, in terms of yield, 2-Me-THF > THF, toluene > DME; (e) even without excess Red-Al, **5** decomposes up to 20% upon heating to 50 °C; (f) diisobutyl aluminum hydride and, surprisingly, lithium aluminum hydride are not successful in this reaction, giving no reaction and inferior yields, respectively.

Direct Coupling of the Vinyl Aluminum Species. Use of the Dvořák protocol with our substrate (Scheme 7) unfortunately provided low conversion to the desired **3** even under scrupulously anhydrous and oxygen-free conditions. Thus, these conditions, effective for electron-deficient iodides, had to be modified to accommodate the reactivity of our substrate 3-bromothiophene (**4b**).

Initially, in an attempt to boost the reactivity of our nucleophilic component, we sought to use directly the more reactive aluminate species (**5,** M = $AlOR_2$**)**, rather than the presumed, less reactive, zinc derivative resulting from the addition of $ZnCl_2$. A screening exercise was initiated[21] however, most Pd:L combinations afforded low conversions primarily due to the immediate catalyst decomposition as indicated by the precipitation of Pd-black. Even the more robust Ni catalysts failed to afford the desired product. Surprisingly, using 3-iodo thiophene afforded significant amounts of the iodo olefin **9** in an apparent Al−I exchange.

When the same screen was performed in the presence of $ZnCl_2$ it was found that $Pd(OAc)_2/P(t\text{-}Bu)_3$ combination afforded 90% conversion to the desired product **3** along with 10% of the disubstituted olefin **10** (Scheme 8).

Furthermore, although the reaction initially proceeded rapidly at ambient temperature, significant amounts of Pd black could be seen precipitating out of the reaction within 20−30 min thus preventing complete conversion. Moreover, multiple repetitions of the reaction without any "apparent" change in the procedure, afforded irreproducible results with up to 20% of **10** forming and premature catalyst decomposition. It is worth noting that in these reactions the vinyl aluminum or zinc species had not decomposed as shown by quenching portions of the mixture with I_2. Only the vinyl iodo compound, **9**, was formed with only traces of olefin **10**.

In order to solve the relative instability of the catalyst with bulky electron rich phosphines, we turned our attention to the N-heterocyclic carbene species that have been highly popular the last several years.[22] Some initial screens with generally successful carbene[23] catalysts gave no evidence of the desired product **3** under a variety of conditions. However, in these reactions, we did not observe any catalyst decomposition as in the case of the phosphine-based catalysts. Interestingly, the best catalyst to date, achieving sufficient reactivity and stability at ambient temperature was the commercially available PEPPSI catalyst (Scheme 9 and Table 2).[24] Following this initial success, several experiments were dedicated to the understanding of solvent effects, the source of Zn (II) and the equivalents of Zn needed for a successful transformation (Table 2).

From these results it was shown that quenching the excess Red-Al with ethyl acetate is important for the success of the reaction (entries 1, 2). Furthermore (entries 5−8) 0.5 equiv of $ZnCl_2$ appears to be the optimal amount, consistent with Dvořák's observations. Other commonly used sources of Zn (entries 9−12) did not give satisfactory results, while metal salts such as $MgBr_2-Et_2O$ also did not effect the desired transformation.

Further optimization brought to light several other essential parameters: the optimal solvent for the hydroalumination/coupling reaction is 2-methyltetrahydrofuran and polar coordinating solvents such as NMP were not appropriate solvents

(20) Control experiments had established that this transformation proceeds in almost quantitative yield.

