Palladium-Catalyzed Hydroarylation of Propiolamides. A Regio- and Stereocontrolled Method for Preparing 3,3-Diarylacrylamides

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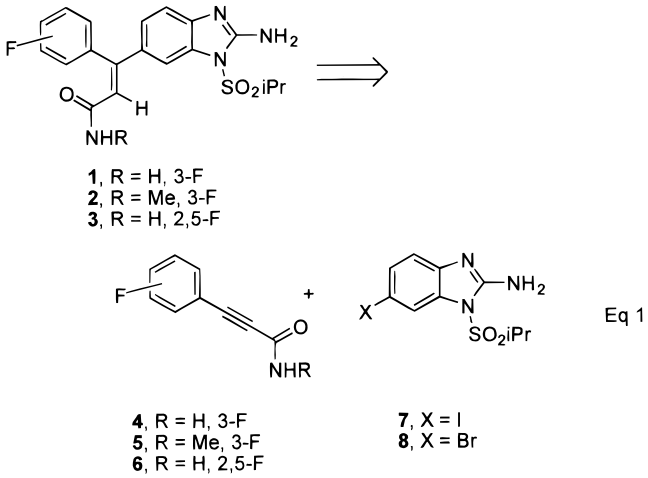
A general regio- and stereoselective synthesis of 3,3-diarylacrylamides is reported. Palladium-catalyzed coupling reactions of propiolamides with aryl halides provide arylpropiolamides. A subsequent hydroarylation reaction of these arylpropiolamides with aryl halides, catalytic palladium, an amine base, and formic acid in refluxing ethyl acetate provides 3,3-diarylacrylamides regio- and stereoselectively. The unique stereo- and regiocontrol is presumed to proceed through careful reaction parameters that allow intramolecular coordination of the propiolamide amide functionality to the transient palladium−alkyne complex. Palladium-catalyzed hydroarylation of propiolamides has not been studied; however, preliminary results from related systems suggest that regioselective addition can be achieved. The methodology as a synthesis tool is demonstrated in an efficient route to previously difficult-to-prepare potent, benzimidazole antiviral targets. In addition, the synthesis scope is explored where, by judicious choice of reaction sequence and aryl iodide, either the *Z*- or *E*-geometric isomer of a given pair of 3,3-diarylacrylamides is independently prepared.

Introduction

The 3,3-diarylacrylamide structure is present in a variety of biologically active molecules. When one of the aryl units is substituted with a carboxyalkanamide or a carboxyalkenamido group, these derivatives are effective in antagonizing the spasmogenic activity of the slow-reacting substance of anaphylaxis (SRS-A) in human subjects.[1] Therefore, this class of compounds is useful for preventing and treating certain obstructive airway diseases, notably allergic bronchial asthma and allergic rhinitis. Additionally, a variety of 3,3-diarylacrylamides are active fungicides in various microbicidal compositions.[2] Specifically, 3-aryl-3-benzimidazole acrylamides can function as agents to treat viral growth.[3]

Since one geometric isomer is usually more active than the other (or at times the other stereoisomer is totally inactive), versatile, stereoselective syntheses of these targets are advantageous. Thus far, 3,3-diarylacrylamides have been prepared by methods such as the Wittig and related reactions, Peterson olefination, Heck reaction, or simply by dehydration of a carbinol. While these reactions are suitable methods, many of them produce mixtures of the (*E*)- and (*Z*)-isomers.

In conjunction with projected syntheses of antirhinoviral agents **1**−**3** (eq 1), our need to develop a practical route to stereospecific 3,3-diarylacrylamides led to an investigation of the palladium-catalyzed hydroarylation reaction[4−7] of propiolamides. The synthesis strategy was to incorporate a key hydroarylation reaction step to establish the geometric 3,3-diarylacrylamide relationship. This convergent approach involved preparation of 2-aminobenzimidazole **7** or **8** and propiolamides **4**−**6**. The palladium-catalyzed hydroarylation reaction between **7** or **8** and **4**−**6** would provide 3,3-diarylacrylamides **1**−**3**.



Eq 1

Hydroarylation reactions of substituted acetylenes with aryl iodides in the presence of palladium catalyst, formic acid, and base are known to result in high stereo- and regioselective formation of trisubstituted olefins. In particular, variations of this methodology have found wide use in the palladium-catalyzed annulation of functionalized carbo- and heterocycles.[8,9] Among the acetylene systems that have been reported are dialkylacetylenes, diarylacetylenes, arylethynylcarbinols, arylethynylsilanes, alkylethynylsilanes, and alkyl 4-hydroxy-2-alkynoates. We have recently investigated the applica-

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(1) Kadin, S. B. U.S. Patent 4,342,781, Aug 3, 1982.
(2) Curtz, J.; Gunter Krummel, M. U.S. Patent 4,912,217, March 27, 1990.
(3) Morwick, T. M.; Paget, C. J. U.S. Patent 4,420,479, Dec 13, 1983.
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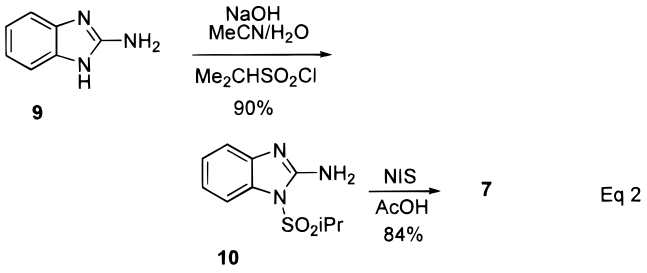
tion of palladium-catalyzed hydroarylation to the propiolamide system for preparing 3,3-diarylacrylamides.[10] Unlike most other acetylene systems where steric factors control the regiochemistry, we reasoned that the amide functionality would play a key role in the regiochemical outcome due to possible coordination of the amide to the transient-metal complex. Herein, we report the use of propiolamides in the palladium-catalyzed hydroarylation reaction. The methodology is developed in terms of the synthesis for antiviral 3,3-diarylacrylamide targets **2** and **3**, which is further extended to include the scope of the general reaction in preparing regio- and stereoselective 3,3-diarylacrylamides.

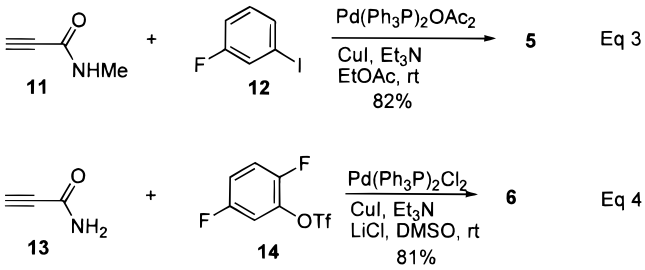
Results and Discussion

Building Blocks. The heterocycles **7** and **8** were prepared from readily available 2-aminobenzimidazole according to eq 2. First, the sulfonamide functionality was introduced by reaction of **9** with isopropylsulfonyl chloride in a solution of acetonitrile and sodium hydroxide. Iodination using *N*-iodosuccinimide in acetic acid provided 6-iodo-2-aminobenzimidazole **7** in an overall yield of 76% from **9**.

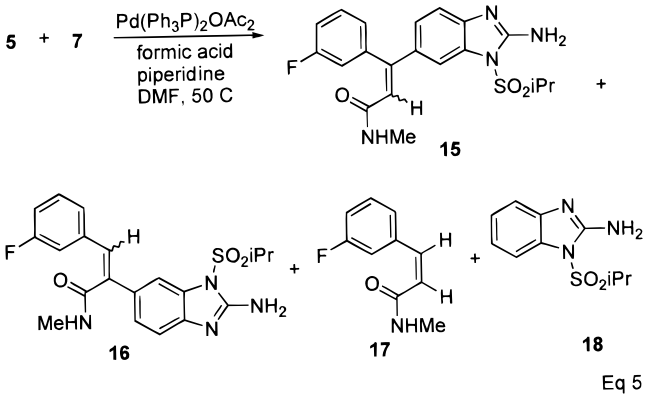


Initial attempts at preparing various arylpropiolamides by the Castro−Stephens[11,12] reaction or its modifications[13−15] employing aryl iodides or aryl triflates with methyl propiolate followed by amination of the ester functionality were not successful due to the low-yielding coupling reaction step. It has been documented that terminal acetylenes containing an electron-withdrawing group directly attached to the ethynyl carbon atom react poorly with aryl halides.[16] With the obvious difference between the ester functionality and amide, we turned our efforts toward cross-coupling reactions of propiolamides and aryl halides or aryl triflates.

