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## COMMUNICATION

## Flash-metathesis for the coupling of sustainable (poly)hydroxyl $\beta$ -methylstyrenes from essential oils†

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**A cross-metathesis procedure was developed to synthesize symmetrical and non symmetrical stilbenes from sustainable resources. The reaction proceeds under solvent-free conditions and at low catalyst loading (down to 0.01 mol%) within a couple of minutes only (TOF up to 6.9 s<sup>-1</sup>), on multi-gram scale. The highly reactive  $\beta$ -methylstyrene substrates were homo-coupled not only as pure synthons but also as components of essential oils that were reacted directly in order to eliminate prior substrate isolation from the overall process.**

The use of sustainable starting materials is one of the main pillars of Green Chemistry and biosourced synthons<sup>1</sup> are now widely used in a variety of applications ranging from commodities to fine chemistry. Beside the highly versatile platform chemicals<sup>2</sup> (e. g. sugar polyols,  $\alpha,\omega$ -diacides or furfural derivatives) obtained from biomass through optimized processes,<sup>3</sup> secondary metabolites naturally occurring in plants are also valuable chemical building-blocks. Furthermore, the challenge of directly transforming botanical extracts containing them<sup>4</sup> deserves attention as it represents a particularly sustainable approach that avoids energy- and/or solvent-consuming preliminary isolation steps.

Among these starting plant-based materials, phenylpropenoids hold great potential as the pendant C3 chain offers a synthetic handle to explore structural diversity through olefin chemistry, including for example oxidations, (cyclo)additions and transition metal-catalyzed C-C bond forming reactions. In particular, the synthetic potential of phenylpropenoids as metathesis<sup>5</sup> partners was demonstrated in a variety of transformations. For example, dos Santos *et coll.* reported on the cross-metathesis (CM) of natural phenylpropenoids of the  $\beta$ -methylstyrene type with acrylates to access the corresponding cinnamates with excellent yields.<sup>6</sup> Similarly, Bruneau *et al.* reported on the hetero-coupling of eugenol derivatives with acrylates, acrylonitrile and acrylamides.<sup>7</sup>

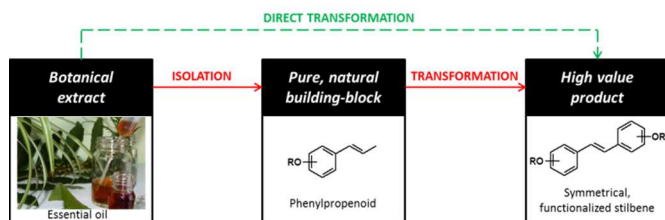
Phenylpropenoids can also undergo self CM as demonstrated in the seminal paper from Grubbs<sup>8</sup> describing the homo-coupling of

eugenol.<sup>9</sup> However, to the best of our knowledge no systematic study has dealt with the use of  $\beta$ -methylstyrenes. Furthermore, even in the case of the  $\beta$ -unsubstituted analogues, this type of reaction has mostly been considered as a side-reaction of hetero-coupling transformations and only a few reports have appeared on self cross-metathesis as a powerful synthetic tool to access symmetrical stilbenes. Notably, using 5 mol% of Grubbs II complex in refluxing CH<sub>2</sub>Cl<sub>2</sub>, Chang developed the homo-coupling of styrenes bearing diverse substituents on the phenyl rings.<sup>10</sup> Similarly, *en route* to an efficient hetero-coupling methodology toward resveratrol derivatives, Delaude *et al.* also used 3-5mol% of Grubbs II complex in refluxing THF or toluene to perform the homo-coupling of various  $\beta$ -unsubstituted styrene derivatives.<sup>11</sup> This transformation was successfully investigated by the same group, including anethole as an example of  $\beta$ -methylstyrene, with novel homobimetallic ruthenium complexes to demonstrate their synthetic utility.<sup>12</sup> However, all these conventional methodologies suffer from the use of organic solvents and/or high catalyst loadings thus hampering their valorization as cheap, green, synthetic tools.<sup>13</sup> Thus, methods to self cross-metathesize styrene derivatives that would circumvent these limitations appear valuable from both the environmental and the economical perspective.

