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## Multicomponent Hosomi–Sakurai reaction on chiral, bio-based, alcohols†

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The multicomponent Hosomi–Sakurai reaction, which gives homoallyl ethers from aldehydes, trimethylsilyl ethers and allyltrimethylsilane, was thoroughly studied using a bio-based aldehyde (protected 5-(hydroxymethyl)tetrahydrofuran-2-carboxyaldehyde) along with trimethylsilyl ethers derived from a variety of (mainly bio-based) alcohols. For comparison, a reactive aromatic aldehyde was also employed. These studies helped to identify the optimal conditions for each aldehyde and provided insight into the scope and limitations of this relatively underexplored multicomponent reaction, one of the few that can incorporate alcohols as diversity inputs.

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### Introduction

Multicomponent reactions (MCRs) are a powerful tool for the diversity-oriented preparation of complex organic molecules from easily available starting materials, with high atom- and step-economy.<sup>1–3</sup> These features make MCRs also very useful in green chemistry, fulfilling several of its principles.<sup>4</sup> The sustainability of this approach can be further enhanced when some or all of the components are bio-based, that is derived from renewable natural sources.<sup>5</sup>

So far, the exploitation of bio-based starting materials has been mainly focused on the production of low-cost commodities and materials, such as biopolymers.<sup>6</sup>

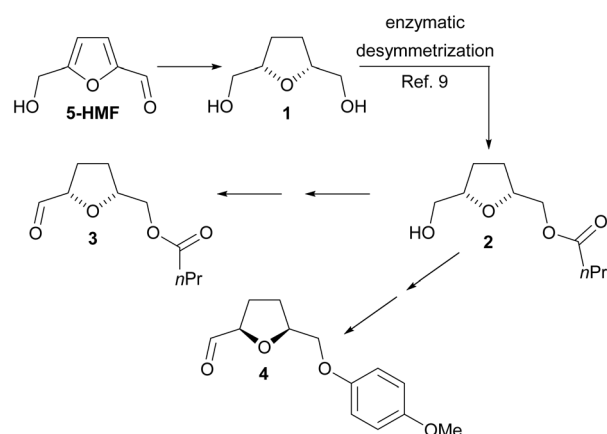
However, it is of great interest to expand their use also in the preparation of bio-based fine chemicals (*e.g.* Active Pharmaceutical Ingredients) with high added value. The diversity-oriented synthesis of complex molecules from biomass is predestined to become an important tool in relieving dependence from oil.

In this context, in recent years we have often investigated the use of bio-based reagents in the Passerini,<sup>7–10</sup> Ugi,<sup>11–14</sup> and Ugi-Joullié<sup>15</sup> MCRs. In all these efforts, the bio-based components were carbonyl compounds, amines, carboxylic acids or isocyanides, but never alcohols. Although alcohols are probably the most abundant among low-cost natural substances,

multicomponent reactions that exploit these building blocks are very rare, unless they are *in situ* converted into carbonyl compounds.<sup>16–19</sup>

Recently, we have pointed our attention to the use, in multicomponent reactions, of aldehydes **3** and **4**, which can be derived, in high enantiomeric excess, from 5-hydroxymethylfurfural (5-HMF). 5-HMF is in turn one of the twelve most interesting bio-based compounds accessible by dehydration processes of lignocellulosic biomass<sup>20,21</sup> and it can be further converted to the *meso* diol **1** by catalytic hydrogenation.<sup>22,23</sup> In 2020, we have reported the successful bio-catalytic desymmetrization of **1** to give aldehydes **3** and **4** (Scheme 1), which have been employed in Zn(II)-mediated diastereoselective Passerini reactions.<sup>9</sup>

In order to extend the potential applications of **3** and **4**, and given our continuous interest in MCRs, as well as in their stereochemical aspects,<sup>24–26</sup> we were interested to explore other



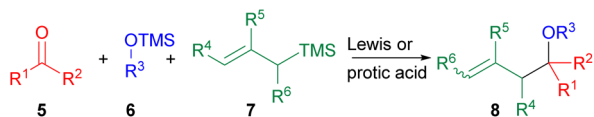
Scheme 1 Previously reported conversion of diol **1** into desymmetrized aldehydes **3** and **4**.

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† Electronic supplementary information (ESI) available: Procedures, optimizations, characterization data, NMR spectra, details of HPLC analyses, and discussion on the assessment of relative configuration. See DOI: <https://doi.org/10.1039/d5ra03165f>





Scheme 2 The Hosomi–Sakurai multicomponent reaction using trimethylsilyl ethers. TMS = trimethylsilyl.

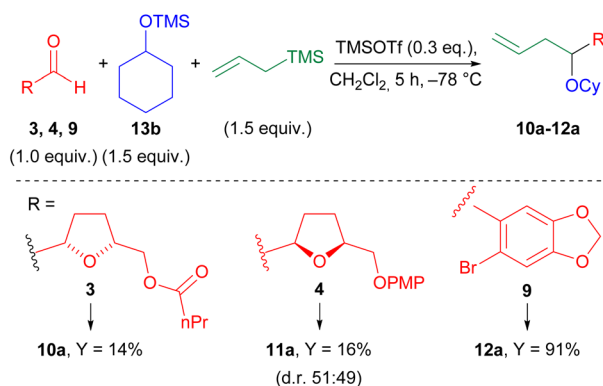
types of multicomponent reactions, especially by combining 3 and 4 with bio-based alcohols.

One of the very few examples of MCRs using alcohols<sup>27</sup> is represented by the so called “multicomponent Hosomi–Sakurai” reaction,<sup>28–34</sup> where a carbonyl compound 5, an alcohol (or its trimethylsilyl ether 6) are combined with an allyl silane 7 in the presence of a Lewis or protic acid, to afford a homoallylic ether 8, with the generation of a new stereogenic centre (unless a symmetric ketone or formaldehyde are used) (Scheme 2).

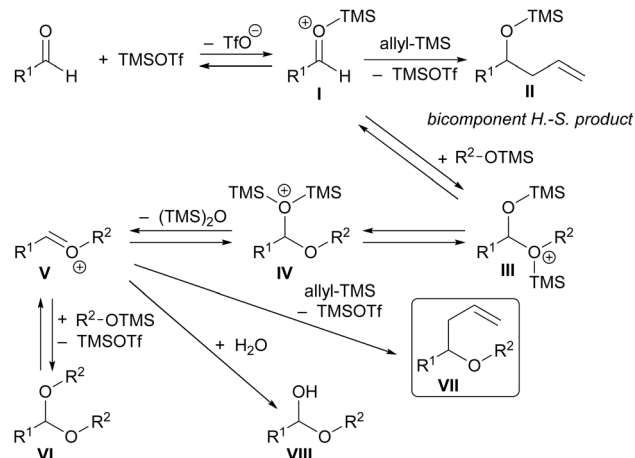
Homoallylic ethers are important building blocks recurrent in natural products.<sup>35</sup> When a silyl ether of the alcohol is used, this reaction is also called “silyl modified Sakurai reaction”.<sup>29</sup> The control of the stereochemical outcome has been studied using chiral silyl ethers<sup>28,36–38</sup> and chiral crotyl silanes.<sup>39–42</sup> To the best of our knowledge, there are very few examples employing chiral aliphatic aldehydes.<sup>33,34</sup> Thus, we decided to study the scope of this MCR on our aldehyde 3 or its analogues bearing different protecting groups. However, we encountered some experimental issues that prompted us to carry out a more systematic study of this reaction. This involved using both achiral and chiral alcohols, including bio-based ones, as well as a less problematic aromatic aldehyde for comparison. Eventually, our efforts have allowed to establish the best experimental conditions for this reaction and to evaluate its scope and limitations. We report here our results, hoping that they can be useful for all those who want to exploit this underexplored MCRs in both target-oriented or diversity-oriented synthesis.

