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Synthesis of *Ortho*/*Ortho*′-Substituted 1,1-Diarylethylenes through Cross-Coupling Reactions of Sterically Encumbered Hydrazones and Aryl Halides

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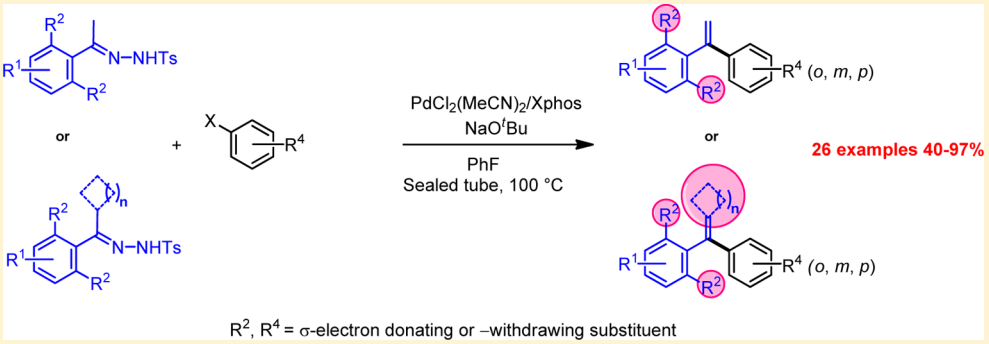
Supporting Information



ABSTRACT: The reactivity of sterically hindered *N*-tosylhydrazones **2** featuring *ortho*/*ortho*′-substituents on the aromatic ring with various *ortho*-, *meta*-, and *para*-substituted aryl halides **3** was investigated. To accomplish successfully this challenging coupling, fine-tuning of the reaction conditions were required. The newly established $PdCl_2(MeCN)_2$/Xphos/NaO-*t*-Bu/F-benzene system in a sealed tube is compatible with a broad spectrum of both coupling partners, regardless of their electronic and steric nature. This protocol has been applied successfully to the synthesis of a xanthene derivative.

INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions have been established as one of the most powerful tools for the construction of C−C bonds.[1] In this context, the development of novel metal-catalyzed cross-coupling processes that do not require stoichiometric organometallic reagents is particularly attractive.[2] Recently, Pd-catalyzed cross-coupling of diazo compounds, pioneered by Van Vranken,[3] has emerged as a new type of cross-coupling reactions; however, diazo compounds without an electron-withdrawing group are usually unstable and thus difficult to handle. *N*-Tosylhydrazones, which are easily prepared from aldehydes or ketones, could be used as generally reliable precursors to diazo compounds.[4] In 2007, Barluenga, Valdés, et al. demonstrated that the procedure for generating in situ the diazo compounds from *N*-tosylhydrazones was compatible with the Pd-catalyzed cross-coupling reaction of aryl halides.[5] Since then, *N*-tosylhydrazones have attracted extensive attention as a new type of versatile coupling partners under transition-metal-catalyzed cross-coupling reactions. In particular, they represent the most important metal−carbenoid precursors capable of undergoing a range of reactions with aryl sulfonates,[6] benzyl halides,[7] alkynes,[8] amines,[9] azoles,[10] arylboronic acid,[11] isocyanides,[12] etc.

Our interest in the 1,1-diarylethylene unit synthesis[13] led us to identify *iso*-combretastatin A-4 (*iso*CA-4), a promising cytotoxic agent with antitubulin and vascular targeting activity.[14] A structure−activity relationship (SAR) study of *iso*CA-4 led us to the design and synthesis of molecules of type **1** (Scheme 1).[15]

In continuation of our earlier work, and in order to have a better understanding of the SAR, a further panel of compounds of type **A** was designed to evaluate the steric effects of the methoxy groups of aromatic rings and/or double-bond substituents on biological activity. These 1,1-diarylolefin derivatives having a di- or tetrasubstituted double bond are characterized by the presence of *ortho*/*ortho*′-substituents on the aromatic rings. Their synthesis was envisioned by coupling of highly sterically hindered *N*-tosylhydrazones **2** with *ortho*-substituted aryl halides **3** under palladium catalysis as outlined in Scheme 2. All our attempts to prepare **4a** by coupling **2a** with **3a** under the standard protocol (Pd_2dba_3/XPhos, LiO-*t*-Bu) developed by Barluenga et al.[5a] or using our previously reported conditions ($PdCl_2(MeCN)_2$/dppp, Cs_2CO_3)[15] resulted in unsatisfactory yields (Table 1, entries 1 and 2). Our attempts to increase the yield of **4a** by using high catalyst loading (up to 15 mol %) and elevated temperatures (up to 130 °C) combined with a prolonged reaction time did not lead to any improvement. These unsuccessful results clearly demonstrate that steric hindrance in both coupling partners plays a

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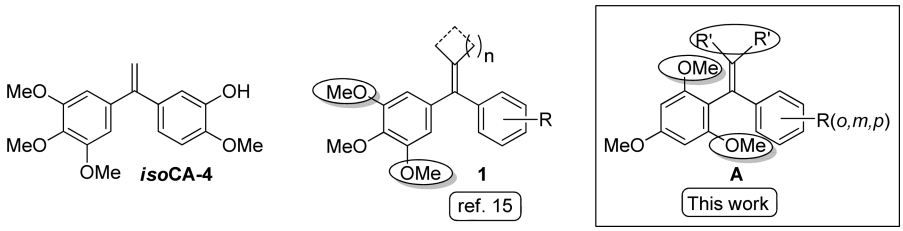
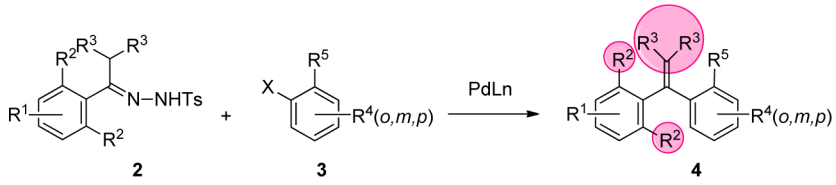
Scheme 1



Scheme 2



critical role in the outcome of this reaction. To address difficulties associated with the reactivity of highly sterically hindered *N*-tosylhydrazones **2**,[16] we decided to reinvestigate this challenging coupling reaction by fine-tuning of the base source, solvent, ligand, and palladium. The results of this study are now reported.

