Catalytic Regioselective Isomerization of 2,2-Disubstituted Oxetanes to Homoallylic Alcohols

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Dedication ((optional))

Abstract: The selective isomerization of strained heterocyclic compounds is an important tool in organic synthesis. An unprecedented regioselective isomerization of 2,2-disubstituted oxetanes to homoallylic alcohols is described. The use of tris(pentafluorophenyl)borane ($B(C_6F_5)_3$), a commercially available Lewis acid was key to obtain good yields and selectivities since other Lewis acids afforded mixtures of isomers and substantial polymerization. The reaction took place under exceptionally mild conditions and very low catalyst loading (0.5 mol %). DFT calculations disclose the mechanistic features of the isomerization and account for the high selectivity displayed by the $B(C_6F_5)_3$ catalyst. The synthetic applicability of the new reaction is demonstrated by the preparation of γ-chiral alcohols using iridium catalyzed asymmetric hydrogenation.

Introduction

Oxetanes are present in numerous drugs and natural products, such as Taxol (Paclitaxel), a well-known antitumoral.[1] They have found significant application in medicinal chemistry[2] since the introduction of an oxetane fragment usually has positive effects in terms of solubility and metabolic stability.[2,3] More recently, 3-substituted oxetanes have been used in polymer chemistry as monomers[4] or cross-linkers,[5] and in opto-electronic devices.[6,7]

The development of new and efficient methods for the preparation of oxetanes has enhanced their role as versatile building blocks in synthetic chemistry.[8,9] Although the ring strain energy of oxetanes (25.4 kcal·mol^{-1}) is only slightly lower than epoxides (26.8 kcal·mol^{-1}), they have been scarcely used compared to epoxides. One of the reasons is that 3-substituted oxetanes show a significantly lower electrophilicity than epoxides so they usually have to be activated by Lewis acids.[8a,10]

Despite of their lower reactivity than epoxides, significant chemistry of 3-substituted oxetanes has been developed focusing on ring-opening reactions[8a,11], including asymmetric versions,[10] and ring-expansion reactions.[12]

On the other hand, 2,2-disubstituted oxetanes are more reactive than the 3-substituted ones due to their facile ring-opening. However, they are also more sensitive to hydrolysis and polymerization. The main reactivity of 2,2-disubstituted oxetanes include reductive ring-opening by titanium[13] or iron[14] complexes, ring expansion[15] to five-membered cyclic ethers and perhydrolysis[16] (Figure 1). The oxetanes have also been used as a lithiation directing groups in aromatic rings.[11,17]

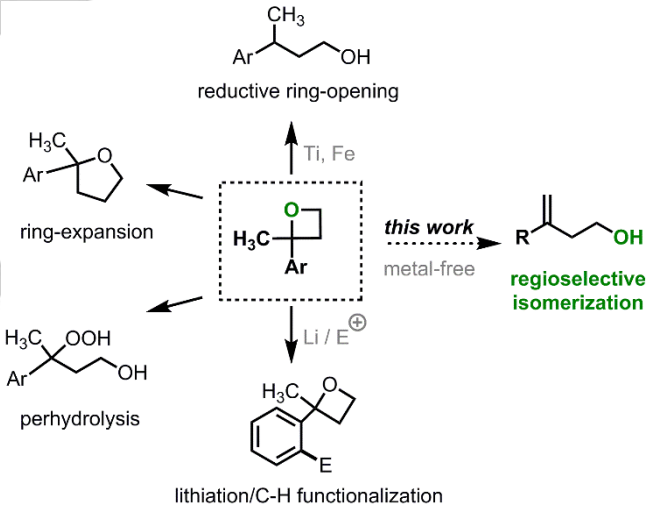

Figure 1. Reactivity of 2,2-disubstituted oxetanes.

Our group has recently explored the metal-catalyzed isomerization of strained heterocyclic compounds (Figure 2). Particularly, we reported the selective iridium-catalyzed isomerization of *N*-sulfonyl aziridines to allylic amines using Crabtree's catalyst (**1**) under very mild conditions and without external activation.[18] Similarly, the conversion of epoxides into aldehydes was achieved by hydrogen activation of reagent **1**.[19] Inspired on these selective transformations, we wondered if 2,2-disubstituted oxetanes would be selectively isomerized when using the appropriate catalyst.