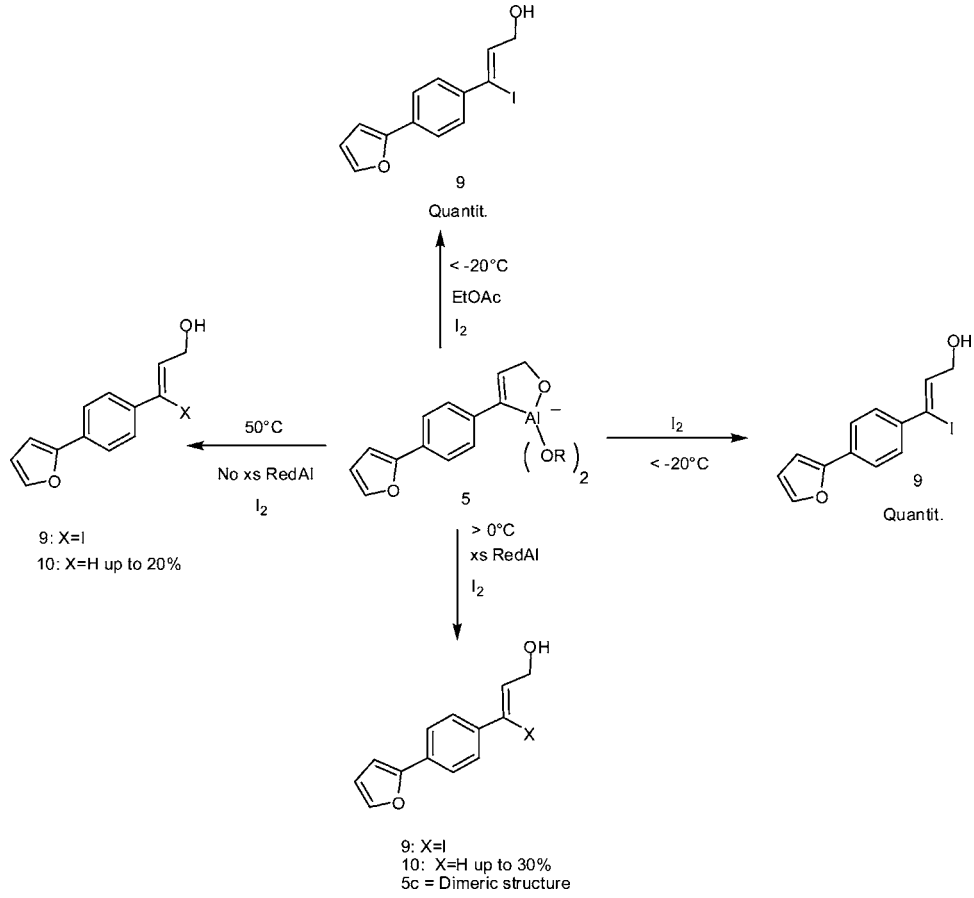
(21) The screen consisted of combinations of the following: Solvents: NMP, THF, Dioxane, Toluene; Pd source: $Pd(OAc)_2$, $Pd_2(dba)_3-CHCl_3$; Ligands: $[OMe_3Ph]_3P$, $[OMe_2Ph]_3P$ *t*-$BuPh_2P$, *t*-Bu_3P, CTQPHOS, DPEPHOS, dppf, P(*o*-tolyl)$_3$, Degussa catCXium kit.

(22) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

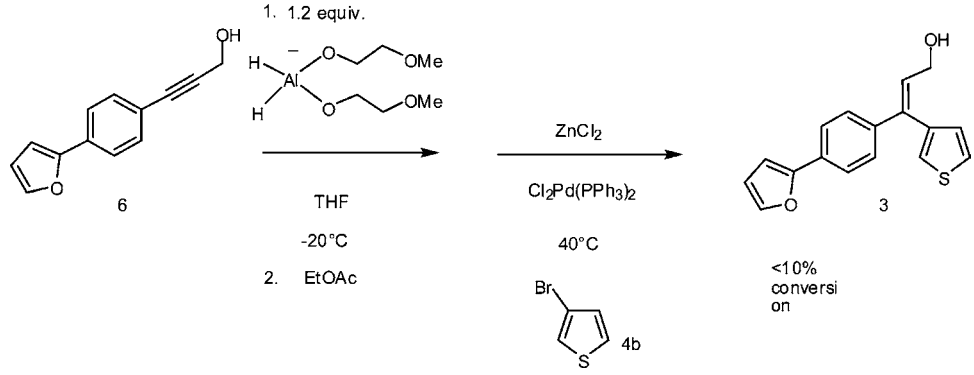
(23) Several of the NHC catalysts pioneered by Nolan (some now commercially available) were investigated: (a) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4020.

