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Expeditious synthesis of 1,1-diarylethylenes related to *iso*combretastatin A-4 (*iso*CA-4) via palladium-catalyzed arylation of *N*-tosylhydrazones with aryl triflates

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ABSTRACT

A quick and efficient entry to 1,1-diarylethylenes via the reaction of polyoxygenated aryl *N*-tosylhydrazones with aryl triflates is described. The reaction employs the catalytic system $Pd(OAc)_2$/XPhos, *t*BuOLi as the base and dioxane as the solvent. A variety of substituents on both the coupling partners' hydrazones and triflates are tolerated. This procedure provides a complementary route to the existing methods for the access to 1,1-diarylethylenes of biological interest.

Combretastatins CA-4 and CA-1 are a very interesting class of cytotoxic agents of natural origin, which have received much attention due to their simple structures, their high potency as cytotoxic and antimitotic agents as well as their ability to selectively damage tumor neovasculature.[1] Despite their remarkable anticancer activities, these *Z*-stilbene compounds are prone to double bond isomerization during storage and administration.[2] The *E*-isomers display dramatically reduced inhibition of cancer cell growth and tubulin assembly.[3] A number of structure–activity relationships (SARs) have been reported for the combretastatins.[4] These studies revealed that the 3,4,5-trimethoxyphenyl unit as well as the cis orientation of the two aromatic rings are a prerequisite for significant biological activities. Therefore, extensive studies have been conducted to prepare various cis-restricted analogues by inserting mainly the *cis*-olefin in a five-membered heterocyclic ring (e.g., pyrazoles, thiazoles, triazoles, imidazoles, etc.).[5]

Our interest in 1,1-diarylethylene unit synthesis,[6,7] combined with our efforts to discover novel potent tubulin assembly inhibitors, related to CA-4,[8] led us to identify a promising class of substances with strong anticancer activities, simply by switching the trimethoxyphenyl nucleus from the C(1) to the C(2) position of the ethylene bridge.[9] In contrast to their natural parent combretastatins A, these synthetic isomers, named *iso*combretastatins A (*iso*CA), are easy to synthesize without the need to control the olefin geometry and constitute the simplest isomers of *iso*CA. The most active compound *iso*CA-4 appears to elicit its tumor cytotoxicity in a fashion similar to CA-4, via inhibition of tubulin polymerization, which then leads to cell cycle arrest in G2/M. As the replacement of the 1,2-ethylene bridge by the 1,1-ethylene one resulted in retention of biological activity, our finding encouraged us to use this bioisostere[10] in future structure–activity relationship studies. To this end, a set of compounds derived from the general structures **1** were considered (Fig. 1), and a versatile synthesis that

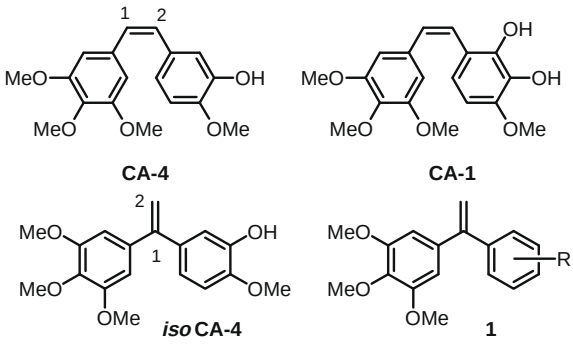

Figure 1. Combretastatins A-1, A-4, synthetic tubulin polymerization inhibitor *iso*CA-4 and target structure **1**.