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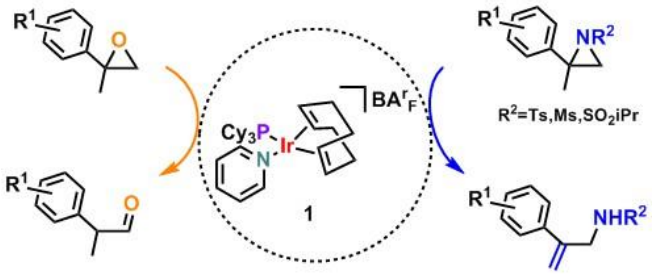


Figure 2. Selective isomerization of heterocyclic compounds catalyzed by Crabtree's catalyst, **1.**

In contrast with the regioselective isomerization of epoxides[20] (also called Meinwald rearrangement) the regioselective isomerization of oxetanes still remains a challenge and, to the best of our knowledge, no synthetic protocols have been described to date. Most probably, the easy polymerization of 2-substituted oxetanes in acidic conditions has hampered their synthetic use.

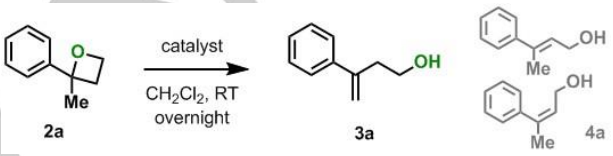
Herein, we report a new catalytic reaction that affords homoallylic alcohols from 2,2-oxetanes in high selectivity using very low loading of tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, as Lewis acid. The subsequent asymmetric hydrogenation allows the preparation of enantioenriched γ-substituted alcohols. Since the preparation 2,2-disubstituted oxetanes using the Corey-Chaykovski reaction[21] is straightforward and environmentally friendly, we believe that the new sequence emerges as a breakthrough in the synthesis of chiral alcohols from ketones.

Results and Discussion

Our preliminary studies began with the synthesis of 2-phenyl-2-methyloxetane **2a**, which was obtained from acetophenone via double Corey-Chaykovsky reaction[21] with good yields without the need of further purification (see the Supporting Information). With **2a** in hand, the isomerization reaction was performed using several catalysts at 5 mol % loading at room temperature, as shown in Table 1. First, we tested Crabtree's catalyst **1** as it gave satisfactory results when using *N*-sulfonyl aziridines[18] and epoxides.[19] However, we observed that, without any external activation, conversion was very low (entry 1, Table 1) being the only product that could be quantified the homoallylic alcohol **3a**. Activation of the catalyst with H_2 to form an Ir-H,H as the catalytic active species led to polymerization (entry 2, Table 1). These disappointing results led us to study a wide range of Lewis-acids. Again, $ZnCl_2$ gave rise to polymerization (entry 3). When moving to milder, inorganic Lewis acids such as $InCl_3$, $IrCl_3$ or $AlCl_3$, **3a** was the major product but the mass balance of the reaction was poor, probably due to polymerization (entries 4-6, Table 1). At that point, we turned our attention to organic Lewis-acids. First, $BF_3{\cdot}Et_2O$ was tested. Full conversion was observed, although the selectivity of the reaction was null: an equimolar mixture of **3a**:(*E*)-**4a**:(*Z*)-**4a** (entry 7, Table 1) was afforded. We then tested a bulky Lewis acid namely $B(C_6F_5)_3$.[22]

Gratifyingly, the reaction in dichloromethane afforded the homoallylic alcohol with excellent yield (82 %) and selectivity (**3a**:**4a**: 98:2, entry 8, Table 1). With this result in hand, we performed a solvent screening. EtOAc, THF and toluene gave excellent conversion and selectivity but the yield was not enhanced (entries 9-11, Table 1). Acetonitrile gave very low conversion (entry 12). The temperature effect was also evaluated and the reaction was performed at 0 ºC in dichloromethane (entry 13). However, no difference with the reaction performed at room temperature was observed. Finally, we reduced the catalyst loading to 0.5 mol %, and the reaction time to 2 h, thus demonstrating the outstanding catalytic activity of $B(C_6F_5)_3$ (entry 14, Table 1). In addition, a gram scale reaction was carried out, affording **3a** with an excellent 84% yield (entry 15).