(24) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Assen, E.; Kantchev, B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2006**, *12*, 4749. O'Brien, C. J.; Assen, E.; Kantchev, B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743.

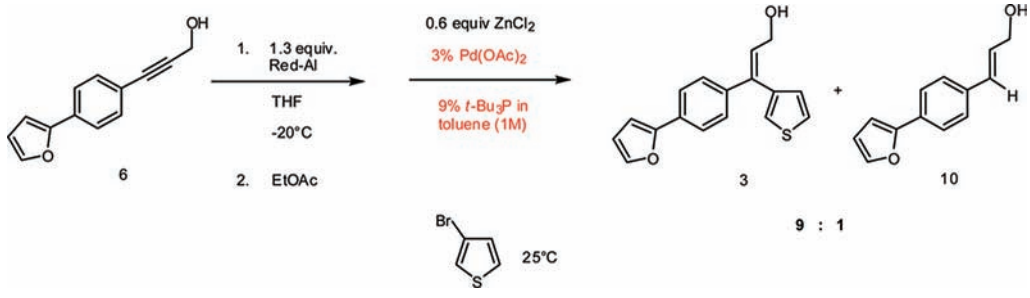
Scheme 6. **Stability study of the vinyl aluminum intermediate**



Scheme 7. **Attempts to prepare 3 using the literature protocol**



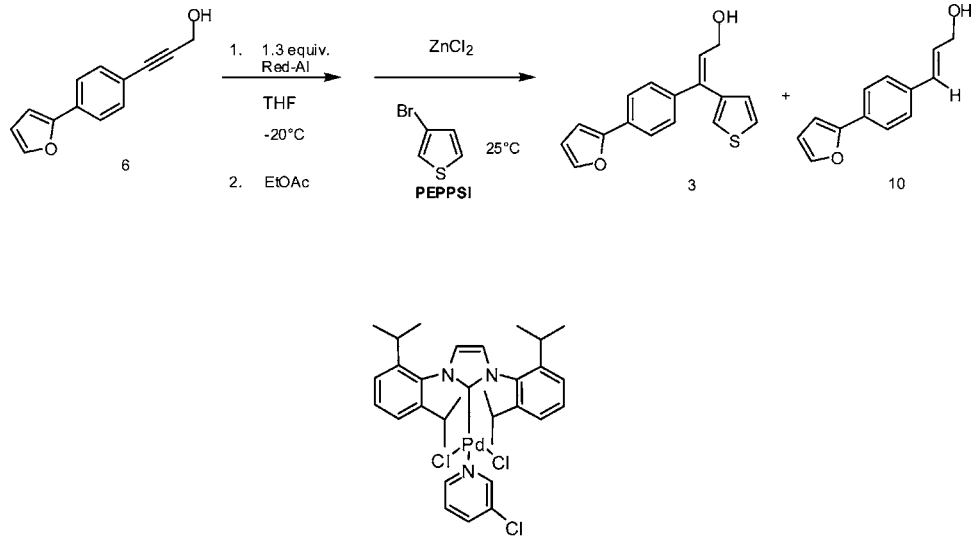
Scheme 8. **Initial success in the synthesis of 3 using *t*-Bu$_3$P as the ligand**



for this reaction. The preferred temperature of the hydroalumination was −30 °C although satisfactory results were obtained also at −20 °C. On the other hand, at 0 °C, the ratio of **3**:**10** was 9−10:1 as opposed to 15:1 at −30 °C.

In the coupling step, the optimal amount of PEPPSI catalyst was determined to be ∼3 mol %. With 1% catalyst the reaction proceeded to ∼86% conversion even after prolonged reaction times.