RESULTS AND DISCUSSION

Initially, the reaction of **2a** (1.2 equiv) with **3a** (1 equiv) under previously reported conditions ($PdCl_2(MeCN)_2$/dppp, Cs_2CO_3, 1,4-dioxane, 100 °C, entry 2)[15] provided **4a** in a low 28% yield (Table 1). This coupling was inefficient and resulted in concomitant formation of the desired compound **4a** and two other byproducts: (i) the Bamford–Stevens[17] alkene **5a**, derived from the evolution of the diazo compound generated from the hydrazone **2a**, and (ii) sulfone **6a** which resulted from decomposition of sulfonylhydrazone. On the basis of the results obtained in entries 2, $PdCl_2(MeCN)_2$ was fixed as the source of palladium, then, we started screening a variety of bases.[18] We were delighted to find that the use of alkoxide bases such as LiOMe, LiO-*t*-Bu or NaO-*t*-Bu leads to improvement of performance of the coupling reaction with yields up to 56% (entries 3–7). With NaO-*t*-Bu[19] as the base, the screening reactions with respect to the solvent revealed that the use of fluorobenzene is superior to all other choices, providing **4a** in 70% yield (entry 12); in this case, byproduct alkene **5a** was not detected by ^{1}H NMR analysis. Other solvents[18] such as toluene, dimethoxyethane (DME), or cyclopentyl methyl ether (CPME) were also effective, albeit affording **4a** with slightly reduced yield. As summarized in Table 1, screening of phosphine ligands revealed that these latter play an important role in the outcome of this transformation. Reactions using other bidentate ligands such as DPEPhos (L5), Xantphos (L6), and dppf (L8) were less efficient than dppp (L7) (compare entries 13 and 14–15). Based on these results, we turned to the use of monodentate biaryl phosphine (Buchwald ligands). The reaction with CyJohnPhos (L3) gave the desired coupling product **4a** in a moderate yield (64%, entry 16), while no reaction occurred with the bulky, electron-rich monodentate phosphine ligand *tert*-butylXphos (L2) (entry 17); in the latter case, the sulfone **6a** became the major product. The use of XPhos (L1) led to the best result, and the desired product **4a** was isolated in a nearly quantitative 96% yield (entry 19). One can note that DavePhos (L4) was also effective, albeit furnishing **4a** with slightly diminished yield (entry 18). Changing the palladium source from $PdCl_2(MeCN)_2$ to Pd_2dba_3 induced a slightly lowering of the reaction yield (compare entries 19 and 20). Entry 21 confirmed the crucial role of NaO-*t*-Bu in this coupling, since its replacement by LiO-*t*-Bu led to a dramatic decrease in the yield. The influence of the temperature was also investigated, and it was confirmed that reactions run at 100 °C gave the best results. Performing the reaction under atmospheric pressure led to **4a** in a similar yield (90%), but 6 h was needed to accomplish the reaction. Finally, reduction of the catalytic loading to 2 mol % of $PdCl_2(MeCN)_2$ and 4 mol % of L1 furnished **4a** in a 90% isolated yield. As a result, the combination of $PdCl_2(MeCN)_2$ (2 mol %), XPhos (4 mol %), NaO-*t*-Bu (3 equiv), and PhF in a sealed tube at 100 °C was fixed as optimal condition.[20] A control experiment revealed that both palladium catalyst and ligand were necessary for the coupling to occur as no coupling product could be formed in the absence of $PdCl_2(MeCN)_2$ or XPhos. It should be noted that the coupling of hydrazone **2a** with aryl halide **3a** is not limited to a small scale (1.25 mmol) as it could be conveniently performed on a 2 g scale for **2a** (5.29 mmol), giving rise **4a** in 92% yield.

With optimal conditions in hand, we subsequently investigated the substrate scope for the Pd-catalyzed coupling of sterically hindered *N*-tosylhydrazone **2a** with various aryl halides possessing different steric and electronic properties. As shown in Table 2, the reaction proceeded smoothly with aryl iodides, bromides, or chlorides having *ortho*-, *meta*-, and *para*-substituents on the aryl ring to give the corresponding products **4b–d** in 72–97% isolated yields (entries 1–7). The reaction displays little dependence upon electronic nature and position of the substituent on the aromatic ring. Electron-rich and electron-poor aryl halides all reacted completely and effectively within 2 h (Table 2, entries 4–13). Additionally, we successfully coupled hydrazone **2a** with 4-iodo-1-methoxy-2-(methoxymethoxy)benzene **3o** and 4-bromo-2-fluoro-1-methoxybenzene **3p**, giving rise to olefins **4k** and **4l**, respectively, which share structural similarity with *iso*CA-4 and *iso*FCA-4, two vascular disrupting agents recently identified by us.[14] Entries 17 and 18 illustrate examples of coupling reactions between hydrazone **2a** with heteroaryl halides, furnishing the corresponding products **4n,o** in good isolated yields.

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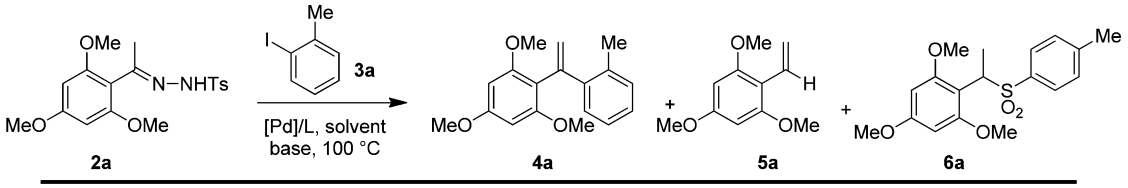
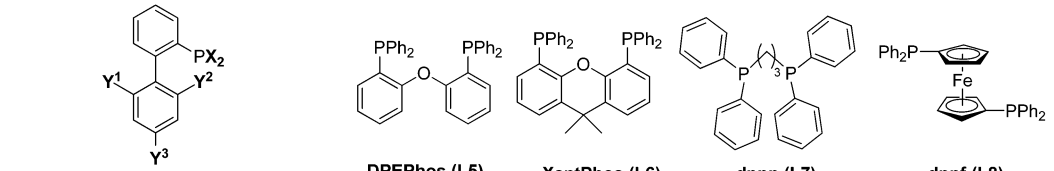
Table 1. Optimization Coupling Reaction of Sterically Hindered *N*-Tosylhydrazones 2a with 4-Iodotoluene 3a under Various Conditions[a]





DPEPhos (L5) XantPhos (L6) dppp (L7) dppf (L8)

X = Cy, $Y^1 = Y^2 = Y^3$ = *i*-Pr : **XPhos (L1)**
X = *t*-Bu, $Y^1 = Y^2 = Y^3$ = *i*-Pr : ***t*-ButylXPhos (L2)**
X = Cy, $Y^1 = Y^2 = Y^3$ = H : **CyJohnPhos (L3)**
X = Cy, $Y^1 = NMe_2$, $Y^2 = Y^3$ = H : **DavePhos (L4)**

entry	[Pd]	L	solvent	base	ratio **4a**/**5a**/**6a**[b]	yield[c] (%)
1	**Pd_2dba_3**	L1	dioxane	LiO-*t*-Bu	30/65/5	15[d]
2	**$PdCl_2(MeCN)_2$**	L7	dioxane	Cs_2CO_3	50/40/10	28
3	$PdCl_2(MeCN)_2$	L7	dioxane	**LiOH**	55/45/0	48
4	$PdCl_2(MeCN)_2$	L7	dioxane	**LiOMe**	48/52/0	40
5	$PdCl_2(MeCN)_2$	L7	dioxane	**KO-*t*-Bu**	50/15/35	38
6	$PdCl_2(MeCN)_2$	L7	dioxane	**LiO-*t*-Bu**	57/43/0	50
7	$PdCl_2(MeCN)_2$	L7	dioxane	**NaO-*t*-Bu**	65/15/20	56
8	$PdCl_2(MeCN)_2$	L7	**DCE**	NaO-*t*-Bu	35/30/35	29
9	$PdCl_2(MeCN)_2$	L7	**Toluene**	NaO-*t*-Bu	63/5/32	57
10	$PdCl_2(MeCN)_2$	L7	**DME**	NaO-*t*-Bu	65/5/30	61
11	$PdCl_2(MeCN)_2$	L7	**CPME**	NaO-*t*-Bu	72/0/28	65
12	$PdCl_2(MeCN)_2$	**L7**	**PhF**	NaO-*t*-Bu	77/0/23	70
13	$PdCl_2(MeCN)_2$	**L5**	PhF	NaO-*t*-Bu	60/15/25	54
14	$PdCl_2(MeCN)_2$	**L6**	PhF	NaO-*t*-Bu	45/45/10	37
15	$PdCl_2(MeCN)_2$	**L8**	PhF	NaO-*t*-Bu	64/12/24	59
16	$PdCl_2(MeCN)_2$	**L3**	PhF	NaO-*t*-Bu	70/15/15	64
17	$PdCl_2(MeCN)_2$	**L2**	PhF	NaO-*t*-Bu	0/35/65	0
18	$PdCl_2(MeCN)_2$	**L4**	PhF	Na-O-*t*Bu	93/7/0	88
19	**$PdCl_2(MeCN)_2$**	**L1**	**PhF**	**NaO-*t*-Bu**	98/2/0	**96**[e,f]
20	Pd_2dba_3	**L1**	PhF	NaO-*t*-Bu	88/7/5	82
21	Pd_2dba_3	**L1**	PhF	LiO-*t*-Bu	67/23/10	59

[a]The reactions were carried out in a sealed tube with **2a** (1.2 mmol), **3a** (1 mmol), [Pd] (5 mol %), ligand (10 mol %), and base (3 equiv) at 100 °C in 4.0 mL of solvent. [b]Total conversion of **2a** was observed in all cases. Ratio was determined by ^{1}H NMR in the crude reaction mixture, see the Supporting Information. [c]Isolated yield of **4a**. [d]When the reaction was carried out at atmospheric pressure, **4a** was isolated in a 17% yield. [e]Performing the reaction in the presence of $PdCl_2(MeCN)_2$ (2 mol %) and **L1** (4 mol %) led to 90% of **4a**. [f]A 92% (1.38 g) yield of **4a** was obtained when the reaction was carried out on a 2.0 g scale of tosylhydrazone **2a** at atmospheric pressure.