Table 1. Screening of conditions for the isomerization of **2a**



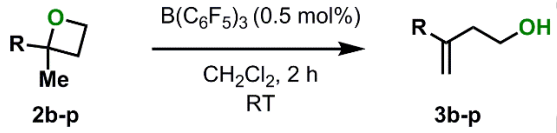
Entry	Catalyst	Solvent	Ratio 3a:4a[a]	Conv. (%)[a]	Yield 3a (%)[b]
1	**1**	DCM	-	35	25
2[c]	**1**	DCM	-	>99	0 [d]
3	$ZnCl_2$	DCM	-	>99	0 [d]
4	$InCl_3$	DCM	4:1	50	39
5	$IrCl_3$	DCM	4:1	>99	34
6	$AlCl_3$	DCM	5:1	>99	51
7	$BF_3{\cdot}Et_2O$	DCM	1:2	>99	30
8	$B(C_6F_5)_3$	DCM	98:2	>99	82
9	$B(C_6F_5)_3$	EtOAc	96:4	>99	70
10	$B(C_6F_5)_3$	THF	98:2	>99	67
11	$B(C_6F_5)_3$	Toluene	98:2	>99	79
12	$B(C_6F_5)_3$	MeCN	-	33	21
13[e]	$B(C_6F_5)_3$	DCM	98:2	>99	80
14[f]	$B(C_6F_5)_3$	DCM	98:2	>99	82, 78[g]
15[h]	$B(C_6F_5)_3$	DCM	98:2	>99	84

The reaction was performed in a sealed vial with 0.1 mmol of **2a,** [0.1 M] and using 5 mol % of catalyst loading. [a] Determined by ^{1}H NMR spectroscopy. [b] ^{1}H NMR yield using mesitylene as internal standard. [c] The reaction was performed in a pressure tube, using H_2 for catalyst activation and, after 1 min, the vessel was fully degassed. [d] Polymerization occurred. [e] The reaction was performed at 0 ºC. [f] 0.5 mol% of catalyst was employed, and the reaction was left stirring for 2 h. [g] Isolated yield, at 0.8 mmol scale. [h] Isolated yield performing the reaction at gram scale, using 0.5 mol% of $B(C_6F_5)_3$.

With the optimal conditions in hand, we explored the substrate scope (Table 2). The aryl group was modified with a range of functionalities. A fluorine atom in *para*- and *ortho*-position was well tolerated (entries 1 and 2, Table 2), affording **3b** and **3c** with complete regioselectivity. In the latter case, the yield was moderate probably due to dimerization of the substrate. A substrate with stronger electron-withdrawing group such as *p*-CF_3 (entry 3, Table 2) afforded the homoallylic alcohol **3d** with high selectivity, albeit in moderate yield. *Para*-substituted

halogen substituents such as *p*–Cl, *p*–Br and *p*-I showed excellent selectivity affording the homoallylic alcohols **3e**, **3g** and **3h** in high yield (entries 4-7, Table 2). In the case of *m*–Cl (**2f**), the yield was high (84%, entry 5, Table 2), but up to 5% of the allylic alcohols **4** were also formed. We then moved on to test the effect of the electron-donating group in the aryl substituent. A methyl group was introduced in both *para*- and *ortho*-position (entries 8 and 9, Table 2). In both cases, the selectivity of the isomerization reaction decreased compared to EWG groups, although **3i** and **3j** were still obtained in good yields. Alternatively, a methoxy group in the *meta*-position enhanced the selectivity ratio **3:4** up to 98%, affording **3k** with an excellent 92% yield (entry 10, Table 2). Furthermore, other relevant functionalities on the aromatic core were tested, such as nitrile (**2l**) and amide (**2m**). For both cases, homoallylic alcohols **3l** and **3m** were obtained in excellent selectivity and in good yields (entries 11 and 12, Table 2), albeit harsher reactions conditions (2 mol% catalyst loading and leaving the reaction overnight, at room temperature or heating) were required. In contrast, bulky group in *para*-position (*p*-*i*Bu) diminished the selectivity, although **3n** was afforded in synthetically useful yield (entry 13, Table 2). The naphthyl group was also studied, affording **3o** in excellent selectivity (92:8) and 83% yield (entry 14, Table 2). Interestingly, the reactivity was not limited to 2-aryl oxetanes. The dialkyl compound 2-cyclohexyl-2-methyl oxetane **2p** (entry 15, Table 2) afforded a 7:3 mixture of the expected product **3p** and the tetrasubstituted allyl alcohol in 56% yield *(*see the Supporting Information).