## Results and discussion

We preliminarily investigated the Hosomi–Sakurai multicomponent reaction by subjecting enantiopure aldehyde 3 to the



Scheme 3 Preliminary results. TMSOTf (trimethylsilyl trifluoromethanesulfonate) was used as freshly prepared 0.3 M solution in  $\text{CH}_2\text{Cl}_2$ ; equiv. = equivalent; Cy = cyclohexyl; Y = yield; d.r. = diastereomeric ratio.



Scheme 4 Putative mechanism of multicomponent Hosomi–Sakurai reaction.

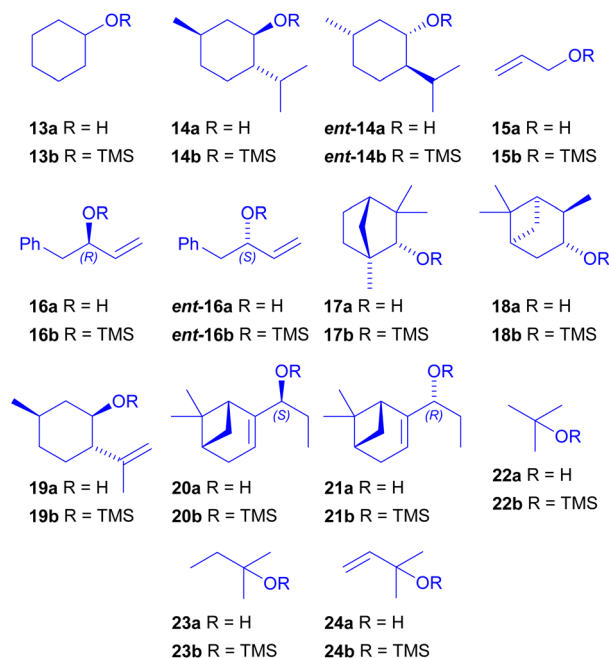
classical conditions reported by Markó *et al.*,<sup>34</sup> using, as partners, cyclohexyloxytrimethyl silane (CyOTMS) 13b, and allyltrimethyl silane (Scheme 3). The preparation of 13b and of the other TMS ethers used at a later time to test the scope of the reaction (Scheme 5) can be easily performed from the corresponding alcohols using stoichiometric  $(\text{TMS})_2\text{NH}$  in the presence of catalytic iodine.<sup>43</sup> At the end of the reaction, TMS ethers are obtained by quick filtration through a silica plug and evaporation to dryness. They are pure enough to be used for the MCR, and can be stored at  $-20\text{ }^\circ\text{C}$  for months.

In the Hosomi–Sakurai multicomponent reaction, we used  $\text{CH}_2\text{Cl}_2$  as the solvent and a freshly prepared solution of TMSOTf in  $\text{CH}_2\text{Cl}_2$  as the catalyst. As shown in Scheme 3, the desired product 10a was obtained in low yield. Hypothesizing an incompatibility of the ester group with TMSOTf, we shifted to aldehyde 4, characterized by a more stable protecting group. This aldehyde is obtained in high yield and as a single enantiomer from desymmetrized alcohol 2 as previously reported by us.<sup>9</sup> Again, only a low yield of product 11a was obtained. Furthermore, the d.r. (HPLC-UV) was found to be quite low (near to 1 : 1).

Scheme 4 shows the putative mechanism of this multicomponent reaction.† The possible side products are the bicomponent product II and the acetal VI. Compound II was formed in significant amounts when the TMS ether of the alcohol was used in stoichiometric amounts, but can be suppressed using 1.5 or 2.0 equiv. of it. On the other hand, we were able to isolate variable amounts of the acetal VI. However, its formation seems to be reversible, as demonstrated by its conversion into multicomponent adduct VII, when treated again with TMSOTf and allyl trimethylsilane.

† Although we were not able to detect hexamethyldisiloxane, which is highly volatile and probably hydrolysed during work-up, its formation can be inferred from the stoichiometry of the reaction. The product has one oxygen less than the three reagents, the same number of hydrogens, and two TMS groups less. Since the reaction is carried out under dry conditions (no water present, unless in traces) and TMS-OTf is catalytic, hexamethyldisiloxane is the only possible stoichiometric product containing the missing oxygen and the two TMS groups.





Scheme 5 Alcohols and TMS ethers used in multicomponent Hosomi-Sakurai reactions of Tables 3 and 4.

Also Markó *et al.*<sup>34</sup> have reported low yields under the same conditions using  $\alpha$ -alkoxyaldehydes. These authors suggested that the low yield could be due to side reactions occurring during work-up and that the product could be converted into hemiacetal **VIII** because of the presence of triflic acid. Although we could detect the acetal **VI**, the hemiacetal **VIII** was never observed, and it is likely to be unstable. Finally, from our evidence, the formation of product **VII** seems to be irreversible under the reaction conditions.<sup>§</sup>

Reasoning that these disappointing results could stem from the particular nature of our aldehyde, we tested 6-bromopiperonal **9**, and the expected product **12a** was eventually obtained in 91% yield in a short reaction time. Aldehyde **9** is non-enolizable, does not contain potentially reactive group, and is also activated towards this reaction, since the dioxolane group can stabilize the intermediate oxocarbenium ion.

This last data pointed out that the conditions that are efficient for “easy” aldehydes, such as **9**, may be not well suited for more complex, aliphatic and not activated aldehydes. We tried to decrease the amount of catalyst to 0.1 equiv. but the reactions became too slow with **4**, and even with **9** it was far from completion after 24 h.

We then used **9** to explore potential substitutes for TMSOTf, aiming to identify a less aggressive Lewis acid that could also work effectively on “difficult” aldehydes like **4** (Table 1). None of them were effective in promoting the reaction, and only using stoichiometric Bi(OTf)<sub>3</sub> we observed tiny traces of the product (entry 3). It is worth noting that Bi(OTf)<sub>3</sub> and iodine left the

<sup>§</sup> Markó *et al.* reported that the yield could be improved by a basic non aqueous work-up (pyridine<sup>34</sup> or EtN(*i*Pr)<sub>2</sub>) (ref. 33). However, in our hands, these basic work-up conditions were influential, whereas addition from the beginning of those bases suppressed completely the activity of the catalyst.