In order to gauge the performance of this catalytic system, the substrate scope with respect to the sterically hindred *N*-tosylhydrazone components has been investigated. As depicted in Table 3, the coupling of pentamethyl-1,2,3,4-tetrahydronaphthalene hydrazone **2b** with 4-iodoanisole **3f** furnished the expected 1,1-diarylethylene **4p** in 76% yield (entry 1). One can note that compound **4p** may be regarded as an analogue of bexarotene (Targretin), an oral antineoplastic agent indicated for cutaneous T cell lymphoma.[21] The results of entries 2 and 3 revealed that the electronic character of the *N*-tosylhydrazone coupling partner did not influence the outcome of the reaction, as component **2c** also reacts successfully, providing the 1,1-diarylethylene products **4q,r** in excellent yields. It is noteworthy that an *ortho* chlorine atom on the aromatic ring is tolerated, enabling further derivatizations through metal-catalyzed cross-coupling techniques. Interestingly, the coupling reaction is also effective even with more challenging *ortho*/*ortho*′-substituted substrates. Accordingly, the reaction of hydrazone **2d** with 2-iodo-1,3,5-trimethylbenzene **3u** gave the expected olefin **4s** in a good 86% yield (entry 4). More interestingly, by increasing the steric hindrance in the hydrazone component, the reaction of **2a** with **3u** still can be performed, giving rise in a moderate 40% yield the 1,1-diarylolefin **4t** featuring *ortho*/*ortho*′-substituents on both of the aromatic rings (entry 5). The effectiveness of our protocol is not restricted to *N*-tosylhydrazones having an *ortho*-substituent on the aromatic ring. Substrates **2e−g** containing a secondary carbon atom alpha to the hydrazone function were also successfully coupled with 4-iodoanisole **3f** to provide tetrasubstituted olefins **4w** and olefins **4u−v** having a cycloalkylidene unit in good yields (entries 6−8). It should be noted that with respect to the reaction yield, this protocol proved to be more efficient than our previously reported

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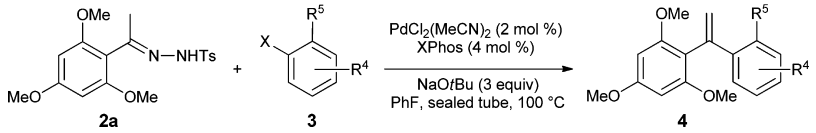
Table 2. Palladium-Catalyzed Coupling of Sterically Hindered *N*-Tosylhydrazone 2a with Various Aryl Halides 3b–s[a]



entry	aryl halide **3**	product	yield (%)[b]
1	**3b,** X = I	**4b**	93
2	**3c**, X = Br	**4b**	85
3	**3d**, X = Cl	**4b**	72
4	**3e**	**4c**	97
5	**3f,** X = I	**4d**	87
6	**3g**, X = Br	**4d**	80
7	**3h**, X = Cl	**4d**	78
8	**3i**	**4e**	96[c]
9	**3j**	**4f**	85
10	**3k**	**4g**	73
11	**3l**	**4h**	52
12	**3m**	**4i**	56
13	**3n**	**4j**	96
14	**3o**	**4k**	93
15	**3p**	**4l**	74
16	**3q**	**4m**	76
17	**3r**	**4n**	63
18	**3s**	**4o**	72

[a]The reactions were carried out in a sealed tube with 2a (1.2 mmol), 3a (1 mmol), [Pd] (2 mol %), Ligand (4 mol %), base (3 equiv) at 100 °C in 4.0 mL of PhF. [b]Yield of isolated product. [c]A 94% (1.43 g) yield of **4e** was obtained when the reaction was carried out on a 2.0 g scale of tosylhydrazone **2a** at atmospheric pressure.

one.[15a] Finally, in hope of further pushing the limit of the degree of steric hindrance of the *N*-tosylhydrazone, we examined the reaction with substrate **2h** possessing both, an *ortho* substituent on the aromatic ring, and a secondary carbon atom alpha to the hydrazine function. Accordingly, we found that if the coupling of **2h** with 2-iodoanisole **3b** failed due to the strong steric hindrance of the two coupling partners (entry 9), the reaction of the same substrate **2h** with 4-bromoanisole **3c** proved to be highly efficient giving rise the desired product **4y** in a 76% isolated yield (entry 10).

Since we had successfully succeeded in coupling *N*-tosylhydrazone **2c** having an *ortho* chorine atom, we undertake to illustrate the potential of this reaction by achieving the coupling of the remaining C–Cl bond through an intramolecular C–O bond-forming process, giving rise to 9-methylenexanthene derivatives. Thus, reaction of **2c** with **3t** under our optimized conditions furnished after removal of the OMOM-protecting group olefin **4z** in a 80% yield (Scheme 3). Next, compound **4z** was subjected to Buchwald–Hartwig coupling by using our optimized conditions; however, 9-methylenexanthene derivative **7** formed could not be isolated as it decomposes during the purification step.[22] To circumvent this problem, we instead considered a one-pot Buchwald–Hartwig coupling followed by a catalytic hydrogenation of the C=C double bond. In a typical experiment, after achieving the intramolecular coupling process, the resulting crude product was treated with Pd/C in AcOEt under hydrogen atmosphere. Thus, under these conditions, we were pleased to observe that the reaction worked very well and provided the desired 3-methoxy-9-methylxanthene **8** in a 56% overall yield (Scheme 3). One can note that in a preliminary result compound **8** could also be synthesized from diaryl ether **9** through an intramolecular *N*-tosylhydrazone coupling with aryl bromide and further reduction of the C=C double bond in a 31% overall yield, despite the fact that the reaction conditions had never been optimized (Scheme 3).

■ CONCLUSION

In summary, we have succeeded in developing an efficient catalytic system for the Pd-catalyzed cross-coupling reaction of sterically encumbered *N*-tosylhydrazones containing an *ortho*/*orho'*-substituent on the aromatic ring. This system overcomes many of the important limitations encountered with highly sterically *N*-tosylhydrazone Pd-coupling processes. The steric

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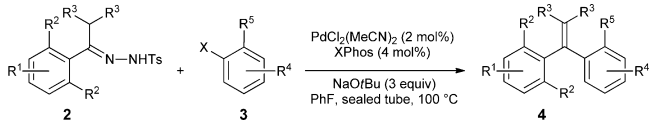
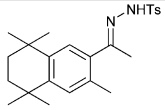
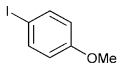
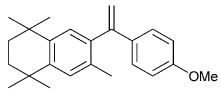
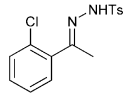
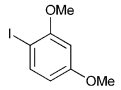
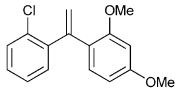
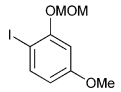
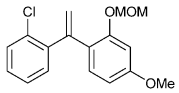
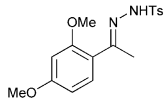
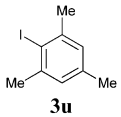
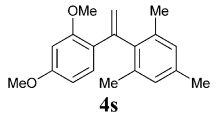
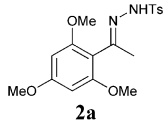
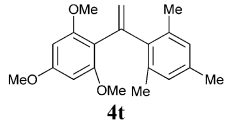
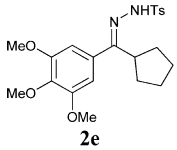
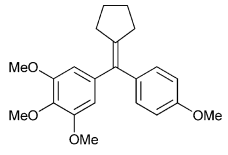
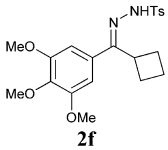
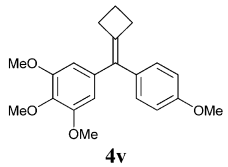
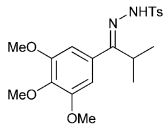
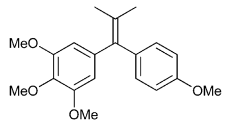
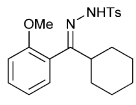
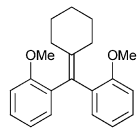
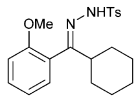
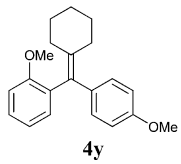
Table 3. Coupling of Various Sterically Hindered *N*-Tosylhydrazones 2a–h with Aryl Halides 3[a]