Propiolamide and *N*-methylpropiolamide were prepared from methyl propiolate [17−20] in 88% and 95% yield, respectively. Both propiolamides were subjected to cross-coupling reaction conditions with a variety of aryl iodides, aryl bromides, and aryl triflates. Unlike methyl propiolate or ethyl propiolate, the propiolamides provide arylpropiolamides in good yields. For example, the coupling of **11** and **12** in the presence of 6 mol % Pd($Ph_3P)_2OAc_2$, 20 mol % CuI, and triethylamine in ethyl acetate at ambient temperature for 6 h provided the coupled product **5** in 82% yield (eq 3). On the other hand, propiolamide **13** reacted with the triflate **14** in the presence of 7 mol % $Pd(Ph_3P)_2Cl_2$, 5 mol % CuI, triethylamine, and LiCl in DMSO at 55 °C for 1 h to provide **3** in 81% yield (eq 4).



Hydroarylation of Propiolamides. Modifying a literature procedure[4] for the palladium-catalyzed hydroarylation reaction, **5** and 1 equiv of the aryl halide **7** were heated in DMF at 50 °C with $Pd(Ph_3P)_2(OAc)_2$, formic acid, and an amine (diethylamine, piperidine, or triethylamine) (eq 5). No reaction occurred with triethylamine, while the reaction with diethylamine provided low yields of the reduced propiolamide, *cis*-alkene **17**. Using piperidine as base provided 10% of **15** as a mixture of geometric isomers in addition to an equal amount of the structural regioisomer **16** also as a mixture. The remainder of the material isolated from this reaction was the dehalogenated benzimidazole **18**. To minimize dehalogenation, **7** was added slowly to the reaction mixture. This approach did not decrease the amount of **18** formed but resulted in an increase of the alkene product **17**. Employing bromobenzimidazole **8** gave similar results. Other hydroarylation conditions were investigated using the same catalyst and replacing the amine/formic acid combination with tetrapropylammonium bromide/sodium formate or potassium carbonate, lithium chloride/formic acid. Neither of these conditions provided the desired product, and only starting materials were recovered. Although excess aryl halide was used in the noted literature reaction, our system was limited to 1 equiv due to the complex nature of the aryl halide. This deviation may have contributed to the outcome of our experimentation.



In an effort to optimize the palladium-catalyzed hydroarylation reaction to provide **2**, several catalysts were examined. The results are summarized in Table 1.

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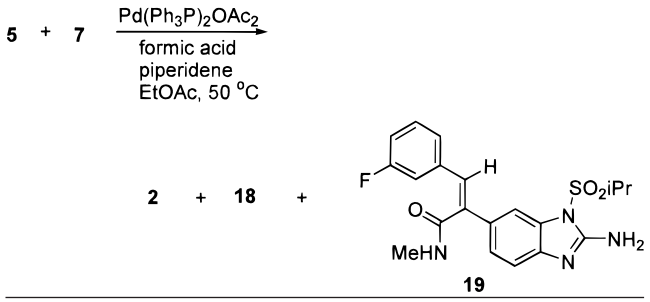
Table 1. Palladium-Catalyzed Hydroarylation in DMF[a]

catalyst	time (h)	yield (%) of **15**[b]	yield (%) of **16**[b]	yield (%) of **18**[b]	isomer ratio (**15**:**16**)
$Pd(Ph_3P)_2(OAc)_2$	>24	7	7	29	1:1
$Pd(MeCN)_2Cl_2$	52	31	27	<5	1.1:1
$Pd(OAc)_2/(o\text{-tol})_3P$	48		trace amounts		2:1

[a] Reactions run using 6−7% catalyst, 3.3 equiv of piperidine, 2.6 equiv of formic acid in DMF at 50−55 °C. [b]Reversed-phase HPLC area percents.

Table 2. Palladium-Catalyzed Hydroarylation in Ethyl Acetate[a]



catalyst	time (h)	yield (%) of **2**[b]	yield (%) of **19**[b]	yield (%) of **18**[b]	isomer ratio (**2**:**19**)
$Pd(MeCN)_2Cl_2$	2	47	11	4	4.4:1
$Pd(dba)_2$	1	55	15	11	3.7:1
$Pd(OAc)_2$	1.5	43	18	12	2.4:1
$PdCl_2$	2	50	19	10	2.6:1
$Pd(TFA)_2$	3	44	22	12	2:1
$Pd(BnCN)_2Cl_2$	1	36	15	6	2.5:1
$Pd(Ph_3P)_2(OAc)_2$	1	20	9	16	2.2:1

[a] Reactions run using 6−7% catalyst, 3.3 equiv of piperidine, 2.6 equiv of formic acid in ethyl acetate at reflux. [b]Reversed-phase HPLC area percents.

Forming the catalyst in situ using $Pd(OAc)_2$ and $(o\text{-tol})_3P$ gave the best isomer ratio; however, the rate of reaction was very slow. $Pd(MeCN)_2Cl_2$ was used to screen for optimal reaction conditions since it gave higher yields of **15** with fewer byproducts.

We started the optimization study with $Pd(MeCN)_2Cl_2$ as catalyst, piperidine as base, formic acid, and the solvent as the variable. At this stage, our goal was to find a solvent that would provide increased yields and a high regioisomer ratio of **15**. Among the solvents investigated, ethyl acetate gave the best isomer ratio of 4.4:1 (**15**:**16**) with decreased reaction time and byproduct formation. Additionally, these conditions minimized formation of geometric isomers for both **15** and **16** where only the *Z*-isomer was observed for both regioisomers. Acetone, 2-butanone, chloroform and toluene, also investigated, were poor solvents for the reaction.

Therefore, ethyl acetate was chosen as the solvent for reinvestigation of the various catalysts since the initial catalyst work was performed with DMF. On the basis of our prior study, we focused on phosphine-free palladium catalysts (Table 2) since these catalysts provided higher yields of **15** relative to regioisomer **16** (see Table 1).

$Pd(MeCN)_2Cl_2$ and $Pd(dba)_2$ gave higher yields, lower byproduct formation, and increased rate of reaction. Both catalysts also gave ratios of the two regioisomers of **2** and **19** in a ratio of approximately 4:1, favoring the desired regioisomer **2**. It is unclear why phosphine-free catalysts gave such significant improvements in the overall yield of products. In palladium-catalyzed hydroarylation, there is evidence that switching the ligand from triphenylphosphine to the more sterically demanding tri-*o*-tolylphosphine ligand affects the regioselectivity and yield.[7] In our system, eliminating the bulky ligand altogether gave higher yields and a major reduction in the amount of dehalogenation byproduct. The phosphine ligand may hinder the requisite palladium−propiolamide coordination, giving rise to an increase in the palladium-catalyzed dehalogenation pathway. Trost and Li[21] also reported that a palladium-catalyzed addition across a carbon−carbon triple bond occurred much more readily and with less decomposition in the absence of ligands. The absence of phosphine ligand on the palladium metal may decrease steric hindrance and increase the potential of the ligandless metal to coordinate with the substrate. However, on the basis of our data, one would therefore expect that $PdCl_2$ would give significantly better yields and improved isomer ratios since it has the least sterically demanding substituents. Although this catalyst gave fairly good yields of product **2** relative to the amount of byproducts **19** and **18**, its selectivity was not much better than that obtained using $Pd(PPh_3)_2(OAc)_2$. Apparently, there may be other factors in the reaction that can account for the success of $Pd(dba)_2$ and $Pd(MeCN)_2Cl_2$.

Table 3. Solvent Effect on Isomer Ratio at 0.02 M[a]

solvent	*T* (°C)	isomer ratio (**2**:**19**)[b]	dielectric constant (ϵ)
EtOAc	77	17:1	6.02
THF	66	20:1	7.6
$CHCl_3$	61	5.8:1	4.9
MeOH	65	3.5:1	32.7
DMF	60	2:1	36.7
MeCN	82	1:1	37.5

[a] Reactions run using 6−7% $Pd(dba)_2$, 3.3 equiv of piperidine, 2.6 equiv of formic acid. [b] Reversed-phase HPLC area percents.

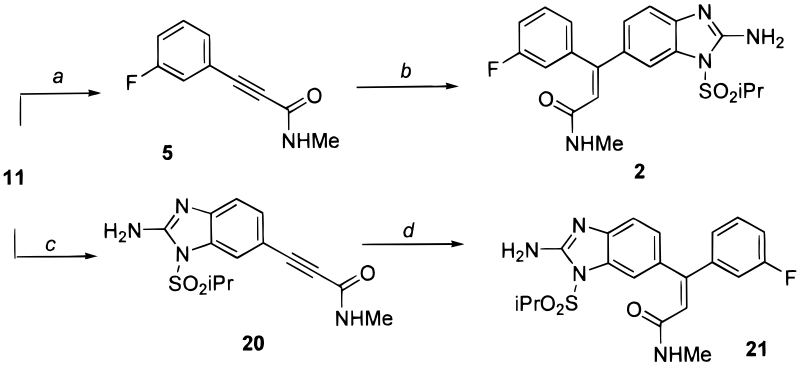
Another parameter that contributed significantly to the optimization of this reaction was concentration. Most of the reactions during the optimization studies were conducted at concentrations of 0.1 M following literature procedures for palladium-catalyzed hydroarylation. Under dilute conditions, such as 0.02 M, an improved isomer ratio was observed. For example, the hydroarylation reaction in refluxing ethyl acetate and $Pd(dba)_2$ at 0.02 M gave a regioisomer ratio of 17:1 (**2**:**19**). Other catalysts also showed improved regioisomer ratios in dilute ethyl acetate. For example, $Pd(PhCN)_2Cl_2$, $PdCl_2$, and $Pd(OAc)_2$ all gave ratios of >6:1 (**2**:**19**). Concentrations less than 0.02 M showed no further improvements.

