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## Ethyl lactate as a renewable carbonyl source for the synthesis of diynones

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**Ethyl lactate, a sustainable feedstock, serves as a highly attractive building block for the synthesis of value-added chemicals such as skipped diynones and, after gold-catalyzed transposition, conjugated diynones. Green solvents are involved in all steps and high yields are obtained for the final diynones which, in several cases, are isolated in pure form without any purification.**

One of the main goals of Green Chemistry is to switch from depleting raw materials to renewable sources, which is described in the 7<sup>th</sup> principle. Therefore, the concept of renewability<sup>1</sup> could be considered crucial nowadays and the development of sustainable processes that employ eco-friendly and readily available biomass-derived feedstocks for the synthesis of value-enhanced chemicals constitutes one of the major challenges in chemical research.<sup>2</sup> In this context, lactic acid and lactates are highly functionalized biobased feedstocks that can be catalytically produced from renewable carbohydrates.<sup>3</sup> Hence, ethyl lactate (EL) is a biomass-derived platform molecule that is unexpensive and completely biodegradable within very short times and does not show any potential health risks.<sup>4</sup> It has been described as a sustainable and green solvent with adequate properties for the replacement of organic solvents.<sup>5</sup> Therefore, EL possesses a promising and appealing potential, from the Green Chemistry point of view, to be used as a sustainable feedstock for the preparation of value-added chemicals.<sup>6</sup>

On the other hand, the oxidative cleavage of glycols and related functional groups is a key transformation in organic synthesis widely used for the preparation and transformation of natural products and, more recently, in biomass valorization for the production of renewable feedstocks.<sup>7</sup> Classical procedures for this reaction involve the use of periodic acid or its salts (Malaprade reaction),<sup>8</sup> and lead tetraacetate (Criegee oxidation).<sup>9</sup> These methods suffer from important drawbacks,

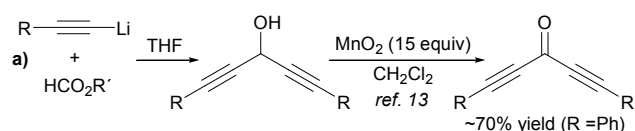
such as the generation of stoichiometric amounts of waste, and so, catalytic and greener alternatives have been recently developed in order to avoid the environmental concerns of the classical reagents, mainly by introducing alternative oxidants and improving the atom-economy.<sup>10</sup> However, none of the reported cleaner procedures solve all the chemoselectivity and reactivity issues. Another approach to minimize the environmental impact caused by the use of classical reagents, like sodium metaperiodate, is their replacement by silica gel-supported NaIO<sub>4</sub> as a reagent for the oxidative cleavage of glycols.<sup>11</sup> This procedure, reported by Shing and Zhong,<sup>11a</sup> has several advantages such as the low cost of both the oxidant and the support, and a simple workup by filtration that affords pure carbonyl compounds in very high yields. However, the required use of a nonpolar solvent like CH<sub>2</sub>Cl<sub>2</sub> that solves the solubility problems, instead of aqueous alcohols or THF, also presents obvious environmental concerns.

Diynones are highly electrophilic substrates and possess multiple reaction sites, which make them useful starting materials for the preparation of a variety of interesting carbo and heterocycles.<sup>12</sup> The general method for their preparation is based on the oxidation of a secondary 1,4-diyn-3-ol, generated from the double addition of lithium or magnesium acetylides to alkyl formates (Scheme 1a).<sup>13</sup> Although well-established and with good overall yields around 70%, this two-step sequence employs a high excess (up to 15 equiv) of oxidants such as manganese dioxide, barium manganate, or PCC, in CH<sub>2</sub>Cl<sub>2</sub>, that leads to a considerable amount of waste with severe environmental as well as human health issues. Following with our interest in the development of cleaner synthetic methodologies, mainly involving oxygen-atom-transfer reactions under dioxomolybdenum(VI)-catalysis,<sup>14</sup> and considering our recently reported method for the oxidative cleavage of glycols with DMSO,<sup>15</sup> we envisaged that a new approach for synthesizing symmetrical skipped diynones could involve the oxidative cleavage of the corresponding 1,1,-dialkynyl-1,2-diols, which are easily available from biomass-derived EL (Scheme 1b).