Scheme 9. **Efficient Coupling Using PEPPSI™ to Form 3**



PEPPSI

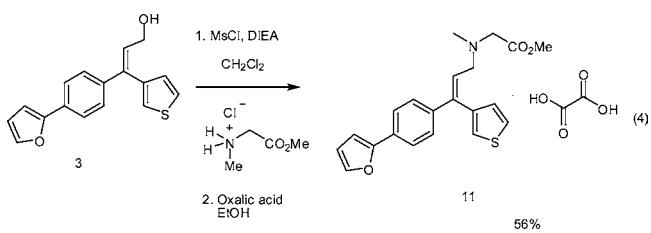
It is worth noting that the coupling reaction is most likely completely selective for the desired product and the amount of **10** observed was actually formed during the hydroalumination reaction (entry 7). This was shown by quenching a portion of the reaction with EtOAc followed by iodine. There, the ratio of **9** to **10** was 94:6, similar to the amount of **10** observed during the preparation of **3**. Finally, the allylic alcohol **3** was shown to be sensitive to acid workup, and thus a basic workup (K, Na tartrate) is needed for the removal of the aluminum salts to avoid decomposition of the product.

Filtration of the reaction mixture through a silica pad or treatment with Silica*Bond*-Thiol followed by EtOH−H_2O crystallization succeeded in achieving low metal content in the final intermediate. Thus Pd, Cu, and Al levels were <50, 10, and 3 ppm, respectively, in the isolated **3** and were <10 ppm in the final active pharmaceutical ingredient (API).

Final Coupling. The transformation of **3** to **11** was significantly more challenging than first anticipated due to the reactivity of the corresponding electron-rich allylic system and the reduced nucleophilicity of the sarcosine nitrogen. The preliminary results are shown below. Further work will be needed to optimize the final steps of synthesis.

Initial attempts to repeat established procedures, from a previous route, produced only low yields of the desired product **11**. The remainder of the mass balance was identified as the impurities shown in Figure 1.

Although work in this area continues, we have been able to produce the desired **1** with a low-temperature reaction (eq 4)



by managing the order of addition of the reagents. Thus, **3** was mixed with sarcosine methyl ester-HCl and diisopropyl ethyl amine in CH_2Cl_2 cooled to 0 °C, and MsCl was added dropwise. After aqueous workup and addition of oxalic acid, the desired compound **11** was isolated in 56% yield as the oxalate salt. The DIEA adduct **12** (~25%) was removed during the aqueous workup. Hydrolysis of **11** afforded the API, **1**, in almost quantitative yield. The Pd content of the API was <10 ppm, thus validating our initial synthetic strategy.

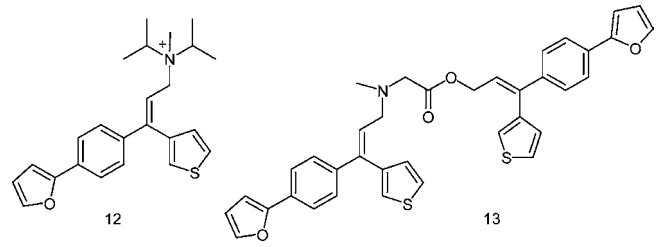


Figure 1

Experimental Section

All experiments were carried out using standard glassware, and the used reagents and solvents were standard technical grade reagents and solvents used without any purification. The phosphine ligands used in the screening experiments were purchased from Acros, Aldrich, or Strem and were used without any purification. HPLC analyses were performed on reversed-phase columns (Waters XTerra RP 3.5 μm, 4.6 mm × 50 mm) in gradient mode (ammonium acetate buffer to acetonitrile) with UV detection (254 nm). GLC analyses were performed on Hewlett-Packard 5890 series II (capillary column HP 5, 10 m) in temperature gradient mode (50 to 300 °C, rate 10 °C/min.) with FID detection. High-resolution mass spectra were performed on Jeol-JMS-T100LP (DART ionization). NMR spectra were recorded on a Bruker AV 400 and 360 MHz instruments. Palladium determinations were performed by AAS on a Varian SpectrAA-880.

