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Palladium-Catalyzed One-Pot Reaction of Hydrazones, Dihaloarenes, and Organoboron Reagents: Synthesis and Cytotoxic Activity of 1,1-Diarylethylene Derivatives

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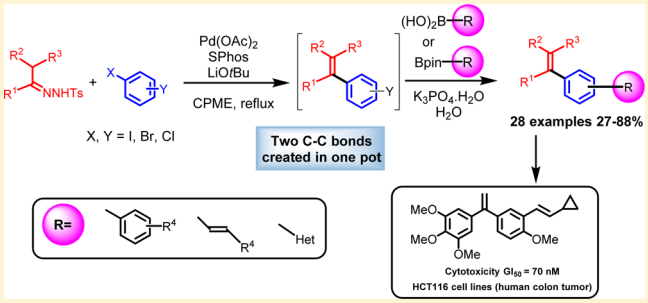
Supporting Information

ABSTRACT: A new three-component assembly reaction between *N*-tosylhydrazones, dihalogenated arenes, and boronic acids or boronate esters was developed, producing highly substituted 1,1-diarylethylenes in good yields. The two C−C bonds formed through this coupling have been catalyzed by a single Pd-catalyst in a one-pot fashion. It is noted that the one-pot pinacol boronate cross-coupling reaction generally provides products in high yields, offers an expansive substrate scope, and can address a broad range of aryl, styrene, vinyl, and heterocyclic olefinic targets. The scope of this one-pot coupling has been also extended to the synthesis of the 1,1-diarylethylene skeleton of the natural product ratanhine. The new compounds were evaluated for their cytotoxic activity, and this allowed the identification of compound **4ab** that exhibits excellent antiproliferative activity in the nanomolar concentration range against HCT116 cancer cell lines.



INTRODUCTION

A fascinating myriad of adventurous and unique palladium-catalyzed transformations are found frequently to be key steps in target-oriented synthesis, affording complex natural products and pharmacologically active compounds.[1] Thus, the desire for quick and easy access to complex structures is still a major task for the organic chemist in the 21st century. On the other hand, concerns related to pollution or sustainability are increasing worldwide. In this light, the development of new simple synthetic methods allowing time and cost savings while reducing waste and hazardous byproducts is an essential and major challenge. In this context, palladium cascade reactions are particularly attractive and have generated considerable interest over the years in comparison to traditional stepwise methodologies. It represents a powerful tool capable of rapid generation of diverse and complex molecules from readily available simple starting materials.[2] Cascade reaction has various advantages over classical stepwise strategy, such as operational simplicity and environmental friendliness.[3] During the past decade, particular attention has been given to autotandem catalysis, in which a single catalyst activates mechanistically distinct reactions in a single reactor.[4]

N-Tosylhydrazones have been proven to be very useful for the in situ generation of nonstabilized diazo compounds through Bamford−Stevens reaction.[5] Recently, Barluenga et al. reported a palladium-catalyzed cross-coupling reaction between *N*-tosylhydrazones and aryl halides for the preparation of polysubstituted olefins.[6] Since then, important transformations such as cross-couplings,[7] oxidative cross-couplings[8] or domino reactions have been emerging.[9] On the basis of our long-standing experience, in the chemistry of 1,1-diarylethylenes[10] combined with our efforts to discover novel isocombretastatin A-4 derivatives,[11] as promising antineoplastic agents (Scheme 1),[12] led us to study a series of Pd-[13] or Cu[14]-catalyzed cross-coupling reactions of *N*-tosylhydrazones with different partners to generate a library of potentially actives compounds.

In connection with these studies, and in order to increase the diversity of new potential active compounds, we envisaged to create two distinct C−C bonds in a one-step reaction using one catalyst, following the strategy depicted in Scheme 1. The first C−C bond will be created through a carbene migratory insertion strategy and the second one by a Suzuki−Miyaura coupling reaction. In comparison to the previous synthesis of similar compounds, which needs 4 to 5 steps including 1,2 addition, oxidation, Wittig reaction, coupling, and deprotection (Scheme 1A),[12] this strategy will lead to a time-saving and a reduction of the number of steps. We have chosen the Suzuki−Miyaura cross-coupling reaction, because it is nowadays one of the most common C−C bond forming methods in organic synthesis, due to (i) mild reaction conditions, (ii) both academic and industrial

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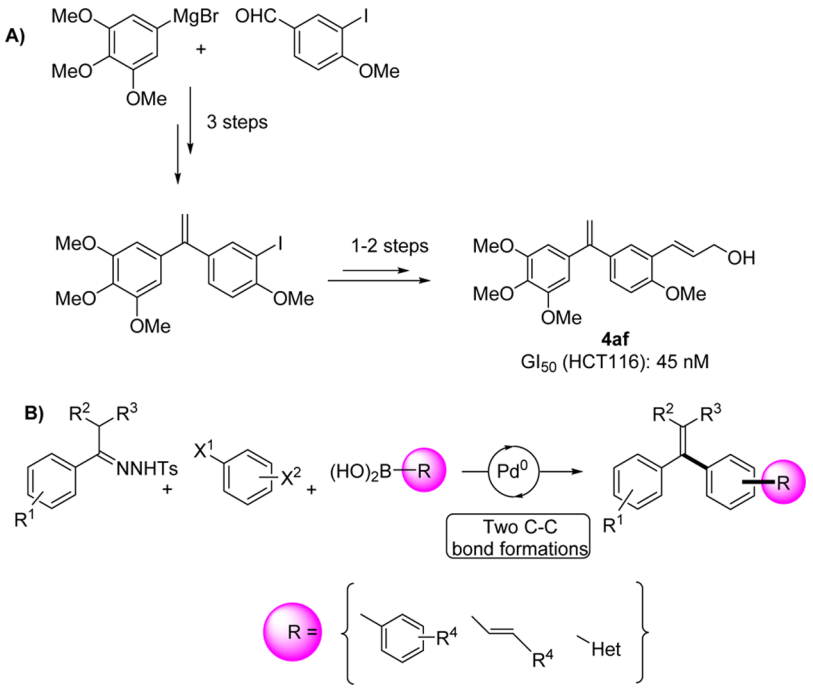
Scheme 1. (A) Synthesis of Isocombretastatin A-4 Derivative 4af; (B) This Work: One-Pot Pd-Catalyzed Reactions Involving Hydrazones, Dihaloarenes, and Boronic Acid Derivatives



interest for this reaction, and (iii) its tolerance toward functional groups. In addition, organoboron reagents display many advantages including stability, no toxicity, easy handling, and commercial availability.[15] Here we describe a strategy that directly addresses this gap in synthetic methodology and presents a single-flask, catalytic two C−C bond formation from *N*-tosylhydrazones, dihalogenated arenes, and organoboron reagents.

RESULTS AND DISCUSSION

This study might seem to be trivial, since we can think that the conditions of coupling for the first and the second steps are known separately. But the challenge is to find the best conditions able to catalyze simultaneously and efficiently the two couplings in a one-pot manner. In the search for effective conditions, the reaction was carried out with *N*-tosylhydrazone **1a**, 1-choloro-4-iodobenzene **2a** and phenylboronic acid **3a** with various palladium sources, ligands, solvents, and additives to form olefin **4a**, as summarized in Table 1. Initially, for the formation of the first C−C bond between hydrazone **1a** and 1-chloro-4-iodobenzene **2a**, we used Pd_2dba_3/XPhos as a catalytic system, LiO-*t*-Bu as a base at reflux in dioxane, following reported conditions (entry 1).[6] After completion of the reaction as judged by TLC, we added potassium phosphate tribasic monohydrate ($K_3PO_4{\cdot}H_2O$), and phenylboronic acid for the second coupling. Accordingly, the desired product **4a** was obtained in an encouraging yield of 25% (Table 1, entry 1). If Xphos and Sphos ligands catalyze the first coupling effectively, Sphos was found to be more powerful for the second Suzuki−Miyaura coupling, affording the required product **4a** in a 50% yield (entry 2). Switching from $K_3PO_4{\cdot}H_2O$ to anhydrous K_3PO_4 did not produce the desired product, instead, the intermediate 1-chloro-4-(1-(*p*-tolyl)vinyl)benzene was obtained as the major product accompanied by the 1,1-biphenyl as side product (entry 3).

This result clearly suggests the role played by water for the second reaction and led us to examine its effect as additive in this cross-coupling (entries 4−5). Adding 5 equiv of water for the second coupling led to a significant improvement in the yield, furnishing compound **4a** in a 60% yield, whereas with 50 or 100 equiv of water the yield decreased up to 15% (entries 5−6). Water and base are required to activate the boronic acid leading to the formation of the tetrahedral anion $[ArB(OH)_3]^-$.[16] A further investigation of various solvents revealed that cyclopentyl methyl ether (CPME) is more efficient than dioxane or toluene (entries 4, 7 and 8). Finally, from the optimized result of entry 8, we further changed the palladium source (entries 9−10), compared to other sources of palladium, $Pd(OAc)_2$ leads to the formation of expected compound **4a**, with a good yield of 84%. This represents an average of 92% yield for both steps of this coupling process. As a result, the combination of $Pd(OAc)_2$/SPhos and LiO-*t*-Bu in refluxing CPME for the first step and then phenylboronic acid, $K_3PO_4{\cdot}H_2O$ and water (5 equiv) for the second step was fixed, as optimal conditions.

We next explored the scope of this reaction with various hydrazones, dihaloarenes, and boronic acids, the results are summarized in Table 2. The reaction is general with respect to *N*-tosylhydrazone partners, both electron-rich and electron-poor hydrazones (compounds **4b−d**) have been efficiently coupled. *N*-Tosylhydrazones derived from aliphatic ketone provided good yield (**4h**). However, the coupling with *N*-tosylhydrazone of chromanone gives a slightly lower yield (**4e**). To gauge the performance of this catalytic system, the substrate scope with respect to boronic acid partners (compounds **4f−4k**) has been examined. When styryl boronic acid was used as a new coupling partner, unfortunately, no trace of **4k** was detected in the crude reaction mixture. Finally, the third component of this reaction, dihaloarene, was studied. Switching the halide atom from *para*-position to *meta*-position on the aryl ring of **2** did not influence the yields (compounds **4l,m**). However, no product was obtained with 1-chloro-2-iodobenzene as coupling partner (**4o**). Interestingly, our catalytic system was also effective with dihaloheterocycle, despite the fact that the reaction conditions had

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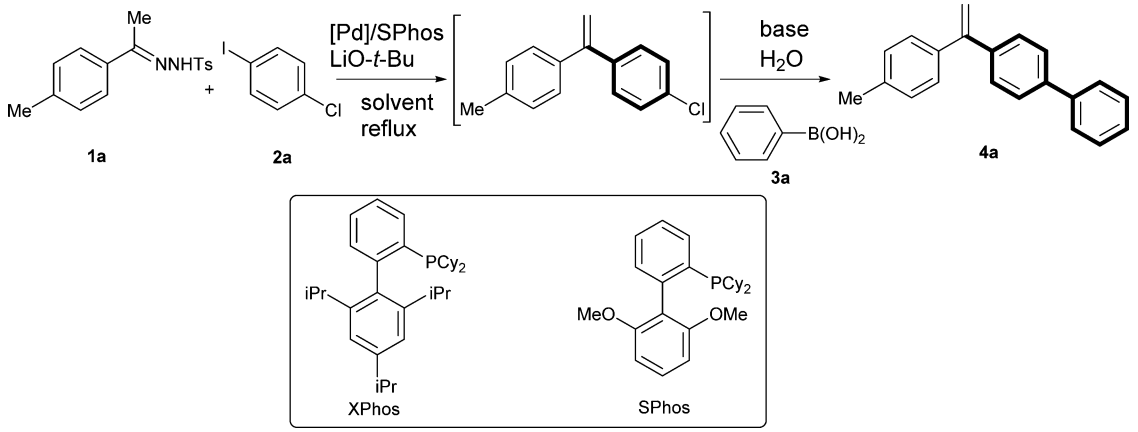
Table 1. Optimization of the Pd-Catalyzed Migratory Insertion/Suzuki−Miyaura Coupling One-Pot Reaction[a]



entry	[Pd]/ligand	solvent	base[b]	H_2O (equiv)[b]	**4a** yield (%)[d]
1	$Pd_2dba_3{\cdot}CHCl_3$[c]	dioxane	$K_3PO_4{\cdot}H_2O$	0	25
2	$Pd_2dba_3{\cdot}CHCl_3$	dioxane	$K_3PO_4{\cdot}H_2O$	0	50
3	$Pd_2dba_3{\cdot}CHCl_3$	dioxane	K_3PO_4	0	traces[e]
4	$Pd_2dba_3{\cdot}CHCl_3$	dioxane	$K_3PO_4{\cdot}H_2O$	5	60
5	$Pd_2dba_3{\cdot}CHCl_3$	dioxane	$K_3PO_4{\cdot}H_2O$	50	15
6	$Pd_2dba_3{\cdot}CHCl_3$	dioxane	$K_3PO_4{\cdot}H_2O$	100	12
7	$Pd_2dba_3{\cdot}CHCl_3$	toluene	$K_3PO_4{\cdot}H_2O$	5	60
8	$Pd_2dba_3{\cdot}CHCl_3$	CPME	$K_3PO_4{\cdot}H_2O$	5	73
9	$PdCl_2(MeCN)_2$	CPME	$K_3PO_4{\cdot}H_2O$	5	65
10	$Pd(OAc)_2$	CPME	$K_3PO_4{\cdot}H_2O$	5	84

[a]First step: Reactions were performed with hydrazone **1a** (1.1 equiv), dihaloarene **2a** (1 equiv, 1 mmol), LiO-*t*-Bu (2.4 equiv), Pd source (4 mol %), ligand (8 mol %), in 8 mL of solvent at reflux. [b]Second step: phenylboronic acid (1.5 equiv), H_2O, and base (3 equiv) were added after completion of the first step. [c]Xphos was used as a ligand instead of SPhos. [d]Yield of product **4a**. [e]1-Chloro-4-(1-(*p*-tolyl)vinyl)benzene was obtained as the major product accompanied by the 1,1-biphenyl side product.

never been optimized. Thus, an indole, a pyridine, or a quinolone core can be included in the final products (**4p−r**).