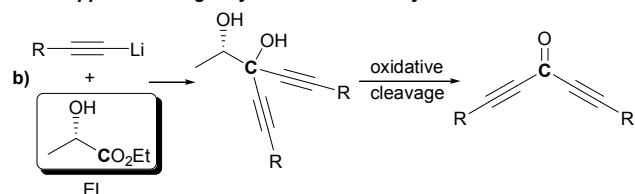
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## General method for the synthesis of diynones:



## Our approach using ethyl lactate as carbonyl source:



**Scheme 1** General method for the synthesis of skipped diynones and our proposed approach from EL.

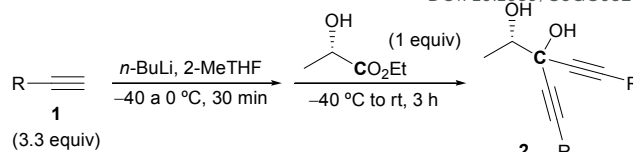
Although the preparation of 1,1,-dialkynyl-1,2-diols **2** from EL has already been reported by its treatment with lithium acetylides (3 equiv),<sup>16</sup> the moderate to good yields obtained, as well as the use of THF as solvent and LiBr as additive, make this procedure susceptible of improvement from the Green Chemistry point of view. We tried to solve these drawbacks by using 2-MeTHF as solvent, which is a renewable alternative to THF, can be produced from lignocellulosic biomass, and presents additional advantages such as lower water miscibility, higher stability, lower volatility, easiness to degrade, and lower toxicity.<sup>17</sup> Gratifyingly, the employment of 2-MeTHF and a slight excess of the corresponding lithium acetylide (3.3 equiv) gave rise to high yields of the expected dialkynyl glycols **2** without the addition of LiBr (Table 1).<sup>18</sup> This general method was successfully performed on a wide variety of alkynes **1**, including aromatic substituted with both electron-withdrawing and electron-donating groups (entries 1, 9–11), heteroaromatic (entries 7–8), (cyclo)alkyl (entries 2–4), alkenyl (entries 5–6), as well as those derived from propargyl alcohols, ethers or amines (entries 12–15). Moreover, silyl-protected alkyne **1p** also allowed the preparation of the corresponding glycol **2p** in high yield (entry 16) and, significantly, 1,2-diol **2q** bearing terminal alkynes could be efficiently accessed from the reaction of EL with commercially available ethynylmagnesium bromide (entry 17). In addition, similar results were obtained for the preparation of **2b** and **2f** using methyl lactate instead of EL. It is worth noting that when starting alkyne **1** possesses a low boiling point, the corresponding crude glycol **2** is obtained pure enough for the next step in an almost quantitative yield.<sup>19</sup>

With an efficient procedure for accessing 1,1,-dialkynyl-1,2-diols **2** in our hands, and considering the second step of our initial proposal, we needed to develop a method for the oxidative cleavage of glycols **2**. We selected diol **2a** as model substrate and tested our recently developed method for this type of oxidations that uses DMSO as stoichiometric oxidant under dioxomolybdenum(VI)-catalysis (Scheme 2).<sup>15</sup> However, under the reported conditions, a low yield of the desired diynone **3a** was obtained, which could not be improved by

**Table 1** Synthesis of bispropargyl diols **2** from ethyl lactate<sup>a</sup>

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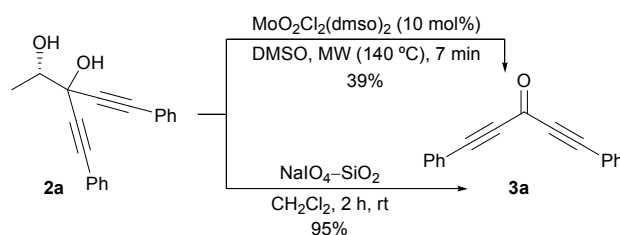