Table 2. Study of the substrate scope.

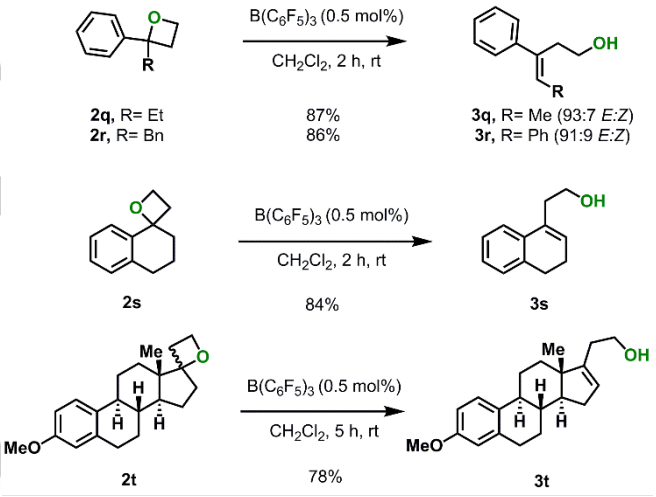


2b-p **3b-p**

Entry		R	Ratio 3:4[a]	Conv. (%)[a]	Yield 3 (%)[b]
1	**2b**	*p*-F-C_6H_4-	97:3	>99	77[f]
2[c]	**2c**	*o*-F-C_6H_4-	>99	>99	57
3	**2d**	*p*-CF_3-C_6H_4-	99:1	>99	54
4	**2e**	*p*-Cl-C_6H_4-	>99	>99	95
5	**2f**	*m*-Cl-C_6H_4-	95:5	>99	84
6	**2g**	*p*-Br-C_6H_4-	>99	>99	86
7[c]	**2h**	*p*-I-C_6H_4-)	>99	>99	70
8	**2i**	*p*-Me-C_6H_4-	96:4	>99	79
9	**2j**	*o*-Me-C_6H_4-	91:9	>99	63
10	**2k**	*m*-OMe-C_6H_4-	98:2	>99	92
11[d]	**2l**	*m*-CN-C_6H_4-	>99	>99	55
12[e]	**2m**	*m*-$CONMe_2$-C_6H_4-	>99	>99	68
13	**2n**	*p*-*i*Bu-C_6H_4-	88:12	>99	70[f]
14	**2o**	2-Naphthyl	92:8	>99	83[f]
15	**2p**	cyclohexyl	99:1	>99	56[g]

The reaction was performed in a sealed vial using 0.4 mmol of **2** and 0.5 mol % of catalyst loading. [a] Determined by ^{1}H NMR spectroscopy from the crude. [b] Isolated yield. [c] 1 mol% of catalyst was used, leaving the reaction stirring overnight. [d] 2 mol% of catalyst was used, heating to 40 ºC and leaving the reaction stirring overnight. [e] 2 mol% of catalyst was used, leaving the reaction stirring overnight. [f] Allylic alcohols **4** could not be completely removed from the product by column chromatography. [g] A mixture of homoallylic alcohols (7:3) was also obtained. (see the Supporting Information).