To increase the scope of our one-pot reaction and find solution for coupling with 2-phenylvinylboronic acid (compound **4k**), or for the formation of sterically hindered products such as compound **4o**, we thought to use pinacol boronic esters instead of boronic acids. Under normal laboratory conditions, boronic acids exist as a mixture of monomer, dimer, and boroxine.[17] This drawback can be overcome by the use of boronate esters which are air and water stable and exist only in a monomeric form in nature. Further advantages of boronate esters include ease of preparation and practicality of purification by column chromatography.[18]

Initially, we first replaced phenylboronic acid **3a** by phenylboronic ester **5a** in our previous protocol (Table 3, entry 1). Under these conditions, we obtained **4a** in a promising 50% yield. We have previously noticed in this one pot reaction that the water played a critical role for complete conversion of starting materials. Thus, in the presence of water (50 equiv) **4a** was isolated in a 62% yield (entry 3). Screening with respect to the solvent revealed that CPME could be replaced by dioxane, providing **4a** in a similar yield (entry 5). The yield could be further improved by using potassium hydroxide as a base in place of potassium phosphate (entry 7). Finally, we confirmed that the use of 50 equiv of water were optimal, while using 100 equiv furnished a lower yield of **4a** (entry 8). With the optimized conditions in hand, the scope of this reaction was then explored (Table 4). Compound **4s** was obtained in a good yield, similar to that obtained with boronic acid (Table 2, **4l**). In a further exploration of our boronic ester based protocol, we decided to focus on the synthesis of examples that did not work using boronic acid as the coupling partner. Notably, in these conditions, *ortho*-dihaloarene substrate was coupled efficiently, furnishing **4t** in a satisfactory yield, whereas no product was obtained when using boronic acid as coupling partner (compare **4o** in Table 2, with **4t** in Table 4). A similar trend was observed when achieving the one pot reaction with styrylboronic ester instead of boronic acid derivative (see Table 2, compound **4k**, and Table 4, compound **4x**). Finally, heterocyclic (**4v**) or vinylboronate (**4w**) can also participate in the coupling with good yield.

To highlight the power and the usefulness of this Pd-catalyzed cascade reaction, we synthesized several analogues of isocombretastatin A-4 (compounds **4y−4ae**) in order to explore their cytotoxic activity. Thus, using commercially available starting materials, in one step and with only one purification, we obtained a small library of compounds with potential antiproliferative activity. Next, a further deprotection of compound **4ae** using TBAF furnished product **4af** (Table 4), one of our lead compounds, with antiproliferative activity against a panel of cancer cell lines.[12]

Thus, **4af** was obtained in a two-step sequence (2 purifications by column chromatography) in a 52% overall yield, whereas in the precedent work (Scheme 1A), this molecule was synthesized in 5 steps (5 purifications by column chromatography) in an 18% overall yield. This result demonstrates the usefulness of our protocol, which should accelerate the discovery of promising cytotoxic agents.

To illustrate the usefulness of the cross-coupling method, we embarked in the synthesis of the 1,1-diarylethylene skeleton of

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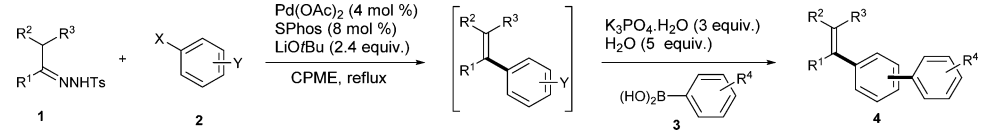
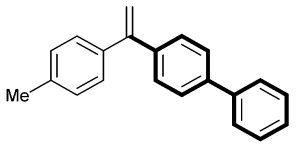
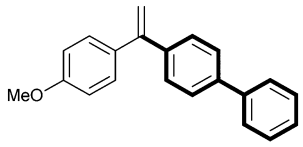
Table 2. Scope of Pd-Catalyzed Migratory Insertion/Suzuki−Miyaura Coupling One-Pot Reaction[a,b]

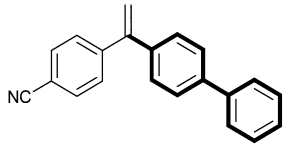




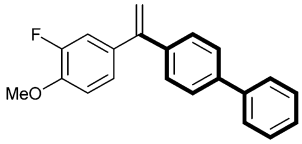
4a, 84% (X = I, Y = Cl)



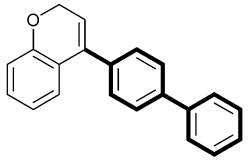
4b, 66% (X = I, Y = Cl)



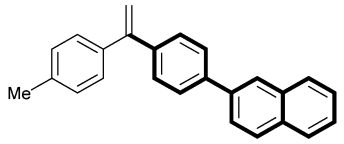
4c, 48% (X = I, Y = Cl)



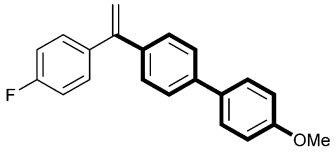
4d, 60% (X = I, Y = Cl)



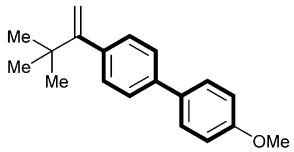
4e, 45% (X = I, Y = Cl)



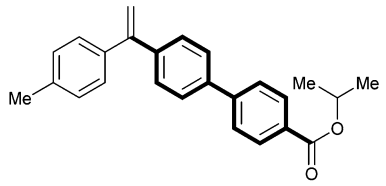
4f, 75% (X = I, Y = Cl)



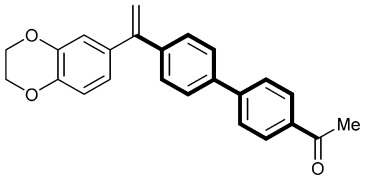
4g, 82% (X = I, Y = Br)



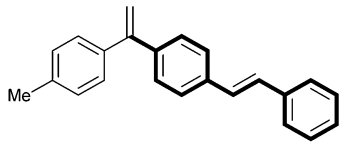
4h, 65% (X = I, Y = Cl)



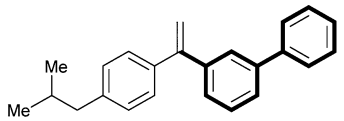
4i, 64% (X = I, Y = Cl)



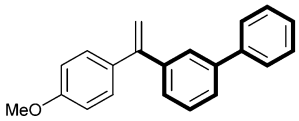
4j, 51% (X = I, Y = Cl)



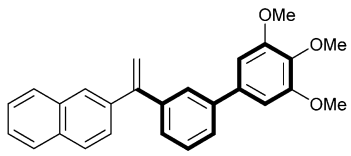
4k, 0% (X = I, Y = Br)



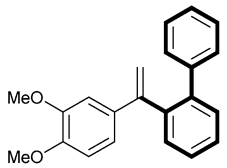
4l, 88% (X = I, Y = Br)



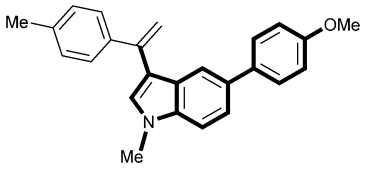
4m, 82% (X = I, Y = Br)



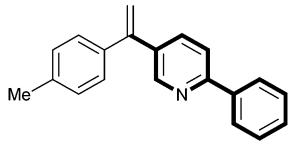
4n, 63% (X = I, Y = Br)



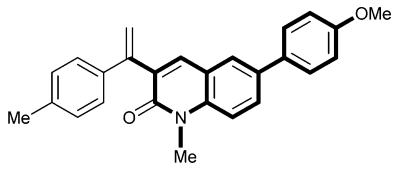
4o, 0% (X = I, Y = Cl)



4p, 27% (X =Br, Y = Br)



4q, 54% (X = I, Y = Cl)



4r, 31% (X = Br, Y = Br)

[a]First step: Reactions were performed with hydrazone **1** (1.1 equiv), dihaloarene **2** (1 equiv, 1 mmol), LiO-*t*-Bu (2.4 equiv), $Pd(OAc)_2$ (4 mol %), SPhos (8 mol %), in 8 mL of CPME at reflux. Second step: boronic acid 3 (1.5 equiv), H_2O (5 equiv), and $K_3PO_4·H_2O$ (3 equiv) were added after completion of the first step. [b]Yield of product **4**.

the natural product ratanhine. The total synthesis of this molecule, extracted from Ratanhiae radix,[19] was reported by Burke and co-workers using an iterative cross-coupling strategy with a trivalent *N*-methyliminodiacetic acid (MIDA) ligand.[20]

The dihaloarene partner **2i** was synthesized according to Burke procedure from 2-iodo-5-methoxyphenol **6** through an alkylation and bromination sequence (Scheme 2, part A).[20] The pinacol boronate **5k** was synthesized in a two steps sequence from the benzofuran **8** involving an iridium catalyzed C−H borylation coupling (Scheme 2, part B).[21] Because of its instability, compound **5k** was used directly for the next coupling sequence without purification.

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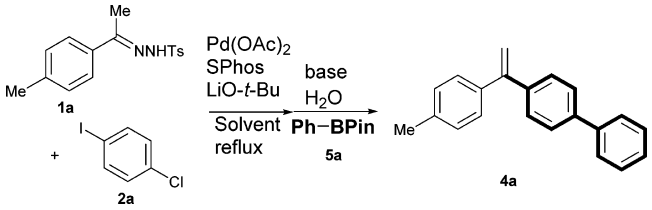
Table 3. Coupling with Phenylboronic Acid Pinacol Ester[a]



entry	solvent	base[a]	H_2O (equiv)[b]	4a yield (%)[c]
1	CPME	$K_3PO_4{\cdot}H_2O$	5	50
2	CPME	$K_3PO_4{\cdot}H_2O$	none	33
3	CPME	$K_3PO_4{\cdot}H_2O$	50	62
4	toluene	$K_3PO_4{\cdot}H_2O$	50	34
5	dioxane	$K_3PO_4{\cdot}H_2O$	50	70
6	dioxane	K_2CO_3	50	76
7	dioxane	KOH	50	89
8	dioxane	KOH	100	43

[a]First step: reactions were performed with hydrazone **1a** (1.1 equiv), dihaloarene **2a** (1 equiv, 1 mmol), LiO-*t*-Bu (2.4 equiv), Pd source (4 mol %), ligand (8 mol %), in 8 mL of solvent at reflux. [b]Second step: phenylboronic acid pinacol ester **5a** (1.5 equiv), additive, and base (3 equiv) were added after completion of the first step. [c]Yield of product **4a**.

For the synthesis of *N*-tosylhydrazones **1**, we need first to find an appropriate protective group on the phenol function of **1**, which should be compatible with our coupling protocol achieved under basic conditions. In addition, its deprotection should be orthogonal to the MOM-protective group present on **2i**. To this end, a screening of various protective groups has been realized using a simplified model for the coupling between **2j** and protected hydrazones **1n−t** (Scheme 3).

The coupling of aryl iodide **2j** with unprotected (R = H) or protected (R = Acyl or silyl group) hydrazones **1o−s** under our standard protocol were, however, unsuccessful. Ultimately, the use of *para*-methoxybenzyl group (PMB) provided the coupling product **4ag** with a 60% yield (Scheme 3).

Having defined the best protective group, we next turned to perform the synthesis of the building block **1u**. This latter was synthesized in a good overall yield from the commercially available acetophenone **10** in three steps including benzylation, Suzuki−Miyaura coupling,[22] and hydrazone formation (Scheme 3, bottom part).

Finally, we performed the one pot coupling reaction between hydrazone **1u**, dihaloarene **2i,** and pinacol boronate **5k** under our standard conditions. Accordingly, the desired product **4ah** was obtained with a promising 45% yield (Scheme 4). To access the formal synthesis of ratanhine, it remains to achieve the deprotection of the PMB group and the installation of the benzoyl group. Different known protocols were tested to achieve the deprotection of the PMB group of **4ah**. However, no traces of the desired compound were detected using as reagents DDQ,[23] CAN[24] or $AgSbF_6$.[25] Only traces of the desired product were observed accompanied by degradation of starting material **4ah**. Even if this step remains difficult to perform, we demonstrated the potential of our methodology in the synthesis of the 1,1-diaryethylene framework of natural product ratanhine.

