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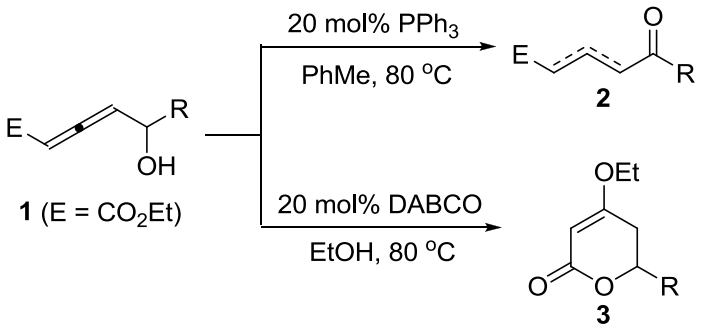
Graphical Abstract



Lewis Base-Catalyzed Divergent Isomerizations of 5-Hydroxyl-2,3-dienoate

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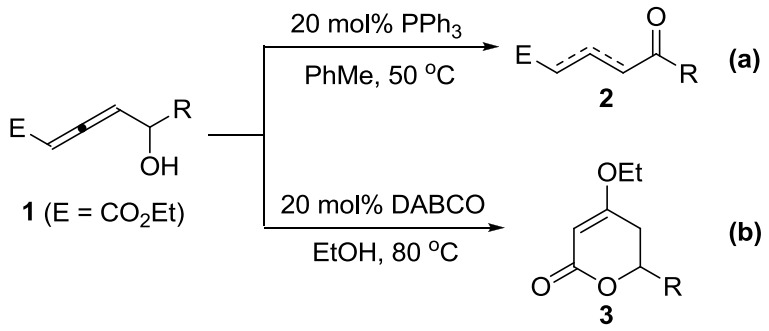
Abstract: A divergent isomerization of 5-hydroxyl-2,3-dienoate **1** catalyzed by Lewis base has been developed, the phosphine catalyst leads to 5-oxohex-2(3)-enoates **2** while DABCO catalyst affords 3-ethoxy α,β-unsaturated lactone **3**.

Keywords: Lewis Base; isomerization; 5-hydroxyl-2,3-dienoate

Lewis base catalysis has emerged as a rapidly growing area of research interest and has been a robust synthetic tool to produce numerous densely functionalized compounds.[1] The catalytic use of Lewis base has been most intensively investigated and demonstrated in such as Morita-Baylis-Hillman reaction[2], Rauhut-Currier reaction[3], Lu's type cycloaddtion[4], [2+2] cycloaddition[5], umpolung addition[6] and so on. With sharp contrast to the highly active situation of the above-mentioned reactions, rare efforts have been devoted to the phosphine-catalyzed isomerization of activated allene and alkyne to (*E*,*E*)-1,3-diene. No variant of this isomerization, to the best of our knowledge, has been developed since it was independently discovered by Trost and Lu in 1990s,[7] although its synthetic applications have been elegantly demonstrated.[8] Herein, we report a novel phosphine-catalyzed isomerization of 5-hydroxyl-2,3-dienoate **1** to 5-oxohex-2(3)-enoates **2** (Scheme 1a). Furthermore, it is interesting to find that the isomerization of **1** is switched to afford lactone **3** when DABCO is instead used as the catalyst (Scheme 1b).