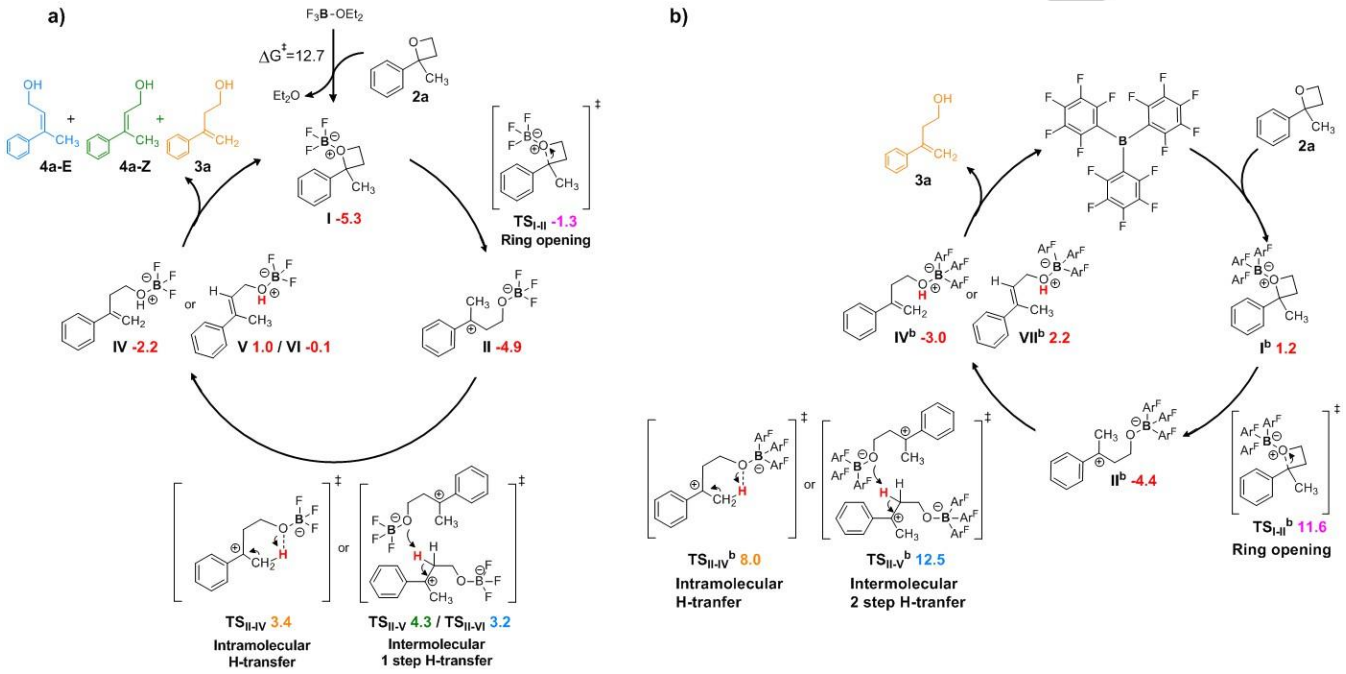
To prove the versatility of this reaction, we also modified the methyl group to other alkyl groups, such as an ethyl (**2q**) or benzyl group (**2r**). The corresponding trisubstituted homoallylic alcohols **3q** and **3r** were formed in good yields, with high *E* selectivity with respect to *Z* (Scheme 1). Also, bicyclic oxetane **2s**, synthesized from α-tetralone, proved highly reactive, exclusively affording homoallylic alcohol **3s** in 84% isolated yield (Scheme 1). Finally, the applicability of this methodology is exemplified by the synthesis of estrone derivative **3t**, which is a potential novel precursor for the development of further bioactive compounds. For this purpose, starting from estrone 3-methyl ether, the corresponding oxetane **2t** was synthesized in high yield affording a mixture of diastereomers (see the Supporting Information) which was directly treated with 0.5 mol% of $B(C_6F_5)_3$. After 5 h, the homoallylic alcohol **3t** was obtained with a 78% yield. The synthesis of this novel compound shows a new derivatization pathway for steroids and related compounds.



Scheme 1. Substrate scope with other alkyl substituents.