Entry	R	Product	Yield <sup>b</sup> (%)
1	Ph	<b>2a</b>	84 (94)
2	<i>n</i> -Bu	<b>2b</b>	89 (95)
3	<i>c</i> -C <sub>3</sub> H <sub>5</sub>	<b>2c</b>	83 (95)
4	(CH <sub>2</sub> ) <sub>2</sub> Ph	<b>2d</b>	74 (87)
5	<i>c</i> -C <sub>6</sub> H <sub>9</sub> <sup>c</sup>	<b>2e</b>	75 (93)
6	C(CH <sub>3</sub> )=CH <sub>2</sub>	<b>2f</b>	74 (89)
7	3-Th <sup>d</sup>	<b>2g</b>	70 (–) <sup>e</sup>
8	2-Th <sup>f</sup>	<b>2h</b>	75 (–) <sup>e</sup>
9	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>2i</b>	74 (86)
10	3-FC <sub>6</sub> H <sub>4</sub>	<b>2j</b>	72 (92)
11	2,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>2k</b>	73 (–) <sup>e</sup>
12	CH <sub>2</sub> N(Me)Ph	<b>2l</b>	71 (90)
13 <sup>g</sup>	CH <sub>2</sub> O(4-MeOC <sub>6</sub> H <sub>4</sub> )	<b>2m</b>	66 (84)
14 <sup>g</sup>	CH <sub>2</sub> O[3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ]	<b>2n</b>	70 (85)
15 <sup>h</sup>	C(Me) <sub>2</sub> OH	<b>2o</b>	62 (–) <sup>e</sup>
16	Si( <i>i</i> -Pr) <sub>3</sub>	<b>2p</b>	80 (89)
17 <sup>i</sup>	H	<b>2q</b>	84 (87)

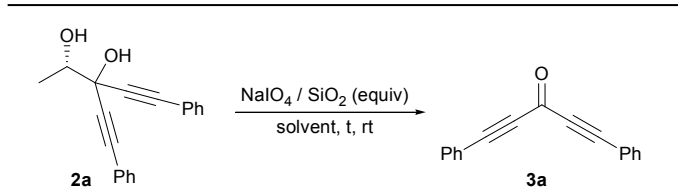
<sup>a</sup> Reaction conditions: **1** (3.4 mmol), *n*-BuLi (3.3 mmol) in 2-MeTHF (10 mL) followed by addition of EL (1 mmol). <sup>b</sup> Isolated yield after column chromatography, in brackets crude yields of almost pure compounds (see ESI). <sup>c</sup> 1-Cyclohexenyl. <sup>d</sup> 3-Thienyl. <sup>e</sup> Not determined. <sup>f</sup> 2-Thienyl. <sup>g</sup> EtMgBr (4 mmol) was used instead of *n*-BuLi. <sup>h</sup> *n*-BuLi (6.6 mmol) was used. <sup>i</sup> Commercially available ethynyl magnesium bromide in THF (5 equiv) was used and the reaction was refluxed overnight.

varying the temperature or reaction time,<sup>20</sup> likely due to competitive decomposition of the final product. Following this methodology, slightly better yields could be obtained for the oxidative cleavage of diols **2b** and **2e**, which afforded the corresponding diynones **3b** and **3e** in only moderate yields (45–50%). We next thought about the use of NaIO<sub>4</sub>–SiO<sub>2</sub> as potential reagent for the oxidative cleavage of model glycol **2a**. Gratifyingly, under the reported conditions,<sup>11a</sup> with CH<sub>2</sub>Cl<sub>2</sub> as solvent and 1.6 equiv of supported NaIO<sub>4</sub>, diynone **3a** was isolated in almost quantitative yield and in pure form by simple filtration of the supported reagent (Scheme 2).

Although this last procedure seems highly appropriate for our proposed synthesis of skipped diynones, the employment of a chlorinated solvent led us to try to re-optimize the



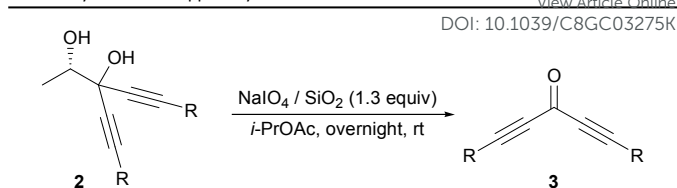
**Scheme 2** Oxidative cleavage of glycol **2a**.

**Table 2** Optimization of the reaction conditions for the oxidative cleavage of **2a** with NaIO<sub>4</sub>-SiO<sub>2</sub><sup>a</sup>

Entry	Solvent	NaIO <sub>4</sub> (equiv)	Time (h)	Conversion <sup>b</sup> (%)	Yield <sup>c</sup> (%)
1	CH <sub>2</sub> Cl <sub>2</sub>	1.6	2	100	95
2	MeOH	1.8	2	60	–
3	MeOH	1.8	6	84	–
4	MeOH	1.6	16	100	95
5	EtOH	1.8	2	31	–
6	EtOH	1.8	6	64	–
7	EtOH	1.6	16	100	93
8	EtOAc	1.8	4	88	–
9	EtOAc	1.8	7	100	96
10	<i>i</i> -PrOAc	1.8	2	62	–
11	<i>i</i> -PrOAc	1.8	7	100	97
12	<i>i</i> -PrOAc	1.5	16	100	97
13	<i>i</i> -PrOAc	1.3	16	100	96
14	<i>i</i> -PrOAc	1.1	16	85	–
15	<i>i</i> -PrOAc	2.5	5	100	97