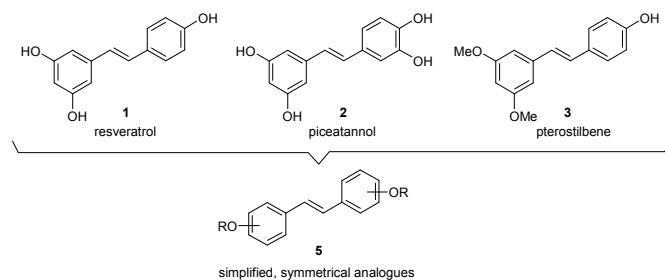
In our continued efforts toward the synthesis of resveratrol-like compounds,<sup>14</sup> we report herein a practical, solvent-free self CM method with low catalyst loading for the homo-coupling of sustainable  $\beta$ -methylstyrenes. This class of *internal* olefins which had been only poorly studied was found to be highly reactive. In addition, these substrates could be used not only as isolated, pure synthons but also as components of complex mixtures within the direct transformation of essential oils, hence saving the preliminary isolation step among the overall process (Scheme 1).

Being structurally simplified analogues, the obtained symmetrical, functionalized stilbenes **5** are accessible alternatives to natural (*E*)-polyhydroxystilbene derivatives,<sup>15,16</sup> such as the phytoalexins resveratrol **1**, piceatannol **2** and pterostilbene **3** (Fig. 1) that are able to modulate various pathological as well as physiological pathways. In particular, resveratrol **1** is now well-established as a valuable

cosmetic ingredient owing to its anti-oxidant<sup>17</sup> and its antimicrobial<sup>18</sup> activities.



**Scheme 1** Direct transformation versus conventional two-step process



**Fig. 1** (*E*)-polyhydroxystilbene derivatives

In order to access the scarce, naturally occurring stilbene **5a**,<sup>19</sup> preliminary experiments were performed with isoeugenol **4a** (Scheme 1) that were inspired by the procedure described by Grubbs *et al.* for the homo-coupling of eugenol.<sup>8</sup> Thus, a mixture of neat **4a** and 1 mol% precatalyst **A** (Grubbs II, see Table 1) was stirred at room temperature (r.t.) under vacuum. After 30min, the reaction mixture had solidified. Although the catalyst remained active,<sup>20</sup> analysis of a crude sample by <sup>1</sup>H NMR revealed that the conversion of **4a** had stopped at 67%. Interestingly, only the (*E*)-stereoisomer was formed.<sup>21</sup> Considering that the harsher procedure reported by Meier<sup>22</sup> may lead to a higher conversion before interruption, **A** (1 mol%) was added to pre-heated **4a** (90°C). Satisfyingly, the procedure was efficient and the reaction was extremely fast: before it stopped, conversion had reached 92% in less than 1 minute. To the best of our knowledge this is the first example of solvent-free self cross-metathesis of functionalized phenylpropenoids of the  $\beta$ -methylstyrene type, *ie* bearing an *internal* olefin moiety.<sup>23</sup> As the Grubbs precatalysts are flammable, for the sake of lab safety it was attempted to pre-mix the substrate and the precatalyst at r.t. before heating up to 90°C. We were pleased to obtain a similar result (91% conversion in 1.75 minutes) and this experiment served as the bottom line for further optimization.