Scheme 1. Lewis Base-Catalyzed Divergent Isomerizations of 2,3-dienoate **1**

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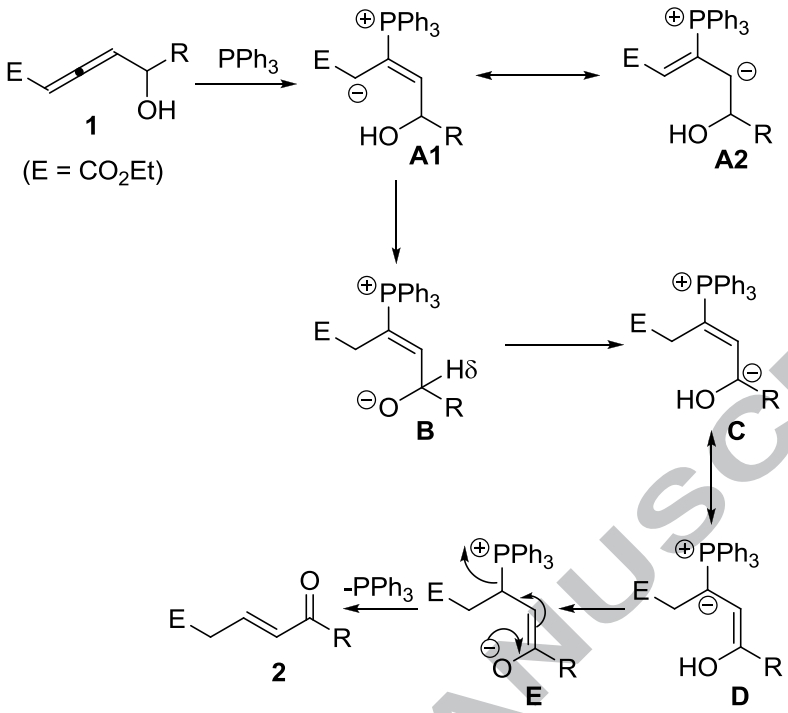


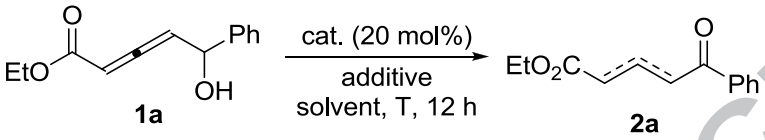
Scheme 2. Working Hypothesis for Phosphine-Catalyzed Isomerization of **1** to **2**

Our design plan was prompted by the generally accepted mechanism for the PPh_3-catalyzed isomerization of allenoate. The working hypothesis for the isomerization of **1** to **2** is depicted in Scheme 2. Addition of triphenylphosphine to allenoate **1** results in the formation of zwitterionic resonants **A1** and **A2**. Then, the former intermediate **A1** undergoes continuous proton shifts to generate intermediate **C**. In the case of phosphine-catalyzed isomerization of allenoate, an acid co-catalyst is typically required to facilitate the corresponding proton shifts.[9] The hydroxyl group of allenoate **1** might play a similar role as the acid co-catalyst. Thus, no requirement of external acid co-catalyst could be anticipated for the isomerization of **1** to **2**. Subsequently, intermediate **D**, which is a resonance form of **C**, undergoes proton shift to form intermeidate **E**, which is followed by 1,4-elimination of phosphine catalyst to give product **2**. As part of our ongoing effort in Lewis base catalysis,[10] we set out to investigate this possibility.

Thus, we initially chose compound **1a** as the model substrate in order to establish an optimal reaction conditions (Table 1). With 20 mol% triphenylphosphine as the catalyst and toluene as the solvent, we were delighted to find that the isomerization of **1a** smoothly occurred at room temperature, affording product **2a** in 54% yield (Table 1, entry 1). When the reaction was carried out at 50 ^{o}C, the yield of **2a** was improved to 80%, and further elevating the temperature proved unnecessary (Table 1, entries 2

and 3). Based on these results, some other phosphines, such as tris(4-fluorophenyl)phosphine, tris(furan-2-yl)phosphine as well as tributylphosphine, were also explored. However, they did not exhibit any superior performance than PPh_3 (Table 1, entries 4-6). After brief screening of solvent, we identified that toluene was an optimal choice (Table 1, entries 7-9).