Table 1 Screening of the catalysts using 6-bromopiperonal **9** and cyclohexanol TMS ether **13b**<sup>a</sup>

| Entry | Catalyst (equiv.)                        | Yield <sup>b</sup> of <b>12a</b> (%) | Unreacted aldehyde <sup>b</sup> (%) |
|-------|--|--------------------------------------|-------------------------------------|
| 1     | TMSOTf (0.3) <sup>c</sup>                | <sup>d</sup> 91%                     | —                                   |
| 2     | Bi(OTf) <sub>3</sub> (0.3)               | 0%                                   | 93%                                 |
| 3     | Bi(OTf) <sub>3</sub> (1.1)               | 2%                                   | 90%                                 |
| 4     | BF <sub>3</sub> ·Et <sub>2</sub> O (1.1) | 0%                                   | 66%                                 |
| 5     | SnCl <sub>4</sub> (1.1)                  | 0%                                   | 37%                                 |
| 6     | TiCl <sub>4</sub> (1.1)                  | 0%                                   | 26%                                 |
| 7     | I <sub>2</sub> (0.1)                     | 0%                                   | 93%                                 |

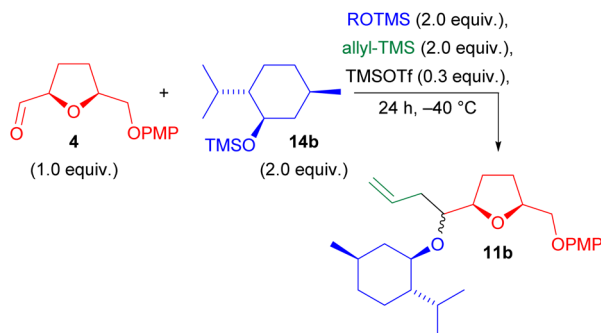
<sup>a</sup> 6-Bromopiperonal **9** (0.30 mmol, 1 equiv.), CyOTMS (1.5 equiv.), Allyl-TMS (1.5 equiv.), catalyst (equiv. indicated in the Table), CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL), -78 °C, 5 h. <sup>b</sup> Calculated by <sup>1</sup>H NMR of the crude using 3,4,5-trimethoxybenzyl alcohol as internal standard (see ESI). <sup>c</sup> Freshly prepared 0.3 M solution in CH<sub>2</sub>Cl<sub>2</sub>. <sup>d</sup> Isolated yield.

aldehyde untouched (entries 2, 3 and 7). On the other hand, stronger Lewis acids led to consumption of the aldehyde, but affording other unidentified products (entries 4–6).

Thus, we returned to using TMSOTf and aldehyde **4**, focusing on optimizing the reaction conditions. This time, we decided to use the TMS ether of (–)-menthol, a cheap bio-based substrate (Table 2). First of all, we noticed that, contrary to aldehyde **9**, the reaction was too slow at -78 °C, and substantial amount of the acetal **VI** (Scheme 4) were isolated. Thus, we decided to work at -40 °C. At this temperature, the multicomponent adduct **11b** was formed in slightly better, but still unsatisfactory, yield, although with a good d.r. (entry 1). A possible explanation of this low yield was attributed to the presence of water. We indeed noted that aldehyde **4** has a strong tendency to stay in its hydrated form thanks to a 5-membered intramolecular hydrogen bond involving the tetrahydrofuran oxygen. Water may be detrimental by destroying the catalyst, at the same time producing triflic acid, which in turn may cause opening of the tetrahydrofuran ring. Actually, during the first set of experiments, we always observed that the recovery of the crude product was much lower than the theoretical, likely because opening of the ring would afford highly polar adducts, which are lost in the aqueous phase during extraction.

In order to overcome these problems, we adopted two strategies: (a) pre-treat the aldehyde with desiccants, to force its dehydration; (b) add a non-soluble base, such as CaCO<sub>3</sub>, able to buffer the system without suppressing catalyst activity. These two changes turned out to be beneficial for the yield. On the other hand, the change of solvent from CH<sub>2</sub>Cl<sub>2</sub> to toluene was beneficial from the point of view of stereoselectivity (entry 3 *vs.* entry 4). Further decrease of polarity of the solvent (entry 6) was not useful.



Table 2 Optimization of the reaction conditions using aldehyde 4 and (–)-menthol TMS ether 14b<sup>a</sup>

| Entry | Aldehyde pre-treatment                     | Solvent                         | Additive                             | Yield <sup>b</sup>      | d.r. <sup>c</sup> |
|-------|--|---------------------------------|--------------------------------------|-------------------------|-------------------|
| 1     | None                                       | CH <sub>2</sub> Cl <sub>2</sub> | None                                 | 20%                     | 81 : 19           |
| 2     | None <sup>d</sup>                          | Toluene                         | None                                 | 20%                     | 92 : 8            |
| 3     | 3 Å MS <sup>e</sup>                        | CH <sub>2</sub> Cl <sub>2</sub> | None                                 | 67%                     | 81 : 19           |
| 4     | 3 Å MS <sup>e</sup>                        | Toluene                         | None                                 | 58%                     | 92 : 8            |
| 5     | P <sub>2</sub> O <sub>5</sub> <sup>f</sup> | Toluene                         | None                                 | — <sup>g</sup>          | —                 |
| 6     | 3 Å MS <sup>e</sup>                        | Pentane/toluene 85 : 15         | None                                 | 54%                     | 92 : 8            |
| 7     | 3 Å MS <sup>e</sup>                        | THF                             | None                                 | 20%                     | 84 : 16           |
| 8     | 3 Å MS <sup>e</sup>                        | <b>Toluene</b>                  | <b>CaCO<sub>3</sub> (0.3 equiv.)</b> | <sup>h</sup> <b>71%</b> | <b>92 : 8</b>     |
| 9     | 3 Å MS <sup>e</sup>                        | Toluene                         | CaCO <sub>3</sub> (1.0 equiv.)       | 57%                     | 92 : 8            |
| 10    | 3 Å MS <sup>e</sup>                        | Toluene <sup>i</sup>            | 3 Å MS <sup>i</sup>                  | 42%                     | 92 : 8            |

<sup>a</sup> Scale: 0.24 mmol of 4. Concentration: 0.2 M. TMSOTf was used as a freshly prepared 0.3 M solution in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Determined by HPLC-UV using 1,2-dimethoxybenzene as internal standard (see ESI). <sup>c</sup> The diastereomeric ratio was determined by HPLC. <sup>d</sup> The aldehyde was used directly after chromatography. <sup>e</sup> After the chromatography the aldehyde was taken up in the desired reaction solvent, and kept overnight over freshly activated 3 Å MS (rods). <sup>f</sup> After the chromatography the aldehyde was kept overnight in a desiccator over P<sub>2</sub>O<sub>5</sub> under vacuum. <sup>g</sup> Unreacted aldehyde was detected by TLC. <sup>h</sup> Isolated yield on 0.50 mmol was 65%. <sup>i</sup> 55 mg of powdered 3 Å MS were added to the reaction mixture.

The best way to dehydrate aldehyde 4 makes use of molecular sieves, whereas drying in desiccator on P<sub>2</sub>O<sub>5</sub> was ineffective (entry 5). Addition of molecular sieves in the reaction mixture was deleterious (entry 10): it is better to use them to dry the aldehyde, but not to have them left during the reaction. A breakthrough result was obtained using CaCO<sub>3</sub> as insoluble buffering agent (entries 8 and 9) and 0.3 equiv. seemed the optimal amount.