First, we checked whether **A** could be replaced with the cheaper Grubbs I precatalyst **B** (1 mol%). However, the reactivity of **B** proved insufficient to get satisfactory conversion (Table 1, entry 2). We thus focused on **A** and investigated the impact of catalyst loading. Increasing it up to 2 mol% did not bring significant improvement compared to 1 mol% (entry 3). On the other hand, to our satisfaction, the catalyst loading could be decreased down to 0.1% with virtually no impact on the conversion of **4a** after short reaction time (entries 4-6). Following the same reasoning with the temperature parameter, we observed with 1 mol% **A** that heating the mixture at 110°C did not increase conversion compared to 90°C. On the other hand, running the reaction at 50°C or r.t. was detrimental (entries 8 and 9). Thus, at this point the optimized conditions consisted in the utilization of 0.1 mol% **A** at 90°C. In this case, the conversion of **4a** reached 97% in less than 5 min and product **5a** was

isolated in 92% yield. In an attempt to make the procedure more practical for laboratory implementation, the reaction was repeated with our optimized conditions under an *air* atmosphere instead of inert atmosphere. Satisfyingly, the conversion to stilbene **5a** was similar to the conversion obtained under argon (compare entries 6 and 10).

**Table 1** Optimization of the self cross metathesis conditions

Entry <sup>a</sup>	Precatalyst	Cat. loading (mol%)	Temp.	%conversion <sup>b</sup>
1	<b>A</b>	1	90°C	91
2	<b>B</b>	1	90°C	23 <sup>c</sup>
3	<b>A</b>	2	90°C	92
4	<b>A</b>	0.5	90°C	92
5	<b>A</b>	0.25	90°C	93
6	<b>A</b>	0.1	90°C	97
7	<b>A</b>	1	110°C	92
8	<b>A</b>	1	50°C	84
9	<b>A</b>	1	r.t.	71
10 <sup>d</sup>	<b>A</b>	0.1	90°C	92

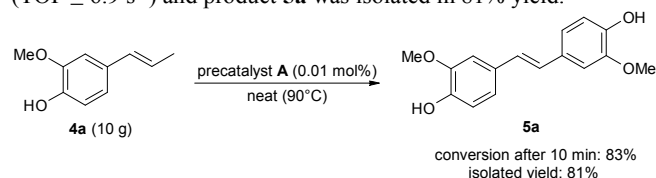
<sup>a</sup> Reaction conditions: neat isoeugenol **4a** (6 mmol) stirred for 5min with the metathesis catalyst at the indicated temperature under an Ar atmosphere

<sup>b</sup> Conversion of substrate **4a** into product **5a** as determined by <sup>1</sup>H NMR analysis of the crude mixture

<sup>c</sup> Conversion measured after 4h

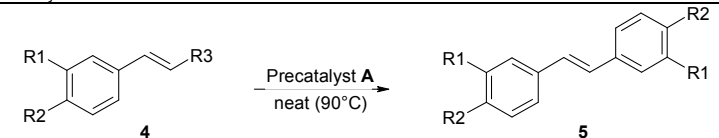
<sup>d</sup> Reaction performed under an air atmosphere

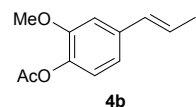
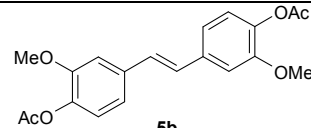
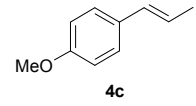
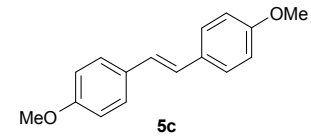
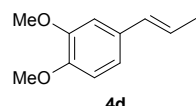
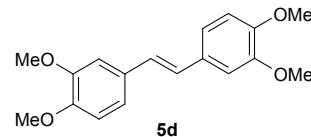
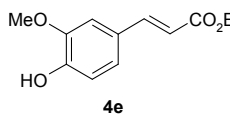
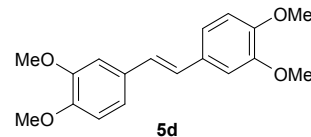
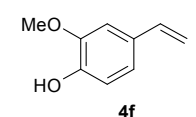
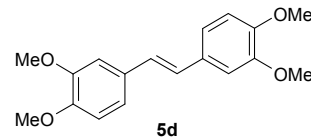
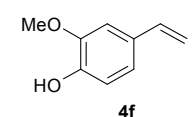
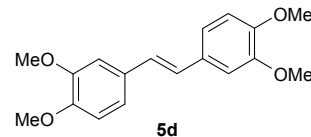
In order to explore the synthetic utility of our method, we further optimized the conditions to access stilbene **5a** with the aim of performing the reaction on a multi-gram, preparative scale. Given that the precatalyst's contribution to the overall cost might be a limitation, we tested the reaction with decreased catalyst loading. We found that 91% conversion of **4a** on a 1g scale could be reached with a concentration of **A** as low as 0.01mol%. These conditions were applied to perform the reaction with 10g of isoeugenol **4a** (Scheme 2). Satisfyingly, after only 10 min, the conversion was 83% (TOF  $\geq 6.9$  s<sup>-1</sup>) and product **5a** was isolated in 81% yield.