Table 1. Optimization of Reaction Conditions for Isomerization of **1a** to **2a**.[a]

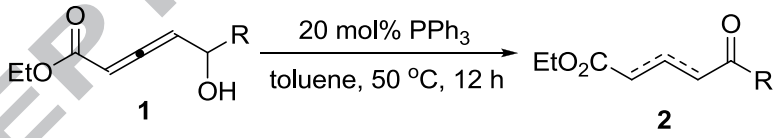


1a **2a**

entry	cat.	solvent	T (^oC)	Yield (%)[b]
1	PPh_3	toluene	25	54
2	PPh_3	toluene	50	80
3	PPh_3	toluene	80	67
4	$P(4\text{-F-}C_6H_4)_3$	toluene	50	72
5	$P(2\text{-furan})_3$	toluene	50	64
6	$(nBu)_3P$	toluene	50	58
7	PPh_3	THF	50	63
8	PPh_3	MeOH	50	45
9	PPh_3	DCM	50	73

[a] Reaction conditions: 1a (0.2 mmol), phosphine (0.04 mmol), 4 mL solvent. [b] Isolated yield.

Table 2. Phosphine-catalyzed Isomerization of **1** to **2a**

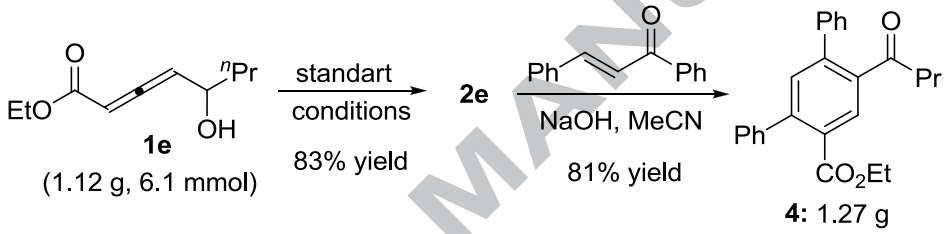


1 **2**

entry	**1** (R)	2	Yield (%)[b]
1	**1a** (Ph)	**2a**	80
2	**1b** (4-Me-C_6H_4)	**2b**	54
3	**1c** (4-MeO-C_6H_4)	**2c**	73
4	**1d** (4-Br-C_6H_4)	**2d**	54
5	**1e** (nPr)	**2e**	92
6	**1f** [-$(CH_2)_2$Ph]	**2f**	85
7	**1g** [-$(CH_2)_2$OTBS]	**2g**	85
8	**1h** (styryl)	**2h**	NR[c]
9	**1i** (H)	**2i**	NR[c]

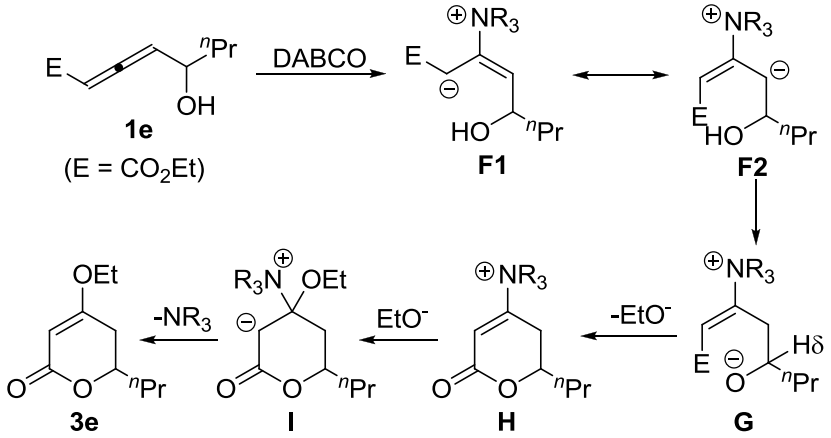
[a] Reaction conditions: 1a (0.2 mmol), phosphine (0.04 mmol), 4 mL toluene. [b] Isolated yield. [c] NR = no reaction.

With the optimized reaction condtions in hand, we then investigated the scope and limitation of the PPh_3-catalyzed isomerization of **1** to **2**. The results are summarized in Table 2. In general, the triphenylphosphine-catalyzed isomerization can be achieved with aryl- and alkyl-substituted substrates. The aromatic ring can bear an electron-donating or an electron-withdrawing group. However, the electronic influence of aromatic substituent shows no monotonous relationship with the corresponding product yield (Table 2, entries 1-4). Alkyl-substituted substrates exhibit much better performance, affording products **1e**-**1g** in excellent yields (Table 2, entries 5-7). It should be noted that substrate **1h** bearing a styryl group and **1i** were found to be inert under the optimized conditions and both were recovered in 95% yield, demonstrating the limitation of this isomerization (Table 2, entries 8 and 9).



