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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⁻¹), on multi-gram scale. The highly reactive β-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 are now widely used in a variety of applications ranging from commodities to fine chemistry. Beside the highly versatile platform chemicals (e.g. sugar polyols, α,ω-diacides or furfural derivatives) obtained from biomass through optimized processes, secondary metabolites naturally occurring in plants are also valuable chemical building-blocks. Furthermore, the challenge of directly transforming botanical extracts containing them 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 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 β-methylstyrene type with acrylates to access the corresponding cinnamates with excellent yields. Similarly, Bruneau et al. reported on the hetero-coupling of eugenol derivatives with acrylates, acrylonitrile and acrylamides. Phenylpropenoids can also undergo self CM as demonstrated in the seminal paper from Grubbs describing the homo-coupling of eugenol. However, to the best of our knowledge no systematic study has dealt with the use of β-methylstyrenes. Furthermore, even in the case of the β-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 CH₂Cl₂, Chang developed the homo-coupling of styrenes bearing diverse substituents on the phenyl rings. Similarly, en route to an efficient hetero-coupling methodology toward resveratrol derivatives, Delaude et al. also used 3-5 mol% of Grubbs II complex in refluxing THF or toluene to perform the homo-coupling of various β-unsubstituted styrene derivatives. This transformation was successfully investigated by the same group, including anethole as an example of β-methylstyrene, with novel homobimetallic ruthenium complexes to demonstrate their synthetic utility. 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. 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, we report herein a practical, solvent-free self CM method with low catalyst loading for the homo-coupling of sustainable β-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 are accessible alternatives to natural (E)-polyhydroxystilbene derivatives such as the phytoalexins resveratrol, piceatannol and pterostilbene (Fig. 1) that are able to modulate various pathological as well as physiological pathways. In particular, resveratrol is now well-established as a valuable...
cosmetic ingredient owing to its anti-oxidant\textsuperscript{17} and its antimicrobial\textsuperscript{18} 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,\textsuperscript{19} preliminary experiments were performed with isoeugenol 4a (Scheme 1) that were inspired by the procedure described by Grubbs \textit{et al.} for the homo-coupling of eugenol.\textsuperscript{8} 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 30 min, the reaction mixture had solidified. Although the catalyst remained active,\textsuperscript{20} analysis of a crude sample by \textit{1} NMR revealed that the conversion of 4a had stopped at 67%. Interestingly, only the (E)-stereoisomer was formed.\textsuperscript{21} Considering that the harsher procedure reported by Meier\textsuperscript{22} 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 stopped, conversion had reached 92\% in less than 1 min. 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.\textsuperscript{23}

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 \textit{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).

\begin{table}
\centering
\small
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Precatalyst & Cat. loading (mol\%) & Temp. & \%conversion \tabularnewline
\hline
1 & A & 0.1 & 90°C & 92 \%
2 & B & 1 & 90°C & 23 \%
3 & A & 2 & 90°C & 92 \%
4 & A & 0.5 & 90°C & 92 \%
5 & A & 0.25 & 90°C & 93 \%
6 & A & 0.1 & 90°C & 97 \%
7 & A & 1 & 110°C & 92 \%
8 & A & 1 & 50°C & 84 \%
9 & A & 1 & r.t. & 71 \%
10 & A & 0.1 & 90°C & 92 \%
\hline
\end{tabular}
\caption{Optimization of the self cross metathesis conditions}
\end{table}

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 1 g scale could be reached with a concentration of A as low as 0.01mol\%. These conditions were applied to perform the reaction with 10 g of isoeugenol 4a (Scheme 2). Satisfyingly, after only 10 min, the conversion was 83\% (TOF \(\geq 6.9\ s^{-1}\)) and product 5a was isolated in 81\% yield.

\begin{table}
\centering
\small
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Precatalyst (0.01 mol\%) & Temp. & %conversion \tabularnewline
\hline
5a & 4a (10 g) & \textit{air} (90°C) & 83 \%
\hline
\end{tabular}
\caption{Flash-metathesis on multi-gram scale}
\end{table}

Using our optimized conditions (Table 1, entry 6), we then explored the scope of the methodology to access diversely substituted (\textit{E})- polyhydroxystilbene derivatives 5\textsuperscript{24} on a preparative scale by reacting other styrene substrates of natural origin 4.\textsuperscript{25} 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,\textsuperscript{12} conversion was complete as observed by \textit{1}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,\textsuperscript{5} 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,\textsuperscript{20} 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.\textsuperscript{27} By analogy to the kinetics studies...
Table 2  Flash-metathesis of various renewable styrene substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>%conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4b</td>
<td>5b</td>
<td>94</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>4c</td>
<td>5c</td>
<td>&gt;98</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>4d</td>
<td>5d</td>
<td>&gt;98</td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td>4e</td>
<td>5a</td>
<td>&lt;2</td>
<td>n. d.</td>
</tr>
<tr>
<td>5</td>
<td>4f</td>
<td>5a</td>
<td>30</td>
<td>87%</td>
</tr>
</tbody>
</table>

- 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
- Conversion of substrate 4 into product 5 as determined by \(^1\)H NMR analysis of the crude mixture
- Isolated yield
- Reaction performed on 4.5 mmol of styrene 4e
- 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,\(^{28}\) this may be attributed to the much higher reactivity of the ethyldiene−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 β-substituted styrene 4a. Given that most precedents for the formation of polyhydroxystilbene derivatives through CM rely on the utilization of β-unsubstituted styrenes,\(^{10,11}\) the superiority of β-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 4 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\(^{29}\) that contain anethole 4c as their major constituent\(^{30}\) 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 \(^1\)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.\(^{31}\)