Biological Results. New 1,1-diarylethylenes **4** having a trimethoxyphenyl unit (**4y−4ac**) as well as compound **4ah** were evaluated for their in vitro cytotoxicity against HCT116 cell lines (human colon tumor) using isocombretastatin A-4 (isoCA-4) as the reference compound (Table 5). The GI_{50} values (drug concentration required to decrease cell growth by 50%) of isoCA-4 analogs are listed in Table 5. The results clearly reveal that the size of the substituent at the 3′-position of isoCA-4 skeleton plays a critical role in cell growth inhibition. Introduction of a benzene or pyrazole rings at the 3′-position (compounds **4y** and **4aa**) resulted in a significant decrease in cytotoxicity, probably owing to steric considerations and absence of hydrogen bond. Compound **4z** having a pyridine group at this position was evaluated and showed promising antiproliferative activity, with GI_{50} = 300 nM. Finally the best antiproliferative activity was obtained with compound **4ab** having a small cyclopropylvinyl group on position 3′ of 1,1-diarylethylene which exhibited significant antiproliferative activities, with GI_{50} values of 70 nM against HCT116 cells. This structure−activity relationship study demonstrate that the replacement of the hydroxymethyl moiety of **4af** by a cyclopropyl moiety led only to slight decrease of the growth inhibition.

CONCLUSION

In summary, a one-pot catalytic reaction of *N*-tosylhydrazones, dihaloarenes, and organoboron reagents into substituted 1,1-diarylethylenes is described. This sequence, which requires only one palladium catalyst, allows the formation of two distinct C−C bonds in a one-pot fashion. One bond was created through an aryl migratory insertion on palladium carbene specie and the other by a Suzuki−Miyaura coupling. Moderate to excellent yields were obtained with a wide range of the three coupling partners. Two different conditions are disclosed, one for boronic acids and the other for pinacol boronates. As a general rule, yields are higher and scope is broader with conditions developed for the coupling of pinacol boronate. This one pot reaction was successfully applied to the synthesis of a library of potential or proven cytotoxic agents.

EXPERIMENTAL SECTION

General Methods. Solvent peaks were used as reference values, with $CDCl_3$ at 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR, with CD_3COCD_3 at 2.05 ppm for ^{1}H NMR and 29.84 ppm for ^{13}C NMR. Chemical shifts δ are given in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m) and broad singlet (bs). Reaction courses and product mixtures were routinely monitored by TLC on silica gel, and compounds were visualized with phosphomolybdic acid/Δ, anisaldehyde/Δ, or vanillin/Δ. Flash chromatography was performed using silica gel 60 (40−63 mm, 230−400 mesh) at medium pressure (200 mbar). Fluorobenzene was used as received, dioxane, dichloromethane, cyclohexane and tetrahydrofuran were dried using the procedures described in D. Perrin Purification of Laboratory Chemicals.[26] Organic extracts were, in general, dried over $MgSO_4$ or Na_2SO_4. High-resolution mass spectra were recorded with the aid of a MicrOTOF-Q II. All products reported showed ^{1}H and ^{13}C NMR spectra in agreement with the assigned structures.

Typical Pd-Catalyzed One-Pot Catalysis of *N*-Tosylhydrazones with Dihaloarenes and Boronic Acids. A 20 mL round-bottom flask with a condenser under an argon atmosphere was charged with *N*-tosylhydrazone (1.1 equiv, 1.1 mmol), $Pd(OAc)_2$ (9 mg, 4 mol %), SPhos (32 mg, 8 mol %), dihaloarene (1.0 equiv, 1 mmol) and LiO-*t*-Bu (192 mg, 2.4 equiv, 2.4 mmol). Then 8 mL of CPME was added via syringe at room temperature. The flask was put into a preheated oil bath and stirred at reflux for 2 h (or until completion of the reaction as judged by TLC). Then boronic acid (1.5 equiv), $K_3PO_4{\cdot}H_2O$ (690 mg, 3 equiv, 3 mmol) and water (0.09 mL, 5 equiv, 5 mmol) were added and reflux was continued for 4 h (or until completion of the reaction as judged by TLC). The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through Celite. The solvents were evaporated under reduce

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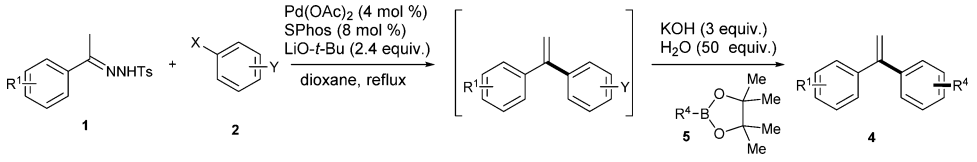
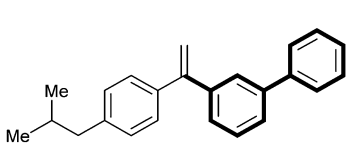
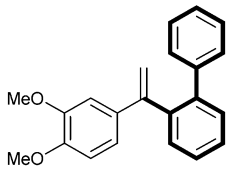
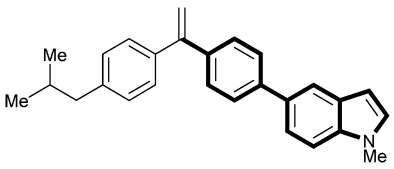
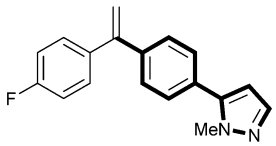
Table 4. Scope of the Pd-Catalyzed Migratory Insertion/Suzuki–Miyaura Coupling Cascade Reaction Using Pinacol Boronate Esters[a,b]

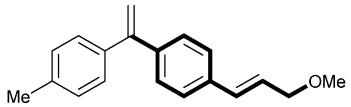


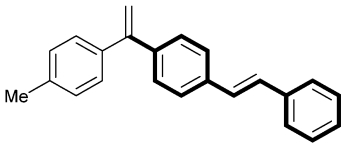

4s, 85% (X = I, Y = Br)

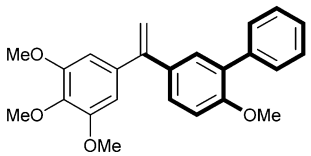

4t, 60% (X = I, Y = Cl)

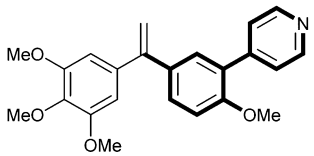

4u, 85% (X = I, Y = Cl)

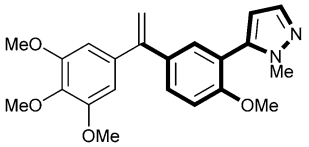

4v, 71% (X = I, Y = Cl)

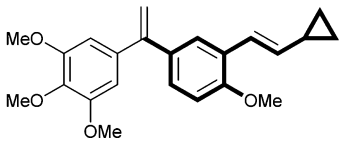

4w, 69% (X = I, Y = Cl)[c]

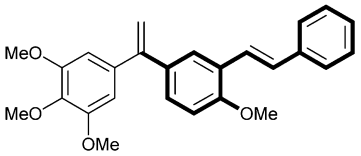

4x, 52% (X = I, Y = Cl)

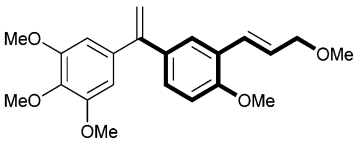

4y, 46% (X = I, Y = Br)

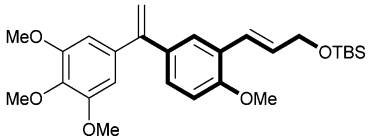

4z, 85% (X = I, Y = Br)

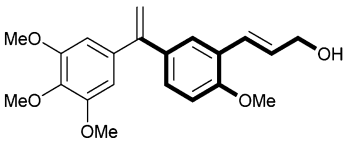

4aa, 66% (X = I, Y = Br)


4ab, 61% (X = I, Y = Br)[c]


4ac, 47% (X = I, Y = Br)


4ad, 46% (X = I, Y = Br)[c]


4ae, 64% (X = I, Y = Br)[c]


4af, 82%[d]

[a]First step: Reactions were performed with hydrazone **1** (1.1 equiv), dihaloarene **2** (1 equiv, 1 mmol), LiO-*t*-Bu (2.4 equiv), $Pd(OAc)_2$ (4 mol %), SPhos (8 mol %), in 8 mL of dioxane at reflux. Second step: boronic ester **5** (1.5 equiv), H_2O (50 equiv), and KOH (3 equiv) were added after completion of the first step. [b]Yield of product **4**. [c]K_2CO_3 was used instead of KOH. [d]**4af** was obtained from **4ae** by using TBAF in THF.

pressure and the crude residue was purified by chromatography on silica gel.

Typical Pd-Catalyzed One-Pot Catalysis of *N*-Tosylhydrazones with Dihaloarenes and Boronic Acid Pinacol Esters. A 20 mL round-bottom flask with a condenser under an argon atmosphere was charged with *N*-tosylhydrazone (1.1 equiv, 1.1 mmol), $Pd(OAc)_2$ (9 mg, 4 mol %), SPhos (32 mg, 8 mol %), dihaloarene (1.0 equiv, 1 mmol) and LiO-*t*-Bu (192 mg, 2.4 equiv, 2.4 mmol). Then 8 mL of dioxane was added via syringe at room temperature. The flask was put into a preheated oil bath and stirred at reflux for 1 h 45 min (or until completion of the reaction as judged by TLC). Then boronic ester (1.5 equiv), KOH (168 mg, 3 equiv, 3 mmol) and water (0.9 mL, 50 equiv, 50 mmol) were added, and reflux was continued for 18 h (or until completion of the reaction as judged by TLC). The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through Celite. The solvents were evaporated under reduce pressure and the crude residue was purified by chromatography on silica gel.

*4-(1-(p-Tolyl)vinyl)-1,1-biphenyl (**4a**).* Flash chromatography on silica gel (Cyclohexane) afforded 230 mg of **4a** (0.84 mmol, yield 84%). White solid, mp 200–202 °C. TLC R_f = 0.63 (Cyclohexane, SiO_2). IR (neat) 1477, 1508, 1456, 1404, 1263, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69–7.61 (m, 2H, H^{Ar}), 7.61–7.55 (m, 2H, H^{Ar}), 7.51–7.33 (m, 5H, H^{Ar}), 7.33–7.27 (m, 2H, H^{Ar}), 7.21–7.16 (m, 2H, H^{Ar}), 5.50 (d, J = 1.3 Hz, 1H, =CH), 5.47 (d, J = 1.3 Hz, 1H, =CH), 2.40 (s, 3H, Ar–CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.6 (C), 140.9 (C), 140.8 (C), 140.6 (C), 138.7 (C), 137.7 (C), 129.0 (2CH), 128.9 (2CH), 128.8 (2CH), 128.4 (2CH), 127.5 (CH), 127.2 (2CH), 127.0 (2CH), 113.8 (CH2), 21.3 (CH_3). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{21}H_{19}$ 271.1487 found 271.1495.

