One-pot hydrosilylation-protodesilylation of functionalized diarylalkynes: a highly selective access to *Z*-stilbenes. Application to the synthesis of combretastatin A-4.

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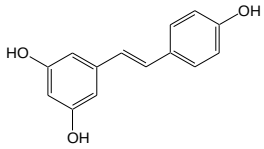
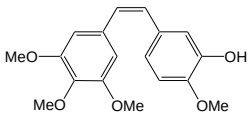
Abstract— An efficient stereoselective synthesis of *Z*-stilbenes has been developed from diarylalkynes *via* a new hydrosilylation-protodesilylation process. Scope and limitation of this method to prepare stereoselectively a wide range of (Z)-stilbenes in a one-pot way is presented. A concise application to the preparation of combretastatin A-4 (**CA-4**), a vascular targeting agent inhibitor of tubulin polymerisation is described.

A large number of stilbene (1,2-diphenylethylene) derivatives have been isolated from various plant species and exhibit a large panel of biological activities such as, antineoplastic, antiangiogenesis, cytotoxic and inhibitory of cell proliferation.[1] Beside *trans* stilbene derivatives and one of their leader, Resveratrol, a large number of their *cis* homologues were isolated, synthesized and evaluated. The most promising of these stilbenes thus far are combretastatins and particularly, the combretastatin A-4 (CA-4), due to its biological activities combined to its structural simplicity (Scheme 1).[2]



Resveratrol



Combretastatin A-4 (CA-4)

Scheme 1

If the access of *trans* stilbenes is well-documented,[3] there are only few methodologies that give access to their *cis* counterparts. The most popular approach is based on the *Z* selective-Lindlar[4] semi reduction of diarylalkynes but suffer from several drawbacks as (*Z*) to (*E*) isomerisation, over reduction to the alkane making purifications tedious and problems with reproductibility.

As a part of our research devoted to anticancer agents,[5] that target tubulin,[6] we wished to synthesize the natural product CA-4 as a reference molecule since, to our knowledge; CA-4 is not commercially available anymore. The chemical synthesis of CA-4 has been tackled in a variety of ways.[1b,7] while these reactions are suitable methods, many of them either display low stereoselectivity or do not tolerate sensitive functionalities. Therefore, alternative routes for the synthesis of CA-4 are welcome. A recent work describing the synthesis of CA-4 and analogues by hydrolysis of Ti(II)-alkynes complexes,[8] prompted us to publish our preliminary results in the *Z*-semi reduction of alkynes field.

Recently, we showed that heterogeneous platinum oxide (PtO_2) is a very efficient catalyst for the hydrosilylation of *para* and *ortho* substituted diarylalkynes. The H–Si bond addition proceeds in a stereoselective *cis*-fashion[9] and the regioselectivity of the reaction was found to be governed by *ortho*-directing effects (ODE)[10] rather than the nature of the platinum catalysts. We reasoned that this efficient hydrosilylation of internal arylalkynes could be efficiently exploited to give, after linkage of the C–Si bond, *Z*-stilbenes of high biological interest. We present in this communication a convenient one-pot procedure for the *Z*-selective semi reduction of diarylalkynes *via* a hydrosilylation-protodesilylation sequence.

To define optimal reaction conditions, we have studied initially the hydrosilylation of diarylalkynes **1a** and **1b** as

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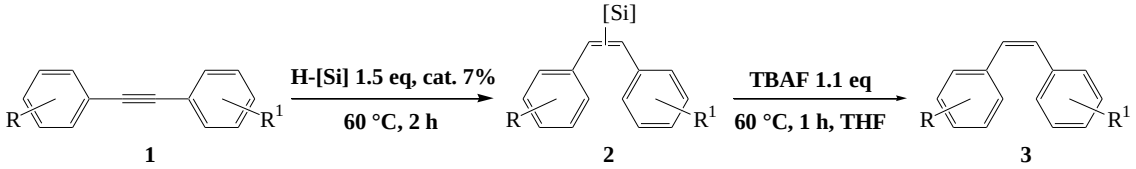