Synthesis of 2-(4-Bromophenyl)furan (7a). A 10 L vessel under N_2 was charged with 4-bromo(iodo)benzene (301 g; 1.06 mol), 2-furanboronic acid (148.81 g; 1.25 mol), triphenylphosphine (13.95 g; 0.05 mol), tetra-*n*-butylammonium bromide

Table 2. **Evaluation of reaction parameters in the direct coupling reaction of aluminate 5 with 3-bromothiophene**

entry	quench with EtOAc[a]	Zn source	Zn (mol %)	solvent	ratio of 3:10 (yield)
1	no	$ZnCl_2$ (0.5 M THF)	30	THF	80:20
2	no	$ZnCl_2$ (0.5 M THF)	30	THF	66:34
3	yes	$ZnCl_2$ (0.5 M THF)	100	THF	74:26
4	yes	$ZnCl_2$ (0.5 M THF)	0	THF	50:50
5	yes	$ZnCl_2$ (0.5 M THF)	30	THF	88:12
6	yes	$ZnCl_2$ (0.5 M THF)	50	THF	92:8
7	yes	$ZnCl_2$ (0.5 M THF)	50	Me-THF	94:6 (75%)
8	yes	$ZnCl_2$ (0.5 M THF)	60	THF	88:12
9	yes	$ZnCl_2$ (0.5 M THF)	70	THF	85:15
10	yes	$ZnCl_2$-TMEDA	100	DME−NMP (1:1)	64:36 20% E-isomer
11	yes	$ZnCl_2$-TMEDA	50	DME−NMP (1:1)	63:37 20% E-isomer
12	yes	$Zn(OAc)_2$	50	THF	no reaction

[a] *yes*: the reaction was first quenched with ethyl acetate to decompose excess RedAl before $ZnCl_2$ was added. *no*: $ZnCl_2$ was added directly to the reaction mixture.

(377.29 g; 1.1 mol), sodium carbonate (225.53 g; 2 mol), palladium on carbon 10% (60.20 g; 56.57 mmol), tetrahydrofuran (3.72 L), and water (3.72 L). The reaction mixture was heated at 60 °C for 20 h (until gas chromatography showed no unreacted starting material). After cooling to room temperature, the reaction mixture was filtered over decalite. The organic layer was separated and washed with a saturated NaCl solution (2 L), concentrated under reduced pressure, and exchanged with ethanol to a final volume of 2.27 L. The product was crystallized by slow addition of water at ambient temperature to afford 266 g of **7a** (94% yield; Pd content <10 ppm).

Synthesis of 3-[4-(2-Furyl)phenyl]-2-propyn-1-ol (6). A 500 mL flask equipped with a mechanical stirrer was charged with *N*-methylpyrrolidone (100 mL) and degassed by bubbling nitrogen at 60 °C for 15 min. The solvent was cooled to ambient temperature, and the reagents were added in the following order: 2-(4-bromophenyl)furan **7a** (22.31 g; 100 mmol), copper(I) iodide (761.8 mg, 4 mmol), 1-butanamine (11.88 mL, 120 mmol), and tetrakis-(triphenylphosphine) palladium (2.31 g, 2 mmol). The reaction mixture was heated to 50 °C, and a solution of 2-propyn-1-ol (6.99 mL, 120 mmol) in *N*-methylpyrrolidone (10 mL) was added slowly over 1 h (syringe pump: 17 mL/h). The reaction mixture was transferred to a separation funnel and treated with water (400 mL) and isopropyl acetate (IPAc) (100 mL). The water layer was extracted a second time with isopropyl acetate (100 mL). The combined organic layers were washed twice with an ammonia solution (20 mL of saturated ammonia diluted in 100 mL of water) until colorless. The organic layer was concentrated in vacuo to afford 16 g of crude product which can be further purified by chromatography through a pad of silica gel (Silica:**6** = 3:1, elution with toluene). Alternatively, the IPAc solution was azeotropically dried (KF ~200 ppm) and the mixture treated with Silica*Bond*-Thiol (10 g/mmol of Pd) and activated carbon (Norit A supra, 10 wt %) The solvent was switched to toluene (5 mL/g) and heptane was added (5 mL/g), to afford 74% yield of the desired compound (silica gel; dichloromethane) or crystallization (1:3 toluene−heptane). Yield **6**: 14.6 g (74%; Pd content 120−150 ppm; Cu < 20 ppm).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dt, J = 8.37, 1.73 Hz, 2 H), 7.44 (d, J = 1.51 Hz, 1 H), 7.42 (ddd, J = 8.31, 1.51, 1.26 Hz, 2 H), 6.63 (d, J = 3.27 Hz, 1 H), 6.44 (dd, J = 3.27, 1.76 Hz, 1 H), 4.48 (s, 2 H), 2.00 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.36 (1 C), 142.49 (1 C), 132.03 (2 C), 130.83 (1 C), 123.59 (2 C), 121.32 (1 C), 111.76 (1 C), 105.93 (1 C), 88.08 (1 C), 85.69 (1 C), 51.57 (1 C). M^+ found = 198.0687; calcd = 198.0681.