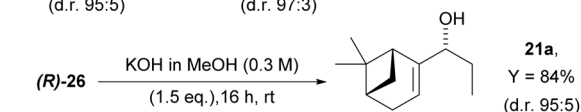
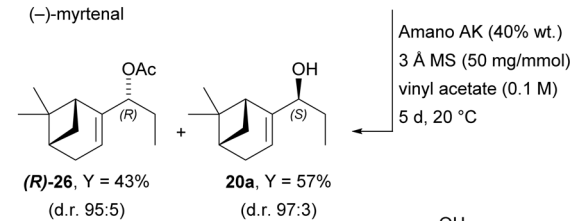
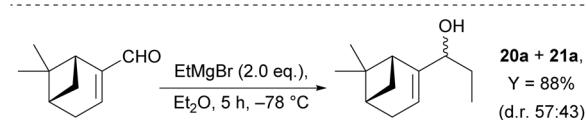
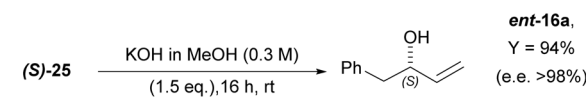
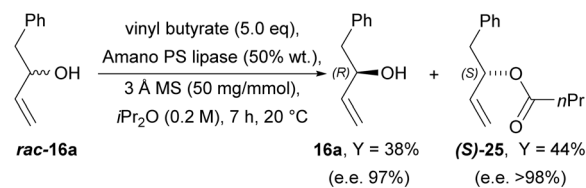
With this optimization, the yield was increased to 71%, with an excellent diastereoselective ratio (92 : 8) (entry 8).

Having identified the optimal conditions for 4 (Table 2, entry 8) and 9 (Table 1, entry 1), we moved to the reaction scope (Scheme 5) testing primary (15b), secondary (13b–14b and 16b–21b) and tertiary (22b–24b) silyl ethers. As can be seen, most of the secondary alcohols were chosen due to their natural origin. All chiral alcohols of Scheme 5 employed were enantiopure.

Apart from allyloxytrimethylsilane 15b, trimethylsilyl ethers are not commercially available, but they can be easily prepared from the corresponding alcohol as above described.<sup>43</sup>

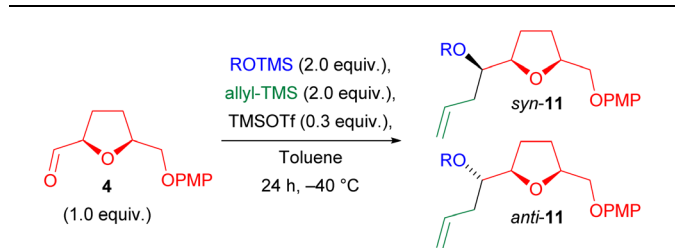
Some of the alcohols were commercially available: cyclohexanol 13a, (–)-menthol 14a, (+)-menthol *ent*-14a, (+)-fencyl alcohol 17a, (–)-isopinocampheol 18a, (–)-isopulegol 19a, and tertiary alcohols 22a–24a. The others were prepared as reported in Scheme 6.

The racemic alcohol *rac*-16a was obtained in one step from phenylacetaldehyde<sup>44</sup> and resolved by biocatalysis using Amano



Scheme 6 Synthesis of non-commercial alcohols.



**Table 3** Scope of multicomponent Hosomi–Sakurai reactions of aldehyde **4** and allyltrimethylsilane with the silyl ethers depicted in Scheme 5<sup>a</sup>

| Entry | TMS ether               | Prod       | Special conditions | Yield <sup>b</sup> | Syn/ <i>anti</i> ratio <sup>c</sup> |
|-------|-------------------------|------------|--------------------|--------------------|-------------------------------------|
| 1     | <b>13b</b>              | <b>11a</b> | None               | 70%                | 65 : 36 <sup>d</sup>                |
| 2     | <b>14b</b>              | <b>11b</b> | None               | 65%                | 92 : 8 <sup>e</sup>                 |
| 3     | <i>ent</i> - <b>14b</b> | <b>11c</b> | None               | 70%                | 32 : 68 <sup>d</sup>                |
| 4     | <b>15b</b>              | <b>11d</b> | None               | <sup>f</sup> <21%  | n.d                                 |
| 5     | <b>15b</b>              | <b>11d</b> | 0 °C               | 55%                | 48 : 52 <sup>d</sup>                |
| 6     | <b>16b</b>              | <b>11e</b> | None               | 66%                | 57 : 43 <sup>d</sup>                |
| 7     | <i>ent</i> - <b>16b</b> | <b>11f</b> | None               | 57%                | 27 : 73 <sup>d</sup>                |
| 8     | <b>17b</b>              | <b>11g</b> | None               | 66%                | 90 : 10 <sup>e</sup>                |
| 9     | <b>19b</b>              | —          | None               | — <sup>g</sup>     | n.d                                 |
| 10    | <b>20b</b>              | —          | None               | — <sup>h</sup>     | n.d                                 |
| 11    | <b>21b</b>              | —          | None               | — <sup>h</sup>     | n.d                                 |
| 12    | <b>22b</b>              | —          | None               | — <sup>i</sup>     | n.d                                 |
| 13    | <b>24b</b>              | —          | None               | — <sup>i</sup>     | n.d                                 |

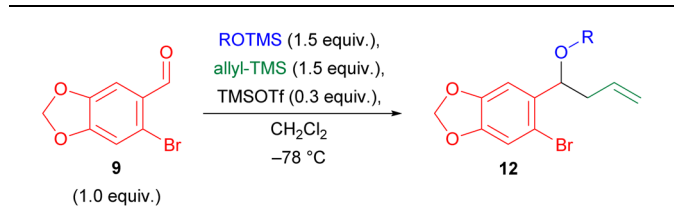
<sup>a</sup> Standard condition of entry 8 of Table 2 were followed, unless otherwise noted. <sup>b</sup> Isolated yield. <sup>c</sup> The diastereomeric ratio was determined by HPLC or <sup>1</sup>H NMR (see ESI for details). <sup>d</sup> *Anti* isomer was faster running in TLC (PE/Et<sub>2</sub>O). <sup>e</sup> *Syn* isomer was faster running in TLC (PE/Et<sub>2</sub>O). <sup>f</sup> The acetal **VI** was the main product (79 : 21 ratio acetal **VI**/**11d**). <sup>g</sup> Prins adduct **30** was formed (see text). <sup>h</sup> A dimeric ether was formed (see text). <sup>i</sup> No reaction.

PS lipase.<sup>45</sup> The non-reactive enantiomer **16a**<sup>46</sup> was isolated with excellent yield and e.e., whereas the acylated (*S*)-**25** was hydrolysed under basic conditions affording the other enantiomer *ent*-**16a** in excellent yield and e.e.<sup>47</sup>

Although the diastereomeric secondary alcohols **20a–21a** were previously synthesized by Seebach by addition of diethylzinc under asymmetric catalysis,<sup>48</sup> we found more convenient a biocatalytic approach. The addition of EtMgBr to commercially available (–)-myrtenal **25** proceeds in high yield, but with poor substrate induced diastereoselectivity and a 57 : 47 mixture of inseparable epimers was detected by <sup>1</sup>H NMR.