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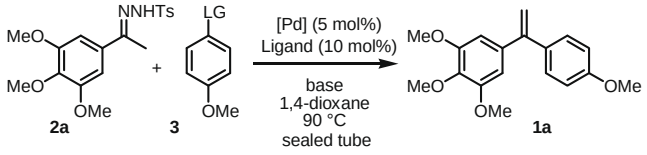
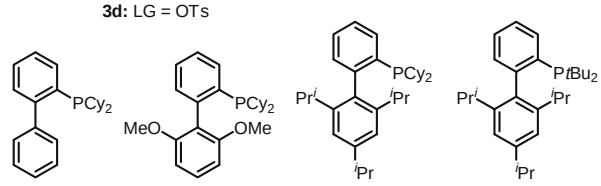
Table 1
Initial studies for Pd-catalyzed Barluenga coupling of *N*-tosylhydrazone **2a** with **3**[a]



3a: LG = OTf
3b: LG = Im (Im = Imidazolylsulfonate)
3c: LG = ONfF
3d: LG = OTs



L1: CyJohnPhos **L2**: S-Phos **L3**: XPhos **L4**: *t*BuXPhos

Entry	[Pd]/Ligand	LG	Base	Yield[b] (%)
1	$Pd_2(dba)_3$/**L3**	OTf	*t*BuOLi	54[c]
2	$Pd_2(dba)_3$/**L3**	OTf	*t*BuOLi	84
3	$Pd_2(dba)_3$/**L3**	OTf	*t*BuOK	34
4	$Pd_2(dba)_3$/**L3**	OTf	Cs_2CO_3	23
5	$Pd_2(dba)_3$/**L3**	OTf	K_3PO_4	50
6	$Pd_2(dba)_3$/**L3**	OTf	Li_2CO_3	0
7	Pd/C/**L3**	OTf	*t*BuOLi	13
8	$Pd(OH)_2$/C/**L3**	OTf	*t*BuOLi	30
9	**$PdCl_2(MeCN)_2$/L3**	**OTf**	***t*BuOLi**	**89**
10	**$Pd(OAc)_2$/L3**	**OTf**	***t*BuOLi**	**91**
11	$Pd(OAc)_2$/**L1**	OTf	*t*BuOLi	82
12	$Pd(OAc)_2$/**L2**	OTf	*t*BuOLi	55
13	$Pd(OAc)_2$/**L4**	OTf	*t*BuOLi	19
14	$Pd(OAc)_2$/**L3**	OSO_2Im	*t*BuOLi	70
15	$Pd(OAc)_2$/**L3**	ONfF	*t*BuOLi	52
16	$Pd(OAc)_2$/**L3**	OTs	*t*BuOLi	5

[a] All reactions were heated in a sealed tube in dioxane using **2a** (1 equiv), **3** (1 equiv), [Pd] (5 mol %), Ligand (10 mol %) and base (2 equiv) at 90 °C for 3 h.
[b] Isolated yield of **1a**.
[c] Reaction was performed at 90 °C at atmospheric pressure.

would allow the incorporation of a variety of aryl substituents was therefore needed.

Typically, the synthesis of the most active compound *iso*CA-4 was performed by the reaction of 3,4,5-trimethoxyacetophenone *N*-tosylhydrazone[11] **2a** with 2-*t*butyldimethylsilyloxy-4-iodoanisole. Thus, when using $Pd_2(dba)_3$ (10 mol %) as a catalyst and Xphos (20 mol %) as a ligand, the coupling reaction gave the desired product *iso*CA-4 in a 75% yield.[12] This synthetic approach proved to be suitable for the synthesis of the others *iso*combretastatins A-1 to A-5[9a] since no stoichiometric organometallic reagent was employed and also, in view of the simple transformation of the acetophenones into their corresponding *N*-tosylhydrazones. Although this reaction has been investigated with aryl halides,[9a,11] there is no report employing the use of aryl triflates. Extension of this coupling reaction to include aryl triflates as electrophiles[13] is especially important since these substrates can be easily synthesized from phenol sources and consequently can be revealed at a late stage in a synthetic sequence. The commercial availability of phenol derivatives will make this approach sufficiently diversity oriented, thus fulfilling the recent demand for the generation of large combinatorial chemical libraries. Herein we report our studies in the synthesis of 1,1-diarylethylenes **1** from the coupling of polyoxygenated *N*-tosylhydrazone **2** with aryl triflates.