Since ethyl acetate has a lower dielectric constant than DMF and possesses different coordinating ability, the possibility of a relationship between dielectric constant of the solvent and regiochemical outcome was examined. Table 3 lists six of the solvents that were investigated at 0.02 M. The temperature was held at 60 °C for DMF and at reflux for the other solvents, giving a range of approximately 60−82 °C.[22] Although dilute refluxing THF provided a similar ratio as ethyl acetate, this reaction progressed much more slowly.

(21) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, *28*, 6625.

(22) *Lange's Handbook of Chemistry*, 13th ed.; Dean, J. A., Ed.; McGraw-Hill: St. Louis, 1985. Although the dielectric constants used were derived at 25 °C for a given solvent, the reactions in Table 3 were conducted at 60−82 °C.

Scheme 1[a]



[a] Reaction conditions: (a) = 3-FC_6H_4I, $Pd(Ph_3P)_2Cl_2$, CuI, Et_3N, EtOAc; (b) = **7**, $Pd(dba)_2$, piperidine, HCOOH, EtOAc, 70 °C; (c) = **7**, $Pd(Ph_3P)_2OAc_2$, CuI, Et_3N, EtOAc; (d) = 3-FC_6H_4I, $Pd(dba)_2$, piperidine, HCOOH, EtOAc, 70 °C.

As anticipated, it appears that a general trend does exist between the ratio of regioisomers and the dielectric constant of the reaction solvent. For the most part, as the dielectric constant of the solvent decreased, the isomer ratio increased in favor of **2**. Methanol, DMF, and acetonitrile, all with high dielectric constants, provided poor regioisomer ratios, while ethyl acetate and THF with low dielectric constants provided high regioisomeric ratios.

Combining data from the optimization studies, the optimum reaction conditions that were developed included $Pd(dba)_2$ or $Pd(MeCN)_2Cl_2$ as catalyst; diethylamine or piperidine as base; formic acid; and 0.02 M of propiolamide **5** in refluxing ethyl acetate. Using these conditions, **2** was obtained in 81% yield. The success of the process development is evident when one compares the optimized reaction conditions to the reaction parameters established in the literature for the palladium-catalyzed hydroarylation of acetylenes. The reaction time was reduced from >24 to 2 h. Significantly less byproduct formation occurred under the optimized conditions, and the regioisomeric ratio of **2** was improved from 1:1 to >17:1 in favor of **2**. These improvements also increased the yield from 10% to 81%.

Similar reaction conditions used for the preparation of **2** were applied to the formation of **3**. Thus, **6** was reacted with **7** to provide **3** in 75% isolated yield with a regioisomer[23] ratio of 4.2:1. Although the reaction for preparing **3** was not optimized, we were somewhat disappointed that the reaction conditions developed for preparing **2** did not give higher isomeric ratios for this target.

Another area where the optimized reaction conditions for preparing **2** did not perform as expected was in the attempted preparation of the opposite geometric isomer **21** (Scheme 1) by simply reversing the order of propiolamide preparation and hydroarylation reaction. Thus, **7** was coupled to *N*-methylpropiolamide in the presence of $Pd(Ph_3P)_2(OAc)_2$ to give **20** in 96.2% yield. Reaction of **20** with 3-fluoroiodobenzene under various hydroarylation conditions provided no significant amount of **21**. This difference in the outcome of the two types of hydroarylation reaction approaches coupled with the low isomeric ratio in the formation of **3** led to a study of the general scope for the palladium-catalyzed hydroarylation of propiolamides.

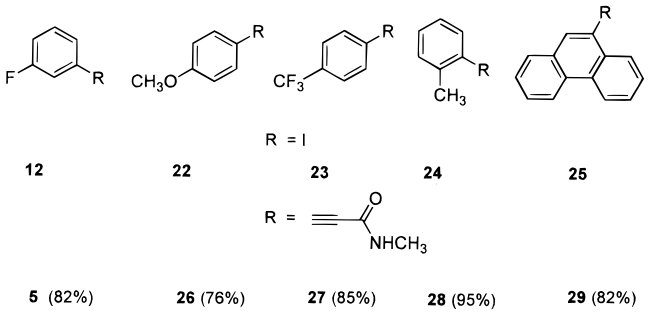


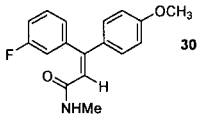
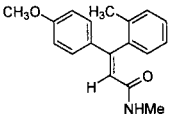
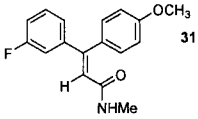
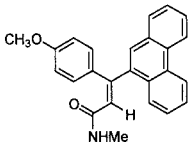
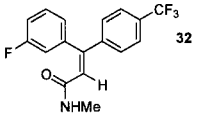
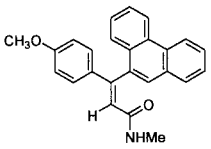
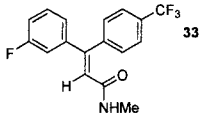
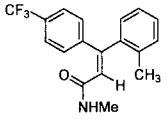
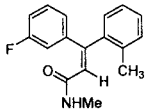
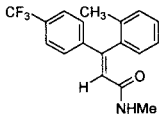
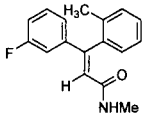
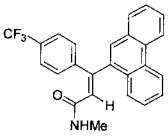
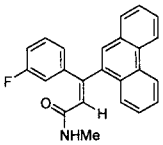
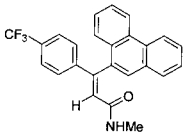
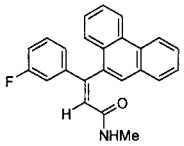
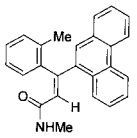
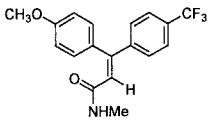
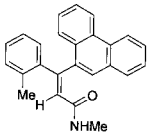
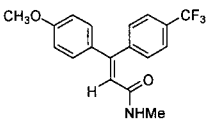
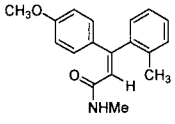
Figure 1. Coupling partners used in the palladium-catalyzed hydroarylation reactions.

Reaction Scope. For consistency and ease in product analysis by ^1H NMR, the *N*-methyl derivative of propiolamide was used in the study. Therefore, in addition to **5**, four other aryl-*N*-methylpropiolamides were prepared in an attempt to explore the effect of electron density or steric influence in the hydroarylation reaction. *N*-Methylpropiolamide **11** was reacted with anisyl iodide (**22**), methyl 4-iodobenzoate (**23**), 2-iodotoluene (**24**), and 9-iodophenanthrene (**25**) using the procedure similar to eq 3 to give *N*-methyl-3-arylpropiolamides **26**−**29** in 76−95% yield (Figure 1). These various arylpropiolamides were then reacted with the same selection of aryl iodides to produce pairs of geometric isomers (Table 4). The palladium-catalyzed hydroarylation reaction of arylpropiolamides **5** and **26**−**29** with aryl iodides **12** and **22**−**35** proceeded cleanly with few exceptions to provide each of the geometric isomers.[23]

The results summarized in Table 4 indicate that electron density in either coupling partner had very little effect on the reaction's yield or regioselectivity. For example, aryl groups with electron-donating substituents such as **22** and **26** gave results similar to those of groups with electron-withdrawing substituents such as **23** and **27**. Large aromatic rings such as phenanthrene in **25** and **29** also provided excellent yields and regioselectivities. In the cases where the aromatic ring of the propiolamide was substituted at the 2-position, the reactions proceeded smoothly. However, in two reactions examined where 2-iodotoluene (**24**) was used as a coupling partner, the attempted hydroarylation reaction was very slow, providing only traces of the 3,3-diarylacrylamide **34** or **44**. In these cases, reduction of the acetylene to the cis olefin product occurred.

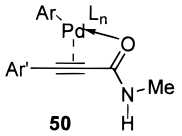
(23) Structural assignments were made on the basis of spectroscopic analyses (NMR), and X-ray crystallographic analyses were also obtained for compound **3** and (*Z*)-*N*-methyl-3-(1-naphthyl)-3-(9-phenanthryl)-2-propenamide.