Table 1. Hydrosilylation-protodesilylation sequence; access to *Z*-stilbenes **3**

entry	diarylalkyne **1**	H-[Si]	catalyst	yield[a] of **2**[b] (%)		yield[a] of **3** (%)		*Z*/*E* ratio[c]
1	**1a** R = 4-OMe, R^1 = H	**1**: $HSiEt_3$	PtO_2	**2a-1**	97	**3a**	58	85/15
2	"	**2**: $HSiPh_2Me$	"	**2a-2**	93	"	49	100/0
3	"	**3**: $HSi(OEt)_3$	"	**2a-3**	70	"	80	100/0
4	**"**	**4**: **$HSiOEtMe_2$**	**PtO_2**	**2a-4**	**86**	"	**90**	100/0
5	"	"	$PtCl_2$	**2a-4**	44	"	nd[d]	nd[d]
6	"	"	Pt/C	**2a-4**	38	"	-	-
7	"	"	$PtCl_4$	**2a-4**	56	"	-	-
8	"	"	H_2PtCl_6	**2a-4**	mixture	"	-	-
9	**1b** R = 2,3,4-OMe, R^1 = H	**4**: $HSiOEtMe_2$	PtO_2	**2b-4**	87	**3b**	77	98/2
10	"	**3**: $HSi(OEt)_3$	"	**2b-3**	78		84	98/2
11	"	**4**: $HSiOEtMe_2$	"	**2b-4**	87		88[e]	100/0
12	**1c** R = 2,3,4-OMe, R^1 = 3-OH, 4-OMe	"	"	**2c-4**	70[f]	**CA-4**	69	100/0

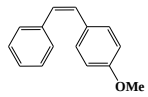
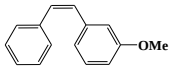
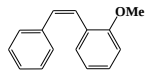
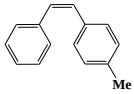
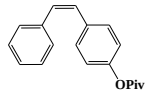
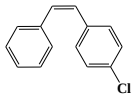
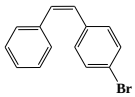
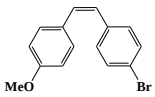
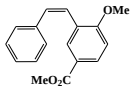
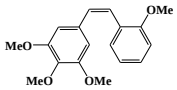
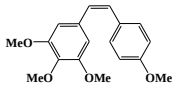
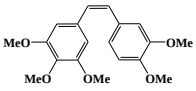
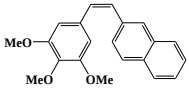
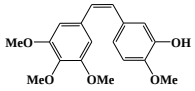
[a] Isolated yield.
[b] Mixture of regioisomers (ratio not determined).
[c] *Z*:*E* Ratios quoted as a percentage composition of total yield as estimated from ^{1}H NMR spectra.
[d] Not determined.
[e] Protodesilylation was achieved at RT.
[f] 4 eq of $HSiOEtMe_2$ were required.