Initial studies were performed by coupling 3,4,5-trimethoxyacetophenone *N*-tosylhydrazone (**2a**) and aryl triflate **3a**, as model substrates using $Pd_2(dba)_3$ (5 mol %), Xphos (10 mol %) and *t*BuOLi (2 equiv) in dioxane at 90 °C. Under these conditions (conventional atmospheric pressure reaction), **1a** was formed in a modest 54% yield (entry 1). Fortunately, a much higher yield was obtained under pressure by running the reaction in a sealed tube (84%, entry 2). As summarized in Table 1, the nature of the base has an influence on the outcome of the reaction. *t*BuOLi appeared the base of choice to secure the 1,1-diarylethylene **1a** formation since performing the same reaction with *t*BuOK, Cs_2CO_3 or K_3PO_4 led to lower yields (entries 3–6). The screening was continued with respects to palladium source and ligands. We were pleased to find that the catalytic activity of $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ proved to be similar to $Pd_2(dba)_3$ leading to **1a** in excellent yields (89–91%, entries 9 and

Table 2
Synthesis of 1,1-diarylethylene **1**[a]

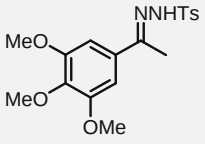
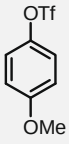
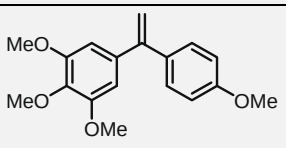
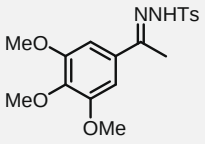
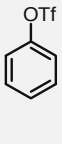
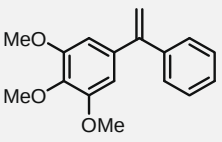
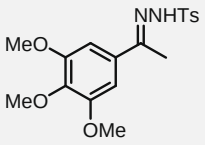
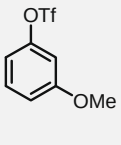
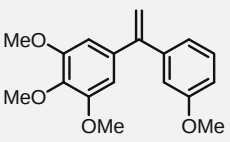
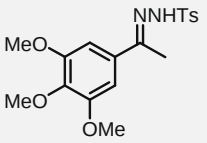
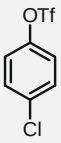
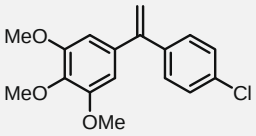
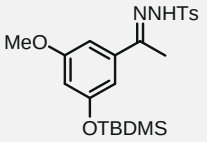
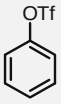
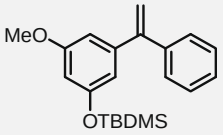
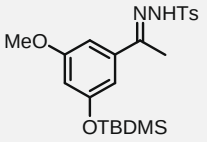
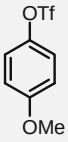
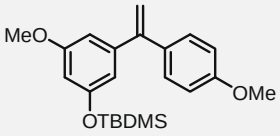
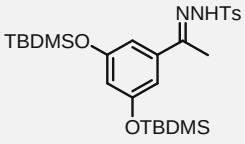
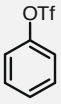
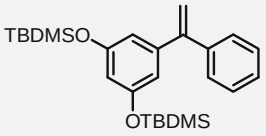
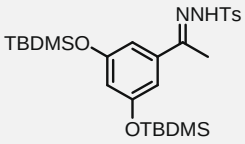
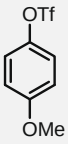
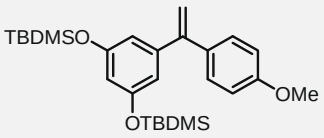
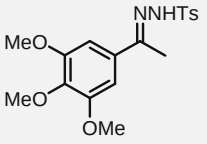
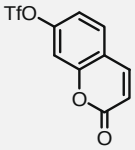
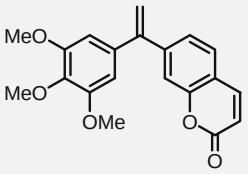
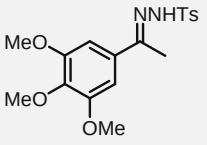
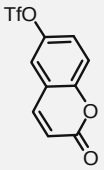
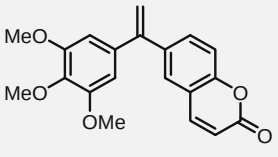
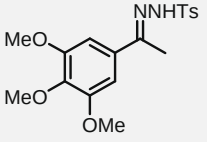
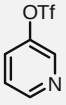
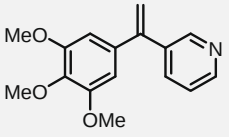
Entry	Hydrazone **2**	ArOTf **3**	Product **1**	Yield[b] (%)
1	 **2a**	 **3a**	 **1a**	91
2	 **2a**	 **3e**	 **1b**	90
3	 **2a**	 **3f**	 **1c**	75