Table 4. Palladium-Catalyzed Hydroarylation of Propiolamides[a]

Aryl Propiolamide	Aryl Iodide	Reaction time (h)	Product	Yield (%)	Aryl Propiolamide	Aryl Iodide	Reaction time (h)	Product	Yield (%)
5	**22**	5	 **30**	80	**28**	**22**	23	 **41**	88
26	**12**	5	 **31**	85	**26**	**25**	5	 **42**	72
5	**23**	5	 **32**	75	**29**	**22**	18	 **43**	83
27	**12**	5	 **33**	64	**27**	**24**	6	 **44**	0
5	**24**	18	 **34**	0	**28**	**23**	24	 **45**	85
28	**12**	12	 **35**	68	**27**	**25**	4	 **46**	89
5	**25**	3	 **36**	77	**29**	**23**	18	 **47**	77
29	**12**	6	 **37**	83	**28**	**25**	18	 **48**	90
26	**23**	4	 **38**	50	**29**	**24**	18	 **49**	62
27	**22**	4	 **39**	22					
26	**24**	5	 **40**	82					

[a] All reactions were carried out with 1 equiv of arylpropiolamide and aryl iodide, $Pd(dba)_2$ (7 mol %) in refluxing ethyl acetate (0.02 mmol of arylpropiolamide/L of solvent).

Taking into consideration the key features of the optimized reaction for preparing regioselective 3,3-diarylacrylamides, i.e., the phosphine-free catalysts, low-coordinating solvents, and low reaction concentrations, we can propose that the high regioselective hydroarylation reaction of arylpropiolamides is mediated by a key coordinated amide complex (Figure 2). Therefore, the regioselectivity of insertion for this process appears to



50

Figure 2. Possible transient palladium-propiolamide complex.

follow the pattern established by others[24−26] in which the aryl group adds to the less hindered carbon of the alkyne functionality and the palladium group adds to the more hindered carbon. Using this rationale, the amide functionality would be viewed as larger than a phenyl. However, this explanation does not fully account for instances where one geometric isomer forms readily while the other does not. This is illustrated in the attempted formation of **21**, **34**, and **44**. The rationale also does not explain the low regioselectivity observed in the formation of **3**. In these reactions, a combination of coordination and steric influences may play a major role in the overall reaction outcome.

Hydroxyl coordination has been proposed to affect the palladium-catalyzed reaction of aryl iodides with allylic alcohols.[7] In our case, the results suggest that the amide functionality coordinates to the palladium center. Phosphine ligands, coordinating solvents, and high concentration of amide may all compete with the possible transient palladium complex to provide reactions that are nonselective or nonhydroarylation reactions. In an attempt to form either geometric isomer by judicious choice of aryl iodide in the arylpropiolamide formation and the hydroarylation reaction, two very different transient palladium complexes are formed. The two complexes become more distinct when the arypropiolamide is a heteroaryl such as **20**, which contains other coordinating sites in addition to the carbon−carbon triple bond.

Conclusion

The palladium-catalyzed hydroarylation reaction between an aryl propiolamide and an aryl iodide has proven to be a practical means for preparing 3,3-diarylacrylamides. In most cases, regio- and stereocontrol was obtained when the reaction was performed under dilute conditions employing phosphine-free Pd(0) catalyst and low-coordinating solvents such as ethyl acetate. The methodology was applied to a variety of arylpropiolamides and aryl iodides for which the reaction was found to be generally regio- and stereoselective. Among the exceptions is 2-iodotoluene, where no hydroarylation reaction took place. The methodology is particularly useful since either the (*Z*)- or (*E*)-isomer of a given 3,3-diarylacrylamide could be prepared by judicious choice of the arylpropiolamide coupling reaction and the hydroarylation reaction. Finally, the utility of the methodology was demonstrated with a convergent synthesis of antirhinoviral agents **2** and **3**.

Experimental Section

General Methods. All reagents and solvents were obtained from Aldrich, Fluka, or Johnson Matthey and were used without further purification. All reactions were performed under a dry nitrogen atmosphere unless specified otherwise. Reaction progress was monitored by thin-layer chromatography (TLC) or HPLC analyses. TLC analyses were performed with 0.25 mm silica gel plates containing F-254 indicator and visualized using UV light (254 nm) or phosphomolybdic acid indicator. Flash column chromatography was performed with 32−63 μm silica gel packing.[27]

Melting and boiling points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded as specified for each experiment with chemical shift recorded as parts per million. Combustion analyses were performed by Eli Lilly and Co. Physical Chemistry Microanalytical Laboratory.

Preparation of 2. To a reaction vessel were added **7** (7.94 g, 21.8 mmol), **5** (5.00 g, 28.2 mmol), and ethyl acetate (750 mL) to form a solution at ambient temperature. To this solution were added $Pd(MeCN)_2Cl_2$ (0.40 g, 1.5 mmol) and piperidine (7.1 mL, 71.8 mmol) followed by formic acid (2.10 g, 55.7 mmol). This mixture was heated to reflux for 5 h, adding additional **5** (0.445 g) after 1 h before the mixture was cooled to room temperature. About half of the solvent was removed under vacuum before dilution with water. The layers were separated and the organics washed two times with water and once with brine, dried over $MgSO_4$, and concentrated to a residue. This material was crystallized from EtOAc to obtain purified product (5.75 g, 60.0% yield): IR ($CHCl_3$) 1638, 1610, 1580, 1546, 1442, 1360 cm^{-1}; ^{1}H NMR (250 MHz; DMSO-d_6) δ 7.98 (d, J = 4.50 Hz, 1H), 7.41−6.93 (m, 9H), 6.43 (s, 1H), 3.85 (m, 1H), 2.57 (d, J = 4.75 Hz, 3H), 1.24 (d, J = 7.00, 6H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.3, 163.6, 159.7, 153.7, 148.2, 143.2, 142.1, 133.2, 132.2, 131.6, 129.5, 125.5, 124.5, 121.0, 116.0, 114.1, 111.2, 55.9, 25.4, 15.7; MS (FD^+) calcd for $C_{20}H_{21}FN_4O_3S$ 416.47, found 416.0 (M^+, 100). Anal. Calcd for $C_{20}H_{21}FN_4O_3S$: C, 57.68; H, 5.08; F, 4.56; N, 13.45; S, 7.70. Found: C, 58.29; H, 5.07; F, 4.69; N, 12.99; S, 7.15.

Preparation of 3. Compound **7** (6.185 g, 0.0169 mol), $Pd(dba)_2$ (0.388 g, 0.675 mmol), and diethylamine (5.8 mL, 56.1 mmol) were dissolved in ethyl acetate (750 mL). Into an addition funnel was placed **6** (3.07 g, 0.0169 mol) in ethyl acetate (60 mL). Formic acid (1.5 mL, 39.8 mmol) was added all at once to the addition funnel. The contents of the reaction vessel were heated to reflux before the solution of **6**, and formic acid was slowly added to the reaction mixture over several hours. The mixture was refluxed overnight. Additional **6** (0.705 g) in ethyl acetate (15 mL) was added along with formic acid (0.09 mL) as a means to drive the reaction to completion. After being refluxed overnight again, the mixture was cooled to room temperature, and half of the solvent was removed under vacuum. The remaining solution was washed with water, 1.0 N NaOH, and brine, dried ($MgSO_4$), and concentrated to 8.282 g (53%) of a yellow solid: IR (CH_2Cl_2) 3461, 3386, 3148, 1677, 1645, 1594, 1544, 1490, 1426, 1269, 1255, 1153, 1042, 832, 687, 512 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.44 (s, 1H), 7.26−6.96 (m, 8H), 6.63 (s, 1H), 3.85 (m, 1H), 1.25 (d, J = 6.75 Hz, 6H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.9, 153.8, 143.5, 142.9, 131.8, 131.6, 129.4, 129.1, 128.9, 123.7, 122.2, 116.5, 116.2, 110.4, 56.0, 15.7; MS (FD^+) calcd for $C_{19}H_{18}N_4O_3F_2S$ 420.437, found 420.1 (M^+, 100). Anal. Calcd for $C_{19}H_{18}N_4O_3F_2S$: C, 54.28; H, 4.32; N, 13.33; S, 7.63; F, 9.04. Found: C,54.02; H, 4.44; N, 13.18; S, 7.40; F, 9.31.

2-(3-Fluorophenyl)propiolamide (4). Propiolamide **13** (1.75 g, 25.3 mmol), 1-fluoro-3-iodobenzene (3.76 g, 16.9 mmol), $Pd(Ph_3P)_2(OAc)_2$ (0.941 g, 1.26 mmol), copper(I) iodide (0.649 g, 3.40 mmol), and triethylamine (7.11 mL, 50.9 mmol) were stirred in ethyl acetate (25 mL) at room temperature. Additional propiolamide (1.07 g) was added after several hours. The mixture was allowed to stir at room temperature for another 6 h before dilution with water, and the layers were separated. The organics were washed with water and brine, dried over $MgSO_4$, and concentrated to tan solid (2.109 g, 76.3%): IR ($CHCl_3$) 3522, 3403, 3015, 2221, 1672, 1582, 1367, 1582, 1367, 1278 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.25

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(br s, 1H), 7.8 (br s, 1H), 7.6−7.3 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.6, 160.4, 153.9, 131.2, 128.6, 118.8, 117.7, 85.1, 81.6; MS (FD$^+$) calcd for C_9H_6NOF 163.15, found 163.1 (M^+, 100). Anal. Calcd for C_9H_6NOF: C, 66.26; H, 3.71; N, 8.59; F, 11.64. Found: C, 64.30; H, 3.73; F, 10.28; N, 7.39.