model substrates and their subsequent desilylation. The results are summarized in Table 1. Preliminary experiment was carried out using $HSiEt_3$ (1.5 eq), PtO_2 (7 mol%) at 60 °C in the absence of solvent as we previously reported.[9] In this case, a mixture of vinylsilanes was obtained with a quantitative yield after purification on silica gel. However, the desilylation of the vinylsilanes mixture using TBAF (1.5 eq) at 60 °C afforded a moderate yield of *Z*-**3a** together with significant amounts of *E*-**3a** (entry 1). A survey of the sequence hydrosilylation-protodesilylation sequence of alkyne **1a** under the same conditions in the presence of other representative silanes, including $HSiPh_2Me$, $HSi(OEt)_3$ and $HSiOEtMe_2$ was conducted (entries 2-4). In these cases, we were pleased to observe the formation of a single *Z*-**3a** stereoisomer whatever the nature of the silane used and the better overall yield was obtained with the non-toxic[11] $HSiOEtMe_2$ (77% for the two steps, entry 4). Encouraged by this result, the effect of $PtCl_4$, $PtCl_2$ and Pt/C on the outcome of the hydrosilylation reaction was investigated. None of these platinum catalysts led to better results than those achieved with PtO_2 (entries 5-7). One can note that H_2PtCl_6 (Speier's catalyst), which is considered to be the catalyst of choice for *cis*-hydrosilylation of internal alkynes[12] was not efficient and led to a complex mixture (entry 7). Having defined the best conditions [PtO_2 (7 mol%), $HSiOEtMe_2$ (1.5 eq), 60 °C then TBAF (1.5 eq), 0 °C] *Z*-stilbene **3b** bearing a 3,4,5-trimethoxyaryl moiety was prepared and isolated with good yield (entry 9). Careful inspection of the ^{1}H NMR spectrum of the crude reaction mixture indicated that the stilbene **3b** was formed in a 98:2/*Z*:*E* ratio. A similar result was obtained when using $HSi(OEt)_3$ instead of $HSiOEtMe_2$ (entry 10). Finally, the best result in terms of yield and *Z*-stereoselectivity was observed when the desilylation step of the vinylsilane **2b-4** was achieved at room temperature (entry 11). In this case, *Z*-stilbene **3b** was obtained as a single *Z* stereoisomer in a 77% overall isolated yield (based on alkyne **1b**). We then applied this two stages process to prepare the target natural product **CA-4**[13] from diarylalkyne **1c**. We were delighted to observe that the hydrosilylation-protodesilylation proceeded extremely efficiently to give the desired **CA-4** as a single *Z*-isomer with good yield (entry 12).

From a practical point of view of the synthetic chemist, we explored the process in a one-pot manner. Thus, after the

hydrosilylation step, the excess of the volatile $HSiOEtMe_2$ was removed to achieve the protodesilylation step with TBAF (3 eq) at 0 °C for a better *Z*-stereoselectivity. Scope and limitations of this one-pot process using various functionalized diarylalkynes **1** are summarized in Table 2.

Table 2. One-pot access to *Z*-stilbenes **3** from diarylalkynes **1**

entry	alkynes	stilbenes		*Z*/*E* ratio[a]	yield[b]
1	**1a**		**3a**	**100/0**	77
2	**1d**		**3d**	**100/0**	90
3	**1e**		**3e**	**100/0**	75
4	**1f**		**3f**	**100/0**	51
5	**1g**		**3 g**	**100/0**	49[c]
6	**1h**		**3 h**	**100/0**	65
7	**1i**		**3i**	**100/0**	79
8	**1j**		**3j**	**>95/5**	51
9	**1k**		**3k**	**100/0**	95
10	**1l**		**3l**	**>95/5**	62
11	**1m**		**3m**	**>95/5**	75
12	**1n**		**3n**	**90/10**	73
13	**1o**		**3o**	**88/12**	78
14	**1c**		**CA-4**	**90/10**	67

[a] *Z*:*E* Ratios quoted as a percentage composition of total yield as estimated from ^{1}H NMR spectra.
[b] Isolated yield.
[c] Unoptimized yield.

Diarylalkynes **1a**, **1d-f** substituted with an electron donating group (OMe, Me) have been transformed successfully to their corresponding stilbenes **3** in good yields (entries 1-4). It should be noted that the position of the substituent on the aromatic ring had no influence on the *Z*-stereochemistry of the stilbenes formed (entries 1-3). A similar result (total *Z*-stereocontrol) has been obtained from **1g** bearing a pivaloyl ester function but with a moderate unoptimized 49% yield (entry 5). We were also pleased to observe that halogenated substituted arylalkynes **1h** and **1i** afforded the expected stilbenes **3h** and **3i** respectively with acceptable yields and again as single *Z*-stereoisomers (entries 6 and 7). When the push-pull diarylalkynes **1j** was employed as a substrate, it was found that the *Z*-stereochemistry of this one-pot process was slightly reduced. In this case, traces of the *E*-stilbene were detected by ^{1}H NMR spectroscopy. This PtO_2-catalyzed hydrosilylation-protodesilylation one-pot process can be performed also with alkyne **1k** bearing a methoxycarbonyl group as illustrated in entry 9. In this case again a total *Z*-stereochemistry associated with a nearly quantitative yield was observed (95%).