<sup>a</sup> Reaction conditions: **2a** (0.2 mmol) in the corresponding solvent (2 mL). <sup>b</sup> Determined by <sup>1</sup>H-NMR analysis of the crude. Only **3a** and **2a** are present in the crude for not complete conversion examples. <sup>c</sup> Isolated yield.

reaction conditions in order to look for an eco-friendly alternative to the previously established use of CH<sub>2</sub>Cl<sub>2</sub> (Table 2, entry 1). Accordingly, we started this study by testing different and greener solvents and also by adjusting the reaction time and the amount of the oxidant for each one. MeOH and EtOH were tried out as they are typically used in homogeneous oxidations with NaIO<sub>4</sub>. Both of them proved to be compatible with this reaction, although longer reaction times and/or higher amounts of the oxidant were required to reach complete conversion (Table 2, entries 2–7). In addition, in these solvents some leaching of the supported reagent seemed to take place. Then, we turned our attention to more environmental-friendly carboxylic esters as solvents and we checked that AcOEt was also an efficient reaction media for this transformation (entries 8 and 9). Looking for an even more eco-friendly solvent we decided to use *i*-PrOAc, which is recognized as one of the greenest solvents and,<sup>21</sup> gratifyingly, we found that the oxidative cleavage also took efficiently place (entries 10–15). We could determine the optimum conditions for complete cleavage of **2a** leading to an almost quantitative yield of **3a** (entry 13), although the reaction time could be shortened by using a higher amount of the oxidant (entries 11 and 15). Interestingly, treatment of **2a** with NaIO<sub>4</sub> in *i*-PrOAc did not led to any transformation after 24 h showing that the supported oxidant presents significant advantages over the non-supported one besides its easy removal. It is also worthy to note that in all the cases diynone **3a** was isolated in pure form after simple filtration of the supported reagent, as the only byproduct of the process, acetaldehyde, is easily removed along with the solvent by evaporation under reduced pressure.

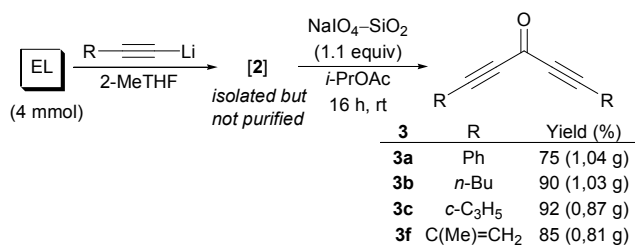
**Table 3** Synthesis of skipped diynones **3**<sup>a</sup>

Entry	Starting diol	R	Product	Yield <sup>b</sup> (%)
1	<b>2a</b>	Ph	<b>3a</b>	95
2	<b>2b</b>	<i>n</i> -Bu	<b>3b</b>	98
3	<b>2c</b>	<i>c</i> -C <sub>3</sub> H <sub>5</sub>	<b>3c</b>	91
4	<b>2d</b>	(CH <sub>2</sub> ) <sub>2</sub> Ph	<b>3d</b>	93
5	<b>2e</b>	<i>c</i> -C <sub>6</sub> H <sub>9</sub> <sup>c</sup>	<b>3e</b>	96
6	<b>2f</b>	C(Me)=CH <sub>2</sub>	<b>3f</b>	97
7	<b>2g</b>	3-Th <sup>d</sup>	<b>3g</b>	92
8	<b>2h</b>	2-Th <sup>e</sup>	<b>3h</b>	94
9	<b>2i</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>3i</b>	88
10	<b>2j</b>	3-FC <sub>6</sub> H <sub>4</sub>	<b>3j</b>	96
11	<b>2k</b>	2,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3k</b>	93
12	<b>2l</b>	CH <sub>2</sub> N(Me)Ph	<b>3l</b>	82
13	<b>2m</b>	CH <sub>2</sub> O(4-MeOC <sub>6</sub> H <sub>4</sub> )	<b>3m</b>	93
14	<b>2n</b>	CH <sub>2</sub> O[3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ]	<b>3n</b>	95
15	<b>2o</b>	C(Me) <sub>2</sub> OH	<b>3o</b>	93
16	<b>2p</b>	Si( <i>i</i> -Pr) <sub>3</sub>	<b>3p</b>	96
17 <sup>f</sup>	<b>2q</b>	H	<b>3q</b>	85 <sup>g</sup>