***N*-Methyl 2-(3-fluorophenyl)propiolamide (5).** 1-Fluoro-3-iodobenzene (20.0 g, 90.1 mmol), triethylamine (37.5 mL, 269.0 mmol), $Pd(Ph_3P)_2(OAc)_2$ (4.0 g, 5.35 mmol), and copper(I) iodide (3.4 g, 17.98 mmol) were stirred in ethyl acetate (250 mL) at room temperature. *N*-Methylpropiolamide **11** (14.1 g, 170.0 mmol) was added in portions over several hours as the mixture was stirred at room temperature, monitoring by HPLC. This mixture was diluted with water and additional ethyl acetate, and the layers were separated. The aqueous layer was extracted with additional ethyl acetate, and the combined organic layers were washed twice with water and once with brine, dried over anhydrous $MgSO_4$, and concentrated to give a dark solid. Reslurrying in cold toluene gave the purified product (13.09 g, 82.0% yield): mp 91−93 °C; IR ($CHCl_3$) 3449, 3008, 2222, 1612, 1584, 1521, 1488, 1437, 1428, 1415, 1299, 1266, 1250, 1235, 1167, 1150, 951, 875 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (br d, J = 4.05 Hz, 1H), 7.54−7.39 (m, 4H), 2.70 (d, J = 4.78 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.80, 81.28, 84.57, 117.54, 118.57, 128.41, 131.14, 152.38, 160.14, 163.39; MS (FD$^+$) calcd for $C_{10}H_8FNO$ 177.18, found 177 (M^+, 100). Anal. Calcd for $C_{10}H_8FNO$: C, 67.79; H, 4.55; F, 10.72; N, 7.91. Found: C, 67.64; H, 4.57; F, 10.68; N, 7.69.

Preparation of 6. DMSO (50 mL), 2,5-difluorophenyltriflate (10.5 g, 40 mmol), propiolamide **13** (3.0 g, 44 mmol), $Pd(Ph_3P)_2Cl_2$ (2.0 g, 2.85 mmol), copper iodide (381 mg, 2 mmol), lithium chloride (5.08 g, 120 mmol), and triethylamine (10.10 g, 100 mmol) were combined and heated to 80 °C in a 250 mL round-bottom flask with reflux condenser. TLC analysis (silica, 100% ethyl ether, UV) was used to monitor the reaction's progress. After 3 h, additional propiolamide (∼300 mg) was added to the reaction. After an additional 2 h, the reaction was cooled to room temperature, diluted with water (20 mL), and filtered through a pad of silica gel using ethyl ether. The resulting filtrate was diluted with water and the organic portion separated. The combined organic extracts were washed with 1 N NaOH, 1 N HCl, and brine before being dried over anhydrous $MgSO_4$. After drying, the solution was concentrated and purified by crystallization from toluene (4.9 g, 68%): mp 92−93 °C; IR (KBr) 3409, 3190, 3049, 2218, 1651, 1605, 1498, 1396, 1282, 1200, 1138, 1098, 900, 852, 761, 696, 600 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.31−7.15 (m, 1 H), 7.15−7.00 (m, 2 H), 6.90−6.5 (br s, 1 H), 6.40−6.90 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 120.3, 119.9, 119.2, 118.9, 117.0, 116.6, 87.4, 77.8; MS *m/e* (rel int) 181 (M^+, 100). Anal. Calcd for $C_9H_5F_2NO$: C, 59.68; H, 2.78; F, 20.98; N, 7.73. Found: C, 59.78; H, 2.77; F, 20.69, N, 7.74.

Preparation of 7. Compound **10** (520 g, 2.18 mol) was added to acetic acid (3.9 L) to form a solution. *N*-Iodosuccinimide (488.8 g, 2.2 mol) was added and the reaction mixture heated to 55 °C. After 5 h, the reaction mixture was cooled to ambient temperature and the product crystallized from solution. Water was used to dilute the slurry before filtering to collect 674 g (84%) of compound **7**: IR ($CHCl_3$) 3516, 3482, 3401, 3022, 1628, 1556, 1450, 1383, 1361, 1290, 1228, 1192, 1176, 1049, 776, 730, 681 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (d, J = 1.48 Hz, 1 H), 7.44 (dd, J = 8.2, 1.58 Hz, 1 H), 7.10 (br s, 2 H), 7.50 (dd, J = 8.34, 1.65 Hz, 1 H), 3.90 (m, 1 H), 1.21 (d, J = 6.72 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.9, 142.1, 132.9, 132.7, 119.9, 118.2, 82.5, 55.7, 15.6; MS *m/z* (rel int) 365 (M^+, 100). Anal. Calcd for $C_{10}H_{12}IN_3O_2S$: C, 32.89; H, 3.31; N, 11.38. Found: C, 33.07; H, 3.39; N, 11.38.

Preparation of 10. Acetonitrile (44 mL), water (4.0 mL), sodium hydroxide (1.92 g, 45.1 mmol), and 2-aminobenzimidazole (3.0 g, 22.5 mmol) were stirred at room temperature to form a solution. At ambient temperature, 2-propanesulfonyl chloride (3.2 g, 22.5 mmol) was added. After 2 h, the reaction was diluted with water and cooled to 15 °C and then filtered to isolate **10** (6.4 g, 90%): IR ($CHCl_3$) 3516, 3481, 3400, 3022, 1682, 1556, 1450, 1383, 1361, 1256, 1228, 1192, 1176, 1049, 940, 776, 730, 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (d, J = 8.01 Hz, 1 H), 7.33 (d, J = 7.84 Hz, 1 H), 7.21 (t, J = 7.70 Hz, 1 H), 7.07 (t, J = 7.77 Hz, 1 H), 6.95 (br s, 2 H), 3.65 (m, 1 H), 1.39 (d, J = 6.86 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 141.1, 130.9, 124.3, 121.0, 116.2, 111.8, 55.6, 15.7; MS *m/e* (rel int) 239 (M^+, 100). Anal. Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.19; H, 5.48; N, 17.56. Found: C, 49.43; H, 5.41; N, 16.80.

***N*-Methylpropiolamide (11).** Methylamine (40% in water, 22.0 mL) in an equal volume of methanol was cooled to −78 °C for the dropwise addition of methyl propiolate (20.1 g, 0.238 mol) over 15 min via an addition funnel. The reaction mixture was stirred for 3 h at −78 °C before being warmed to room temperature. The solvent was removed at 25 °C under vacuum, and the resulting solid was slurried in methanol to remove any water. The slightly yellow solid was slurried in diethyl ether and cooled to −30 °C before being filtered to obtain a white crystalline solid (18.7, 95%): mp 88 °C; IR ($CHCl_3$) 3691, 3450, 3303, 3025, 3016, 2948, 2338, 2113, 1164, 1523, 1416, 1359, 1252, 1205, 1164, 1051, 1003, 868 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (br s, 1 H), 4.0 (s, 1 H), 2.56 (d, J = 4.89 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.67, 75.23, 78.24, 152.05. Anal. Calcd for C_4H_5NO: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.88; H, 6.12; N, 16.99.

Propiolamide (13). Aqueous ammonia (14.0 mL, 29% in water) was cooled to −78 °C for the dropwise addition of methyl propiolate (4.2 g, 50.2 mmol) over 15 min via an addition funnel. The mixture was stirred for 1 h at −78 °C before being warmed to room temperature. The solvent was removed at 25 °C under vacuum to obtain 3.04 g (87.7%) product: mp 60.5−62 °C; IR ($CHCl_3$) 3295, 2111, 1664, 1614, 1384, 1134, 657, 592, 543 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 7.1 (br s, 1H), 6.9 (br s, 1H), 3.0 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 154.3, 77.8, 74.3. Anal. Calcd for C_3H_3NO: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.26; H, 4.61; N, 20.48.

Preparation of 14. To a flask were added 2,5-difluorophenol (30.0 g, 230 mmol) and methylene chloride (150 mL) to form a solution. The solution was cooled to 0 °C, and pyridine (20.0 g, 253 mmol) was added. A methylene chloride solution of trifluoromethanesulfonyl anhydride (84.5 g, 300 mmol) was added dropwise to the reaction mixture at 0 °C. After addition, the resulting reaction mixture was stirred at room temperature for 4 h. Workup involved filtering the reaction mixture to remove the corresponding pyridine salt and the filtrate washed with 0.5 N HCl solution followed by a brine wash. After being dried over anhydrous $MgSO_4$, the methylene chloride solution was concentrated to a residue. The residue was purified by vacuum distillation to provide 52 g (84%) of pure product as a colorless liquid: bp 70 °C (13 mmHg); IR ($CHCl_3$) 1616, 1511, 1476, 1420, 1301, 1246, 1135, 1003, 790, 780, 748, 682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.18 (m, 1 H), 7.17−7.0 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 111.2, 111.6, 116.0, 116.4, 116.5, 117.7, 118.0; MS *m/e* (rel int) 262 (M^+, 100). Anal. Calcd for $C_7H_3F_5O_3$: C, 32.07; H, 1.15; F, 36.24. Found: C, 31.87; H, 1.15; F, 36.37.