We exploited again the use of biocatalysis to selectively convert one epimer into the acetate, which can be easily separated from the unreacted epimeric alcohol by chromatography. We ran a screening of lipases (see ESI†) and Amano AK lipase emerged as the best in terms of selectivity and reaction rate, giving selectively alcohol **20a**. Finally, the acetate group of (*R*)-**26** was removed under basic hydrolysis affording the corresponding alcohol **21a** in excellent yield. The configuration of epimeric **20a** and **21a** was assessed by Mosher's esters analysis (see ESI†) and the results are in agreement with the Kazlauskas's rule for lipase preference in acylation of secondary alcohols.<sup>49</sup>

The results of multicomponent Hosomi–Sakurai reaction with the TMS ethers shown in Scheme 5 are reported in Table 3

**Table 4** Scope of multicomponent Hosomi–Sakurai reactions of aldehyde **9** and allyltrimethylsilane with the silyl ethers depicted in Scheme 5<sup>a</sup>

| Entry | TMS ether               | Product    | Time  | Yield <sup>b</sup> | D.r. <sup>c</sup> |
|-------|-------------------------|------------|-------|--------------------|-------------------|
| 1     | <b>13b</b>              | <b>12a</b> | 5 h   | 91%                | —                 |
| 2     | <b>14b</b>              | <b>12b</b> | 4 h   | 87%                | 55 : 45           |
| 3     | <b>15b</b>              | <b>12c</b> | 2 h   | 82%                | —                 |
| 4     | <i>ent</i> - <b>16b</b> | <b>12d</b> | 1 h   | 89%                | 82 : 18           |
| 5     | <b>17b</b>              | <b>12e</b> | 1, 5h | 60%                | 52 : 48           |
| 6     | <b>18b</b>              | <b>12f</b> | 6 h   | 49%                | 52 : 48           |
| 7     | <b>19b</b>              | —          | 4 h   | — <sup>d</sup>     | —                 |
| 8     | <b>23b</b>              | —          | 6 h   | No reaction        | —                 |

<sup>a</sup> Standard condition of entry 1 of Table 1 were followed, unless otherwise noted. <sup>b</sup> Isolated yield. <sup>c</sup> The diastereomeric ratio was determined by HPLC (see ESI). Relative configuration not determined. <sup>d</sup> Prins products were formed (see text).

for chiral aldehyde **4** and in Table 4 for achiral 6-bromopiperonal **9**. Ethers **12a** and **12c** were obtained as racemic mixtures. All the remaining ethers **11** or **12**, derived from chiral enantiopure substrates were obtained as pure enantiomers.¶

Allyloxytrimethylsilane **15b**, a primary silyl ether, afforded the expected product in excellent yield by reaction with **9** (Table 4, entry 3). On the other hand, starting from **4**, and using standard conditions (–40 °C), the <sup>1</sup>H NMR of the crude product showed a 79 : 21 ratio of acetal **VI**/**11d**. However, when we submitted again the crude product to the same reaction conditions (catalyst, allyl trimethylsilane, –40 °C), a progress of the reaction was observed (45 : 55 acetal **VI**/**11d**). This confirms that the acetal is a possible intermediate of the reaction. We postulated that in the case of primary groups, the acetal has a lower tendency to give the key intermediate oxocarbenium ion **V**, due to a lower benefit following the steric release. In this scenario, a higher temperature might be beneficial; in fact, the desired products were obtained in 55% yield when the reaction was carried out at 0 °C (entry 5). The diastereomeric ratio was near to 1 : 1. However, the epimers can be easily separated by chromatography, as in all the other examples of Table 3, and this was crucial for the assessment of the relative stereochemistry (see below).

¶ Loss of enantiopurity under reaction conditions is very unlikely and was not observed by HPLC with chiral stationary phase (see ESI†). In the case of aldehyde **4**, which has two stereogenic centers, no epimerization was observed in all cases. Racemization would imply simultaneous inversion of both stereocenters, which is impossible. Furthermore, in reaction of **4** with chiral TMS ethers (e.g. **14b**), more than 2 diastereomers would have been observed, and this was not the case. Racemization of chiral TMS ethers is also highly unlikely, and again, in reactions with aldehyde **4**, this would have led to more than two diastereomers.



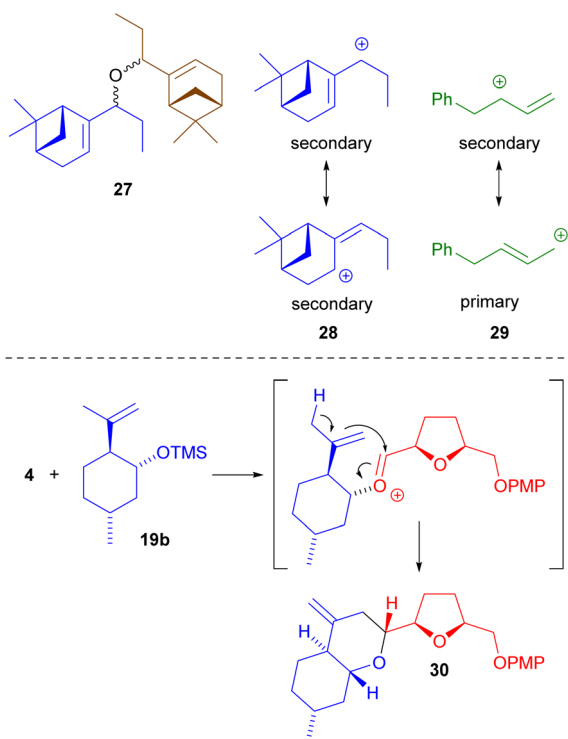
Secondary silyl ethers proved to be the best partner in the Hosomi–Sakurai multicomponent reaction and a good variety of bio-based silyl ethers were employed.

As expected, the reactions starting from 6-bromopiperonal **9** were cleaner and the yields were higher than those from aldehyde **4**. This is due to the high reactivity of **9**, which allowed the reactions to be performed at  $-78\text{ }^{\circ}\text{C}$  in few hours, whereas **4** required a higher temperature ( $-40\text{ }^{\circ}\text{C}$ ) and longer reaction times. Anyway, even TMS ethers of bulky secondary alcohols were able to afford in satisfactory yields adducts **11** or **12** starting from both aldehydes.

With the aim to explore post MCR cyclizations based on ring closing metathesis (RCM), we were particularly interested in TMS ethers containing double bonds, especially those of natural origin, such as **19b–21b**. However, the outcomes were somehow surprising. While allyl ethers **16b** and *ent*-**16b** led to the expected products, starting from allyl ethers **20b** and **21b**, we could only isolate, either for **4** or **9**, a diastereomeric mixture of ethers **27** (Scheme 7), together with unreacted aldehyde.

Ethers **27** may derive from the formation of the carbocation **28**. The different behaviour of **20b–21b** compared to **16b**, may be due to a subtle difference in stability of carbocation **28** compared to **29**. Indeed, carbocation **28** has two resonance forms that are both secondary, whereas one of the forms of **29** is primary (Scheme 7).