*4-(1-(4-Methoxyphenyl)vinyl)-1,1-biphenyl (**4b**).* Chromatography on silica gel (AcOEt/Cyclohexane, 0/100 to 1/99) afforded 188 mg of

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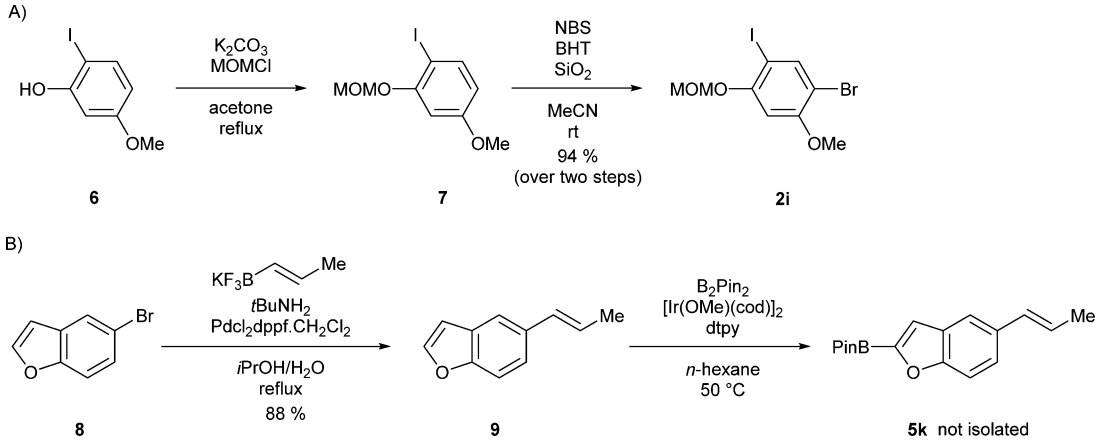
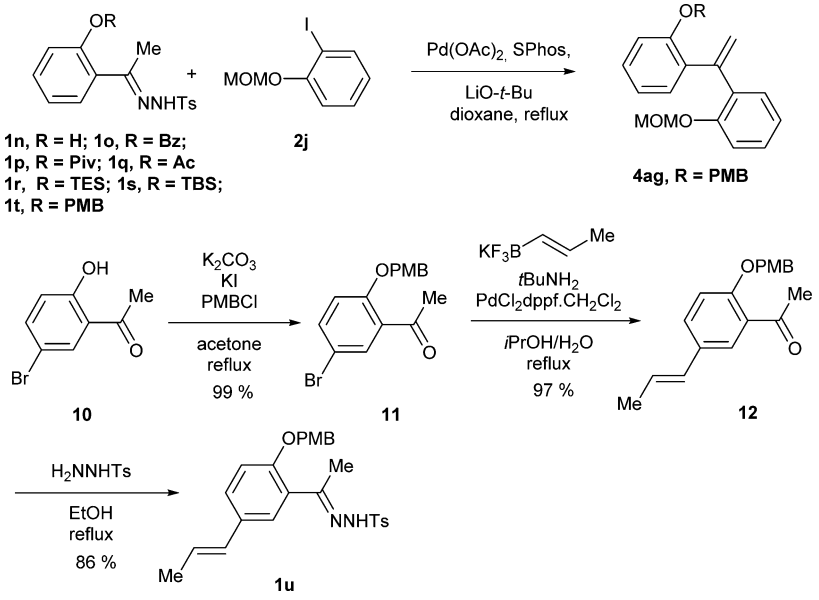
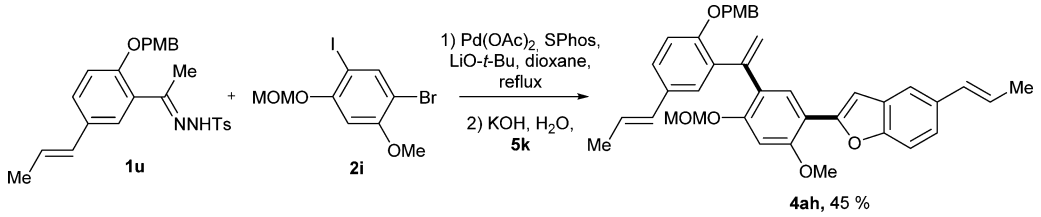
Scheme 2. Synthesis of Building Blocks 2i and 5k



Scheme 3. Top: Optimization of the Coupling between Hydrazone 1n−t and Aryl Iodide 2j; Bottom: Synthesis of Building Block 1u



Scheme 4. Pd-Catalyzed One Pot Reaction for the Synthesis of 4ah



4b (0.66 mmol, yield 66%). White solid, mp 163−164 °C. TLC R_f = 0.22 (Cyclohexane, SiO_2). IR (neat) 1606, 1508, 1471, 1249, 1112, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.67−7.55 (m, 4H, H^{Ar}), 7.50−7.40 (m, 4H, H^{Ar}), 7.37−7.30 (m, 3H, H^{Ar}), 6.91 (d, J = 8.9 Hz, 2H, H^{Ar}), 5.44 (d, J = 1.3 Hz, 1H, =CH), 5.43 (d, J = 1.3 Hz, 1H, =CH), 3.85 (s, 3H, Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 159.5 (C), 149.3 (C), 140.9 (2C), 140.6 (C), 134.1 (C), 129.6 (2CH), 128.9 (2CH), 128.8 (2CH), 127.5 (CH), 127.2 (2CH), 127.0 (2CH), 113.7 (2CH), 113.1 (CH_2), 55.5 (CH_3). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{21}H_{19}O$ 287.1430 found 287.1435.

4-(1-([1,1-Biphenyl]-4-yl)vinyl)benzonitrile ***(4c).*** Chromatography on silica gel (DCM/Cyclohexane, 0/100 to 30/70) afforded 135 mg of **4c** (0.48 mmol, yield 48%). White solid, mp 149−150 °C. TLC R_f = 0.22 (DCM/Cyclohexane, 10/90, SiO_2). IR (neat) 2360 (C≡N stretch), 1647, 1488, 1456, 1418, 1275 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.71−7.55 (m, 6H, H^{Ar}), 7.53−7.42 (m, 4H, H^{Ar}), 7.42−7.31 (m, 3H, H^{Ar}), 5.66 (d, J = 0.6 Hz, 1H, =CH), 5.56 (d, J = 0.6 Hz, 1H, =CH). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 148.5 (C), 146.2 (C), 141.3 (C), 140.6 (C), 139.2 (C), 132.3 (2CH), 129.1 (2CH), 129.0 (2CH), 128.7 (2CH), 127.7 (CH), 127.3 (2CH), 127.2 (2CH), 119.0 (C), 116.8 (CH_2), 111.6 (C). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{21}H_{16}N$ 282.1283 found 282.1299.

4-(1-(3-Fluoro-4-methoxyphenyl)vinyl)-1,1-biphenyl ***(4d).*** Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 1/99) afforded 182 mg of **4d** (0.60 mmol, yield 60%). White solid, mp 145−147 °C. TLC R_f = 0.24 (Cyclohexane, SiO_2). IR (neat) 1519, 1276, 1260,

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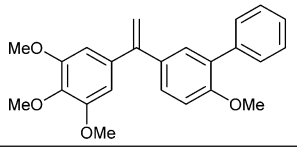
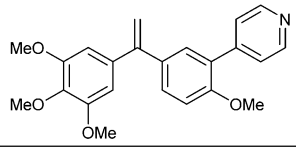
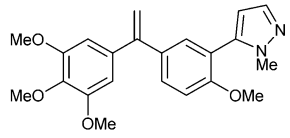
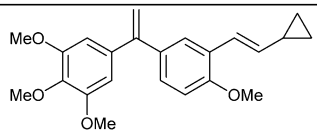
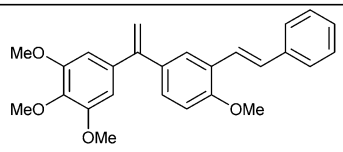
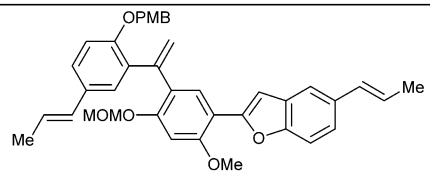
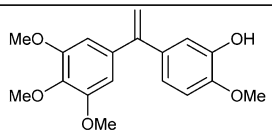
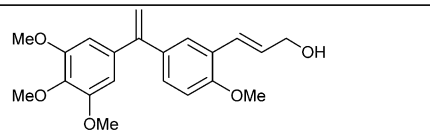
Table 5. Cytotoxic Activity of Selected Substituted 1,1-Diarylethylenes 4, against HCT-116 Cells[a]

Cytotoxicity against HCT116 cells

Cpnd			
GI_{50} (nM)[b]	**4y: NA[c]**	**4z: 300 ± 25**	**4aa: NA[c]**
			
GI_{50} (nM)[b]	**4ab: 70 ± 4**	**4ac: NA[c]**	**4ah: NA[c]**
			
GI_{50} (nM)[b]	***iso*CA-4: 2 ± 0.2**	**4af: 45 ± 3**	

[a]HCT116 human colon carcinoma cells. [b]GI_{50}: compound concentration required to decrease cell growth by 50% following 72 h treatment with the tested drug; values represent the average ± SD of three experiments. [c]NA = not active.

1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69−7.57 (m, 4H, H^{Ar}), 7.52−7.33 (m, 5H), 7.20−7.08 (m, 2H, H^{Ar}), 6.95 (t, J = 8.6 Hz, 1H, H^{Ar}), 5.47 (d, J = 0.9 Hz, 1H, =CH), 5.45 (d, J = 1.0 Hz, 1H, =CH), 3.93 (s, 3H, Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 152.2 (C, d, J = 243.8 Hz), 148.4 (C), 147.5 (C, d, J = 10.9 Hz), 140.9 (C), 140.8 (C), 140.2 (C), 134.8 (d, J = 6.3 Hz), 128.9 (2CH), 128.8 (2CH), 127.5 (CH), 127.2 (2CH), 127.1 (2CH), 124.2 (CH, d, J = 3.0 Hz), 116.1 (CH, d, J = 18.8 Hz), 114.0 (CH_2), 113.1 (d, J = 1.2 Hz), 56.5 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{21}H_{18}OF$ 305.1342 found 305.1339.

4-([1,1-Biphenyl]-4-yl)-2H-chromene ***(4e)***. Chromatography on silica gel (DCM/Cyclohexane, 0/100 to 2/98) afforded 127 mg of **4e** (0.45 mmol, yield 45%). Yellow solid, mp 88−90 °C. TLC R_f = 0.27 (Cyclohexane, SiO_2). IR (neat) 1601, 1483, 1462, 1447, 1302, 1223, 1115 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70−7.60 (m, 4H, H^{Ar}), 7.52−7.33 (m, 5H, H^{Ar}), 7.23−7.16 (m, 1H, H^{Ar}), 7.10 (dd, J = 7.7, 1.6 Hz, 1H, H^{Ar}), 6.97−6.85 (m, 2H, H^{Ar}), 5.87 (t, J = 4.0 Hz, 1H, =CH), 4.89 (d, J = 4.0 Hz, 2H, O−CH_2−CH). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 155.0 (C), 140.8 (2C), 137.4 (C), 137.0 (C), 129.4 (CH), 129.2 (2CH), 129.0 (2CH), 127.5 (CH), 127.2 (2CH), 127.2 (2CH), 126.0 (CH), 123.8 (C), 121.3 (CH), 120.1 (CH), 116.4 (CH), 65.4 (CH_2). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{21}H_{17}O$ 285.1279 found 285.1275.

2-(4-(1-(p-Tolyl)vinyl)phenyl)naphthalene ***(4f)***. Chromatography on silica gel (Cyclohexane) afforded 239 mg of **4f** (0.75 mmol, yield 75%). White solid, mp 146−147 °C. TLC R_f = 0.15 (Heptane, SiO_2). IR (neat) 1607, 1501, 1330, 1119, 1017 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.10 (bs, 1H), 7.99−7.84 (m, 3H, H^{Ar}), 7.80 (dd, J = 8.6, 1.7 Hz, 1H, H^{Ar}), 7.72 (d, J = 8.5 Hz, 2H, H^{Ar}), 7.58−7.46 (m, 4H, H^{Ar}), 7.33 (d, J = 8.1 Hz, 2H, H^{Ar}), 7.21 (d, J = 7.9 Hz, 2H, H^{Ar}), 5.53 (d, J = 1.0 Hz, 1H, =CH), 5.50 (s, 1H, =CH), 2.42 (s, 3H, Ar−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.7 (C), 140.9 (C), 140.5 (C), 138.7 (C), 138.2 (C), 137.7 (C), 133.8 (C), 132.8 (C), 129.1 (2CH), 128.9 (2CH), 128.6 (CH), 128.4 (3CH), 127.8 (CH), 127.2 (2CH), 126.4 (CH), 126.1 (CH), 125.8 (CH), 125.6 (CH), 113.9 (CH_2), 21.3 (CH_3). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{25}H_{21}$ 321.1638 found 321.1642.

4-(1-(4-Fluorophenyl)vinyl)-4′-methoxy-1,1-biphenyl ***(4g)***. Chromatography on silica gel (Et_2O/Cyclohexane, 0/100 to 1/99) afforded 250 mg of **4g** (0.82 mmol, yield 82%). White solid, mp 143−144 °C. TLC R_f = 0.31 (Cyclohexane, SiO_2). IR (neat) 1502, 1316, 1288, 1249, 1158 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.57 (d, J = 7.4 Hz, 2H, H^{Ar}), 7.54 (d, J = 7.1 Hz, 2H, H^{Ar}), 7.42−7.32 (m, 4H, H^{Ar}), 7.06 (d, J = 8.8 Hz, 2H, H^{Ar}), 7.00 (d, J = 8.9 Hz, 2H, H^{Ar}), 5.50 (d, J = 1.0 Hz, 1H, =CH), 5.42 (d, J = 1.0 Hz, 1H, =CH), 3.87 (s, 3H, Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 162.5 (C, d, J = 245.3 Hz), 159.3 (C), 148.7 (C), 140.3 (C), 139.6 (C), 137.6 (C, d, J = 3.8 Hz), 133.2 (C), 130.0 (2CH, d, J = 8.3 Hz), 128.6 (2CH), 128.0 (2CH), 126.5 (2CH), 115.1 (2CH, d, J = 21.0 Hz), 114.3 (2CH), 114.0 (CH_2), 55.4 (CH_3). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{21}H_{18}FO$ 305.1336 found 305.1338.