Table 2 (*continued*)

Entry	Hydrazone **2**	ArOTf **3**	Product **1**	Yield[b] (%)
4	 **2a**	 **3g**	 **1d**	69
5	 **2b**	 **3e**	 **1e**	94
6	 **2b**	 **3a**	 **1f**	97
7	 **2c**	 **3e**	 **1g**	90
8	 **2c**	 **3a**	 **1h**	74
9	 **2a**	 **3f**	 **1i**	75
10	 **2a**	 **3g**	 **1j**	66
11	 **2a**	 **3e**	 **1k**	52[c]

[a] All reactions were heated in a sealed tube in dioxane using **2a** (1 equiv), **3** (1 equiv), $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %) and *t*BuOLi (2 equiv) at 90 °C for 3 h.
[b] Isolated yield of **1**.
[c] Not optimized.

10). Pd/C or $Pd(OH)_2$ however, showed moderate catalytic activities (entries 7 and 8) since **1a** was formed in lower yields than those obtained with $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$. Evaluation of ligands revealed that Xphos (**L3**) and CyJohnPhos (**L1**) have a similar efficiency and are superior to all other choices (entries 11–13). Finally we examined the effect of the leaving group (LG) of the electrophilic coupling partner. A comparative study revealed that the reactivity of triflate **3a** is superior to that of imidazolylsulfonate **3b** (entry 14) and nonaflate **3c** (entry 15) whereas the coupling failed when using tosylate **3d** (entry 16). Considering its high catalytic activity $Pd(OAc)_2$ was our choice for further experimentation. In summary, the best conditions were found to require: **2a** (1 equiv), **3a** (1 equiv), $Pd(OAc)_2$ (5 mol %), Xphos (10 mol %), *t*BuOLi (2 equiv), dioxane in a sealed tube at 90 °C for 3 h.[14] It should be noted that microwave heating is also effective for this reaction. However, if the reaction time is reduced (~0.5 h),[15] a slightly lower yield (78%) was obtained.

After these optimization studies, we applied this catalytic system for the coupling of various aryl triflates and polyoxygenated tosylhydrazones **2** to assess the scope of the developed reaction conditions (Table 2). First, 3,4,5-trimethoxyacetophenone *N*-tosylhydrazone **2a** was reacted with various aryl triflates **3** to afford the corresponding 1,1-diarylethylenes **1a–c** (entries 1–3). Running the reaction from aryl triflate **3g** bearing a para sp2-carbon-chlorine bond, the coupling reaction gave selectively **1d** in a 69% yield (entry 4). Among these substrates, the coupling reaction worked efficiently even in the case of alkaline sensitive tosylhydrazones **2b** and **2c** bearing silyloxy groups in good to excellent yields (entries 5–8). Heteroaromatic triflates **3f–e** also were coupled successfully with hydrazone **2a** and provided the desired coupling products **1i–k** in a satisfactory yield (entries 9–11), despite the fact that the reaction conditions with these heterocyclic substrates had never been optimized.