Also the failure to obtain the expected products using tertiary TMS ethers **22b–24b** may be ascribed to the formation of stable carbocations, which can lead to oligomerization–polymerization reactions, leaving the aldehydes unreacted.



Scheme 7 Unexpected products of some multicomponent Hosomi–Sakurai reactions.

In the literature, there is only one example of multicomponent Hosomi–Sakurai reaction employing a tertiary TMS ether, namely **24b**,<sup>34</sup> but, in our hands, we were not able to detect any multicomponent product with it. Also by removing the double bond, and using **22b** or **23b**, no product was obtained.

We can conclude that the reaction is possible unless the TMS ether is able to form a relatively stable carbocation, either tertiary or allylic and doubly secondary, such as **28**.

On the other hand, when using the TMS ether **19b**, obtained from (–)-isopulegol, aldehyde **4** was consumed, although not affording the expected product. In this case, after the formation of the oxocarbenium intermediate, an intramolecular Prins cyclization occurred affording compound **30**, that was isolated in 41% yield, along with minor amounts of its stereoisomers/regioisomers (Scheme 7).<sup>50</sup> The relative configuration of this interesting product, being (*R*) at the new stereogenic center, was assumed because the hydrogen bound to it seems to be axial from the coupling constants. Also with **9** a similar behaviour was observed, but the mixture was in this case more complex and we were not able to isolate a single isomer.

As far as it concerns diastereoselectivity, with achiral alcohols aldehyde **4** reacts giving typically low to moderate induction, in favour of the *syn* isomer. Interestingly, in our previous work concerning Passerini reaction with the same aldehyde, the *anti* isomers were instead favoured.<sup>9</sup>

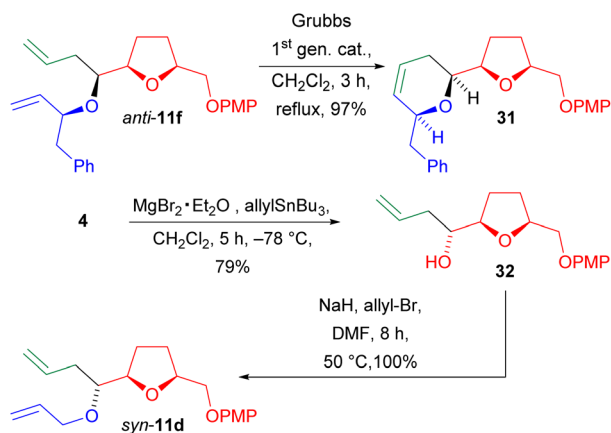
With chiral TMS ethers, matched–mismatched cases were observed. It is well known that in “double asymmetric synthesis”, where two enantiopure substrates interact, the two diastereofacial selectivities may either oppose each other (“mismatched case”) or act in concert (“matched case”).<sup>51,52</sup> In particular, with (–)-menthol **14b**, a matched case allowed to reach the highest d.r. of 92:8 for the *syn* product. With (+)-menthol *ent*-**14b** (mismatched case), the *anti* isomer was preferred, indicating that the main control was put forth by **14b**. With **16b** and *ent*-**16b**, a matched–mismatched combination was again in action, but this time the matched combination favoured the *anti* isomer of **11g**. With (+)-fenchyl alcohol **17b**, probably we are in presence of another matched case, although, due to unavailability of the (–) enantiomer, we could not demonstrate that.

With 6-bromopiperonal **9** a good diastereoselectivity was achieved only with **16b** (or *ent*-**16b**, which gave identical d.r. ratios), whereas with other chiral TMS ethers, the asymmetric induction was low, even with (–)-menthol **14a** and (+)-fenchyl alcohol **17a**, which seemed quite selective with aldehyde **4**.

As a first preliminary example of post-MCR transformation, we carried out a cyclization through Ring Closing Metathesis on the *anti* stereoisomer of **11f** to give **31** as shown in Scheme 8, which involves cyclization of the *anti* stereoisomer of **11f** to give **31**.

The relative configuration of compounds **11f**, was assessed through NMR studies on dihydropyran **31**. In the case of **11d**, the relative configuration was demonstrated by an independent synthesis of the *syn* isomer from **32**, in turn obtained in high yield (79%) and d.r. (99:1) by allylation of aldehyde **4** with allyltributyltin at  $-78\text{ }^{\circ}\text{C}$  under the catalysis of  $\text{MgBr}_2$  (Scheme 8) to afford bicomponent product **32**, whose configuration was demonstrated by Mosher ester analysis (see ESI†). Moreover,





Scheme 8 Ring closing metathesis and transformations made for the determination of relative configuration.

although **32** is a new compound, the analogue with another protecting group (benzyl) has been previously obtained by the same allylation reaction and the configuration established by us is in agreement with the one proposed in that work.<sup>53,54</sup>

For **11a–c**, and **11g**, we used NMR analogies with the spectra of **11d** and **11f** (see ESI†).

On the contrary, the relative configuration of ethers **12b**, **12d**, **12e**, **12f**, derived from 6-bromopiperonal **9**, was not determined.

## Conclusions

In conclusion, we have carried out a comprehensive study on the scope and limitations of the multicomponent Hosomi–Sakurai reaction using TMS ethers of various alcohols, with a particular emphasis on those of terpenic origin. For this study, we employed two complementary aldehydes: one is aromatic and highly activated for this reaction, making it less critical, while the other, derived from biomass, is more critical due to being acid-labile and highly prone to hydration.

Nevertheless, we have successfully developed conditions well suited for both. As far as it concerns the alcohol counterpart, reactions works very well with TMS ethers of secondary alcohols, even the bulky ones, unless they are able to form relatively stable carbocations. TMS ethers of tertiary alcohols are not suited for this MCR. TMS ethers of primary alcohols may be used, but at higher temperatures, being inclined to form acetals too. Thus we have mainly focussed on secondary alcohols. The use of these conditions for other bio-based TMS ethers (including also carbohydrate-derived ones), in combination with various (biobased or not) aldehydes is in progress.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Author contributions

Conceptualization: LB, RR, CL, AB. Funding acquisition: LB, RR. Resources: CL, LM. Data analysis: CL, LB, RR, LM.