4-(3,3-Dimethylbut-1-en-2-yl)-4′-methoxy-1,1-biphenyl ***(4h)***. Chromatography on silica gel (AcOEt/Cyclohexane, 0/100 to 1/99) afforded 173 mg of **4h** (0.65 mmol, yield 65%). White solid, mp 108−109 °C. TLC R_f = 0.24 (Cyclohexane, SiO_2). IR (neat) 1522, 1496, 1360, 1287, 1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.55 (d, J = 8.8 Hz, 2H, H^{Ar}), 7.48 (d, J = 8.3 Hz, 2H, H^{Ar}), 7.20 (d, J = 8.3 Hz, 2H, H^{Ar}), 6.98 (d, J = 8.8 Hz, 2H, H^{Ar}), 5.21 (d, J = 1.6 Hz, 1H, =CH), 4.82 (d, J = 1.6 Hz, 1H, =CH), 3.86 (s, 3H, Ar−OCH_3), 1.16 (s, 9H, ^{t}Bu). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 159.8 (C), 159.2 (C), 142.1 (C), 138.9 (C), 133.7 (C), 129.5 (2CH), 128.2 (2CH), 125.7 (2CH), 114.3 (2CH), 111.8 (CH_2), 55.5 (CH_3), 36.3 (C), 29.9 ($3CH_3$). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{19}H_{23}O$ 267.1743 found 267.1755.

Isopropyl 4′-(1-(p-tolyl)vinyl)-[1,1-biphenyl]-4-carboxylate ***(4i)***. Chromatography on silica gel (AcOEt/Cyclohexane, 0/100 to 1/99) afforded 227 mg of **4i** (0.64 mmol, yield 64%). Yellow solid, mp 157−159 °C. TLC R_f = 0.11 (Cyclohexane, SiO_2). IR (neat) 1711 (C=O

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stretch), 1608, 1511, 1273, 1179, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.12 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.68 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.60 (d, J = 8.3 Hz, 2H, H^{Ar}), 7.45 (d, J = 8.3 Hz, 2H, H^{Ar}), 7.28 (d, J = 8.2 Hz, 2H, H^{Ar}), 7.17 (d, J = 7.9 Hz, 2H, H^{Ar}), 5.48 (s, 2H, =CH_2), 5.29 (hept, J = 6.3 Hz, 1H, CH−$(CH_3)_2$), 2.39 (s, 3H, Ar−CH_3), 1.40 (d, J = 6.2 Hz, 6H, CH−$(CH_3)_2$). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 166.1 (C), 149.5 (C), 145.1 (C), 141.7 (C), 139.4 (C), 138.5 (C), 137.8 (C), 130.2 (2CH), 129.9 (C), 129.1 (2CH), 129.0 (2CH), 128.3 (2CH), 127.1 (2CH), 126.9 (2CH), 114.1 (CH_2), 68.5 (CH), 22.1 ($2CH_3$), 21.3 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{25}H_{25}O_2$ 357.1855 found 357.1857.

1-(4′-(1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)vinyl)-[1,1-biphenyl]-4-yl)ethanone ***(4j)***. Chromatography on silica gel (AcOEt/Cyclohexane, 1/99 to 10/90) afforded 182 mg of **4j** (0.51 mmol, yield 51%). White solid, mp 165−166 °C. TLC R_f = 0.30 (AcOEt/Cyclohexane, 20/80, SiO_2). IR (neat) 1680 (C=O stretch), 1604, 1504, 1267, 1248, 1123 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.04 (d, J = 8.5 Hz, 2H, H^{Ar}), 7.71 (d, J = 8.5 Hz, 2H, H^{Ar}), 7.60 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.45 (d, J = 8.4 Hz, 2H, H^{Ar}), 6.92−6.89 (m, 1H, H^{Ar}), 6.87−6.84 (m, 2H, H^{Ar}), 5.44 (d, J = 1.1 Hz, 1H, =CH), 5.42 (d, J = 1.1 Hz, 1H, CH), 4.28 (bs, 4H, O−CH_2−CH_2−O), 2.64 (s, 3H, CO−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 197.8 (C), 148.9 (C), 145.4 (C), 143.6 (C), 143.3 (C), 141.7 (C), 139.2 (C), 136.0 (C), 134.8 (C), 129.1 (4CH), 127.2 (2CH) 127.1 (2CH), 121.6 (CH), 117.3 (CH), 117.1 (CH), 113.8 (CH_2), 64.6 (CH_2), 64.5 (CH_2), 26.8 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{24}H_{21}O_3$ 357.1491 found 357.1487.

3-(1-(4-Isobutylphenyl)vinyl)-1,1-biphenyl ***(4l)***. Chromatography on silica gel (Cyclohexane) afforded 274 mg of **4l** (0.88 mmol, yield 88%). Yellow oil. TLC R_f = 0.51 (Cyclohexane, SiO_2). IR (neat) 1597, 1509, 1477, 1450, 1382, 1327 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60−7.52 (m, 4H, H^{Ar}), 7.48−7.38 (m, 3H, H^{Ar}), 7.38−7.27 (m, 4H, H^{Ar}), 7.12 (d, J = 8.2 Hz, 2H, H^{Ar}), 5.51 (d, J = 1.2 Hz, 1H, =CH), 5.46 (d, J = 1.2 Hz, 1H, =CH), 2.50 (d, J = 7.2 Hz, 2H, Ar−CH_2), 1.97−1.82 (m, 1H, CH−$(CH_3)_2$), 0.93 (d, J = 6.6 Hz, 6H, CH−$(CH_3)_2$). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.9 (C), 142.3 (C), 141.5 (C), 141.1 (C), 141.1 (C), 138.6 (C), 129.0 (2CH), 128.7 (2CH), 128.5 (CH), 127.9 (2CH), 127.4 (CH), 127.3 (CH), 127.2 (2CH), 127.2 (CH), 126.5 (CH), 113.8 (CH_2), 45.2 (CH_2), 30.2 (CH), 22.4 ($2CH_3$). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{24}H_{25}$ 313.1956 found 313.1955.

3-(1-(4-Methoxyphenyl)vinyl)-1,1-biphenyl ***(4m)***. Chromatography on silica gel (DCM/Cyclohexane, 0/100 to 1/99) afforded 234 mg of **4m** (0.82 mmol, yield 82%). White solid, mp 68−70 °C. TLC R_f = 0.35 (Heptane, SiO_2). IR (neat) 1603, 1509, 1246, 1178 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.74−7.59 (m, 4H, H^{Ar}), 7.59−7.45 (m, 3H, H^{Ar}), 7.45−7.36 (m, 4H, H^{Ar}), 7.02−6.89 (m, 2H, H^{Ar}), 5.54 (d, J = 1.2 Hz, 1H, =CH), 5.51 (d, J = 1.2 Hz, 1H, =CH), 3.89 (s, 3H, Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.5 (C), 149.6 (C), 142.5 (C), 141.2 (2C), 134.0 (C), 129.5 (2CH), 128.9 (2CH), 128.7 (CH), 127.5 (CH), 127.4 (CH), 127.3 (2CH) 127.3 (CH), 126.6 (CH), 113.7 (CH_2), 113.3 (2CH), 55.4 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{21}H_{19}O$ 287.1436 found 287.1448.

2-(1-(3′,4′,5′-Trimethoxy-[1,1-biphenyl]-3-yl)vinyl)naphthalene ***(4n)***. Chromatography on silica gel (DCM/Cyclohexane, 1/99 to 2/98) afforded 250 mg of **4n** (0.63 mmol, yield 63%). Yellow oil. TLC R_f = 0.23 (DCM/Cyclohexane, 10/90, SiO_2). IR (neat) 1584, 1508, 1457, 1397, 1126 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.91−7.77 (m, 4H, H^{Ar}), 7.62−7.33 (m, 7H, H^{Ar}), 6.80 (s, 2H), 5.69 (d, J = 1.0 Hz, 1H, =CH), 5.63 (d, J = 1.0 Hz, 1H, =CH), 3.93 (s, 6H, 2 Ar−OCH_3), 3.90 (s, 3H, Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 153.6 (2C), 150.1 (C), 142.3 (C), 141.6 (C), 138.8 (C), 137.9 (C), 137.2 (C), 133.5 (C), 133.2 (C), 128.8 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 126.8 (CH), 126.4 (CH), 126.4 (CH), 126.3 (CH), 115.3 (CH_2), 104.8 (2CH), 61.1 (CH_3), 56.4 ($2CH_3$). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{27}H_{25}O_3$ 397.1804 found 397.1803.

5-(4-Methoxyphenyl)-1-methyl-3-(1-(p-tolyl)vinyl)-1H-indole ***(4p)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/70) afforded 96 mg of **4p** (0.27 mmol, yield 27%). Yellow oil. TLC R_f = 0.26 (AcOEt/Cyclohexane, 20/80, SiO_2). IR (neat) 1550, 1505, 1382, 1243, 1177 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.85−7.81 (m, 1H, H^{Ar}), 7.55 (d, J = 8.9 Hz, 2H, H^{Ar}), 7.40 (d, J = 9.2 Hz, 2H, H^{Ar}), 7.27 (d, J = 8.2 Hz, 2H, H^{Ar}), 7.20 (d, J = 1.6 Hz, 1H, H^{Ar}), 7.18−7.12 (m, 2H, H^{Ar}), 6.97 (d, J = 8.8 Hz, 2H, H^{Ar}), 5.39 (s, 2H, =CH_2), 3.88 (s, 3H, Ar−OCH_3), 3.80 (s, 3H, N−CH_3), 2.33 (s, 3H, Ar−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, CD_3COCD_3) δ (ppm) 159.0 (C), 152.2 (C), 140.4 (C), 138.3 (C), 138.1 (C), 134.3 (C), 129.6 (2CH), 129.0 (4CH), 127.9 (CH), 127.9 (C), 127.0 (C), 123.4 (CH), 120.1 (CH), 117.2 (C), 115.1 (2CH), 112.4 (CH_2), 110.2 (CH), 55.5 (CH_3), 33.0 (CH_3), 21.2 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{25}H_{24}NO$ 354.1858 found 354.1859.

2-Phenyl-5-(1-(p-tolyl)vinyl)pyridine ***(4q)***. Chromatography on silica gel (AcOEt/Cyclohexane, 0/100 to 1/99) afforded 145 mg of **4q** (0.54 mmol, yield 54%). White solid, mp 78−79 °C. TLC R_f = 0.26 (AcOEt/Cyclohexane, 2/98, SiO_2). IR (neat) 1588, 1474, 1455, 1362, 1106 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.75 (d, J = 0.9 Hz, 1H, H^{Ar}), 8.06 (d, J = 6.9 Hz, 2H, H^{Ar}), 7.79−7.66 (m, 2H, H^{Ar}), 7.57−7.40 (m, 3H, H^{Ar}), 7.29 (d, J = 8.1 Hz, 2H, H^{Ar}), 7.20 (d, J = 8.0 Hz, 2H, H^{Ar}), 5.57 (s, 1H, =CH), 5.54 (s, 1H, =CH), 2.42 (s, 3H, Ar−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.6 (C), 149.3 (CH), 146.8 (C), 139.2 (C), 138.2 (C), 137.7 (C), 136.4 (CH), 135.7 (C), 129.3 (2CH), 129.1 (CH), 128.9 (2CH), 128.1 (2CH), 127.0 (2CH), 119.8 (CH), 114.9 (CH_2), 21.3 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{20}H_{18}N$ 272.1439 found 272.1439.

6-(4-Methoxyphenyl)-1-methyl-3-(1-(p-tolyl)vinyl)quinolin-2(1H)-one ***(4r)***. Chromatography on silica gel (AcOEt/Cyclohexane, 2/98 to 5/95) afforded 114 mg of **4r** (0.31 mmol, yield 31%). Yellow solid, mp 150−151 °C. TLC R_f = 0.20 (AcOEt/Cyclohexane, 20/80, SiO_2). IR (neat) 1641 (C=O stretch), 1567, 1496, 1247, 1181 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83−7.73 (m, 3H, H^{Ar}), 7.56 (d, J = 8.9 Hz, 2H, H^{Ar}), 7.41 (d, J = 8.7 Hz, 1H, H^{Ar}), 7.29 (d, J = 8.1 Hz, 2H, H^{Ar}), 7.14 (d, J = 7.9 Hz, 2H, H^{Ar}), 7.01 (d, J = 8.8 Hz, 2H, H^{Ar}), 5.69 (d, J = 1.5 Hz, 1H, =CH), 5.64 (d, J = 1.5 Hz, 1H, =CH), 3.87 (s, 3H, Ar−OCH_3), 3.75 (s, 3H, N−CH_3), 2.35 (s, 3H, Ar−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.3 (C), 159.4 (C), 146.1 (C), 138.9 (C), 137.9 (CH), 137.9 (C), 137.6 (C), 135.0 (C), 134.0 (C), 132.4 (C), 129.2 (2CH), 129.1 (CH), 128.0 (2CH), 126.8 (2CH), 126.4 (CH), 120.9 (C), 116.7 (CH_2), 114.6 (3CH), 55.5 (CH_3), 30.0 (CH_3), 21.3 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{24}NO_2$ 382.1807 found 382.1807.