2 3 4

entry	hydrazone 1	aryl halide 2	product	yield (%)[b]
1	 **2b**	 **3f**	 **4p**	76
2	 **2c**	 **3n**	 **4q**	87
3	**2c**	 **3t**	 **4r**	93[c]
4	 **2d**	 **3u**	 **4s**	86
5	 **2a**	**3u**	 **4t**	40
6	 **2e**	**3f**	 **4u**	91[d]
7	 **2f**	**3f**	 **4v**	86[d]
8	 **2g**	**3f**	 **4w**	84[d]
9	 **2h**	**3b**	 **4x**	0[e]
10	 **2h**	**3c**	 **4y**	76

[a]The reactions were carried out in a sealed tube with **2** (1.2 mmol), **3** (1 mmol), [Pd] (2 mol %), ligand (4 mol %), and base (3 equiv) at 100 °C in 4.0 mL of PhF. [b]Yield of isolated product. [c]A 93% (1.75 g) yield of **4r** was obtained when the reaction was carried out on a 2.0 g scale of tosylhydrazone **2c** at atmospheric pressure. [d]**4u** was obtained in 68% isolated yield, **4v** in 80% isolated yield, and **4w** in 64% isolated yield by using our initial conditions ($PdCl_2(MeCN)_2$/dppp, Cs_2CO_3, 1,4-dioxane, 100 °C, entry 2, Table 1).[15a] [e]No reaction is observed even when using high catalyst loading of $PdCl_2(MeCN)_2$ (15 mol %), XPhos (30 mol %).

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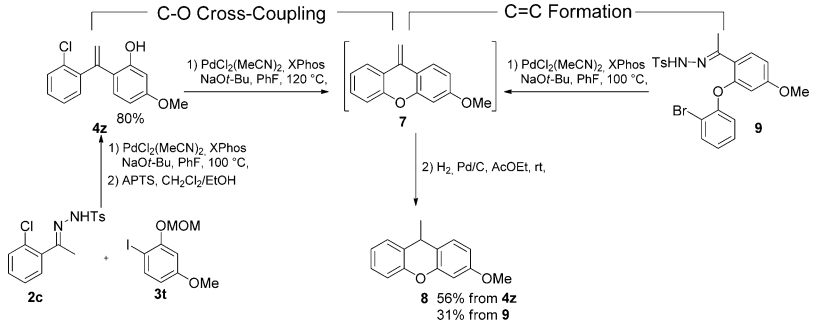
Scheme 3. Synthesis of 3-Methoxy-9-methylxanthene Derivative 8



hindrance effect on the outcome of the reaction was studied both on the aryl moiety of the *N*-tosylhydrazone, and on the aryl halide partner. The catalytic system based on $PdCl_2(MeCN)_2$/Xphos/NaO-*t*-Bu/F-benzene in a sealed tube is very general with regard to both coupling partners, and coupling occurs with good to excellent yields in most of the studied cases.

EXPERIMENTAL SECTION

General Methods. Solvent peaks were used as reference values, with $CDCl_3$ at 7.26 ppm for ^1H NMR and 77.16 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 under a UVP Mineralight UVGL-58 lamp (254 nm) and 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 *Purification of Laboratory Chemicals*.[23] Organic extracts were, in general, dried over $MgSO_4$ or Na_2SO_4. All products reported showed ^1H and ^{13}C NMR spectra in agreement with the assigned structures.

General Procedure for Preparation of Hydrazones.[24] To a rapidly stirred suspension of *p*-toluenesulfonohydrazide (5 mmol) in dry methanol (10 mL) at 60 °C was added the ketone (5 mmol) dropwise. Within 5−60 min, the *N*-tosylhydrazone began to precipitate. The mixture was cooled to 0 °C, and the product was collected on a Büchner funnel, washed with petroleum ether, and then dried in vacuo to afford the pure product.

*(E)-4-Methyl-N′-(1-(2,4,6-trimethoxyphenyl)ethylidene)-benzenesulfonohydrazide (**2a**):* white solid (1.68 g, 89% yield); mp 197−199 °C; TLC R_f = 0.26 (EtOAc/cyclohexane, 3/7, SiO_2); IR (neat, cm^{-1}) 3190, 1606, 1583, 1496, 1456, 1415, 1382, 1337, 1186, 1156, 1126, 1049, 911; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.82 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.11 (s, 2H), 3.84 (s, 3H), 3.63 (s, 6H), 2.46 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.1 (C), 157.4 (2C), 151.4 (C), 143.5 (C), 136.4 (C), 129.4 (2CH), 128.0 (2CH), 103.2 (C), 91.0 ($2CH_3$), 55.8 ($2CH_3$), 55.7 (CH_3), 23.9 (CH_3), 21.7 (CH_3); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{18}H_{22}N_2NaO_5S$ 401.1142, found 401.1137.

*(E)-4-Methyl-N′-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)ethylidene)benzenesulfonohydrazide (**2b**):* white solid (1.67 g, 81% yield); mp 223−225 °C; TLC R_f = 0.49 (EtOAc/cyclohexane, 3/7, SiO_2); IR (neat) 3196, 2961, 2362, 1497, 1380, 1340, 1168, 1092, 1060, 899, 812; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.78 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.19 (s, 1H), 7.13 (s, 1H), 6.66 (s, 1H), 2.45 (s, 3H), 2.12 (s, 3H), 1.94 (s, 3H), 1.67 (s, 4H), 1.29 (m, 6H), 1.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.9 (C), 146.8 (C), 144.1 (C), 144.0 (C), 135.9 (C), 131.1 (C), 130.9 (C), 129.7 (2CH), 129.3 (CH), 127.9 (2CH), 124.0 (CH), 35.0 (CH_2), 35.0 (CH_2), 34.4 (C), 34.2 (C), 32.0 ($2CH_3$), 31.9 ($2CH_3$), 25.0 (CH_3), 21.8 (CH_3), 18.4 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{24}H_{33}N_2O_2S$ 413.2257, found 413.2235.

*(Z/E)-N′-(1-(2,4-Dimethoxyphenyl)ethylidene)-4-methylbenzene-sulfonohydrazide (**2d**):* white solid (1.60 g, 92% yield); mp 147−149 °C; TLC R_f = 0.44 (EtOAc/cyclohexane, 3/7, SiO_2); IR (neat) 1596, 1506, 1468, 1209, 1186, 1161, 1033; The presence of *Z*/*E* isomers in a ratio 2:1 complicates the NMR spectroscopic data. Data for major *Z* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80 (d, J = 8.3 Hz, 2H), 7.46 (bs, 1H), 7.31 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 6.52 (dd, J = 8.4, 2.3 Hz, 1H), 6.46 (d, J = 2.2 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 2.43 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (ppm) 162.3 (C), 156.4 (C), 153.3 (C), 143.8 (C), 136.1 (C), 129.6 (CH), 129.5 (2CH), 128.0 (2CH), 115.2 (C), 106.0 (CH), 99.3 (CH), 55.7 ($2CH_3$), 25.0 (CH_3), 21.7 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{17}H_{21}N_2O_4S$ 349.1222, found 349.1206.