Investigation: AC, LP, CL. Supervision: CL, LM. Writing of draft: CL, LB. Writing: editing and review: RR, LM.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- 1 A. Dömling, W. Wang and K. Wang, Chemistry and Biology Of Multicomponent Reactions, *Chem. Rev.*, 2012, **112**, 3083–3135.
- 2 L. Banfi, A. Basso, C. Lambruschini, L. Moni and R. Riva, Synthesis of seven-membered nitrogen heterocycles through the Ugi multicomponent reaction, *Chem. Heterocycl. Compd.*, 2017, **53**, 382–408.
- 3 L. Banfi, A. Basso, C. Lambruschini, L. Moni and R. Riva, The 100 facets of the Passerini reaction, *Chem. Sci.*, 2021, **12**, 15445–15472.
- 4 R. C. Cioc, E. Ruijter and R. V. A. Orru, Multicomponent reactions: advanced tools for sustainable organic synthesis, *Green Chem.*, 2014, **16**, 2958–2975.
- 5 L. Banfi, C. Lambruschini, L. Moni and R. Riva, in *RSC Green Chemistry*, ed. R. Ballini, Royal Society of Chemistry, 2019, vol. 2019-January, pp. 115–140.
- 6 Z. Wang, M. S. Ganewatta and C. Tang, Sustainable polymers from biomass: Bridging chemistry with materials and processing, *Prog. Polym. Sci.*, 2020, **101**, 101197.
- 7 L. Moni, L. Banfi, A. Basso, E. Martino and R. Riva, Diastereoselective Passerini Reaction of Biobased Chiral Aldehydes: Divergent Synthesis of Various Polyfunctionalized Heterocycles, *Org. Lett.*, 2016, **18**, 1638–1641.
- 8 G. Vitali Forconesi, L. Banfi, A. Basso, C. Lambruschini, L. Moni and R. Riva, Synthesis of Polyoxygenated Heterocycles by Diastereoselective Functionalization of a Bio-Based Chiral Aldehyde Exploiting the Passerini Reaction, *Molecules*, 2020, **25**, 3227.
- 9 L. Moni, L. Banfi, D. Cartagenova, A. Cavalli, C. Lambruschini, E. Martino, R. V. A. Orru, E. Ruijter, J. M. Saya, J. Sgrignani and R. Riva, Zinc(ii)-mediated diastereoselective Passerini reactions of biocatalytically desymmetrised renewable inputs, *Org. Chem. Front.*, 2020, **7**, 380–398.



- 10 G. Vitali Forconesi, A. Basso, L. Banfi, D. Gugliotta, C. Lambruschini, M. Nola, R. Riva, V. Rocca and L. Moni, Total Synthesis of 4-epi-Bengamide E, *Molecules*, 2024, **29**, 1715.
- 11 C. Lambruschini, D. Galante, L. Moni, F. Ferraro, G. Gancia, R. Riva, A. Traverso, L. Banfi and C. D'Arrigo, Multicomponent, fragment-based synthesis of polyphenol-containing peptidomimetics and their inhibiting activity on beta-amyloid oligomerization, *Org. Biomol. Chem.*, 2017, **15**, 9331–9351.
- 12 D. Galante, L. Banfi, G. Baruzzo, A. Basso, C. D'Arrigo, D. Lunaccio, L. Moni, R. Riva and C. Lambruschini, Multicomponent Synthesis of Polyphenols and Their In Vitro Evaluation as Potential  $\beta$ -Amyloid Aggregation Inhibitors, *Molecules*, 2019, **24**, 2636.
- 13 C. Lambruschini, A. Basso, L. Moni, A. Pinna, R. Riva and L. Banfi, Bicyclic Heterocycles from Levulinic Acid through a Fast and Operationally Simple Diversity-Oriented Multicomponent Approach, *Eur. J. Org. Chem.*, 2018, **2018**, 5445–5455.
- 14 C. Lambruschini, I. Demori, Z. El Rashed, L. Rovegno, E. Canessa, K. Cortese, E. Grasselli and L. Moni, Synthesis, Photoisomerization, Antioxidant Activity, and Lipid-Lowering Effect of Ferulic Acid and Feruloyl Amides, *Molecules*, 2021, **26**, 89.
- 15 V. Cerulli, L. Banfi, A. Basso, V. Rocca and R. Riva, Diversity oriented and chemoenzymatic synthesis of densely functionalized pyrrolidines through a highly diastereoselective Ugi multicomponent reaction, *Org. Biomol. Chem.*, 2012, **10**, 1255–1274.
- 16 B. Paul, M. Maji, K. Chakrabarti and S. Kundu, Tandem transformations and multicomponent reactions utilizing alcohols following dehydrogenation strategy, *Org. Biomol. Chem.*, 2020, **18**, 2193–2214.
- 17 T. Nguansavanh and J. Zhu, Alcohols in Isonitrile-Based Multicomponent Reaction: Passerini Reaction of Alcohols in the Presence of O-Iodoxybenzoic Acid, *Angew. Chem., Int. Ed.*, 2006, **45**, 3495–3497.
- 18 F. Drouet, G. Masson and J. Zhu, Ugi Four-Component Reaction of Alcohols: Stoichiometric and Catalytic Oxidation/MCR Sequences, *Org. Lett.*, 2013, **15**, 2854–2857.
- 19 L. Moni, L. Banfi, R. Riva and A. Basso, External-Oxidant-Based Multicomponent Reactions, *Synthesis*, 2016, **48**, 4050–4059.
- 20 R. J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres and J. G. de Vries, Hydroxymethylfurfural, a versatile platform chemical made from renewable resources, *Chem. Rev.*, 2013, **113**, 1499–1597.
- 21 G. V. López and W. Porcal, Renewable carbon resource from biomass: building molecular architectures from furanic platforms, *Pure Appl. Chem.*, 2024, **96**, 1271–1277.
- 22 Y. Nakagawa, M. Tamura and K. Tomishige, Supported Metal Catalysts for Total Hydrogenation of Furfural and 5-Hydroxymethylfurfural, *J. Jpn. Petrol. Inst.*, 2017, **60**, 1–9.
- 23 T. Buntara, S. Noel, P. H. Phua, I. Melián-Cabrera, J. G. de Vries and H. J. Heeres, Caprolactam from Renewable Resources: Catalytic Conversion of 5-Hydroxymethylfurfural into Caprolactone, *Angew. Chem., Int. Ed.*, 2011, **50**, 7083–7087.
- 24 C. Lambruschini, L. Moni and L. Banfi, Diastereoselectivity in Passerini Reactions of Chiral Aldehydes and in Ugi Reactions of Chiral Cyclic Imines, *Eur. J. Org. Chem.*, 2020, **2020**, 3766–3778.
- 25 S. Caputo, L. Banfi, A. Basso, A. Galatini, L. Moni, R. Riva and C. Lambruschini, Diversity-Oriented Synthesis of Various Enantiopure Heterocycles by Coupling Organocatalysis with Multicomponent Reactions, *Eur. J. Org. Chem.*, 2017, **2017**, 6619–6628.
- 26 A. Pinna, A. Basso, C. Lambruschini, L. Moni, R. Riva, V. Rocca and L. Banfi, Stereodivergent access to all four stereoisomers of chiral tetrahydrobenzo[f][1,4]oxazepines, through highly diastereoselective multicomponent Ugi–Joullié reaction, *RSC Adv.*, 2020, **10**, 965–972.
- 27 A. G. Németh, G. M. Keserű and P. Ábrányi-Balogh, A novel three-component reaction between isocyanides, alcohols or thiols and elemental sulfur: a mild, catalyst-free approach towards O-thiocarbamates and dithiocarbamates, *Beilstein J. Org. Chem.*, 2019, **15**, 1523–1533.
- 28 A. Mekhafia and I. E. Markó, The silyl modified sakurai (SMS) reaction. An efficient and versatile one-pot synthesis of homoallylic ethers, *Tetrahedron Lett.*, 1991, **32**, 4779–4782.
- 29 T. Jacques, I. E. Markó and J. í. Pospíšil, in *Multicomponent Reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2005, ch. 13, pp. 398–452.
- 30 D. Kampen, A. Ladépêche, G. Claßen and B. List, Brønsted Acid-Catalyzed Three-Component Hosomi–Sakurai Reactions, *Adv. Synth. Catal.*, 2008, **350**, 962–966.
- 31 H. Sakurai, K. Sasaki, J. Hayashi and A. Hosomi, Chemistry of organosilicon compounds. 191. Acetalization of carbonyl compounds with alkoxyasilanes catalyzed by iodotrimethylsilane. One-pot allylation reactions of carbonyl compounds to homoallyl ethers using an allylsilane, *J. Org. Chem.*, 1984, **49**, 2808–2809.
- 32 T. Watahiki, Y. Akabane, S. Mori and T. Oriyama, Iron(III) Chloride-Catalyzed Convenient One-Pot Synthesis of Homoallyl Benzyl Ethers Starting from Aldehydes, *Org. Lett.*, 2003, **5**, 3045–3048.
- 33 J. Pospíšil and I. E. Markó, Total Synthesis of Jerangolid D, *J. Am. Chem. Soc.*, 2007, **129**, 3516–3517.
- 34 J. Pospisil, T. Kumamoto and I. E. Marko, Highly diastereoselective silyl-modified sakurai multicomponent reaction, *Angew. Chem., Int. Ed.*, 2006, **45**, 3357–3360.
- 35 M. Yus, J. C. Gonzalez-Gomez and F. Foubelo, Diastereoselective allylation of carbonyl compounds and imines: application to the synthesis of natural products, *Chem. Rev.*, 2013, **113**, 5595–5698.
- 36 M. Teruaki, O. Masahiro and M. Norikazu, An Efficient and Convenient Method for the Asymmetric Allylation of Aldehydes with Allyltrimethylsilane Catalyzed by Diphenylboryl Triflate, *Chem. Lett.*, 1987, **16**, 1121–1124.
- 37 L. F. Tietze, K. Schiemann and C. Wegner, Enantioselective Synthesis of Tertiary Homoallylic Alcohols via Diastereoselective Addition of Allylsilanes to Ketones, *J. Am. Chem. Soc.*, 1995, **117**, 5851–5852.