3-(1-(4-Isobutylphenyl)vinyl)-1,1-biphenyl ***(4s)***. Chromatography on silica gel (Cyclohexane) afforded 265 mg of **4s** (0.85 mmol, yield 85%). Yellow oil. TLC R_f = 0.51 (Cyclohexane, SiO_2). IR (neat) 1597, 1509, 1477, 1450, 1382, 1327 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60−7.52 (m, 4H, H^{Ar}), 7.48−7.38 (m, 3H, H^{Ar}), 7.38−7.27 (m, 4H, H^{Ar}), 7.12 (d, J = 8.2 Hz, 2H, H^{Ar}), 5.51 (d, J = 1.2 Hz, 1H, =CH), 5.46 (d, J = 1.2 Hz, 1H, =CH), 2.50 (d, J = 7.2 Hz, 2H, Ar−CH_2), 1.97−1.82 (m, 1H, CH−$(CH_3)_2$), 0.93 (d, J = 6.6 Hz, 6H, CH−$(CH_3)_2$). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.9 (C), 142.3 (C), 141.5 (C), 141.1 (C), 141.1 (C), 138.6 (C), 129.0 (2CH), 128.7 (2CH), 128.5 (CH), 127.9 (2CH), 127.4 (CH), 127.3 (CH), 127.2 (2CH), 127.2 (CH), 126.5 (CH), 113.8 (CH_2), 45.2 (CH_2), 30.2 (CH), 22.4 ($2CH_3$). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{24}H_{25}$ 313.1956 found 313.1955.

2-(1-(3,4-Dimethoxyphenyl)vinyl)-1,1-biphenyl ***(4t)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/80) afforded 190 mg of **4t** (0.60 mmol, yield 60%). White solid, mp 83−85 °C. TLC R_f = 0.50 (AcOEt/Cyclohexane, 30/70, SiO_2). IR (neat) 1579, 1510, 1462, 1318, 1225, 1135 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.30 (m, 4H, H^{Ar}), 7.24−7.10 (m, 5H, H^{Ar}), 6.66−6.60 (m, 3H, H^{Ar}), 5.50 (d, J = 1.3 Hz, 1H, =CH), 5.12 (d, J = 1.3 Hz, 1H, =CH), 3.81 (s, 3H, Ar−OCH_3), 3.74 (s, 3H, Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.2 (C), 148.4 (C), 148.3 (C), 141.6 (C), 141.3 (C), 140.9 (C), 134.5 (C), 130.7 (CH), 130.1 (CH), 129.0 (2CH), 127.7 (CH), 127.6 (2CH), 127.0 (CH), 126.5 (CH), 112.0 (CH), 114.9 (CH_2), 110.5 (CH), 110.4 (CH), 55.8 (CH_3), 55.8 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{22}H_{21}O_2$ 317.1542 found 317.1543.

5-(4-(1-(4-Isobutylphenyl)vinyl)phenyl)-1-methyl-1H-indole ***(4u)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 2/98) afforded 311 mg of **4u** (0.85 mmol, yield 85%). Yellow solid, mp

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131−133 °C. TLC R_f = 0.31 (Cyclohexane, SiO_2). IR (neat) 1604, 1509, 1482, 1420, 1336, 1245 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.90 (d, J = 1.2 Hz, 1H, H^{Ar}), 7.66 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.54 (dd, J = 8.5, 1.7 Hz, 1H, H^{Ar}), 7.45 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.41 (d, J = 8.5 Hz, 1H, H^{Ar}), 7.35 (d, J = 8.2 Hz, 2H, H^{Ar}), 7.16 (d, J = 8.2 Hz, 2H, H^{Ar}), 7.10 (d, J = 3.1 Hz, 1H, H^{Ar}), 6.57 (dd, J = 3.1, 0.6 Hz, 1H, H^{Ar}), 5.51 (d, J = 1.3 Hz, 1H, =CH), 5.48 (d, J = 1.3 Hz, 1H, =CH), 3.83 (s, 3H, N−CH_3), 2.54 (d, J = 7.2 Hz, 2H, Ar−CH_2), 2.00−1.87 (m, 1H, CH−$(CH_3)_2$), 0.97 (d, J = 6.6 Hz, 6H, CH−$(CH_3)_2$). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.9 (C), 1421 (C), 141.5 (C), 139.7 (C), 139.1 (C), 136.5 (C), 132.5 (C), 129.6 (CH), 129.1 (C), 129.1 (2CH), 128.7 (2CH), 128.2 (2CH), 127.1 (2CH), 121.4 (CH), 119.4 (CH), 113.4 (CH_2), 109.6 (CH), 101.5 (CH), 45.3 (CH_2), 33.1 (CH_3), 30.4 (CH), 22.6 ($2CH_3$). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{27}H_{28}N$ 366.2222 found 366.2220.

5-(4-(1-(4-Fluorophenyl)vinyl)phenyl)-1-methyl-1H-pyrazole ***(4v)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/80) afforded 197 mg of **4v** (0.71 mmol, yield 71%). White solid, mp 77−78 °C. TLC R_f = 0.59 (AcOEt/Cyclohexane, 50/50, SiO_2). IR (neat) 1601, 1507, 1224, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.52 (d, J = 1.9 Hz, 1H, H^{Het}), 7.40 (s, 4H, H^{Ar}), 7.33 (dd, J = 8.8, 5.4 Hz, 2H, H^{Ar}), 7.05 (t, J = 8.7 Hz, 2H, H^{Ar}), 6.33 (d, J = 1.9 Hz, 1H, H^{Het}), 5.51 (s, 1H, =CH), 5.47 (s, 1H, =CH), 3.93 (s, 3H, N−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 162.8 (C, d, J = 245.3 Hz), 148.5 (C), 143.3 (C), 141.5 (C), 138.7 (CH), 137.3 (C, d, J = 3.0 Hz), 130.4 (C), 130.1 (2CH, d, J = 8.3 Hz), 128.7 (2CH), 128.5 (2CH), 115.3 (2CH, d, J = 21.0 Hz), 115.0 (CH_2), 106.3 (CH), 37.7 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{18}H_{16}FN_2$ 279,1298 found 279.1301.

(E)-1-(3-Methoxyprop-1-en-1-yl)-4-(1-(p-tolyl)vinyl)benzene ***(4w)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 10/90) afforded 182 mg of **4w** (0.69 mmol, yield 69%). Yellow oil. TLC R_f = 0.37 (AcOEt/Cyclohexane, 20/80, SiO_2). IR (neat) 1508, 1457, 1379, 1184, 1119 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.33 (d, J = 8.5 Hz, 2H, H^{Ar}), 7.27 (d, J = 8.0 Hz, 2H, H^{Ar}), 7.18 (d, J = 7.9 Hz, 2H, H^{Ar}), 6.66 (d, J = 16.0 Hz, 1H, =CH), 6.33 (dt, J = 15.9, 6.0 Hz, 1H, =CH), 5.46 (d, J = 1.2 Hz, 1H, =CH), 5.44 (d, J = 1.2 Hz, 1H, =CH), 4.14 (dd, J = 6.0, 1.4 Hz, 2H, CH_2−OCH_3), 3.43 (s, 3H, OCH_3), 2.40 (s, 3H, Ar−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.6 (C), 141.1 (C), 138.7 (C), 137.7 (C), 136.3 (C), 132.2 (2CH), 129.0 (2CH), 128.6 (2CH), 128.3 (2CH), 126.4 (2CH), 126.2 (CH), 113.7 (CH_2), 73.2 (CH_2), 58.1 (CH_3), 21.3 (CH_3). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{19}H_{21}O$ 265,1592 found 265.1613.

(E)-1-Methyl-4-(1-(4-styrylphenyl)vinyl)benzene ***(4x)***. Chromatography on silica gel (Cyclohexane) afforded 155 mg of **4x** (0.52 mmol, yield 52%). White solid, mp 144−146 °C. TLC R_f = 0.43 (Cyclohexane, SiO_2). IR (neat) 1604, 1509, 1446, 1327, 1264 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60−7.47 (m, 4H, H^{Ar}), 7.44−7.34 (m, 4H, H^{Ar}), 7.34−7.25 (m, 3H, H^{Ar}), 7.23−7.14 (m, 4H, H^{Ar}), 5.49 (d, J = 1.3 Hz, 1H, =CH), 5.46 (d, J = 1.2 Hz, 1H, =CH), 2.41 (s, 3H, Ar−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 149.7 (C), 141.1 (C), 138.7 (C), 137.7 (C), 137.5 (C), 136.9 (C), 129.0 (2CH), 128.9 (CH), 128.8 (2CH), 128.7 (2CH), 128.4 (CH), 128.4 (2CH), 127.8 (CH), 126.7 (2CH), 126.4 (2CH), 113.7 (CH_2), 21.3 (CH_3). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{23}H_{21}$ 297.1643 found 297.1640.

2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1,1-biphenyl ***(4y)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/80) afforded 172 mg of **4y** (0.46 mmol, yield 46%). Yellow oil. TLC R_f = 0.61 (AcOEt/Cyclohexane, 30/70, SiO_2). IR (neat) 1578, 1504, 1410, 1342, 1233, 1124 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.57−7.50 (m, 2H, H^{Ar}), 7.50−7.29 (m, 5H, H^{Ar}), 6.98 (d, J = 8.5 Hz, 1H, H^{Ar}), 6.64 (s, 2H, H^{Ar}), 5.46 (d, J = 1.2 Hz, 1H, =CH), 5.39 (d, J = 1.2 Hz, 1H, =CH), 3.92 (s, 3H, Ar−OCH_3), 3.85 (s, 9H, 3Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.4 (C), 152.9 (2C), 149.5 (C), 138.3 (C), 137.9 (C), 137.5 (C), 133.8 (C), 130.8 (CH), 130.4 (C), 129.6 (2CH), 128.5 (CH), 128.0 (2CH), 127.1 (CH), 112.8 (CH_2), 110.9 (CH), 105.7 (2CH), 60.9 (CH_3), 56.2 ($2CH_3$), 55.7 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{24}H_{25}O_4$ 377.1753 found 377.1756.

4-(2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)vinyl)phenyl)pyridine ***(4z)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 30/70) afforded 322 mg of **4z** (0.85 mmol, yield 85%). Yellow oil. TLC R_f = 0.22 (AcOEt/Cyclohexane, 30/70, SiO_2). IR (neat) 1578, 1504, 1411, 1345, 1235, 1125 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.62−8.60 (m, 2H, H^{Ar}), 7.46−7.44 (m, 2H, H^{Ar}), 7.40−7.35 (m, 2H, H^{Ar}), 6.97 (d, J = 9.2 Hz, 1H, H^{Ar}), 6.57 (s, 2H, H^{Ar}), 5.41 (s, 1H, =CH), 5.37 (s, 1H, =CH), 3.88 (s, 3H, Ar−OCH_3), 3.86 (s, 3H, Ar−OCH_3), 3.82 (s, 6H, 2Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.4 (C), 153.0 (2C) 149.5 (2CH), 149.1 (C), 146.1 (C), 138.0 (C), 137.1 (C), 134.2 (C), 130.3 (CH), 130.0 (CH), 127.4 (C), 124.3 (2CH), 113.1 (CH_2), 111.1 (CH), 105.7 (2CH), 60.9 (CH_3), 56.2 ($2CH_3$), 55.7 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{23}H_{24}NO_4$ 378.1705 found 378.1712.

5-(2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)vinyl)phenyl)-1-methyl-1H-pyrazole ***(4aa)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 25/75) afforded 251 mg of **4aa** (0.66 mmol, yield 66%). Yellow oil. TLC R_f = 0.33 (AcOEt/Cyclohexane, 30/70, SiO_2). IR (neat) 1579, 1503, 1462, 1411, 1342, 1251, 1126 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.50 (d, J = 1.9 Hz, 1H, H^{Het}), 7.40 (dd, J = 8.6, 2.4 Hz, 1H, H^{Ar}), 7.27 (d, J = 2.3 Hz, 1H, H^{Ar}), 6.95 (d, J = 8.6 Hz, 1H, H^{Ar}), 6.55 (s, 2H, H^{Ar}), 6.22 (d, J = 1.9 Hz, 1H, H^{Het}), 5.40 (d, J = 1.1 Hz, 1H, =CH), 5.35 (d, J = 1.1 Hz, 1H, =CH), 3.87 (s, 3H, Ar−OCH_3), 3.84 (s, 3H, Ar−OCH_3), 3.81 (s, 6H, 2Ar−OCH_3), 3.73 (s, 3H, N−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.8 (C), 153.0 (2C), 149.0 (C), 140.1 (C), 138.4 (CH), 138.1 (C), 137.2 (C), 133.8 (C), 131.4 (CH), 130.3 (CH), 119.6 (C), 113.2 (CH_2), 110.8 (CH), 106.9 (CH), 105.8 (2CH), 61.0 (CH_3), 56.3 ($2CH_3$), 55.7 (CH_3), 37.3 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{22}H_{25}N_2O_4$ 381.1814 found 381.1812.