*(E)-N′-(Cyclohexyl(2-methoxyphenyl)methylene)-4-methylbenze-nesulfonohydrazide (**2h**):* white solid (1.45g, 75% yield); mp 123−125 °C; TLC R_f = 0.48 (EtOAc/cyclohexane, 3/7, SiO_2); IR (neat, cm^{-1}) 2928, 2853, 2364, 1597, 1490, 1451, 1382, 1341, 1290, 1242, 1167, 1093, 1020, 990, 908, 814; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.79 (d, J = 8.3 Hz, 2H), 7.41−7.28 (m, 3H), 7.14 (s, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.82 (dd, J = 7.5, 1.7 Hz, 1H), 3.59 (s, 3H), 2.45 (s, 3H), 2.41−2.26 (m, 1H), 1.84−1.51 (m, 4H), 1.32−1.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2 (C), 155.6 (C), 143.7 (C), 136.0 (C), 131.1 (CH), 129.4 (2CH), 128.6 (2CH), 128.1 (2CH), 121.6 (C), 121.5 (CH), 111.5 (CH), 55.5 (CH_3), 45.9 (CH_3), 30.1 ($2CH_2$), 26.1 ($2CH_2$), 21.8 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{21}H_{27}N_2O_3S$ 387.1742, found 387.1730.

Typical Procedure for Pd-Catalyzed *N*-Tosylhydrazones Coupling with Aryl Halides. *N*-Tosylhydrazone (1.2 mmol), $PdCl_2(MeCN)_2$ (0.02 mmol, 2 mol %), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (0.04 mmol, 4 mol %), and 4 mL of PhF were mixed under argon for 5 min at rt. NaO-*t*-Bu (3.0 mmol) was then added, the reaction mixture was stirred for an additional 1 min, and finally, aryl halide (1.0 mmol) was added. The resulting mixture was stirred at 100 °C in a sealed tube for 1−2 h until completion of reaction as judged by TLC analysis. 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 reduced pressure, and the crude residue was purified by flash chromatography on silica gel.

*1,3,5-Trimethoxy-2-(1-(o-tolyl)vinyl)benzene (**4a**).* After 2 h at 100 °C in a sealed tube, compound **4a** was obtained as a white solid (256 mg, 90% yield), mp 72−74 °C. A 92% (1.38 g) yield of **4a** was obtained when the reaction was carried out on a 2.0 g scale of tosylhydrazone **2a** at atmospheric pressure for 4 h: TLC R_f = 0.59 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat) 1603, 1581, 1494, 1453, 1413, 1334, 1224, 1203, 1161, 1125, 1036, 950, 908, 811; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)7.22−7.15 (m, 1H), 7.14−7.01 (m, 3H), 6.14 (s, 2H), 5.47 (d, J = 2.2 Hz, 1H), 5.41 (d, J = 2.2 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.5 (C), 158.6 (2C), 143.3 (C), 141.6 (C), 135.3 (C), 130.2 (CH), 129.1 (CH), 126.4 (CH), 125.2 (CH), 120.6 (CH_2), 114.4 (C),

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91.2 (2CH), 56.0 ($2CH_3$), 55.4 (CH_3), 20.2 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{18}H_{21}O_3$ 285.1485, found 285.1476.

*1,3,5-Trimethoxy-2-(1-(2-methoxyphenyl)vinyl)benzene (**4b**).* After 1 h at 100 °C in a sealed tube, compound **4b** was obtained as a white solid (279 mg, 93% yield): mp 98−100 °C; TLC R_f = 0.44 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}): 2835; 2359, 2329, 1605, 1583, 1490, 1466, 1453, 1434, 1412, 1335, 1282, 1243, 1224, 1203, 1182, 1160, 1124, 1052, 1026, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.15 (td, J = 7.7, 1.7 Hz, 1H), 7.05 (dd, J = 7.6, 1.7 Hz, 1H), 6.92−6.76 (m, 2H), 6.17 (s, 2H), 6.03 (d, J = 2.4 Hz, 1H), 5.41 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.3 (C), 158.7 (2C), 157.5 (C), 138.1 (C), 131.2 (C), 130.0 (CH), 127.8 (CH), 120.8 (CH_2), 120.4 (CH), 114.6 (C), 111.6 (CH), 91.1 (2CH), 56.1 ($2CH_3$), 55.8 (CH_3), 55.4 (CH_3); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{18}H_{20}NaO_4$ 323.1254, found 323.1255.

*1,3,5-Trimethoxy-2-(1-(3-methoxyphenyl)vinyl)benzene (**4c**).* After 1 h at 100 °C in a sealed tube, compound **4c** was obtained as a colorless oil (291 mg, 97% yield): TLC R_f = 0.49 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 2939, 2836, 2361, 2018, 1603, 1577, 1499, 1487, 1467, 1453, 1412; 1335, 1284, 1224, 1203, 1184, 1158, 1123, 1050, 1037, 950. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.17 (t, J = 7.9 Hz, 1H), 6.96−6.88 (m, 2H), 6.77 (dd, J = 8.1, 1.7 Hz, 1H), 6.20 (s, 2H), 5.95 (d, J = 1.4 Hz, 1H), 5.21 (d, J = 1.3 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.8 (C), 159.6 (C), 158.9 (2C), 142.6 (C), 141.1 (2C), 129.0 (CH), 118.7 (CH), 116.7 (CH_2), 112.5 (CH), 111.9 (CH), 91.1 (2CH), 56.2 ($2CH_3$), 55.5 (CH_3), 55.3 (CH_3); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{18}H_{20}NaO_4$ 323.1254, found 323.1246.

*1,3,5-Trimethoxy-2-(1-(4-methoxyphenyl)vinyl)benzene (**4d**).* After 1 h at 100 °C in a sealed tube, compound **4d** was obtained as a white solid (261 mg, 87% yield): mp 121−123 °C; TLC R_f = 0.61 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}): 3185, 2999, 2837, 2358, 2181, 2131, 1603, 1582, 1511, 1467, 1454, 1412, 1335, 1247, 1225, 1204, 1181, 1160, 1123, 1052, 1033, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 6.21 (s, 2H), 5.86 (d, J = 1.5 Hz, 1H), 5.10 (d, J = 1.5 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.70 (C), 159.04 (C), 158.84 (2 C), 140.64 (C), 133.51 (C), 127.12 (2 CH), 114.36 (CH_2), 113.5 (2CH), 112.8 (C), 91.2 (2CH), 56.2 ($2CH_3$), 55.5 (CH_3), 55.3 (CH_3); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{18}H_{20}NaO_4$ 323.1254, found 323.1244.

*2-(1-(2-Fluorophenyl)vinyl)-1,3,5-trimethoxybenzene (**4e**).* After 2 h at 100 °C in a sealed tube, compound **4e** was obtained as a white solid (276 mg, 96% yield); mp 72−74 °C; A 94% (1.43 g) yield of **4e** was obtained when the reaction was carried out on a 2.0 g scale of tosylhydrazone **2a** at atmospheric pressure for 4 h: TLC R_f = 0.53 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat) 1584, 1225, 1204, 1157, 1127, 905, 812; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.21−6.83 (m, 4H), 6.18 (s, 2H), 5.97 (d, J = 1.5 Hz, 1H), 5.45 (d, J = 1.6 Hz, 1H), 3.84 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.7 (C), 160.6 (d, J = 258.2 Hz, C) 158.8 (2C), 135.8 (C), 130.0 (d, J = 3.2 Hz, CH), 129.6 (d, J = 11.9 Hz, C), 128.2 (d, J = 8.4 Hz, CH), 123.6 (d, J = 3.3 Hz, CH), 121.7 (d, J = 7.4 Hz, CH_2), 115.8 (d, J = 23.3 Hz, CH), 113.1 (C), 91.1 (2CH), 56.1 (2 CH_3), 55.5 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) −113.9; HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{17}H_{18}FO_3$ 289.1234, found 289.1223.