Preparation of 20. The iodobenzimidazole **7** (6.63 g, 18.2 mol), $Pd(Ph_3P)_2(OAc)_2$ (1.09 g, 1.46 mmol), copper(I) iodide (0.702 g, 3.69 mmol), and *N*-methylpropiolamide **11** (2.08 g, 25.1 mmol) were taken up in DMSO (140 mL). Triethylamine (7.26 mL, 52.1 mmol) was added and the mixture stirred at room temperature. Additional **11** (3.24 g) was added in portions. After 4 h, water was added, and the resulting solid was filtered off. This solid was reslurried in toluene to give 5.17 g of product. The filtrate was extracted with methylene chloride, washed with water and then brine, dried over $MgSO_4$, and concentrated under vacuum to give another 0.433 g of product. The combined crude material was crystallized from ethyl acetate (5.5 g, 96.2%): IR (CH_2Cl_2) 3437, 3087, 2982, 2211, 1673, 1610, 1554, 1474, 1445, 1358, 1275, 1259, 1235, 1176, 1154, 1038, 688, 606, 592 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (m, 1H), 7.65−7.25 (m, 5H), 3.95 (m, 1H), 2.67 (d, J = 4.78 Hz, 3H), 1.33 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.3, 153.0, 144.3, 131.2, 129.0, 116.2, 115.5, 110.8, 84.2, 82.9, 55.7, 25.8, 15.5; MS (FD$^+$) calcd for $C_{14}H_{16}N_4O_3F$ 320.37, found 320.3 (M^+, 100). Anal. Calcd for

$C_{14}H_{16}N_4O_3F$: C, 52.49; H, 5.03; N, 17.49; S, 10.01. Found: C, 51.14; H, 4.95; N, 16.76; S, 9.58.

3-(4-Anisyl)-*N*-methylpropiolamide (26). General Procedure A. *N*-Methylpropiolamide (6.1 g, 72.8 mmol), 4-iodoanisole (13.58 g, 58.04 mmol), $Pd(Ph_3P)_2(OAc)_2$ (3.4 g, 4.5 mmol), copper iodide (2.2 g, 11.6 mmol), and triethylamine (24.2 mL, 173.6 mmol) were stirred in ethyl acetate (200 mL) at room temperature. After 1 h (7.1 g, 85.9 mmol), *N*-methylpropiolamide was added in portions, along with water (75 mL). After another hour, additional water (75 mL) was added, and the mixture was separated into the two layers. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum at room temperature to a solid, which was reslurried in ethyl acetate and cooled to −10 °C and then filtered to provide 8.4 g (76%) of product: mp 123−124 °C; IR ($CHCl_3$) 2222, 1649, 1606, 1511, 1288, 1252, 1173, 835 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 8.61 (d, J = 4.75 Hz, 1H), 7.51 (d, J = 9.01 Hz, 2H), 7.01 (d, J = 8.76 Hz, 2H), 3.81 (s, 3H), 2.68 (d, J = 4.50 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 160.6, 153.1, 133.9, 114.6, 111.7, 83.4, 83.2, 55.4, 25.8; MS (FD^+) calcd for $C_{11}H_{11}NO_2$ 189.22, found 189.0 (M^+, 100). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.83; H, 6.10; N, 7.44.

***N*-Methyl-3-(9-phenanthryl)propiolamide (29). General Procedure B**. *N*-Methylpropiolamide (1.96 g, 23.56 mmol), 9-iodophenanthrene (5.93 g, 19.49 mmol), $Pd(Ph_3P)_2(OAc)_2$ (1.15 g, 1.54 mmol), copper iodide (0.743 g, 3.90 mmol), and triethylamine (6.0 mL, 43.05 mmol) were stirred at room temperature in 130 mL of DMSO overnight. The mixture was diluted with water and extracted with ethyl acetate. The organics were washed with water and brine, dried over $MgSO_4$, and concentrated to a tan solid. This solid was reslurried in toluene and filtered to give 4.13 g (82% yield) of product: mp 140−142 °C; IR ($CHCl_3$) 3450, 2219, 2205, 1651, 1520, 1494, 1453, 1264, 1242 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 8.98 (d, J = 4.50 Hz, 1H), 8.96−7.70 (m, 9H), 2.81 (d, J = 4.75 Hz, 3H); ^{13}C (63 MHz, DMSO-d_6) δ 152.8, 134.0, 130.4, 130.3, 130.0, 129.6, 129.0, 128.8, 127.9, 127.8, 127.5, 126.2, 123.5, 123.0, 116.3, 88.4, 81.0, 26.0; MS (FD^+) calcd for $C_{18}H_{13}NO$ 259.31, found 259.1 (M^+, 100). Anal. Calcd for $C_{18}H_{13}NO$: C, 83.38; H, 5.05; N, 5.40. Found: C,83.30; H, 5.05; N, 5.52.

3-[4-α,α,α-Trifluoromethyl)phenyl]-*N*-methylpropiolamide (27). Product was obtained as a white crystalline solid in 85% yield: mp 160−162 °C; IR ($CHCl_3$) 3449, 2232, 1656, 1617, 1532, 1524, 1510, 1415, 1405, 1284, 1173, 1135, 1107, 1070, 1018, 844 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 8.85 (d, J = 4.5 Hz, 1H), 7.85 (m, 4H), 2.72 (d, J = 5.0 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 152.3, 132.8, 125.92, 125.87, 125.7, 124.3, 85.9, 81.1, 25.9; MS (FD^+) calcd for $C_{11}H_8F_3NO$ 227.19, found 227 (M^+, 100). Anal. Calcd for $C_{11}H_8F_3NO$: C, 58.16; H, 3.55; N, 6.17; F, 25.09. Found: C, 58.12; H, 3.52; N, 6.17; F, 24.87.

***N*-methyl-3-(2-tolyl)propiolamide (28).** Product was obtained as a white solid in 95% yield: mp 52−55 °C; IR ($CHCl_3$) 3451, 3012, 2222, 1650, 1523, 1487, 1415, 1295, 1283, 1278 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, J = 7.5 Hz, 1H), 7.32−7.10 (m, 3H), 6.07 (br s, 1H), 2.91 (d, J = 4.9 Hz, 3H), 2.44 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 154.2, 141.3, 132.7, 129.8, 129.6, 125.7, 120.0, 86.7, 83.5, 26.5, 20.5; MS (FD^+) calcd for $C_{11}H_{11}NO$ 173.22, found 173.0 (M^+, 100). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.04; H, 6.42; N, 8.15.

General Procedure for the Hydroarylation of Arylpropiolamides. Arylpropiolamide, aryl iodide (1 equiv), and $Pd(dba)_2$ (7 mol %) were dissolved in ethyl acetate (0.02 mmol of arylpropiolamide/L of solvent). Diethylamine (3.3 equiv) was added, followed by formic acid (2.6 equiv), and the solution was heated to reflux until reaction completion. The reaction was then cooled to room temperature and washed with dilute HCl, dilute NaOH, and finally brine. The organics were dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum. Product was isolated from the crude mixture by either flash column chromatography (3% MeOH/$CHCl_3$; silica) or crystallization (1:1 EtOAc/Et_2O). All products were isolated as solids.

(*Z*)-3-(4-Anisyl)-3-(3-fluorophenyl)-*N*-methyl-2-propenamide (30): yield 80%; mp 165−168 °C; IR ($CHCl_3$) 3460, 3008, 1653, 1606, 1582, 1512, 1255, 1179 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.88 (d, J = 4.5 Hz, 1H), 7.37−7.32 (q, J = 7.2 Hz, 1H), 7.16−7.11 (m, 3H), 6.93−6.89 (m, 4H), 6.38 (s, 1H), 3.75 (s, 3H), 2.53 (d, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.2, 159.8, 147.2, 141.9, 141.8, 132.9, 129.5, 128.8, 125.3, 120.7, 116.1, 115.8, 113.9, 55.2, 25.3; MS (FD^+) calcd for $C_{17}H_{16}NO_2F$ 285.32, found 285.1 (M^+, 100). Anal. Calcd for $C_{17}H_{16}NO_2F$: C, 71.56; H, 5.65; N, 4.91; F, 6.66. Found: C, 71.51; H, 5.63; N, 4.95; F, 6.38.