(E)-5-(1-(3-(2-Cyclopropylvinyl)-4-methoxyphenyl)vinyl)-1,2,3-trimethoxybenzene ***(4ab)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/80) afforded 223 mg of **4ab** (0.61 mmol, yield 61%). Yellow oil. TLC R_f = 0.73 (AcOEt/Cyclohexane, 30/70, SiO_2). IR (neat) 1582, 1499, 1461, 1412, 1331, 1246, 1126 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37 (d, J = 2.2 Hz, 1H, H^{Ar}), 7.12 (dd, J = 8.5, 2.3 Hz, 1H, H^{Ar}), 6.82−6.75 (m, 2H, H^{Ar} + =CH), 6.56 (s, 2H, H^{Ar}), 5.72 (dd, J = 15.9, 8.9 Hz, 1H, =CH), 5.36 (d, J = 1.3 Hz, 1H, =CH), 5.33 (d, J = 1.3 Hz, 1H, =CH), 3.88 (s, 3H, Ar−OCH_3), 3.87 (s, 3H, Ar−OCH_3), 3.81 (s, 6H, 2Ar−OCH_3), 1.66−1.51 (m, 1H, CH−$(CH_2)_2$), 0.85−0.76 (m, 2H, CH−$(CH_2)_2$), 0.54−0.46 (m, 2H, CH−$(CH_2)_2$). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.1 (C), 153.0 (2C), 149.9 (C), 137.9 (C), 137.6 (C), 136.2 (CH), 133.8 (C), 127.8 (CH), 126.6 (C), 126.3 (CH), 122.0 (CH), 112.7 (CH_2), 110.5 (CH), 105.8 (2CH), 61.2 (CH_3), 56.3 ($2CH_3$), 55.7 (CH_3), 15.2 (CH), 7.5 ($2CH_2$). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{23}H_{27}O_4$ 367.1909 found 367.1913.

(E)-1,2,3-Trimethoxy-5-(1-(4-methoxy-3-styrylphenyl)vinyl)-benzene ***(4ac)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/80) afforded 191 mg of **4ac** (0.47 mmol, yield 47%). Yellow oil. TLC R_f = 0.42 (AcOEt/Cyclohexane, 30/70, SiO_2). IR (neat) 1579, 1505, 1456, 1338, 1248, 1127 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.64 (d, J = 2.2 Hz, 1H, H^{Ar}), 7.59−7.47 (m, 3H, H^{Ar}), 7.39−7.34 (m, 2H, H^{Ar}), 7.29−7.23 (m, 2H, H^{Ar}), 7.13 (d, J = 16.5 Hz, 1H, =CH), 6.90 (d, J = 8.6 Hz, 1H, H^{Ar}), 6.62 (s, 2H, H^{Ar}), 5.45 (d, J = 1.2 Hz, 1H, =CH), 5.41 (d, J = 1.2 Hz, 1H, =CH), 3.94 (s, 3H, Ar−OCH_3), 3.92 (s, 3H, Ar−OCH_3), 3.85 (s, 6H, 2Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.9 (C), 153.0 (2C), 149.7 (C), 138.0 (C), 138.0 (C), 137.5 (C), 133.9 (C), 129.6 (CH), 128.9 (CH), 128.7 (2CH), 127.6 (CH), 126.7 (2CH), 126.5 (CH), 126.2 (C), 123.5(C), 112.9 (CH_2), 110.7 (CH), 105.8 (2CH), 61.1 (CH_3), 56.3 ($2CH_3$), 55.8 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{26}H_{27}O_4$ 403.1909 found 403.1909.

(E)-1,2,3-Trimethoxy-5-(1-(4-methoxy-3-(3-methoxyprop-1-en-1-yl)phenyl)vinyl)benzene ***(4ad)***. Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/80) afforded 171 mg of **4ad** (0.46 mmol, yield 46%). Yellow oil. TLC R_f = 0.65 (AcOEt/Cyclohexane, 30/70, SiO_2). IR (neat) 1584, 1499, 1456, 1412, 1331, 1247, 1125 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.46 (d, J = 2.3 Hz, 1H, H^{Ar}), 7.21 (dd, J = 8.5, 2.3 Hz, 1H, H^{Ar}), 6.91 (d, J = 16.1 Hz, 1H, =CH), 6.83

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(d, J = 8.6 Hz, 1H, H^{Ar}), 6.55 (s, 2H, H^{Ar}), 6.28 (dt, J = 16.1, 6.1 Hz, 1H, =CH), 5.37 (d, J = 1.2 Hz, 1H, =CH), 5.33 (d, J = 1.2 Hz, 1H, =CH), 4.09 (dd, J = 6.1, 1.4 Hz, 2H, CH_2−OCH_3), 3.88 (s, 3H, Ar−OCH_3), 3.87 (s, 3H, Ar−OCH_3), 3.81 (s, 6H, 2Ar−OCH_3), 3.38 (s, 3H, CH_2−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.8 (C), 153.0 (2C), 149.7 (C), 137.9 (C), 137.5 (C), 133.8 (C), 128.9 (CH), 127.5 (CH), 127.2 (2CH), 125.5 (C), 112.8 (CH_2), 110.6 (CH), 105.7 (2CH), 73.7 (CH_2), 61.0 (CH_3), 58.1 (CH_3), 56.3 ($2CH_3$), 55.7 (CH_3). HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{22}H_{27}O_5$ 371.1858 found 371.1858.

(E)-tert-Butyl((3-(2-methoxy-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-phenyl)allyl)oxy)dimethylsilane ***(4ae).*** Chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 20/80) afforded 301 mg of **4ae** (0.64 mmol, yield 64%). Yellow oil. TLC R_f = 0.43 (AcOEt/Cyclohexane, 10/90, SiO_2). IR (neat) 1583, 1501, 1462, 1332, 1255, 1126 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45 (d, J = 2.3 Hz, 1H, H^{Ar}), 7.19 (dd, J = 8.5, 2.3 Hz, 1H, H^{Ar}), 6.90 (dt, J = 15.9, 1.6 Hz, 1H, =CH), 6.82 (d, J = 8.5 Hz, 1H, H^{Ar}), 6.57 (s, 2H, H^{Ar}), 6.28 (dt, J = 16.0, 5.2 Hz, 1H, =CH), 5.38 (d, J = 1.2 Hz, 1H, =CH), 5.34 (d, J = 1.2 Hz, 1H, =CH), 4.35 (dd, J = 5.2, 1.7 Hz, 2H,, CH_2−OCH_3), 3.88 (s, 3H, Ar−OCH_3), 3.86 (s, 3H, Ar−OCH_3), 3.81 (s, 6H, 2Ar−OCH_3), 0.94 (s, 9H, ^{t}Bu), 0.10 (s, 6H, Si−$(CH_3)_2$). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.7 (C), 153.0 (2C), 149.8 (C), 138.0 (C), 137.6 (C), 133.8 (C), 130.4 (CH), 128.5 (CH), 127.1 (CH), 126.0 (C), 124.6 (CH), 112.7 (CH_2), 110.6 (CH), 105.8 (2CH), 64.5 (CH_2), 61.0 (CH_3), 56.3 ($2CH_3$), 55.7 (CH_3), 26.1 ($3CH_3$), 18.6 (C), −5.0 ($2CH_3$). HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{27}H_{38}NaO_5Si$ 493.2386 found 493.2390.

(E)-3-(2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)vinyl)phenyl)-prop-2-en-1-ol ***(4af).*** To a solution of **4ae** (246 mg, 0.5 mmol) in 5 mL of THF is added TBAF (1.0 M in THF) (1 mL, 1 mmol) at 0 °C. The resulting mixture is stirred 2h at room temperature. Solvents are removed under reduce pressure and the crude mixture is purified by chromatography. Chromatography on silica gel (DCM/Cyclohexane, 0/100 to 20/80) afforded 146 mg of **4af** (0.41 mmol, yield 82%). Colorless oil. TLC R_f = 0.20 (AcOEt/Cyclohexane, 20/80, SiO_2). IR (neat) 1580, 1504, 1456, 1411, 1338, 1240, 1126 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45 (d, J = 2.2 Hz, 1H, H^{Ar}), 7.21 (dd, J = 8.5, 2.3 Hz, 1H, H^{Ar}), 6.91 (d, J = 16.1 Hz, 1H, =CH), 6.84 (d, J = 8.5 Hz, 1H, H^{Ar}), 6.55 (s, 2H, H^{Ar}), 6.37 (dt, J = 16.0, 5.8 Hz, 1H, =CH), 5.37 (d, J = 1.2 Hz, 1H, =CH), 5.34 (d, J = 1.2 Hz, 1H, =CH), 4.32 (d, J = 5.1 Hz, 2H, CH_2−OCH_3), 3.88 (s, 3H, Ar−OCH_3), 3.88 (s, 3H, Ar−OCH_3), 3.81 (s, 6H, 2Ar−OCH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 156.6 (C), 152.9 (2C), 149.5 (C), 137.8 (C), 137.4 (C), 133.7 (C), 129.7 (CH), 128.8 (CH), 127.0 (CH), 126.0 (CH), 125.3 (C), 112.7 (CH_2), 110.4 (CH), 105.6 (2CH), 64.1 (CH_2), 60.9 (CH_3), 56.2 ($2CH_3$), 55.6 (CH_3). HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{21}H_{25}O_5Na$ 379.1521 found 379.1523.

1-Bromo-5-iodo-2-methoxy-4-(methoxymethoxy)benzene ***(2i).*** 2-Iodo-5-methoxyphenol (**6**) (4 mmol, 1.00 g) and potassium carbonate (12 mmol, 1.67g) were dissolved in acetone (20 mL), and then chloromethyl methyl ether (8 mmol, 0.61 mL) was added at RT. The resulting mixture was stirred at reflux for 3 h. The mixture was cooled to RT, and potassium carbonate was filtered off. The filtrate was concentrated in vacuo. The crude 1-iodo-4-methoxy-2-(methoxymethoxy)-benzene (**7**) was used in the next reaction without further purification. The spectroscopic data were in full accord with those reported previously. TLC R_f = 0.51 (EtOAC/Cyclohexane, 20/80, SiO_2). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.62 (d, J = 8.7 Hz, 1H, H^{Ar}), 6.69 (d, J = 2.7 Hz, 1H, H^{Ar}), 6.38 (dd, J = 8.7, 2.7 Hz, 1H, H^{Ar}), 5.22 (s, 2H, O−CH_2−O), 3.78 (s, 3H, Ar−OCH_3), 3.51 (s, 3H, OCH_3). To a solution of the crude 1-iodo-4-methoxy-2-(methoxymethoxy)benzene (**7**) in acetonitrile (20 mL) were added silica gel (300 mg), butylated hydroxytoluene (14 mg), and *N*-bromosuccinimide (4 mmol, 712 mg). The resulting mixture was stirred at RT for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2/H_2O (100 mL, 1/1, v/v) and vigorously stirred for 5 min. The layers were then separated and the aqueous phase was extracted twice with CH_2Cl_2. Organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The product was isolated by chromatography on silica gel (EtOAc/Cyclohexane, 2/98 to 10/90) as a yellow solid (yield: 1.40 g, 3.8 mmol, 94%). The spectroscopic data were in full accord with those reported previously. TLC R_f = 0.53 (EtOAC/Cyclohexane, 20/80, SiO_2). ^1H NMR (300 MHz, CDCl3) δ (ppm) 7.85 (s, 1H, H^{Ar}), 6.73 (s, 1H, H^{Ar}), 5.22 (s, 2H, O−CH_2−O), 3.87 (s, 3H, Ar−OCH_3), 3.51 (s, 3H, OCH_3).

(E)-5-(Prop-1-en-1-yl)benzofuran ***(9).*** 5-Bromobenzofuran 8 (5 mmol, 985 mg), potassium *trans*-1-propenyltrifluoroborate (5.25 mmol, 772 mg), $PdCl_2$(dppf).CH_2Cl_2 (0.1 mmol, 82 mg) and tBuNH$_2$ (15.75 mmol, 1.7 mL) were dissolved in iPrOH/H_2O (50 mL, 2/1, v/v). The resulting mixture was stirred at reflux under an argon atmosphere for 4 h. The mixture was cooled to room temperature and diluted with water (100 mL), followed by extraction with diethyl ether. Organic layers were combined and washed with HCl (1 N) and brine, dried over $MgSO_4$ and concentrated in vacuo. The product was isolated by chromatography on silica gel (Cyclohexane) as a colorless liquid (yield: 698 mg, 4.4 mmol, 88%). TLC R_f = 0.60 (Cyclohexane, SiO_2). IR (neat) 1597, 1509, 1477, 1450, 1382, 1327. ^1H NMR (300 MHz, CDCl3) δ (ppm) 7.59 (d, J = 2.2 Hz, 1H, H^{Ar}), 7.52 (d, J = 1.6 Hz, 1H, H^{Ar}), 7.41 (d, J = 8.6 Hz, 1H, H^{Ar}), 7.31 (dd, J = 8.6, 1.7 Hz, 1H, H^{Ar}), 6.73 (dd, J = 2.2, 0.9 Hz, 1H, H^{Ar}), 6.49 (dq, J = 15.7, 1.6 Hz, 1H, =CH), 6.20 (dq, J = 15.7, 6.6 Hz, 1H, =CH), 1.90 (dd, J = 6.6, 1.6 Hz, 3H, =CH−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 154.2 (C), 145.3 (CH), 133.1 (C), 131.0 (CH), 127.7 (C), 124.5 (CH), 122.4 (CH), 118.3 (CH), 111.2 (CH), 106.6 (CH), 18.5 (CH_3). HRMS (APCI) $(M + H)^+$ m/z calcd for $C_{11}H_{11}O$ 159.0810 found 159.0810.