*2-(1-(4-Fluorophenyl)vinyl)-1,3,5-trimethoxybenzene (**4f**).* After 1 h at 100 °C in a sealed tube, compound **4f** was obtained as a white solid (245 mg, 85% yield): mp 61−63 °C; TLC R_f = 0.47 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 2835, 2361, 2329, 1603, 1584, 1508, 1467, 1454, 1413, 1336, 1225, 1204, 1160, 1125, 1052, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38−7.19 (m, 2H), 6.93 (t, J = 8.7 Hz, 2H), 6.21 (s, 2H), 5.87 (d, J = 1.0 Hz, 1H), 5.18 (d, J = 1.0 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.2 (C, d, J = 245.7 Hz), 160.9 (C), 158.8 (2C), 140.3 (C), 137.2 (C, d, J = 3.3 Hz), 127.6 (2CH, d, J = 7.7 Hz), 116.2 (CH_2), 114.9 (2CH, d, J = 21.4 Hz), 112.3 (C), 91.1 (2CH), 56.1 ($2CH_3$), 55.5 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) −114.2; HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{17}H_{18}FO_3$ 289.1234, found 289.1231.

*1,3,5-Trimethoxy-2-(1-(4-(trifluoromethyl)phenyl)vinyl)benzene (**4g**).* After 1 h at 100 °C in a sealed tube, compound **4g** was obtained as a colorless oil (247 mg, 73% yield): TLC R_f = 0.47 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 2839, 1604, 1583, 1497, 1468, 1455, 1413, 1322, 1225, 1204, 1160, 1125, 1108, 1079, 1064, 1037, 1014, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.21 (s, 2H), 5.99 (d, J = 1.2 Hz, 1H), 5.32 (d, J = 1.2 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.1 (C), 158.9 (2C), 144.9 (C), 140.2 (C), 129.0 (C, q, J = 32.1 Hz), 126.2 (2CH), 125.1 (2CH, q, J = 3.6 Hz), 124.6 (C, q, J = 271.6 Hz), 118.7 (CH_2), 111.6 (C), 91.1 (2CH), 56.1 ($2CH_3$), 55.5 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) −62.8; HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{18}H_{18}F_3O_3$ 339.1203, found 339.1193.

*tert-Butyl 4-(1-(2,4,6-Trimethoxyphenyl)vinyl)benzoate (**4h**).* After 1 h at 100 °C in a sealed tube, compound **4h** was obtained as yellow oil (192 mg, 52% yield): TLC R_f = 0.64 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}): 2360, 1704 1605, 1583, 1495, 1454, 1412, 1368, 1336, 1294, 1255, 1204, 1162, 1140, 1125, 1106, 1052, 1037, 1016, 950, 907, 864, 849, 813; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.87 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 6.20 (s, 2H), 6.00 (d, J = 1.3 Hz, 1H), 5.30 (d, J = 1.3 Hz, 1H), 3.86 (s, 3H), 3.67 (s, 6H), 1.58 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.0 (C), 161.0 (C), 158.9 (2C), 145.4 (C), 140.7 (C), 130.6 (C), 129.4 (2CH), 125.8 (2CH), 118.4 (CH_2), 111.9 (C), 91.1 (2CH), 80.8 (C), 56.1 ($2CH_3$), 55.5 (CH_3), 28.4 ($3CH_3$); (ESI) $(M + H)^+$ m/z calcd for $C_{22}H_{27}O_5$ 371.1858, found 371.1877.

*4-(1-(2,4,6-Trimethoxyphenyl)vinyl)benzonitrile (**4i**).* After 2 h at 100 °C in a sealed tube, compound **4i** was obtained as a white solid (165 mg, 56% yield): mp 102−104 °C; TLC R_f = 0.47 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 2837, 2224, 1604, 1583, 1468, 1454, 1416, 1336, 1226, 1204, 1161, 1124, 1052, 1036, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.53 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 6.20 (s, 2H), 5.99 (d, J = 1.1 Hz, 1H), 5.37 (d, J = 1.0 Hz, 1H), 3.86 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.3 (C), 158.8 (2C), 146.1 (C), 140.0 (C), 132.1 (2CH), 126.6 (2CH), 119.8 (CH_2), 119.4 (C), 110.5 (C), 91.0 (2CH), 56.0 ($2CH_3$), 55.5 (CH_3); (ESI) $(M + Na)^+$ m/z calcd for $C_{18}H_{17}NNaO_3$ 318.1101, found 318.1096.

*2-(1-(2,4-Dimethoxyphenyl)vinyl)-1,3,5-trimethoxybenzene (**4j**).* After 1 h at 100 °C in a sealed tube, compound **4j** was obtained as a white solid (317 mg, 96% yield): mp 115−117 °C; TLC R_f = 0.33 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}):, 2836, 2253, 2177, 2158, 2017, 1605, 1583, 1570, 1504, 1466, 1453, 1413, 1335, 1295, 1259, 1225, 1205, 1160, 1125, 1076, 1035, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.92 (d, J = 8.5 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 6.35 (dd, J = 8.5, 2.4 Hz, 1H), 6.17 (s, 2H), 6.03 (d, J = 2.4 Hz, 1H), 5.31 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 6H), 3.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.3 (C), 159.6 (C), 158.7 (2C), 137.7 (C), 130.5 (CH), 123.7 (C), 119.2 (CH_2), 114.9 (C), 104.1(CH), 99.2 (CH), 91.1 (2CH), 56.2 ($2CH_3$), 55.7 (CH_3), 55.4 ($2CH_3$), 55.3 (CH_3); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{19}H_{22}NaO_5$ 353.1359, found 353.1360.

*1,3,5-Trimethoxy-2-(1-(4-methoxy-3-(methoxymethoxy)phenyl)-vinyl)benzene (**4k**).* After 1 h at 100 °C in a sealed tube, compound **4k** was obtained as a colorless oil (335 mg, 93% yield): TLC R_f = 0.28 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 2836, 1603, 1581, 1511, 1466, 1454, 1412, 1334, 1299, 1251, 1224, 1202, 1182, 1156, 1121, 1074, 1052, 1030, 982; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (d, J = 2.1 Hz, 1H), 6.85 (dd, J = 8.5, 2.1 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.20 (s, 2H), 5.86 (s, 1H), 5.19 (s, 2H), 5.10 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.70 (s, 6H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.7 (C), 158.8 (2C), 149.5 (C), 146.2 (C), 140.4 (C), 133.8 (C), 120.5 (CH), 114.8 (CH_2), 114.7 (CH), 112.5 (C), 111.3 (CH), 95.9 (CH_2), 91.1 (2CH), 56.2 (CH_3), 56.1 ($2CH_3$), 55.9 (CH_3), 55.4 (CH_3); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{20}H_{24}NaO_6$ 383.1465, found 383.1462.

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*2-(1-(3-Fluoro-4-methoxyphenyl)vinyl)-1,3,5-trimethoxybenzene (**4l**).* After 1 h at 100 °C in a sealed tube, compound **4l** was obtained as a white solid (235 mg, 74% yield): mp 120−122 °C; TLC R_f = 0.54 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}): 812, 875, 910, 950, 1026, 1052, 1109, 1126, 1158, 1183, 1204, 1225, 1271, 1300, 1335, 1413, 1454, 1467, 1515, 1582, 1603, 1728, 2839; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.13−6.95 (m, 2H), 6.83 (t, J = 8.8 Hz, 1H), 6.20 (s, 2H), 5.85 (d, J = 1.2 Hz, 1H), 5.13 (d, J = 1.2 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.9 (C), 158.8 (2C), 153.95 (C), 150.7 (C), 146.9 (C), 139.8 (C), 134.5 (C, d, J = 6.0 Hz), 121.7 (CH, d, J = 3.3 Hz), 115.6 (CH_2), 113.8 (CH, d, J = 19.0 Hz), 113.0 (CH, d, J = 2.2 Hz), 91.1 (2CH), 56.4 (CH_3), 56.2 ($2CH_3$), 55.5(CH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) −134.6; HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{18}H_{20}FO_4$ 319.1340, found 319.1331.