We next embarked on the utilization of this process for the conversion of 3,4,5-trimethoxyarylalkynes to their corresponding *Z*-stilbenes, analogues of CA-4. Starting from 3,4,5-trimethoxyarylalkynes **1l** and **1m** bearing an ortho or a para methoxy group respectively, it was noted that the 3,4,5 trimethoxyaryl unit smoothly affected the *Z*-stereoselectivity (> 95%, entries 10 and 11) providing **3l** and **3m**[14] in good yields. Similarly, we succeeded in the one-pot preparation of known biologically active analogues of **CA-4**, **3n**[15] and **3o**[16] within good yields and high *Z*-stereocontrol (entries 12 and 13).

On account of the large scope of this one-pot procedure, we then attempted to synthesized **CA-4** from the corresponding **1c** having a free phenolic function. Because of the side silylation of the phenol moiety, the desilylation step was conducted at 60 °C. As showed in entry 14, **CA-4** was obtained with fortunately an excellent *Z*-stereoselectivity (*Z*:*E*/90:10) and a good yield. Careful separation on silica gel afforded pure **CA-4** which could be used as reference for biological evaluation of analogues that would be reported in due course.

In summary, we have developed a new mild and efficient method for the synthesis of *Z*-stilbenes from diarylalkynes. This method is complementary to the existing procedures and sometimes could be the method of choice because of its chemoselectivity, simplicity and its excellent *Z*-stereoselectivity. The ease of which several *Z*-stilbenes were obtained with a total *Z*-stereocontrol and good yields encouraged us to prepare efficiently by this way the natural stilbene **CA-4**. Moreover, we demonstrated too that this hydrosilylation-protodesilylation sequence could be achieved in a one- pot way from various diarylalkynes.

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[13] Procedure for the synthesis of **CA-4**: In a 10 mL flask, PtO_2 (10 mg, 0.0035 mmol) and arylalkyne **1c** (0.5 mmol) were placed under nitrogen atmosphere. Dimethylethoxysilane (304 μL, 2 mmol) was introduced via syringe and the mixture was stirred at 60 °C in an oil bath for 1 h. The residue was concentrated and then purified by column chromatography over silica gel to yield the vinylsilanes as a mixture of regioisomers (147 mg; 70%). The mixture of vinylsilanes (147 mg, 0.35 mmol) was treated with TBAF in THF (1 mL, 1 N) at 60 ° C for 1 h. After concentration in *vacuo*, the crude product was purified by column chromatography (SiO_2, Cyclohexane/ EtOAc : 70/30) to afford **CA-4** as a single *Z*-stereoisomer (75 mg; 69%). TLC: R_f 0.46 (Cyclohexane/EtOAc : 70/30, 1/1, SiO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 6H), 3.84 (s, 3H), 3.86 (s, 3H), 5.50 (brs, 1H, OH), 6.40 (d, 1H, *J* = 12.1 Hz), 6.47 (d, 1H, *J* = 12.1 Hz), 6.53 (s, 2H), 6.72 (d, 1H, *J* = 8.2 Hz), 6.80 (dd, 1H, *J* = 8.2 Hz, *J* = 1.8 Hz), 6.92 (d, 1H, *J* = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9 (2 C), 56.1, 60.9, 106.0 (2 C), 110.3, 115.0, 121.1, 129.0, 129.5, 130.6, 132.7, 137.1, 145.2, 145.8, 152.8 (2 C).

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