(E)-4,4,5,5-Tetramethyl-2-(5-(prop-1-en-1-yl)benzofuran-2-yl)-1,3,2-dioxaborolane ***(5k).*** To a flask under argon, containing $[Ir(OMe)(cod)]_2$ (0.03 mmol, 20 mg), 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.06 mmol, 16 mg) and bis(pinacolato)diboron (1 mmol, 254 mg) was added degassed *n*-hexane (6 mL) and (*E*)-5-(prop-1-en-1-yl)-benzofuran **9** (2 mmol, 316 mg). The resulting mixture was stirred at 50 °C under an argon atmosphere for 3 h. The crude product was isolated by filtration on silica gel with EtOAc/Cyclohaxane (200 mL, 7/3, v/v) as a brown oil and used without further purification in the next step. TLC R_f = 0.53 (EtOAc/Cyclohexane, 20/80, SiO_2). ^1H NMR (300 MHz, CDCl3) δ (ppm) 7.55 (d, J = 1.5 Hz, 1H, H^{Ar}), 7.48 (d, J = 8.6 Hz, 1H, H^{Ar}), 7.42−7.34 (m, 2H, H^{Ar}), 6.50 (dq, J = 15.7, 1.6 Hz, 1H, =CH), 6.21 (dq, J = 15.7, 6.6 Hz, 1H, =CH), 1.90 (dd, J = 6.6, 1.6 Hz, 3H, =CH−CH_3), 1.40 (s, 12H, $6CH_3$).

1-(5-Bromo-2-((4-methoxybenzyl)oxy)phenyl)ethanone ***(11).*** 1-(5-Bromo-2-hydroxyphenyl)ethanone **1a** (15 mmol, 3.23 g) was dissolved in acetone (50 mL), then K_2CO_3 (45 mmol, 6.21 g), KI (15 mmol, 2.49 g) and PMBCl (30 mmol, 4.1 mL) were added at RT. The resulting mixture was stirred at reflux overnight. The mixture was cooled to RT, filtered and concentrated in vacuo. The product was isolated by chromatography on silica gel (EtOAc/Cyclohexane, 2/98 to 10/90) as a white solid (yield: 4.99 g, 14.9 mmol, 99%). TLC R_f = 0.60 (EtOAC/Cyclohexane, 20/80, SiO_2). IR (neat) 1671, 1514, 1395, 1249, 1173. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.84 (d, J = 2.6 Hz, 1H, H^{Ar}), 7.52 (dd, J = 8.8, 2.6 Hz, 1H, H^{Ar}), 7.34 (d, J = 8.8 Hz, 2H, H^{Ar}), 6.95−6.88 (m, 3H, H^{Ar}), 5.07 (s, 2H, Ar−OCH_2−Ar), 3.83 (s, 3H Ar−OCH_3), 2.55 (s, 3H, CO−CH_3). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 198.4 (C), 159.9 (C), 157.2 (C), 136.1 (CH), 133.2 (CH), 130.3 (C), 129.5 (2CH), 127.8 (C), 115.0 (CH), 114.3 (2CH), 113.5 (C), 71.0 (CH_2), 55.5 (CH_3), 32.1 (CH_3). HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{16}H_{15}BrO_3Na$ 357,0102 found 357.0094.

(E)-1-(2-((4-Methoxybenzyl)oxy)-5-(prop-1-en-1-yl)phenyl)-ethanone ***(12).*** 1-(5-Bromo-2-((4-methoxybenzyl)oxy)phenyl)-ethanone **11** (5 mmol, 1.68 g), potassium *trans*-1-propenyltrifluoroborate (5.25 mmol, 772 mg), $PdCl_2$(dppf).CH_2Cl_2 (0.1 mmol, 82 mg) and tBuNH$_2$ (15.75 mmol, 1.7 mL) were dissolved in iPrOH/H_2O (50 mL, 2/1, v/v). The resulting mixture was stirred at reflux under an argon atmosphere for 4 h. The mixture was cooled to room temperature and diluted with water (100 mL), followed by extraction with diethyl ether. Organic layers were combined and washed with HCl (1 N) and brine, dried over $MgSO_4$ and concentrated in vacuo. The product was isolated by chromatography on silica gel (EtOAc/Cyclohexane, 2/98 to 10/90) as a white solid (yield: 1.43 g, 4.8 mmol, 97%). TLC R_f = 0.60 (EtOAC/Cyclohexane, 20/80, SiO_2). IR (neat) 1668, 1515, 1494, 1407,

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1243. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70 (d, J = 2.4 Hz, 1H, H^{Ar}), 7.40 (dd, J = 8.6, 2.4 Hz, 1H, H^{Ar}), 7.35 (d, J = 8.7 Hz, 2H, H^{Ar}), 6.96 (d, J = 8.7 Hz, 1H, H^{Ar}), 6.92 (d, J = 8.7 Hz, 2H, H^{Ar}), 6.40−6.28 (m, 1H, =CH), 6.15 (dq, J = 15.7, 6.4 Hz, 1H, =CH), 5.07 (s, 2H, Ar−OCH_2−Ar), 3.82 (s, 3H Ar−OCH_3), 2.56 (s, 3H, CO−CH_3), 1.86 (dd, J = 6.5, 1.5 Hz, 3H, =CH−CH_3). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 200.1 (C), 159.6 (C), 157.0 (C), 130.9 (C), 130.7 (CH), 129.5 (CH), 129.3 (2CH), 128.6 (C), 128.2 (C), 127.7 (CH), 125.0 (CH), 114.1 (2CH), 113.0 (CH), 70.6 (CH_2), 55.3 (CH_3), 32.1 (CH_3), 18.4 (CH_3). HRMS (ESI) (M + Na)$^+$ m/z calcd for $C_{19}H_{20}O_3Na$ 319.1310 found 319.1314.

N′-(1-(2-((4-Methoxybenzyl)oxy)-5-((E)-prop-1-en-1-yl)phenyl)-ethylidene)-4-methylbenzenesulfonohydrazide ***(1u).*** (*E*)-1-(2-((4-Methoxybenzyl)oxy)-5-(prop-1-en-1-yl)phenyl)ethanone (12) (3.5 mmol, 1.04 g) was dissolved in ethanol (10 mL), then *para*-toluenesulfonylhydrazide (4.2 mmol, 0.78 g) was added at RT. The resulting mixture was stirred at reflux for 1 h. The mixture was cooled to RT and the product was isolated by filtration as a white solid (yield: 1.39 g, 3.0 mmol, 86%). TLC R_f = 0.38 (EtOAC/Cyclohexane, 20/80, SiO_2). IR (neat) 1613, 1515, 1493, 1340, 1237, 1166. ^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.81 (d, J = 8.3 Hz, 2H, H^{Ar}), 7.42−7.32 (m, 4H, H^{Ar}), 7.30 (dd, J = 8.6, 2.4 Hz, 1H, H^{Ar}), 7.13 (d, J = 2.3 Hz, 1H, H^{Ar}), 7.03 (d, J = 8.5 Hz, 1H, H^{Ar}), 6.96−6.86 (m, 2H, H^{Ar}), 6.33 (dq, J = 15.8, 1.6 Hz, 1H, =CH), 6.08 (dq, J = 15.7, 6.6 Hz, 1H, =CH), 5.01 (s, 2H Ar−OCH_2−Ar), 3.80 (s, 3H, Ar−OCH_3), 2.85 (bs, 1H, NH), 2.41 (s, 3H, CN−CH_3), 2.15 (s, 3H, Ar−CH_3), 1.85 (dd, J = 6.6, 1.6 Hz, 3H, =CH−CH_3). ^{13}C{1H} NMR (75 MHz, CD_3COCD_3) δ (ppm) 159.6 (C), 155.7 (C), 155.1 (C), 143.5 (C), 136.7 (C), 130.6 (C), 130.1 (CH), 129.4 (2CH), 129.2 (2CH), 129.1 (C), 128.9 (C), 128.1 (2CH), 127.6 (CH), 126.8 (CH), 123.6 (CH), 113.8 (2CH), 112.8 (2CH), 70.0 (CH_2), 54.6 (CH_3), 20.6 (CH_3), 17.6 (CH_3), 17.1 (CH_3). HRMS (ESI) (M + Na)$^+$ m/z calcd for $C_{26}H_{28}N_2O_4SNa$ 487.1667 found 487.1666.

2-(2-Methoxy-5-(1-(2-((4-methoxybenzyl)oxy)-5-((E)-prop-1-en-1-yl)phenyl)vinyl)-4-(methoxymethoxy)phenyl)-5-((E)-prop-1-en-1-yl)-benzofuran ***(4ah).*** A round-bottom flask with condenser under argon, was charged with *N′*-(1-(2-((4-methoxybenzyl)oxy)-5-((*E*)-prop-1-en-1-yl)phenyl)ethylidene)-4-methylbenzenesulfonohydrazide **1u** (1.1 mmol, 512 mg), 1-bromo-5-iodo-2-methoxy-4-(methoxymethoxy)benzene **2i** (1 mmol 373 mg), $Pd(OAc)_2$ (0.04 mmol, 9 mg), Sphos (0.08 mmol 32 mg), lithium-*tert*-butoxide (2.4 mmol, 192 mg), and degassed dioxane (6 mL). The resulting mixture was stirred at reflux for 2 h. Then, potassium hydroxide (3 mmol, 168 mg), degassed water (50 mmol, 0.8 mL), and crude (*E*)-4,4,5,5-tetramethyl-2-(5-(prop-1-en-1-yl)benzofuran-2-yl)-1,3,2-dioxaborolane **5k** (∼2 mmol) dissolved in degassed dioxane (0.5 mL) were added and reflux was continued for 4 h. The mixture was cooled to room temperature, diluted with EtOAc, filtered through Celite, and concentrated in vacuo. The product was isolated by chromatography on silica gel (EtOAc/Cyclohexane, 0/100 to 5/95) as a white solid (yield: 2726 mg, 45%). TLC R_f = 0.48 (EtOAC/Cyclohexane, 20/80, SiO_2). IR (neat) 1514, 1464, 1302, 1216, 1082. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.93 (s, 1H, H^{Ar}), 7.51 (d, J = 1.4 Hz, 1H, H^{Ar}), 7.43−7.33 (m, 2H, H^{Ar}), 7.28−7.15 (m, 4H, H^{Ar}), 6.92 (d, J = 8.7 Hz, 2H, H^{Ar}), 6.83 (d, J = 8.5 Hz, 1H, H^{Ar}), 6.70 (s, 1H, H^{Ar}), 6.59 (d, J = 8.7 Hz, 2H, H^{Ar}), 6.57−6.32 (m, 2H, 2(=CH)), 6.30−6.07 (m, 2H, 2(=CH)), 5.58 (s, 2H, =CH_2), 4.89 (s, 2H, Ar−OCH_2−Ar), 4.81 (s, 2H O−CH_2−O), 4.00 (s, 3H, Ar−OCH_3), 3.50 (s, 3H, Ar−OCH_3), 3.19 (s, 3H, OCH_3), 1.97−1.84 (m, 6H, 2(=CH−CH_3)). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 159.1 (C), 156.9 (C), 155.4 (C), 155.2 (C), 153.2 (C), 153.0 (C), 144.9 (C), 144.8 (C), 133.0 (C), 132.5 (C), 131.5(CH), 130.8 (C), 130.7 (CH), 130.4 (C), 128.9 (2CH), 128.8 (CH), 128.3 (CH), 125.9 (CH), 125.8 (C), 124.1 (CH), 123.7 (CH), 122.0 (CH), 118.9 (CH_2), 117.9 (CH), 113.5 (2CH), 113.3 (C), 112.5 (CH), 110.8 (CH), 104.8 (CH), 99.2 (CH), 94.7 (CH_2), 70.2 (CH_2), 55.9 (CH_3), 55.8 (CH_3), 55.0 (CH_3), 18.6 (CH_3), 18.6 (CH_3). HRMS (ESI) (M + H)$^+$ m/z calcd for $C_{39}H_{39}O_6$ 603.2747 found 603.2750.

Biology. Cancer cell lines were obtained from the American type Culture Cancer cell lines were obtained from the American type Culture Collection (Rockville, MD) and were cultured according to the supplier's instructions. HCT116 colorectal carcinoma cells were grown in RPMI 1640 containing 10% FCS and 1% glutamine. Cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. All cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cell viability was assessed using Promega CellTiter-Blue reagent according to the manufacturer's instructions. Cells were seeded in 96-well plates (5 × 103 cells/well) containing 50 μL growth medium. After 24 h of culture, the cells were supplemented with 50 μL of the tested compound dissolved in DMSO (less than 0.1% in each preparation). After 72 h of incubation, 20 μL of resazurin was added for 2 h before recording fluorescence (λ_{ex} = 560 nm, λ_{em} = 590 nm) using a Victor microtiter plate fluorimeter (PerkinElmer, USA). The GI_{50} corresponds to the concentration of the tested compound that caused a decrease of 50% in fluorescence of drug treated cells compared with untreated cells. Experiments were performed in triplicate. The GI_{50} values for all compounds were compared to the GI_{50} of isoCA-4 and measured the same day under the same conditions.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00880.

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Notes

The authors declare no competing financial interest.

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