<sup>a</sup> Reaction conditions: **2** (0.5 mmol) was treated with NaIO<sub>4</sub> / SiO<sub>2</sub> (1.3 equiv) in *i*-PrOAc (5 mL). <sup>b</sup> Isolated yield. <sup>c</sup> 1-Cyclohexenyl. <sup>d</sup> 3-Thienyl. <sup>e</sup> 2-Thienyl. <sup>f</sup> Carried out in CDCl<sub>3</sub>. <sup>g</sup> Determined by <sup>1</sup>H-NMR.

Moreover, the acetaldehyde solution in *i*-PrOAc could be collected adding further value to this valorization of EL.

Having established the optimized conditions for the oxidative cleavage of glycols **2** with NaIO<sub>4</sub>-SiO<sub>2</sub>, we decided to evaluate the substrate scope (Table 3). Gratifyingly, starting diols **2** bearing (functionalized)aryl and heteroaryl groups as substituents of the alkyne, efficiently underwent the oxidative cleavage (entries 1 and 7–11), as well as those with (cyclo)alkyl and alkenyl groups (entries 2–6), leading to the symmetrical skipped diynones **3a-k** in almost quantitative yields. In the same way, functionalized starting diols **2l-n** also led to the corresponding diynones **3l-o** without any side product (entries 12–15). Finally, silyl-substituted diynone **3p** and terminal diynone **3q** could also be obtained from the corresponding dialkynyl diols **2p** and **2q** (entries 16 and 17). Due to the low boiling point of **3q**, the oxidative cleavage of **2q** was carried out in CDCl<sub>3</sub> and the NMR of the crude shows the clean formation of **3q** along with acetaldehyde (see ESI). It is interesting to note that in all the cases the final diynone **3** was obtained in pure form after a simple filtration and removal of the solvent.



**Scheme 3** Gram-scale preparation of selected skipped diyrones **3** from EL.

Moreover, this methodology is amenable for scale up and can be applied to the preparation of diyrones such as **3a,b,c,f** in gram scale. Interestingly, the corresponding intermediate glycol **2a,b,c,f** does not need to be purified and, after a simple extraction with EtOAc or *i*-PrOAc, it could be used for the subsequent oxidative cleavage with the NaIO<sub>4</sub>-SiO<sub>2</sub> reagent. Moreover, in these gram-scale experiments the amount of the supported oxidant could be reduced up to 1.1 equiv further improving the greenness of the overall procedure (Scheme 3). For instance, starting from 0,709 g of ethyl lactate, 1,036 g (75%) of diynone **3a**, 1,027 g (90%) of diynone **3b**, 0,873 g (91%) of diynone **3c** and 0,806 g (85%) of diynone **3f** could be obtained, respectively. Moreover, it is worthy to note that these skipped diyrones **3** were isolated in pure form without the need of any purification process (only **3a** was purified by column chromatography due to its partial decomposition under the reaction conditions).

Taking advantage from this efficient method for the synthesis of skipped diyrones **3**, and inspired by the work of Gevorgyan and co-workers about the gold-catalyzed 1,3-transposition of ynones,<sup>22</sup> we decided to combine both processes to achieve a new valorization of EL. In their original report, the authors used a cationic gold(I) complex bearing a triarylphosphite ligand as catalytic system, in DCE as solvent, for the transformation of skipped diyrones **3** into their conjugated isomers **4**. After a brief experimentation with diynone **3a** as model, we obtained better results with the cationic gold(I) complex IPrAuNTf<sub>2</sub><sup>23</sup> (Table 4, entries 1–4). To further improve this protocol, and also considering that the availability of DCE is now severely limited in the European Union due to regulatory controls,<sup>24</sup> we thought about replacing this chlorinated solvent by a greener alternative. Whereas toluene and trifluorotoluene resulted to be successful alternatives to DCE (entries 5 and 6), gratifyingly, we found that environmentally-friendly *i*-PrOAc was again a convenient solvent for this Au-catalyzed transformation, although no complete conversion was observed at room temperature (entry 7). Upon increasing the reaction temperature the starting material was consumed (entry 8). Finally, we have also found that under microwave irradiation the reaction time can be dramatically shortened from several hours to 10 minutes (entry 9). The use of *i*-PrOAc as green solvent for this reaction is highly remarkable as few examples of gold-catalyzed processes carried out in safe, non-toxic, biorenewable and cheap solvents have been reported.<sup>25</sup> Under these optimized conditions conjugated diynone **4a** was obtained in high yield from **3a** (entry 9). In an analogous way conjugated diyrones **4b**