Scheme 3. Gram-scale Synthesis of Substituted Benzoate **4**

5-Oxohex-2(3)-enoates **2** are valuable building blocks and are obtained otherwise with multiple synthetic steps.[11] To illustrate this synthetic utility of the PPh_3-catalyzed isomerization, a preparative scale experiment was conducted. Indeed, 1.2 gram of **1e** was subjected to the standard reaction conditions and furnished **2e** being isolated with somewhat lower yield (Scheme 3). The obtained **2e** reacted well with chaltone using the protocol developed by Liu's group,[12] delivering 1.27 gram of benzene derivative **4**.

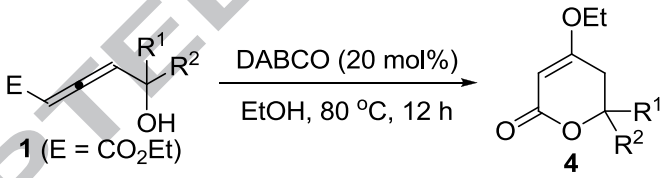


Scheme 4. The Proposal for the DABCO-catalyzed Isomerization of **1e**

Interestingly, when phosphine catalyst for the reaction of **1e** was replaced by catalytic amount of DABCO, lactone product **3e** was isolated instead, albeit only in 32% yield (Scheme 4). These results demonstrate different catalytic behaviors between phosphine and tertiary amine catalysts for the allenoate substrates.[13] The formation of lactone **3e** can be explained by the proposed mechanism as outlined in Scheme 4. 1,4-Addtion of DABCO catalyst to substrate **1e** forms two resonants **F1** and **F2**. Then, the latter undergoes proton shift to generate intermediate **G**, which facilitates intramolecular lactonization to produce intermediate **H** and release a molecule of ethanolate which initiates an addition-elimination process to yield product **3e** and regenerate DABCO catalyst (Scheme 4).[14]

Although we have no supporting data to elucidate these two divergent isomerizations at this stage, we believed that resonant **A1** might be thermodynamically favorable over **A2** in the phosphine case, while resonant **F2** might be favorable in the DABCO case. Furthermore, δH of intermediate **B** locates at allylic position of electron-deficient alken. Thus it might be readily deprotonated. Apparently, δH of intermediate **G** is lack of the corresponding activation effect.

Table 3. DABCO-catalyzed isomerization of **1** to **3a**

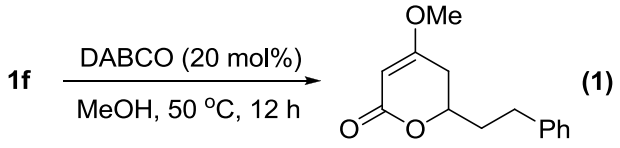


entry	**1** (R_1, R_2)	**3**	Yield (%)[b]
1	**1e** (R_1 = nPr, R_2 = H)	**3e**	92
2	**1f** [R_1 = -$(CH_2)_2$Ph, R_2 = H]	**3f**	90
3	**1g** [R_1 = -$(CH_2)_2$OTBS, R_2 = H]	**3g**	93
4	**1i** (R_1 = H, R_2 = H)	**3i**	87
5	**1j** (R_1 = Bn, R_2 = H)	**3j**	80
6	**1k** (R_1 = Me, R_2 = Me)	**3k**	71
7	**1a** ((R_1 = Ph, R_2 = H)	**3a**	NR[c]
8	**1h** (R_1 = styryl, R_2 = H)	**3h**	NR[c]

[a] Reaction conditions: **1a** (0.2 mmol), DABCO (0.04 mmol), 4 mL solvent. [b] Isolated yield. [c] NR = no reaction.