**Scheme 2** Flash-metathesis on multi-gram scale

Using our optimized conditions (Table 1, entry 6), we then explored the scope of the methodology to access diversely substituted (*E*)-polyhydroxystilbene derivatives **5**<sup>24</sup> on a preparative scale by reacting other styrene substrates of natural origin **4**.<sup>25</sup> The conversion of isoeugenyl acetate **4b**, a phenol-protected analogue of **4a**, reached 94% and product **5b** was isolated in 92% yield. Starting from anethole **4c**,<sup>12</sup> conversion was complete as observed by <sup>1</sup>H NMR analysis of the crude reaction mixture. Stilbene derivative **5c**, which had been previously described as a potential skin care ingredient owing to its antioxidant properties,<sup>16</sup> was obtained in 95%. Similarly, methyl isoeugenol **4d** was fully converted to **5d**, which was isolated in good yield. On the other hand, as expected by comparison with literature precedents,<sup>26</sup> no trace of product **5a** could be detected with the electron-deficient ethyl ferulate **4e** as substrate. Interestingly, under our optimized conditions, the terminal olefin **4f** gave a much lower conversion to **5a** than its more hindered,  $\beta$ -substituted counterpart **4a**.<sup>27</sup> By analogy to the kinetics studies

**Table 2** Flash-metathesis of various renewable styrene substrates


Entry <sup>a</sup>	Substrate	Product	%conversion <sup>b</sup>	Yield <sup>c</sup>
1			94	92%
2			>98	95%
3			>98	84%
4 <sup>d</sup>			<2	n. d.
5			30	n. d.
6 <sup>e</sup>			95	87%

<sup>a</sup> Reaction conditions: neat styrene **4** (33.7 mmol) stirred for 80 min with 0.1 mol% of the Grubbs II precatalyst **A** (0.1 mol%) at 90°C under an Ar atmosphere

<sup>b</sup> Conversion of substrate **4** into product **5** as determined by <sup>1</sup>H NMR analysis of the crude mixture

<sup>c</sup> Isolated yield

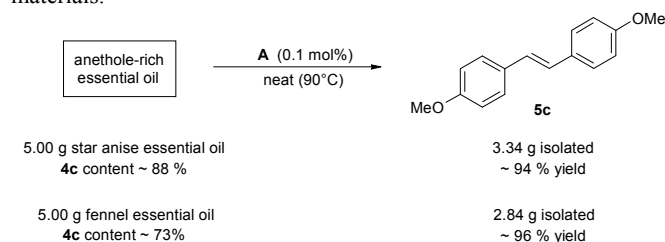
<sup>d</sup> Reaction performed on 4.5 mmol of styrene **4e**

<sup>e</sup> Reaction performed on 6.7 mmol of styrene **4f** with 1 mol% of the Grubbs II precatalyst **A**

previously reported with the Grubbs I pre-catalyst,<sup>28</sup> this may be attributed to the much higher reactivity of the ethylidene–Ru propagating species formed from **A** and the internal olefin **4a**, compared to the methylidene–Ru complex generated from **A** and the terminal olefin **4f**. It is worth noting this gap in reactivity overcomes the steric hindrance effects that are more unfavorable in the case of the  $\beta$ -substituted styrene **4a**. Given that most precedents for the formation of polyhydroxystilbene derivatives through CM rely on the utilization of  $\beta$ -unsubstituted styrenes,<sup>10,11</sup> the superiority of  $\beta$ -methylstyrenes under our reaction conditions suggests that this type of internal olefins may have been overlooked. Hence, we believe these results will motivate further exploration of the potential of this class of substrates as cross-metathesis partners.