(*E*)-3-(4-Anisyl)-3-(3-fluorophenyl)-*N*-methyl-2-propenamide (31): yield 85%, mp 118−122 °C; IR ($CHCl_3$) 3460, 3007, 1652, 1608, 1583, 1511, 1485, 1440, 1292, 1267, 1250, 1177 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.83 (d, J = 4.5 Hz, 1H), 7.38 (q, J = 7.4 Hz, 1H), 7.20−7.14 (m, 1H), 7.08−6.99 (m, 4H), 6.90 (d, J = 8.7 Hz, 2H), 6.35 (s, 1H), 3.77 (s, 3H), 2.54 (d, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.6, 158.9, 146.7, 144.6, 144.5, 130.7, 130.4, 130.3, 124.0, 123.0, 115.0, 114.1, 113.1, 55.0, 25.4; MS (FD^+) calcd for $C_{17}H_{16}NO_2F$: 285.32, found 285.1 (M^+, 100). Anal. Calcd for $C_{17}H_{16}NO_2F$: C, 71.56; H, 5.65; N, 4.91; F, 6.66. Found: C, 70.99; H, 5.99; N, 4.71; F, 6.28.

(*Z*)-3-[4-(α,α,α-Trifluoromethyl)phenyl]-3-(3-fluorophenyl)-*N*-methyl-2-propenamide (32): yield 75%; mp 122−125 °C; IR ($CHCl_3$) 3454, 3008, 1658, 1614, 1583, 1523, 1411, 1326, 1277, 1266, 1247, 1225, 1171, 1114, 1069, 1017, 841 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.04 (d, J = 4.5 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.44−7.35 (m, 3H), 7.20−7.17 (m, 1H), 7.00−6.93 (m, 2H), 6.57 (s, 1H), 2.55 (d, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.9, 160.1, 145.7, 144.7, 140.8, 140.7, 129.9, 129.7, 128.3, 125.5, 125.41, 125.37, 125.3, 116.2, 114.6, 25.4; MS (FD^+) calcd for $C_{17}H_{13}NOF_4$ 323.29, found 323 (M^+, 100). Anal. Calcd for $C_{17}H_{13}NOF_4$: C, 63.16; H, 4.05; N, 4.33; F, 23.52. Found: C, 64.11; H, 4.11; N, 4.25; F, 23.27.

(*E*)-3-[4-(α,α,α-Trifluoromethyl)phenyl]-3-(3-fluorophenyl)-*N*-methyl-2-propenamide (33): yield 64%; IR ($CHCl_3$) 3440, 3008, 1662, 1618, 1584, 1522, 1320, 1170, 1133, 1110, 1067 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 8.07 (d, J = 4.5 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.43−7.33 (m, 3H), 7.25−7.18 (m, 1H), 7.09−6.98 (m, 2H), 6.59 (s, 1H), 2.55 (d, J = 4.5 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 168.8, 160.3, 146.4, 143.1, 132.9, 130.7, 130.6, 130.0, 124.7, 124.62, 124.57, 123.90, 123.85, 115.5, 113.9, 25.4; MS (FD^+) calcd for $C_{17}H_{13}NOF_4$ 323.29, found 323.4 (M^+, 100). Anal. Calcd for $C_{17}H_{13}NOF_4$: C, 63.16; H, 4.05; N, 4.33; F, 23.52. Found: 62.86; H, 4.04; N, 4.45; F, 23.71.

(*Z*)-3-(3-Fluorophenyl)-*N*-methyl-3-(2-tolyl)-2-propenamide (35): yield 68%; IR ($CHCl_3$) 3436, 3007, 1651, 1610, 1596, 1583, 1529, 1485, 1442, 1268 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, J = 4.5 Hz, 1H), 7.42−7.35 (m, 1H), 7.28−7.17 (m, 4H), 7.03−6.98 (m, 3H), 6.67 (s, 1H), 2.54 (d, J = 4.6 Hz, 3H), 2.00 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 164.9, 146.8, 142.6, 138.5, 135.2, 130.7, 130.6, 129.6, 128.7, 127.3, 125.3, 123.3, 122.8, 115.5, 113.3, 25.4, 19.4; MS (FD^+) calcd for $C_{17}H_{16}NOF$ 269.32, found 269 (M^+, 100). Anal. Calcd for $C_{17}H_{16}NOF$: C, 75.82; H, 5.99; N, 5.20; F, 7.05. Found: C, 76.10; H, 6.00; N, 5.14; F, 6.98.

(*E*)-3-(3-Fluorophenyl)-*N*-methyl-3-(9-phenanthryl)-2-propenamide (36): yield 77%; mp 199−201 °C; IR ($CHCl_3$) 3454, 3010, 1658, 1611, 1582, 1521, 1494, 1486, 1268 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 8.84 (t, J = 7.5 Hz, 2H), 8.19 (d, J = 5.0 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.86−7.84 (m, 2H), 7.73−7.52 (m, 4H), 7.31−7.10 (m, 4H), 6.36 (s, 1H), 2.66 (d, J = 4.5 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.7, 145.6, 138.1, 130.9, 130.2, 129.80, 129.77, 129.7, 128.9, 127.6, 127.4, 127.2, 127.0, 126.9, 126.4, 124.82, 124.79, 123.4, 122.9, 115.6, 115.3, 114.9, 114.6, 25.6; MS (FD^+) calcd for $C_{24}H_{18}NFO$ 355.42, found 355.1 (M^+, 100). Anal. Calcd for $C_{24}H_{18}NFO$: C, 81.10; H, 5.11; N, 3.94; F, 5.35. Found: C, 81.12; H, 5.02; N, 3.91; F, 5.23.

(*Z*)-3-(3-Fluorophenyl)-*N*-methyl-3-(9-phenanthryl)-2-propenamide (37): yield 83%; mp 124 °C; IR ($CHCl_3$) 3444, 3009, 1653, 1611, 1583, 1529, 1493, 1486, 1451, 1289, 1266

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (t, J = 8.7 Hz, 2H), 7.90 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.78−7.62 (m, 5H), 7.55−7.50 (m, 1H), 7.26−7.14 (m, 2H), 7.06−6.96 (m, 2H), 6.80 (s, 1H), 5.38 (br s, 1H), 2.39 (d, J = 4.9 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.3, 146.2, 142.2, 142.1, 133.7, 131.0, 130.6, 130.4, 130.1, 130.0, 129.9, 128.9, 127.8, 127.4, 127.3, 127.11, 127.07, 126.0, 125.3, 123.2, 122.7, 122.6, 114.1, 26.1; MS (FD$^+$) calcd for $C_{24}H_{18}NOF$ 355.42, found 355.18 (M$^+$, 100). Anal. Calcd for $C_{24}H_{18}NOF$: C, 81.11; H, 5.10; N, 3.94. Found: C, 80.99; H, 5.17; N, 3.94.

(*Z*)-3-(4-Anisyl)-3-[α,α,α-trifluoromethyl)phenyl]-*N*-methyl-2-propenamide (38): yield 50%; IR ($CHCl_3$) 3450, 3004, 1653, 1606, 1510, 1325, 1251, 1171, 1131, 1068 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.94 (d, J = 5.0 Hz, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.40 (s, 1H), 3.79 (s, 3H), 2.57 (d, J = 4.5 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.6, 159.1, 146.7, 146.2, 130.9, 130.4, 128.9, 128.6, 125.4, 125.3, 125.2, 124.0, 113.3, 55.1, 25.4; MS (FD$^+$) calcd for $C_{18}H_{16}NO_2F_3$ 335.53, found 335.1 (M$^+$, 100). Anal. Calcd for $C_{18}H_{16}NO_2F_3$: C, 64.47; H, 4.81; N, 4.18; F, 16.99. Found: C, 64.35; H, 4.79; N, 4.19; F, 17.22.

(*E*)-3-(4-Anisyl)-3-[α,α,α-trifluoromethyl)phenyl]-*N*-methyl-2-propenamide (39): yield 22%; IR ($CHCl_3$) 3458, 3020, 1660, 1603, 1510, 1325, 1254, 1170, 1131, 1109, 1066, 1034, 1020, 833 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.14 (dd, J = 6.8, 1.9 Hz, 2H), 6.84 (dd, J = 6.8, 2.3 Hz, 2H), 6.30 (s, 1H), 5.44 (d, J = 3.8 Hz, 1H), 3.80 (s, 3H), 2.69 (d, J = 4.9 Hz, 3H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 166.3, 160.3, 149.0, 142.8, 132.6, 129.6, 129.2, 125.13, 125.08, 125.03, 124.97, 120.3, 113.8, 55.2, 26.1; MS (FD$^+$) calcd for $C_{18}H_{16}NO_2F_3$ 335.53, found 335.14 (M$^+$, 100). Anal. Calcd for $C_{18}H_{16}NO_2F_3$: C, 64.47; H, 4.81; N, 4.18. Found: C, 64.33; H, 4.85; N, 4.23.