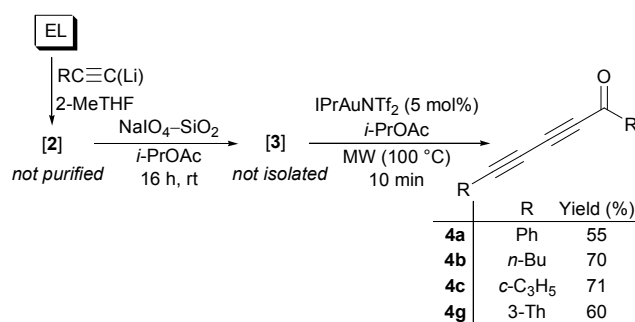
**Table 4** Optimization study with greener solvents for the Au-catalyzed 1,3-transposition of **3a**<sup>a</sup>

Entry	Au catalyst	Solvent	Temp (°C) <sup>b</sup>	Time (h)	Conversion <sup>c</sup> (%)
1 <sup>d</sup>	(ArO) <sub>3</sub> PAuCl/AgBF <sub>4</sub>	DCE	rt	4	10
2 <sup>d</sup>	(ArO) <sub>3</sub> PAuCl/AgSbF <sub>6</sub>	DCE	rt	4	80
3	Ph <sub>3</sub> PAuNTf <sub>2</sub>	DCE	rt	4	90
4	IPrAuNTf <sub>2</sub>	DCE	rt	4	100
5	IPrAuNTf <sub>2</sub>	PhCF <sub>3</sub>	rt	16	100
6	IPrAuNTf <sub>2</sub>	toluene	80 (Δ)	16	100
7 <sup>e</sup>	IPrAuNTf <sub>2</sub>	<i>i</i> -PrOAc	rt	24	60
8	IPrAuNTf <sub>2</sub>	<i>i</i> -PrOAc	80 (Δ)	6	100
9	IPrAuNTf <sub>2</sub>	<i>i</i> -PrOAc	100 (MW)	0,2	100 (81)

<sup>a</sup> Reaction conditions: **3a** (0.2 mmol) in the corresponding solvent (2 mL). <sup>b</sup> In brackets the way of heating (MW: microwave; Δ: conventional heating). <sup>c</sup> Determined by <sup>1</sup>H-NMR analysis of the crude. Only **3a** and **4a** are present in the crude for not complete conversion examples. Isolated yields of crude mixtures were >90% in all the cases. In brackets isolated yield. <sup>d</sup> Ar = (2,4-ditertbutylphenyl). <sup>e</sup> The gold catalyst was added in two portions (2.5 mol% at the beginning of the reaction and 2.5 mol% after 10 h).

and **4c** could be also obtained from the corresponding skipped diyrones **3b** and **3c** in high isolated yields (80–85%).

After this study, a selection of conjugated diyrones **4a-c,g** could be prepared in good to high isolated yields (referred to EL) without any intermediate purification, following the sequence shown in Scheme 4.<sup>26</sup> It is important to note that all the reactions, acetylide addition to EL, oxidative cleavage, and Au-catalyzed transposition, yield the corresponding products in almost pure form allowing the next step to be performed with the crudes. Only final diyrones **4** needed purification in order to remove impurities coming from the gold catalyst. In addition, the solvents employed in these processes (2-MeTHF and *i*-PrOAc) are ecofriendly alternatives to the ones typically used (THF and CH<sub>2</sub>Cl<sub>2</sub> or DCE).



**Scheme 4** Further valorization of EL: synthesis of conjugated diyrones **4**.



## Conclusions

We have demonstrated how a biomass-derived platform molecule, ethyl lactate, serves as a highly efficient, sustainable and environmentally benign C<sub>1</sub> building block for the synthesis of high-added-value chemicals such as symmetrical skipped diynones. To meet the sustainability criteria, THF and halogenated solvents, typically used in the involved reactions, have been replaced by greener alternatives such as 2-MeTHF and *i*-PrOAc, respectively. In addition, the gold-catalyzed transposition of skipped diynones to conjugated ones, but employing environmentally-friendly *i*-PrOAc instead of chlorinated solvents, has been also merged with this valorization of EL.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

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