In conclusion, we have described an efficient and general method for cross coupling of different aryl triflates with polyoxygenated hydrazones catalyzed by the combination of $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ and Xphos ligand in the presence of *t*BuOLi as the base in a sealed tube. In our opinion, this approach seems to be a suitable method for the synthesis of other *iso*combretastatin A analogues. The design of antitumor agents based on the 1,1-diaryethylene scaffold in future structure–activity relationship studies is currently underway; the results of synthetic and biological studies will be reported in due course.

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12. Only 50% of the desired product was obtained when running the coupling reaction with $Pd_2(dba)_3$ (1 mol %) and Xphos (2 mol %).
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14. *General procedure for the synthesis of* **1**. To a dioxane (6 mL) solution of *N*-tosylhydrazone **2** (0.5 mmol), *t*BuOLi (1 mmol), $Pd(OAc)_2$ (0.025 mmol), and X-Phos (0.05 mmol) was added the aryl triflate **3** (0.5 mmol) in dioxane (2 mL). The reaction vessel was sealed, and then heated at 90 °C for 3 h. The resulting suspension was cooled to room temperature and filtered through a pad of Celite eluting with AcOEt, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.
Diarylethylene **1a**: Yield: 91%. R_f (cyclohexane/EtOAc: 6/4) = 0.60. IR (cm^{-1}): 1579, 1507, 1454, 1411, 1346, 1299, 1233, 1174, 1122, 1030, 1004. ^1H NMR: (δ ppm, CD_3COCD_3, 300 MHz): 3.75 (s, 3H, OCH_3), 3.78 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 5.34 (m, 2H, CH_2), 6.60 (s, 2H), 6.92 (d, 2H, J = 8.7 Hz), 7.29 (d, 2H, J = 8.7 Hz). ^{13}C NMR (δ ppm, 75 MHz, CD_3COCD_3): 55.5, 56.4 (2), 60.5, 106.8 (2), 112.7, 114.4 (2), 130.1 (2), 134.4, 138.2 (2), 150.6, 154.1 (2), 160.5.
Diarylethylene **1d**: Yield: 69%. R_f (cyclohexane/EtOAc: 9/1) = 0.58. IR (cm^{-1}): 1579, 1504, 1462, 1410, 1344, 1235, 1125, 1007. ^1H NMR: (δ ppm, $CDCl_3$, 300 MHz): 3.73 (s, 6H, OCH_3), 3.80 (s, 3H, OCH_3), 5.34 (d, 2H, J = 1.0 Hz, CH_2), 6.44 (s, 2H, CH), 7.22 (s, 4H, CH). ^{13}C NMR (δ ppm, 75 MHz, $CDCl_3$): 56.1 (2), 60.9, 105.5 (2), 114.3, 128.4 (2), 129.6 (2), 133.7, 136.8, 137.8, 139.7, 149.0, 153.0 (2).
Diarylethylene **1i**: Yield: 75%. R_f (cyclohexane/EtOAc: 7/3) = 0.28. Mp: 143–145 °C. IR (cm^{-1}): 1719, 1574, 1508, 1453, 1411, 1350, 1221, 1177, 1124, 996. ^1H NMR: (δ ppm, $CDCl_3$, 300 MHz): 3.82 (s, 6H), 3.89 (s, 3H), 5.54 (s, 1H), 5.56 (s, 1H), 6.42 (d, 1H, J = 9.5 Hz), 6.51 (s, 2H), 7.27 (dd, 1H, J = 1.6 Hz, J = 8.0 Hz), 7.35 (d, 1H, J = 1.5 Hz), 7.44 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 9.5 Hz).^{13}C NMR (δ ppm, 75 MHz, $CDCl_3$): 56.0 (2), 60.8, 105.6 (2), 116.1, 116.2, 116.4, 118.2, 124.3, 127.4, 136.0, 138.1, 142.9, 145.1, 148.6, 153.0 (2), 153.9, 160.6.
15. The reaction was conducted according to the general method described above. The reaction vessel was sealed, then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature: 120 °C; time: 30 min; fixed hold time: on; sample absorption: high; pre-stirring: 60 s.