(*E*)-3-(4-Anisyl)-*N*-methyl-3-(2-tolyl)-2-propenamide (40): yield 82%; IR ($CHCl_3$) 3453, 3008, 1654, 1606, 1511, 1294, 1251, 1179, 1033, 838 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.87 (d, J = 4.5 Hz, 1H), 7.25−7.11 (m, 4H), 7.08 (d, J = 8.5, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.85 (s, 1H), 3.74 (s, 3H), 2.58 (d, J = 4.5 Hz, 3H), 1.97 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 166.2, 158.9, 147.9, 142.7, 135.3, 131.0, 130.4, 130.3, 129.4, 127.8, 125.8, 123.3, 113.0, 55.1, 25.5, 19.7; MS (FD$^+$) calcd for $C_{18}H_{19}NO_2$ 281.36, found 281.2 (M$^+$, 100). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.61; H, 6.79; N, 5.20.

(*Z*)-3-(4-Anisyl)-*N*-methyl-3-(2-tolyl)-2-propenamide (41): yield 88%; IR ($CHCl_3$) 3007, 1646, 1605, 1573, 1530, 1512, 1291, 1279, 1254, 1181, 1034, 834 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.77 (d, J = 4.8 Hz, 1H), 7.20−7.10 (m, 5H), 6.95−6.88 (m, 3H), 6.52 (s, 1H), 3.74 (s, 3H), 2.52 (d, J = 4.5 Hz, 3H), 1.98 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.2, 159.7, 146.2, 139.4, 135.1, 132.3, 129.4, 128.6, 128.0, 126.9, 125.2, 119.8, 114.1, 55.2, 25.4, 19.4; MS (FD$^+$) calcd for $C_{18}H_{19}NO_2$ 281.36, found 281.1 (M$^+$, 100). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.60; H, 6.84; N, 5.08.

(*E*)-3-(4-Anisyl)-*N*-methyl-3-(9-phenanthryl)-2-propenamide (42): yield 72%; mp 156−158 °C; IR ($CHCl_3$) 3452, 1653, 1606, 1494, 1451, 1413, 1294, 1252, 1176, 1032, 845 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.83 (m, 2H), 8.07−8.02 (m, 2H), 7.82−7.50 (m, 6H), 7.26 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.21 (s, 1H), 3.70 (s, 3H), 2.66 (d, J = 4.5 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 166.3, 159.1, 146.5, 139.0, 131.1, 131.0, 130.3, 130.2, 130.1, 129.7, 128.8, 127.3, 127.2, 126.8, 126.74, 126.68, 124.5, 123.3, 122.8, 113.3, 55.1, 25.6; MS (FD$^+$) calcd for $C_{25}H_{21}NO_2$ 367.45, found 367.0 (M$^+$, 100). Anal. Calcd for $C_{25}H_{21}NO_2$: 81.72; H, 5.76; N, 3.81. Found: C, 81.81; H, 5.62; N, 3.94.

(*Z*)-3-(4-Anisyl)-*N*-methyl-3-(9-phenanthryl)-2-propenamide (43): yield 83%; mp 176−179 °C; IR ($CHCl_3$) 3435, 3010, 1648, 1604, 1529, 1512, 1274, 1254, 1180 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.81 (m, 2H), 8.05−7.77 (m, 2H), 7.76−7.50 (m, 6H), 7.26 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.75 (s, 1H), 5.29 (br s, 1 H), 3.72 (s, 3H), 2.39 (d, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 160.3, 146.9, 134.6, 132.2, 131.1, 130.6, 130.2, 129.0, 128.9, 128.4, 128.1, 127.5, 127.3, 127.2, 127.0, 126.3, 123.1, 122.6, 122.3, 113.9, 55.2, 26.1; MS (FD$^+$) calcd for $C_{25}H_{21}NO_2$ 367.45, found 367.01 (M$^+$, 100). Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.76; H, 6.02; N, 3.49.

(*Z*)-3-[4-(α,α,α-Trifluoromethyl)phenyl]-*N*-methyl-3-(2-tolyl)-2-propenamide (45): yield 85%; IR ($CHCl_3$) 1653, 1618, 1529, 1411, 1326, 1171, 1131, 1116, 1069, 1016, 844 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.95 (d, J = 4.5 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.27−6.99 (m, 4H), 6.72 (s, 1H), 2.54 (d, J = 4.8 Hz, 3H), 1.99 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 164.8, 146.8, 144.2, 138.3, 135.2, 129.7, 128.8, 127.44, 127.38, 125.63, 125.57, 125.5, 125.4, 124.4, 25.4, 19.4; MS (FD$^+$) calcd for $C_{18}H_{16}NOF_3$ 319.33, found 319.1 (M$^+$, 100). Anal. Calcd for $C_{18}H_{16}NOF_3$: C, 67.71; H, 5.05; N, 4.39. Found: C, 67.54; H, 5.13; N, 4.36.

(*E*)-3-[4-(α,α,α-Trifluoromethyl)phenyl]-*N*-methyl-3-(9-phenanthryl)-2-propenamide (46): yield 89%; mp 209−210 °C; IR ($CHCl_3$) 3450, 3000, 1660, 1617, 1521, 1325, 1170, 1131, 1115, 1074, 1068, 1017, 856 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.85 (t, J = 7.9 Hz, 2H), 8.23 (d, J = 4.5 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.88−7.83 (m, 2H), 7.76−7.53 (m, 8H), 6.43 (s, 1H), 2.66 (d, J = 4.5 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.4, 146.1, 143.3, 138.0, 130.8, 130.3, 128.8, 129.7, 129.5, 128.9, 128.3, 127.8, 127.7, 127.5, 127.3, 127.1, 127.0, 126.3, 124.7, 124.6, 123.5, 122.9, 25.6; MS (FD$^+$) calcd for $C_{25}H_{18}F_3NO$ 405.42, found 405.1 (M$^+$, 100). Anal. Calcd for $C_{25}H_{18}F_3NO$ C, 74.07; H, 4.48; N, 3.46; F, 14.06. Found: C, 74.21; H, 4.53; N, 3.59; F, 14.16.

(*Z*)-3-[4-(α,α,α-Trifluoromethyl)phenyl]-*N*-methyl-3-(9-phenanthryl)-2-propenamide (47): yield 77%; mp 138−139 °C; IR ($CHCl_3$) 3010, 1654, 1617, 1529, 1325, 1171, 1132, 1070, 1016, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (t, J = 9.2 Hz, 2H), 7.91 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.76−7.62 (m, 5H), 7.55−7.45 (m, 5H), 6.84 (s, 1H), 5.44 (d, J = 4.1 Hz, 1H), 2.40 (d, J = 4.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 146.0, 143.3, 133.5, 131.0, 130.6, 130.4, 129.8, 128.9, 127.9, 127.5, 127.4, 127.3, 127.2, 127.1, 126.1, 125.9, 125.6, 125.54, 125.49, 123.3, 122.6, 118.4, 26.1; MS (FD$^+$) calcd for $C_{25}H_{18}F_3NO$ 405.42, found 405.1 (M$^+$, 100). Anal. Calcd for $C_{25}H_{18}F_3NO$: C, 74.07; H, 4.48; N, 3.46. Found: C, 73.98; H, 4.73; N, 3.72.

(*E*)-*N*-Methyl-3-(9-phenanthryl)-3-(2-tolyl)-2-propenamide (48): yield 90%; mp 247−248 °C; IR ($CHCl_3$) 3008, 1651, 1528 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.88 (d, J = 7.87 Hz, 1H), 8.80 (d, J = 8.17 Hz, 1 H), 8.23 (dd, J = 7.94 Hz, J = 0.85 Hz, 1H), 8.00−7.89 (m, 2H), 7.74−7.56 (m, 5H), 6.39 (s, 1H), 2.60 (d, J = 4.60 Hz, 3H), 2.20 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.1, 147.2, 140.0, 138.5, 135.5, 130.9, 130.6, 130.5, 130.0, 129.7, 129.5, 129.1, 128.8, 127.7, 127.4, 127.3, 127.2, 127.0, 126.9, 126.1, 125.2, 123.5, 122.8, 25.5, 20.1; MS (FD$^+$) calcd for $C_{25}H_{21}NO$ 351.47, found 351.1 (M$^+$, 100). Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.17; H, 5.95; N, 4.21.

(*Z*)-*N*-Methyl-3-(9-phenanthryl)-3-(2-tolyl)-2-propenamide (49): yield 62%; mp 144 °C; IR ($CHCl_3$) 3450, 3011, 2219, 2205, 1652, 1521, 1494, 1452, 1415, 1265, 1242 cm^{-1}; ^{1}H NMR (350 MHz, $CDCl_3$) δ 8.77−8.60 (m, 3 H), 8.11 (d, J = 7.62 Hz, 1 H), 7.80 (dd, J = 7.83, 1.1 Hz), 7.70−7.50 (m, 4 H), 7.29 (s, 1 H), 7.25−7.0 (m, 3 H), 6.45 (s, 1H), 2.35 (d, J = 4.52 Hz, 3H), 2.32 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.9, 147.4, 141.3 128.9 127.1, 126.9, 126.8, 122.7, 26.0, 21.2; MS (FD$^+$) calcd for $C_{25}H_{21}NO$ 351.47, found 351.1 (M$^+$, 100). Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.36; H, 5.87; N, 4.41.

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