*2-(1-(2,4,6-Trimethoxyphenyl)vinyl)naphthalene (**4m**).* After 1 h at 100 °C in a sealed tube, compound **4m** was obtained as a white solid (243 mg, 76% yield): mp 106−108 °C; TLC R_f = 0.38 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 1604, 1583, 1498, 1466, 1453, 1413, 1335, 1225, 1203, 1159, 1126, 1051, 1037, 949; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80−7.71 (m, 3H), 7.66−7.57 (m, 2H), 7.46−7.32 (m, 2H), 6.25 (s, 2H), 6.09 (d, J = 1.2 Hz, 1H), 5.31 (d, J = 1.2 Hz, 1H), 3.89 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.9 (C), 159.0 (2C), 141.2 (C), 138.4 (C), 133.6 (C), 133.00 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 125.9 (CH), 125.6 (CH), 124.9 (CH), 124.4 (CH), 117.0 (CH_2), 112.6 (C), 91.2 (2CH), 56.2 ($2CH_3$), 55.5 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{21}H_{21}O_3$ 321.1485, found 321.1479.

*3-(1-(2,4,6-Trimethoxyphenyl)vinyl)pyridine (**4n**).* After 2 h at 100 °C in a sealed tube, compound **4n** was obtained as a white solid (171 mg, 63% yield): mp 74−76 °C; TLC R_f = 0.24 (EtOAc/cyclohexane, 5/5, SiO_2); IR (neat, cm^{-1}) 2839, 1604, 1583, 1497, 1468, 1455, 1413, 1322, 1225, 1204, 1160, 1125, 1108, 1079, 1064, 1037, 1014, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.56 (d, J = 1.6 Hz, 1H), 8.43 (dd, J = 4.8, 1.6 Hz, 1H), 7.58 (dt, J = 8.0, 2.0 Hz, 1H), 7.16 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 6.19 (s, 2H), 5.95 (d, J = 1.2 Hz, 1H), 5.30 (d, J = 1.2 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.2 (C), 158.8 (2C), 148.2 (CH), 147.8 (CH), 138.5 (C), 136.8 (C), 133.2 (CH), 123.0 (CH), 118.4 (CH_2), 111.1 (C), 91.0 (2CH), 56.0 ($2CH_3$), 55.5 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{16}H_{18}NO_3$ 272.1281, found 272.1288.

*1-Methyl-5-(1-(2,4,6-trimethoxyphenyl)vinyl)-1H-indole (**4o**).* After 2 h at 100 °C in a sealed tube, compound **4o** was obtained as a white solid (233 mg, 72% yield); mp 105−107 °C; TLC R_f = 0.43 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}): 2836, 1603, 1582, 1467, 1453, 1411, 1334, 1245, 1224, 1203, 1183, 1156, 1051, 1036, 950; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.50 (d, J = 1.4 Hz, 1H), 7.39 (dd, J = 8.6, 1.7 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 3.1 Hz, 1H), 6.41 (d, J = 3.1 Hz, 1H), 6.26 (s, 2H), 5.96 (d, J = 1.5 Hz, 1H), 5.15 (d, J = 1.5 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 3.71 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.6 (C), 158.9 (2C), 142.2 (C), 138.5 (C), 132.4 (C), 1289.0 (CH), 128.5 (C), 120.2 (CH), 118.6 (CH), 114.0 (CH_2), 113.8 (C), 108.8 (CH), 102.5 (CH), 91.2 (2CH), 56.3 ($2CH_3$), 55.5 (CH_3), 32.9 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{20}H_{22}NO_3$ 324.1594, found 324.1583.

*6-(1-(4-Methoxyphenyl)vinyl)-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene (**4p**).* After 2 h at 100 °C in a sealed tube, compound **4p** was obtained as a white solid (254 mg, 76% yield): mp 80−82 °C; TLC R_f = 0.69 (EtOAc/cyclohexane, 1/9, SiO_2) ; IR (neat) 1608, 1511, 1248, 1177, 1036, 897; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)7.00 (d, J = 8.9 Hz, 2H), 6.92 (s, 1H), 6.86 (s, 1H), 6.61 (d, J = 8.9 Hz, 2H), 5.42 (d, J = 1.6 Hz, 1H), 4.88 (d, J = 1.6 Hz, 1H), 3.58 (s, 3H), 1.77 (s, 3H), 1.49 (s, 4H), 1.09 (s, 6H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)159.2 (C), 149.3 (C), 144.0 (C), 142.2 (C), 139.1 (C), 133.8 (C), 133.0 (C), 128.1 (CH), 128.0 (CH), 127.9 (2CH), 113.7 (2CH), 112.9 (CH_2), 55.4 (CH_3), 35.4 ($2CH_2$), 34.1 (C), 34.0 (C), 32.1 ($4CH_3$), 20.0 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{24}H_{31}O$ 335.2369, found 335.2350.

*1-(1-(2-Chlorophenyl)vinyl)-2,4-dimethoxybenzene (**4q**).* After 1 h at 100 °C in a sealed tube, compound **4q** was obtained as pale yellow oil (238 mg, 87% yield): TLC R_f = 0.73 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat) 1605, 1573, 1503, 1466, 1435, 1300, 1262, 1208, 1165, 1082; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40−7.15 (m, 4H), 7.06 (d, J = 8.6 Hz, 1H), 6.45 (m, 2H), 5.79 (s, 1H), 5.39 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.5 (C), 158.4 (C), 144.6 (C), 142.3 (C), 132.7 (C), 131.2 (CH), 131.1 (CH), 129.6 (CH), 128.2 (CH), 126.4 (CH), 123.0 (C), 119.1 (CH_2), 104.4 (CH), 99.2 (CH), 55.7 (CH_3), 55.4 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{16}H_{16}ClO_2$ 275.0833, found 275.0834.

*1-(1-(2-Chlorophenyl)vinyl)-4-methoxy-2-(methoxymethoxy)-benzene (**4r**).* After 1 h at 100 °C in a sealed tube, compound **4r** was obtained as pale yellow oil (303 mg, 93% yield). A 93% (1.75 g) yield of **4r** was obtained when the reaction was carried out on a 2.0 g scale of tosylhydrazone **2c** at atmospheric pressure for 4 h: TLC R_f = 0.69 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}): 3198, 2177, 2116, 1607, 1573, 1503, 1471, 1432, 1298, 1217, 1153, 1120, 1071, 1007, 923; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39−7.10 (m, 5H), 6.64 (d, J = 2.5 Hz, 1H), 6.53 (dd, J = 8.5, 2.5 Hz, 1H), 5.71 (d, J = 1.7 Hz, 1H), 5.40 (d, J = 1.7 Hz, 1H), 4.95 (s, 2H), 3.80 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.5 (C), 155.5 (C), 144.9 (C), 142.2 (C), 132.7 (C), 131.2 (CH), 131.1 (CH), 129.7 (CH), 128.1 (CH), 126.4 (CH), 124.0 (C), 119.3 (CH_2), 106.5 (CH), 101.8 (CH), 94.4 (CH_2), 55.9 (CH_3), 55.5 (CH_3); HRMS (ESI) $(M + Na)^+$ m/z calcd for $C_{17}H_{17}ClNaO_3$ 327.0758, found 327.0740.

*2-(1-(2,4-Dimethoxyphenyl)vinyl)-1,3,5-trimethylbenzene (**4s**).* After 2 h at 100 °C in a sealed tube, compound **4s** was obtained as a yellow oil (243 mg, 86% yield): TLC R_f = 0.68 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 1605, 1571, 1503, 1291, 1257, 1209, 1160, 1112, 1069, 1033, 902; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.89 (s, 2H), 6.76 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.33 (dd, J = 8.6, 2.4 Hz, 1H), 6.13 (d, J = 2.4 Hz, 1H), 5.19 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.31 (s, 3H), 2.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9 (C), 159.2 (C), 143.2 (C), 140.5 (C), 136.2 (2C), 136.0 (C), 130.7 (CH), 128.2 (2CH), 121.9 (C), 117.9 (CH_2), 104.2 (CH), 99.4 (CH), 55.6 (CH_3), 55.4 (CH_3), 21.2 (CH_3), 20.2 ($2CH_3$); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{19}H_{23}O_2$ 283.1693, found 283.1684.