Synthesis of (*Z*)-3-[4-(2-Furyl)phenyl]-3-(3-thienyl)-2-propen-1-ol (3) (Method 2: Direct Coupling Using the Peppsi Catalyst). A round-bottom flask was charged with intermediate **6** (15 g, 75 mmol) and degassed 2-methyl-tetrahydrofuran (90 mL) and cooled to 0 °C. Sodium bis(2-methoxyethoxy)aluminum hydride (19.8 g, 99 mmol) was added, and the mixture was stirred for 15 min. Ethyl acetate (270 mL) was added to quench the reaction, and 3-bromothiophene was added (neat, 16 g, 99 mmol). The reaction vessel was removed from the cooling bath and treated with zinc dichloride (72 g, 39 mmol) and [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl palladium(II) dichloride (PEPPSI) under an Ar blanket. The reaction mixture was quenched after 3 h at room temperature by addition of saturated aqueous K, Na, tartrate (100 mL) and extracted with 2-methyltetrahydrofuran (300 mL). The organic layer was washed with water, filtered, and concentrated in vacuo. The residue was dissolved in dichloromethane and filtered through a pad of silica gel (90 g). The fractions containing the reaction product were collected and concentrated, yielding crude (*Z*)-3-(4-(2-furyl)phenyl)-3-(3-thienyl)-prop-2-en-1-ol (17.5 g). The product can be further purified by dissolution in ethanol (30 mL), and precipitation by addition of water (24 mL). The precipitate was washed with ethanol−water (1:1, 15 mL) and dried: Yield of **3**: 15.4 g (Pd content < 50 ppm).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (dt, J = 8.40, 2.03 Hz, 2 H), 7.44 (d, J = 1.51 Hz, 1 H), 7.30 (dd, J = 4.91, 3.02 Hz, 1 H), 7.27 (dt, J = 8.69, 1.89 Hz, 2 H), 7.16 (dd, J = 2.83, 1.32 Hz, 1 H), 6.88 (dd, J = 4.91, 1.13 Hz, 1 H), 6.62 (d, J = 3.02 Hz, 1 H), 6.45 (dd, J = 3.21, 1.70 Hz, 1 H), 6.20 (t, J = 6.80 Hz, 1 H), 4.29 (d, J = 6.80 Hz, 2 H), 1.94 (br s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 153.60 (1 C), 142.12 (1 C), 140.39 (1 C), 138.88 (1 C), 138.56 (1 C), 130.11 (1 C), 129.03 (1 C), 127.97 (1 C), 127.76 (2 C), 125.26 (1 C), 124.71 (1 C), 123.50 (2 C), 111.67 (1 C), 105.18 (1 C), 60.52 (1 C). MH^+ found = 283.0783; calcd = 283.0793.