To our delight, the isolated yield of **4e** could be improved to 92% when ethanol was instead used as solvent (Table 3, entry 1). Under these conditions, a wide range of substrates with an alkyl substituent at δC-position smoothly undergo isomerization to

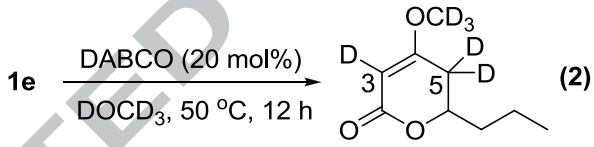
afford the corresponding latones **4** in good to excellent yields (Table 3, entries 1-6). To our surprise, no reaction was observed when substarte **1a** or **1h** was subjected to these reaction conditions (Table 3, entries 7 and 8).



(1)

5f: 90% yield

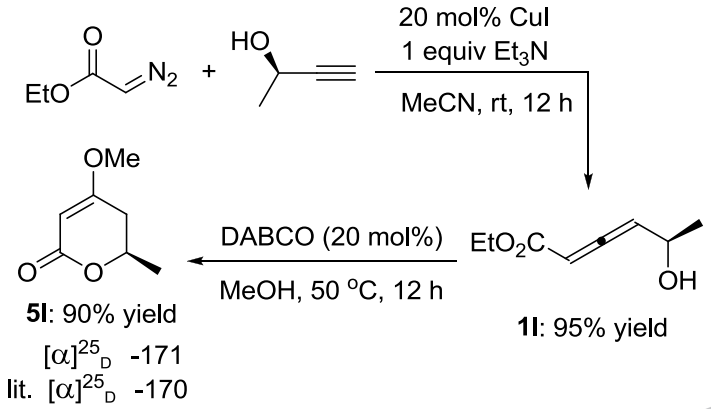
When the DABCO-catalyzed isomerization of **1** was conducted in MeOH solvent, the corresponding 3-methoxy α,β-unsaturated lactone could be obtained. Indeed, with the use of MeOH as the solvent, substrate **1f** was smoothly transformed into (+/-)-dihydrokavain **5f**[15] in 90% yield (eq 1). Furthermore, under the otherwise identical reaction conditions, MeOH-d_4 enabled deuterium-labeled **5e** being isolated in 90% yield, which has 97% D at C3-position and 79% D at C5-position (eq 2). Although numerous methods have been elegantly developed to access the related lactones of widely synthetic and biological interest,[16] the present DABCO-catalyzed isomerization of **1** provides an alternative way, which features mild conditions, simple operation as well as facile deuterium-labeling.



(2)

5e: 90% yield

To further demonstrate the utility of the DABCO-catalyzed isomerization, we sought to undertake a stereospecific synthesis of latone **(R)-5l**, which is an important intermediate for the total synthesis of natural product vioxanthin.[17] Thus, using a modified Fu's Cu-catalyzed protocol,[18] coupling between commercial ethyl 2-diazoacetate and (R)-3-butyn-2-ol (99% ee) afforded (R)-ethyl 5-hydroxyhexa-2,3-dienoate **1l**, which was smoothly converted into **(R)-5l** in 85% yield over the two steps, (Scheme 5). Importantly, the spectroscopic data for the obtained **(R)-5l** in this way is in complete agreement with that in the literatures.



Scheme 5. Synthesis of Lactone **(R)-5l** in Two Steps

In summary, we have developed the Lewis base-catalyzed divergent isomerizations of 5-hydroxyl-2,3-dienoate **1**. The isomerization of **1** to 5-oxohex-2(3)-enoates **2** was achieved by using the phosphine catalyst, which presents a novel variant of phosphine-catalyzed isomerization of activated allene. On the other hand, the DABCO catalyst furnished the isomerization of **1** to 3-ethoxy α,β-unsaturated lactone **3**. Both of the resulted products are important compounds of widely synthetic and biological interest. Further understanding of mechanism via computational studies and synthetic application are ongoing and will be reported in due course.

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