*2-(1-Mesitylvinyl)-1,3,5-trimethoxybenzene (**4t**).* After 2 h at 100 °C in a sealed tube, compound **4t** was obtained as a colorless solid (125 mg, 40% yield): mp 84−85 °C; TLC R_f = 0.68 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 2835, 1604, 1580, 1453, 1412, 1333, 1224, 1204, 1158, 1128, 1054, 952, 907; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.78 (s, 2H), 6.11 (s, 2H), 5.57 (d, J = 2.5 Hz, 1H), 5.32 (d, J = 2.5 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 6H), 2.24 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2 (C), 159.0 (2C), 140.4 (C), 139.1 (C), 136.4 (2C), 135.0 (C), 128.2 (2CH), 122.3 (CH_2), 91.4 (2CH), 55.9 ($2CH_3$), 55.4 (CH_3), 21.1 (CH_3), 20.4 ($2CH_3$); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{20}H_{25}O_3$ 313.1798, found 313.1784.

*5-(Cyclopentylidene(4-methoxyphenyl)methyl)-1,2,3-trimethoxybenzene (**4u**).*[15a] After 2 h at 100 °C in a sealed tube, compound **4u** was obtained as a colorless oil (322 mg, 91% yield): R_f = 0.42 (cyclohexane/EtOAc, 8/2, SiO_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.13 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.39 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.79 (s, 6H), 2.49−2.24 (m, 4H), 1.80−1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.7 (C), 152.7 (2C), 142.6 (2C), 139.4 (C), 135.6 (C), 132.5 (C), 130.0 (2CH), 113.2 (2CH), 106.4 (2CH), 60.8 (CH_3), 56.0 ($2CH_3$), 55.1 (CH_3), 33.4 (CH_2), 33.3 (CH_2), 26.9 (CH_2), 26.8 (CH_2); MS (APCI) $(M + H)^+$ m/z 355.5.

*5-(Cyclobutylidene(4-methoxyphenyl)methyl)-1,2,3-trimethoxybenzene (**4v**).*[15a] After 2 h at 100 °C in a sealed tube, compound **4v** was obtained as a colorless oil (292 mg, 86% yield): R_f = 0.39 (cyclohexane/EtOAc, 8/2, SiO_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.12 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.39 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.78 (s, 6H), 2.93 (t, J = 7.7 Hz, 4H), 2.05 (p, J = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.9 (C), 152.7 (2C), 139.6 (2C), 136.4 (C), 132.8 (C), 132.4 (C), 129.8 (2CH), 113.3 (2CH), 106.0 (2CH), 60.8 (CH_3), 55.9 ($2CH_3$), 55.1

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(CH_3), 32.3 (CH_2), 32.2 (CH_2), 26.8 (CH_2); MS (ESI) $(M + Na)^+$ m/z 363.4.

*1,2,3-Trimethoxy-5-(1-(4-methoxyphenyl)-2-methylprop-1-en-1-yl)benzene (**4w**).*[15a] After 2 h at 100 °C in a sealed tube, compound **4w** was obtained as a colorless oil (276 mg, 84% yield): R_f = 0.37 (cyclohexane/EtOAc, 8/2, SiO_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.07 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.33 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.79 (s, 6H), 1.80 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.8 (C), 152.6 (2C), 139.2 (C), 136.6 (C), 136.2 (C), 135.3 (C), 130.6 (2CH), 130.4 (C), 113.1 (2CH), 106.9 (2CH), 60.8 (CH_3), 56.0 ($2CH_3$), 55.1 (CH_3), 22.7 (CH_3), 22.4 (CH_3); MS (APCI) $(M + H)^+$ m/z 329.2.

*1-(Cyclohexylidene(4-methoxyphenyl)methyl)-2-methoxybenzene (**4y**).* After 2 h at 100 °C in a sealed tube, compound **4y** was obtained as a yellow oil (234 mg, 76% yield): TLC R_f = 0.74 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 2929, 2833, 1607, 1576, 1507, 1488, 1463, 1433, 1282, 1237, 1176, 1029, 993; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.20 (t, J = 7.8 Hz, 1H), 7.14−7.05 (m, 3H), 6.96−6.72 (m, 4H), 3.77 (s, 3H), 3.71 (s, 3H), 2.39−1.96 (m, 4H), 1.85−1.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.8 (C), 157.0 (C), 139.3 (C), 135.4 (C), 132.9 (C), 131.2 (CH), 130.6 (2CH), 129.8 (C), 127.7 (CH), 120.5 (CH), 113.1 (2CH), 111.5 (CH), 55.7 (CH_3), 55.3 (CH_3), 32.9 (CH_2), 31.7 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 27.0 (CH_2); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{21}H_{25}O_2$ 309.1855, found 309.1868.

*1,3,5-Trimethoxy-2-vinylbenzene (side product **5a**):*[25] colorless oil; TLC R_f = 0.60 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}) 1603, 1579, 1454, 1404, 1334, 1230, 1206, 1193, 1155, 1125, 1064, 1039, 1004, 952; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 6.90 (dd, J = 18.0, 12.2 Hz, 1H), 6.14 (s, 2H), 5.95 (dd, J = 18.0, 2.9 Hz, 1H), 5.31 (dd, J = 12.2, 2.9 Hz, 1H), 3.83 (s, 6H), 3.82 (s, 3H); MS (ESI) $(M + H)^+$ m/z 195.2.

*1,3,5-Trimethoxy-2-(1-tosylethyl)benzene (side product **6a**):* colorless oil; TLC R_f = 0.31 (EtOAc/cyclohexane, 2/8, SiO_2); IR (neat, cm^{-1}): 1608, 1587, 1494, 1418, 1285, 1227, 1206, 1121, 1087, 1066, 1037, 950, 918; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.54 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.02 (d, J = 2.0 Hz, 1H), 5.94 (d, J = 2.0 Hz, 1H), 5.00 (q, J = 7.3 Hz, 1H), 3.77 (s, 3H), 3.55 (s, 3H), 3.52 (s, 3H), 2.38 (s, 3H), 1.79 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.7 (C), 161.3 (C), 159.4 (C), 143.5 (C), 136.8 (C), 129.2 (2CH), 128.8 (2CH), 103.5 (C), 91.3 (2CH), 90.4 (CH), 58.0 (CH_3), 55.8 (CH_3), 55.4 (CH_3), 21.6 (CH_3), 13.0 (CH_3); MS (ESI) $(M + Na)^+$ m/z 373.2.

*3-Methoxy-9-methyl-9H-xanthene (**8**).* After purification by flash chromatography on silica gel, compound **8** was obtained as a yellow oil (purity = 96%) (126 mg, 56% yield): TLC R_f = 0.73 (cyclohexane, SiO_2); IR (neat, cm^{-1}) 2935, 1506, 1431, 1033, 958; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm) 7.36−7.30 (m, 1H), 7.23 (m, 2H), 7.07 (m, 2H), 6.70 (dd, J = 8.4, 2.6 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 4.09 (q, J = 7.0 Hz, 1H), 3.82 (s, 3H), 1.43 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm) 160.3 (C), 152.74 (C), 146.7 (C), 130.0 (CH), 129.5 (CH), 128.4 (CH), 127.7 (C), 124.2 (CH), 119.3 (C), 117.0 (CH), 110.9 (CH), 102.0 (CH), 55.7 (CH_3), 33.1 (CH), 27.9 (CH_3); HRMS (ESI) $(M + H)^+$ m/z calcd for $C_{15}H_{15}O_2$ 227.1072, found 227.1081.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details for experiments conditions; copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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