The novelty of the transformation led us to perform a mechanistic study. Our previous studies of iridium-catalyzed isomerization of *N*-sulfonyl aziridines and epoxides (Figure 2) disclosed a two-steps mechanism in which the initial ring-opening step is followed by metal-assisted tautomerization.[18,19] The selectivity of the process depends on the C-H hydrogen involved in the tautomerization. However, the metal-free nature of the oxetane isomerization raises new questions regarding the hydrogen migration step, in particular regarding the identity of the agent assisting the H-migration and how the selectivity homoallylic alcohol (**3**)/allylic alcohol (**4**) is defined. Indeed, the results obtained using the two borane reagents [$BF_3{\cdot}Et_2O$ and $B(C_6F_5)_3$] differ markedly. While the former yields an equimolar mixture of both products, the latter is highly selective toward the homoallylic product (Table 1). To answer these questions, here we studied the isomerization mechanism of 2-phenyl-2-methyloxetane **2a** catalyzed by both $BF_3{\cdot}Et_2O$ and $B(C_6F_5)_3$ Lewis acids. To this end, DFT calculations[23] applying the

B3LYP-D3 functional and treating the DCM solvent with the SMD continuum model were performed (see Computational Details in the Supporting Information).



Scheme 2. DFT computed mechanism (B3LYP-D3 in DCM) for the isomerization of oxetane **2a** to homoallylic **3a** and allylic ***(E)*-4a** and **(*Z*)-4a** alcohols catalyzed by a) $BF_3{\cdot}Et_2O$ and b) $B(C_6F_5)_3$. Relative Gibbs energies (in red) in kcal·mol^{-1} are referred to the separated species; transition state energies are shown in purple, for the ring opening step and orange, blue or green for the proton transfer process entailing the formation of **3a**, ***(E)*-4a** and **(*Z*)-4a**, respectively.

As $BF_3{\cdot}Et_2O$ gave similar yields of both products, we started the mechanistic study using this Lewis acid reagent. The computed catalytic cycle is shown in Scheme 2a. The corresponding Gibbs energy profile can be found at the Supporting Information (Figure S3). The formation of the Lewis-adduct **2a**·BF_3 (**I**) requires the previous displacement of Et_2O by **2a**, which takes places by means of a SN_2 substitution process demanding 12.7 kcal·mol^{-1}. Coordination of boron to the O-oxetane activates the C-O bond for ring opening, that only requires an activation barrier of 4.0 kcal·mol^{-1} (**TS$_{I-II}$**) and leads to the zwitterionic intermediate **II** (-4.9 kcal·mol^{-1}). At this point, the catalytic cycle can follow two different pathways depending on the proton that migrates to the oxygen: proton transfer from methyl group brings the homoallylic alcohol **3a**, while if it happens from the $C_\beta H_2$ group the allylic products (*E*,*Z*)-**4a** are formed. The process leading to **3a** has been characterized as a low barrier (8.3 kcal·mol^{-1}) intramolecular proton transfer involving a six-member ring transition state, **TS$_{II-IV}$**. On the contrary, the formation of the allylic products **4a** via an intramolecular mechanism, involving a four-member ring transition state, can be discarded as it presents a Gibbs energy barrier of 23.8 kcal·mol^{-1} (see the Supporting Information), incompatible with the experimental detection of equimolar amounts of **3a** and **4a** products (Table 1). Therefore, we investigated the possible role of all the bases present in the reaction medium in assisting the proton migration from the $C_\beta H_2$ group to the oxygen. Three O-bases were tested in the intermolecular base-assisted H transfer: the ether oxygen of Et_2O, that of oxetane substrate **2a**, and alkoxide oxygen of intermediate **II**. Base-assisted transition states involving the three species have been computed leading to an energy ordering for the Gibbs energy barrier from **II** that follows the expected basicity order: O-**II** (8.1 kcal·mol^{-1}) < O-**2a** (13.6 kcal·mol^{-1}) < O-Et_2O (15.6 kcal·mol^{-1}) (see the Supporting Information). The favored intermolecular **II**-assisted TS bringing **4a** comes from a head-to-tail adduct of two unities of intermediate **II** (Figure 3a).