- 38 J. Cossrow and S. D. Rychnovsky, Optically pure alpha-(trimethylsilyl)benzyl alcohol: a practical chiral auxiliary for oxocarbenium ion reactions, *Org. Lett.*, 2002, **4**, 147–150.
- 39 J. S. Panek, M. Yang and F. Xu, Diastereoselective additions of chiral (E)-crotylsilanes to in situ generated oxonium ions: a direct asymmetric synthesis of functionalized homoallylic ethers, *J. Org. Chem.*, 1992, **57**, 5790–5792.
- 40 J. Wu, Y. Chen and J. S. Panek, Vinylogous Aldol Products from Chiral Crotylsilanes Obtained by Enantioselective Rh(II) and Cu(I) Carbenoid Si–H Insertion, *Org. Lett.*, 2010, **12**, 2112–2115.
- 41 D. Kim, J. S. Lee, L. Lozano, S. B. Kong and H. Han, Enantioenriched Bifunctional Crotylsilanes for the Asymmetric Synthesis of Orthogonally Protected 2-Methyl-1,3-diols, *Org. Lett.*, 2013, **15**, 5142–5145.
- 42 Y. Chu, Q. Pu, Z. Tang, L. Gao and Z. Song, Enantioselective synthesis of crotyl geminal bis(silane) and its usage for asymmetric Sakurai allylation of acetals, *Tetrahedron*, 2017, **73**, 3707–3713.
- 43 B. Karimi and B. Golshani, Mild and Highly Efficient Method for the Silylation of Alcohols Using Hexamethyldisilazane Catalyzed by Iodine under Nearly Neutral Reaction Conditions, *J. Org. Chem.*, 2000, **65**, 7228–7230.
- 44 A. Ramdular and K. A. Woerpel, Using Neighboring-Group Participation for Acyclic Stereocontrol in Diastereoselective Substitution Reactions of Acetals, *Org. Lett.*, 2020, **22**, 4113–4117.
- 45 A. Chojnacka, R. Obara and C. Wawrzęńczyk, Kinetic resolution of racemic secondary aliphatic allylic alcohols in lipase-catalyzed transesterification, *Tetrahedron:Asymmetry*, 2007, **18**, 101–107.
- 46 S. Purushotham Reddy, B. Chinnababu, V. Shekhar, D. Kumar Reddy, G. V. Bhanuprakash, L. R. Velatoor, J. Venkateswara Rao and Y. Venkateswarlu, Stereoselective synthesis of alpinoid-C and its analogues and study of their cytotoxic activity against cancer cell lines, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4182–4184.
- 47 Q. Gao, Y. Li, L. Chen, L.-J. Xie, X. Shao, Z. Ke and S. Xu, Enantioselective  $\alpha$ -C(sp<sup>3</sup>)-H Borylation of Masked Primary Alcohols Enabled by Iridium Catalysis, *J. Am. Chem. Soc.*, 2025, **147**, 88–95.
- 48 D. Seebach, A. K. Beck, B. Schmidt and Y. M. Wang, Enantio- and diastereoselective titanium-TADDOLate catalyzed addition of diethyl and bis(3-buten-1-yl) zinc to aldehydes a full account with preparative details, *Tetrahedron*, 1994, **50**, 4363–4384.
- 49 R. J. Kazlauskas, A. N. Weissfloch, A. T. Rappaport and L. A. Cuccia, A rule to predict which enantiomer of a secondary alcohol reacts faster in reactions catalyzed by cholesterol esterase, lipase from *Pseudomonas cepacia*, and lipase from *Candida rugosa*, *J. Org. Chem.*, 1991, **56**, 2656–2665.
- 50 M. N. Timofeeva, V. N. Panchenko, A. Gil, S. V. Zakusin, V. V. Krupskaya, K. P. Volcho and M. A. Vicente, Effect of structure and acidity of acid modified clay materials on synthesis of octahydro-2H-chromen-4-ol from vanillin and isopulegol, *Catal. Commun.*, 2015, **69**, 234–238.
- 51 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis, *Angew. Chem., Int. Ed.*, 1985, **24**, 1–30.
- 52 W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. A. Straub and A. D. Palkowitz, Asymmetric synthesis using tartrate ester modified allylboronates. 2. Single and double asymmetric reactions with alkoxy-substituted aldehydes, *J. Org. Chem.*, 1990, **55**, 4117–4126.
- 53 G. Keum, S. B. Kang, Y. Kim and E. Lee, Stereoselection in Radical Cyclization of  $\beta$ -Alkoxyvinyl Sulfoxides: Synthesis of Tetrahydrofuran-yl Allyl Carbinols, *Org. Lett.*, 2004, **6**, 1895–1897.
- 54 G. Keum, C. H. Hwang, S. B. Kang, Y. Kim and E. Lee, Stereoselective Syntheses of Rolliniastatin 1, Rollimembrin, and Membranacin, *J. Am. Chem. Soc.*, 2005, **127**, 10396–10399.