Considering that styrenes **4** are renewable compounds that can be sourced from natural extracts, we reasoned that it would be more valuable from an economical and Green Chemistry standpoint to perform the metathesis transformation one step upstream, directly on the natural extracts<sup>4</sup> rather than on the isolated, pure styrene components. Thus, as a proof-of-concept the synthesis of **5c** was undertaken using star anise and fennel essential oils<sup>29</sup> that contain anethole **4c** as their major constituent<sup>30</sup> and from which **4c** can actually be sourced at the industrial level. Satisfyingly, we observed that our optimized conditions could indeed be applied to these

natural extracts and that the self CM reaction proceeded smoothly on multi-gram scale (Scheme 3). From <sup>1</sup>H NMR analysis of the crude reaction mixtures after 1h, the conversion of anethole **4c** contained in both star anise and fennel essential oils was complete. Stilbene **5c** was isolated in ~ 94 % and ~ 96 % yield respectively, taking into account the proportion of **4c** within these complex starting materials.<sup>31</sup>

**Scheme 3** Direct transformation of essential oils

It is worth noting that the réempatage method employed to purify the desired stilbene is identical whether the starting material is an essential oil or pure anethole. It appears that the other, minor components of the essential oils do not interfere with the metathesis reaction and subsequent purification. They are readily eliminated, as

**Table 3** Optimization of the hetero cross metathesis conditions

Entry <sup>d</sup>	Substrates	Cat. loading	%overall conversion <sup>b</sup>	Product distribution <sup>c</sup> 6ac/5a/5c	Selectivity <sup>c</sup>
1	4a (1 equiv.) + 4c (1 equiv.) R = Me : 4c R = H : 4g	0.002 equiv.	92	40/30/30	6ac/5c 57/43
2	4a (1 equiv.) + 4g (1 equiv.)	0.002 equiv.	94	35/34/31	6ac/5c 53/47
3	4a (1 equiv.) + 4c (5 equiv.)	0.002 equiv.	87	39/5/56	6ac/5a 88/12
4	4a (5 equiv.) + 4c (1 equiv.)	0.002 equiv.	73	25/65/10	6ac/5c 74/26
5	4a (10 equiv.) + 4c (1 equiv.)	0.002 equiv.	67	28/72/traces	6ac/5c >95/<5
6 <sup>d</sup>	4a (10 equiv.) + 4c (1 equiv.)	0.011 equiv.	88	16/84/traces	6ac/5c >95/<5

<sup>a</sup> Reaction conditions: neat mixture of styrenes **4** (3 mmol of limiting reagent) stirred for 30 min with the Grubbs II precatalyst **A** at 90 °C under an Ar atmosphere

<sup>b</sup> Overall conversion of substrates **4** into products **5** and **6** as determined by <sup>1</sup>H NMR analysis of the crude mixture

<sup>c</sup> Indicated molar ratio determined by <sup>1</sup>H NMR analysis of the crude mixture