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
well as the potential corresponding by-products. Consequently, directly transforming the essential oils saves the primary 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 β2methylstyrenes 4a and 4c under the previously optimized conditions, i.e. using 0.1 mol% catalyst relative to the sum of the 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, we transposed this strategy that had been developed with terminal styrenes under conventional conditions to our solvent-free procedure with β2methylstyrenes. 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 5e were observed when 4e 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 3. Optimization of the hetero cross metathesis conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>Cat. loading</th>
<th>%Overall conversion</th>
<th>Product distribution</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a (1 equiv.) 4c (1 equiv.)</td>
<td>0.002 equiv.</td>
<td>92</td>
<td>40/30/30</td>
<td>6ac/5c</td>
</tr>
<tr>
<td>2</td>
<td>4a (1 equiv.) 4g (1 equiv.)</td>
<td>0.002 equiv.</td>
<td>94</td>
<td>35/34/31</td>
<td>6ac/5c</td>
</tr>
<tr>
<td>3</td>
<td>4a (5 equiv.) 4c (5 equiv.)</td>
<td>0.002 equiv.</td>
<td>87</td>
<td>39/5/56</td>
<td>6ac/5a</td>
</tr>
<tr>
<td>4</td>
<td>4a (5 equiv.) 4c (1 equiv.)</td>
<td>0.002 equiv.</td>
<td>73</td>
<td>25/65/10</td>
<td>6ac/5c</td>
</tr>
<tr>
<td>5</td>
<td>4a (10 equiv.) 4c (1 equiv.)</td>
<td>0.002 equiv.</td>
<td>67</td>
<td>28/72/traces</td>
<td>6ac/5c</td>
</tr>
<tr>
<td>6</td>
<td>4a (10 equiv.) 4c (1 equiv.)</td>
<td>0.011 equiv.</td>
<td>88</td>
<td>16/84/traces</td>
<td>6ac/5c</td>
</tr>
</tbody>
</table>

### Table 4. Synthesis of non symmetrical polyhydroxystilbene derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hetero CM product</th>
<th>%Conv.</th>
<th>Selectivity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6ab</td>
<td>91</td>
<td>6ab5b</td>
<td>42%</td>
</tr>
<tr>
<td>2</td>
<td>6ad</td>
<td>91</td>
<td>6ad5d</td>
<td>50%</td>
</tr>
</tbody>
</table>

\[ a \] 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
\[ b \] Overall conversion of substrates 4 into products 5 and 6 as determined by 1H NMR analysis of the crude mixture
\[ c \] Indicated molar ratio determined by 1H NMR analysis of the crude mixture
\[ d \] Reaction performed on 1.5 mmol of styrene 4c
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 β-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.33

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Notes and references

* L’Oréal Research & Innovation, 1 avenue Eugène Schueller, 93600 Aulnay-sous-Bois, France. Email: jhitce@rd.loreal.com
† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, spectroscopic data, GC-MS analysis of the studied essential oils. See DOI: 10.1039/c000000x

9 The reaction proceeds under vacuum and solvent-free conditions with 0.3 mol% of Grubbs I complex. Recently, an improvement of the yield was reported on multi-gram scale with an optimized isolation procedure: B. G. Harvey, C. M. Sahagun, A. J. Guenther, T. J. Groshens, L. R. Cambrea, J. T. Reams and J. M. Mabry, ChemSusChem, 2014, 7, 1964.
16 For the potential of oxygen-functionalized symmetrical stilbenes as cosmetic ingredients, see for example: Faming Zhu and Shengqi, CN 1839809 A, 2006.
20 For the description of the experiment ruling out catalyst irreversible deactivation, see ESI.
21 The olefin configuration was assigned by comparison with previously reported spectroscopic data corroborated by X-ray analysis: see ref. 19.
23 For another example of the self cross-metathesis reaction of anethole under unconventional conditions, see: L. Gulajski, P. Śledź, A. Lupa and K. Grela, Green Chem., 2008, 10, 271.
24 The olefin configuration of 5c was assigned by comparison to previously reported spectroscopic data, see: L.-K. Sy and G. D. Brown, J. Nat. Prod., 1998, 61, 987. The olefin configuration of 5b and 5d was assigned by analogy with 5a and 5c.
25 The β-methylstyrene substrates were used as a mixture of the (E)- and the (Z)-isomer.
27 L. Delaude et coll. had previously observed a similar reactivity difference with an unusual homobimetallic ruthenium complex in toluene: anethole reacted more promptly than its less hindered counterpart 4-methoxystyrone. See ref. 12.
Although the sourcing of phenylpropenoids from essential oils was discussed by E. N. dos Santos et al. in ref. 6, the synthetic potential of the direct transformation of essential oils containing these phenylpropenoids had not been demonstrated.


The relative purity of anethole within the essential oils was determined through semi-quantitative GC/FID analysis: see ESI.


A procedure was developed to expeditely cross-metathetize renewable β-methylstyrenes, used as pure reagents or as components of essential oils.

\[
\text{(Ru) cat.} \quad 0.01-0.1 \text{ mol\% neat}
\]

up to 95% isolated yield