Synthesis of Methyl *N*-[(2*Z*)-3-[4-(2-Furyl)phenyl]-3-(3-thienyl)-2-propen-1-yl]-*N*-methylglycinate Compound with Oxalic Acid (1:1) (11). Allylic alcohol **3** (35 g, 124 mmol) in dichloromethane (372 mL) was cooled to 0 °C and treated with methanesulfonyl chloride (10.1 mL, 130 mmol). Diisopropyl-

ethylamine (23.8 mL, 136.3 mmol) was added dropwise so that the temperature did not exceed 5 °C. The mixture was stirred for 30 min at 0 °C. Solid sarcosine methyl ester hydrochloride salt (19.8 g, 136 mmol) was added in one portion followed by diisopropylethylamine (48 mL, 273 mmol), maintaining the temperature between 0 and 4 °C. The mixture was allowed to stir overnight at this temperature, and then it was quenched with water. The organic layer was washed twice with water, and during the final wash the pH was adjusted to ~10. The organic layer was separated, the solvent was evaporated, and the residue was dissolved in 270 mL of ethanol and heated to 60 °C. Oxalic acid (14.8 g) was added in 180 mL of ethanol, and the mixture was stirred until a precipitate was observed. The latter was stirred overnight, filtered, and dried to afford the oxalate salt **11**. Yield of **11**: 31.7 g (56%). ^{1}H NMR (360 MHz, DMSO-d_6): δ 2.50 (s, 3 H) 3.53 (d, J = 6.70 Hz, 2 H) 3.63−3.64 (m, 2 H) 3.63 (s, 3 H) 5.95 (br s, 2 H) 6.21 (t, J = 6.70 Hz, 1 H) 6.60 (dd, J = 3.36, 1.85 Hz, 1 H) 6.91 (dd, J = 4.89, 1.10 Hz, 1 H) 6.96 (d, J = 3.36 Hz, 1 H) 7.31 (d, J = 8.46 Hz, 2 H) 7.45 (dd, J = 2.90, 1.10 Hz, 1 H) 7.63−7.66 (m, J = 4.89, 2.90 Hz, 1 H) 7.67 (d, J = 8.46 Hz, 2 H) 7.76 (d, J = 1.85 Hz, 1 H). MNa^+ found = 390.1135; calcd = 390.1140.

Synthesis of *N*-[(2*Z*)-3-[4-(2-Furyl)phenyl]-3-(3-thienyl)-2-propen-1-yl]-*N*-methylglycine (1). The oxalate salt **11** (20.2 g, 43.8 mmol) was dissolved in MTBE (160 mL) and treated dropwise with a solution of K_2CO_3 (saturated) in water (160 mL). Stir for 1 h at ambient temperature. The aqueous layer was separated, and the organic was concentrated in vacuo. The residue was dissolved in methanol (160 mL) and treated with NaOH (3 mL, 50% aqueous solution). The mixture was warmed to 60 °C and stirred for 4 h. Upon completion, the mixture was treated with water (120 mL), and formic acid was added (19.6 g, 219 mmol) at 60 °C until precipitation of **1** began after 30 min; the slurry was stirred for 2 h, cooled to room temperature, and stirred overnight. The solid was filtered and washed with methanol−water (100 mL, 1:1 ratio). The filtrate was dried to afford **1**. Yield of **1**: 14.7 g, 95% ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3 H) 3.21 (s, 2 H) 3.42 (d, J = 6.77 Hz, 2 H) 3.46 (br s, 1 H) 6.19 (t, J = 6.67 Hz, 1 H) 6.60 (dd, J = 3.43, 1.79 Hz, 1 H) 6.91 (dd, J = 4.89, 1.24 Hz, 1 H) 6.94 (dd, J = 3.43, 0.46 Hz, 1 H) 7.29 (d, J = 8.53 Hz, 2 H) 7.44 (dd, J = 2.93, 1.24 Hz, 1 H) 7.62 (dd, J = 4.89, 2.93 Hz, 1 H) 7.66 (d, J = 8.53 Hz, 2 H) 7.75 (dd, J = 1.79, 0.46 Hz, 1 H) MH^+ found = 354.1171; calcd = 354.1164. Pd content < 10 ppm.

Supporting Information Available

Spectra of the key compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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