<sup>d</sup> Reaction performed on 1.5 mmol of styrene **4c**

well as the potential corresponding by-products. Consequently, *directly* transforming the essential oils saves the preliminary isolation step to get the metathesis substrate without introducing purification difficulties downstream. The net result for the overall process is thus the economy of one isolation step (Scheme 1). Finally, we attempted to extend the methodology to *hetero* cross-metathesis so as to access non symmetrical stilbenes **6**. Thus, we reacted a 1:1 mixture of β-methylstyrenes **4a** and **4c** under the previously optimized conditions, *ie* using 0.1 mol% catalyst relative to the sum of the equimolar substrates (0.002 equiv.). High conversion was obtained and the desired stilbene **6ac** was formed together with the symmetrical stilbenes **5a** and **5c** resulting from the competing self CM of **4a** and **4c**, respectively (Table 3, entry 1). Although the non symmetrical stilbene **6ac** was the major product, the crude composition corresponded to almost statistical proportions of the three metathesis products. Hypothesizing that selectivity could arise from the gap in reactivity we had observed as a function of the substitution pattern of the substrate olefin moiety, anethole **4c** was replaced by its terminal styrene analogue **4g**. However no improvement was observed (entry 2). As literature precedents demonstrate that using an excess of one of the cross metathesis partners allows for good selectivity,<sup>11,32</sup> we transposed this strategy that had been developed with terminal styrenes under conventional conditions to our solvent-free procedure with β-methylstyrenes. Satisfyingly, using 5 equiv. of one of the partners, selectivity was enhanced: the conversion of the limiting reagent to the non symmetrical stilbene clearly exceeds its conversion to the corresponding self CM product (entries 3 and 4). Furthermore, only trace amounts of symmetrical **5c** were observed when **4c** was reacted with 10 equiv. of **4a** (entry 5). However, as the substrates quantities increased the catalyst concentration got lower, resulting in a moderate 67% overall conversion. Thus, we restored the catalyst loading previously optimized for self CM reactions using 0.1 mol% catalyst relative to the sum of the substrates. Under these conditions,

overall conversion reached 88% while the excellent **6ac/5c** selectivity was maintained (entry 6).

As shown in Table 4, these optimized hetero CM conditions could be employed to form the non symmetrical stilbenes **6ab** and **6ad** with good selectivities. High conversions were observed but these natural-like polyhydroxystilbene derivatives were isolated in moderate yields (42% and 50% yield, respectively) as the high proportion of the major self CM by-product **5a** in the crude mixtures precludes full recovery of the desired non symmetrical stilbenes.

**Table 4** Synthesis of non symmetrical polyhydroxystilbene derivatives

Entry <sup>a</sup>	Hetero CM product	%conv. <sup>b</sup>	Selectivity <sup>c</sup>	Yield <sup>d</sup>
1	6ab	91	6ab/5b 89/11	42%
2	6ad	91	6ad/5d 87/13	50%

<sup>a</sup> Reaction conditions: neat mixture of styrenes **4** (1.5 mmol) and **4a** (15 mmol) stirred for 30 min with 0.011 equiv. of the Grubbs II precatalyst **A** at 90°C under an Ar atmosphere

<sup>b</sup> Overall conversion of substrates **4** and **4a** into products **5** and **6** as determined by <sup>1</sup>H NMR analysis of the crude mixture

<sup>c</sup> Indicated molar ratio determined by <sup>1</sup>H NMR analysis of the crude mixture

<sup>d</sup> Isolated yield

In summary, we have developed a cross-metathesis procedure to access either symmetrical or non symmetrical (*E*)-stilbene derivatives from natural renewable resources, under solvent-free conditions and at low catalyst loading (down to 0.01 mol%). The coupled  $\beta$ -methylstyrenes proved to be highly reactive not only as pure substrates but also within mixtures in the *direct* transformation of essential oils that was implemented to eliminate the preliminary isolation step from the overall process. In practice, conversions up to >98% were obtained in extremely short reaction times (a couple of minutes) and this « flash-metathesis » could be easily performed on multi-gram scale. The obtained stilbene derivatives thus become readily accessible, renewable synthetic platforms that can be further elaborated and efforts are ongoing in our laboratory to access novel resveratrol-like derivatives by using the newly formed double bond as a synthetic handle.<sup>33</sup>

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, spectroscopic data, GC-MS analysis of the studied essential oils. See DOI: 10.1039/c000000x/

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A procedure was developed to expedite cross-metathetize renewable  $\beta$ -methylstyrenes, used as pure reagents or as components of essential oils.