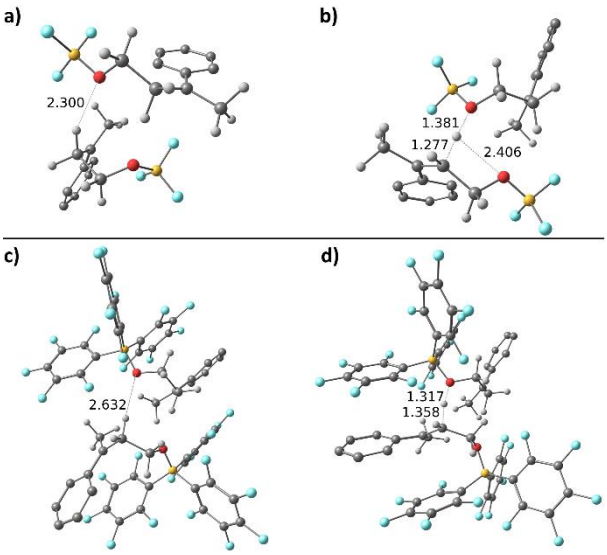


Figure 3. Optimized geometries for: a) adduct of two unities of intermediate **II**; b) concerted intermolecular proton migration transition state, **TS$_{II-VI}$**; c) adduct of two unities of intermediate **II^b**, and d) first step of the proton migration

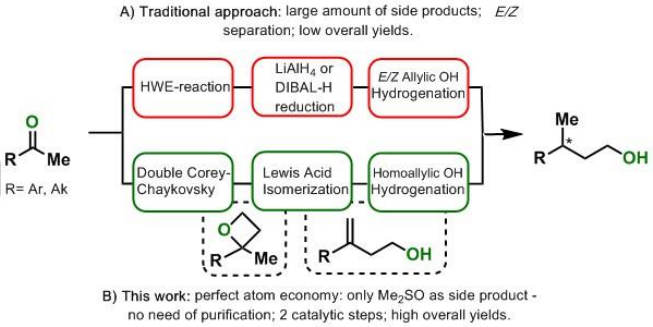
transition state, $TS_{II\text{-}V}{}^{b}$. The most important distances are also reported in Å. Hydrogen atoms of Ph groups have been omitted for clarity.

The proton migration has been characterized as a concerted mechanism in which the C_{β}-H proton, picked by the oxygen of one unity of intermediate **II**, is directly transferred to the oxygen of the second unity to form the allylic alcohol (Figure 3b). Both pro-(*E*), $TS_{III\text{-}V}$ and pro-(*Z*), $TS_{III\text{-}VI}$, show barriers (8.1 and 9.2 kcal·mol^{-1}, respectively) very close to $TS_{II\text{-}IV}$ (8.3 kcal·mol^{-1}). For sake of completeness, the transition state of the base-**II** assisted proton transfer leading to the major product **3a**, has been also characterized. The intermolecular process has an energy barrier of 9.9 kcal·mol^{-1}, 1.6 kcal·mol^{-1} higher than the intramolecular $TS_{II\text{-}IV}$. Taking these data into account, from a micro-kinetics analysis carried out with COPASI software,[24] a 1.0:1.6 mixture of **3a**:**4a** is predicted, highlighting no selectivity of the catalyst (for further details see the Supporting Information).

When using $B(C_6F_5)_3$ (Scheme 2b and Gibbs energy profile at the Supporting Information, Figure S2) no previous substitution is required. According with the lower Lewis acidity of $B(C_6F_5)_3$ respect to BF_3, its interaction with the O-oxetane is weaker and a bit higher barrier (11.6 kcal·mol^{-1}, $TS_{I\text{-}II}{}^{b}$) is required in the ring-opening step that leads to the zwitterionic intermediate II^{b} at -4.4 kcal·mol^{-1}. From II^{b} the homoallylic alcohol **3a** is obtained through an intramolecular H-transfer involving a 6-member ring transition state $TS_{II\text{-}IV}{}^{b}$, requiring a Gibbs energy barrier of 12.4 kcal·mol^{-1}. As with the $BF_3{\cdot}Et_2O$ catalyzed process, the intermolecular base-**II** assisted mechanism displays a higher barrier of 16.0 kcal·mol^{-1}. As for BF_3, the formation of the allylic products via an intramolecular mechanism, entailing a four-member ring transition state, implies high activation energy (21.3 kcal·mol^{-1}, see the Supporting Information). Regarding the base-assisted mechanism, the same basicity trend than for BF_3 reaction has been observed: the **II**-assisted process is favored over the **2a**-assisted proton transfer, with barriers of 16.9 and 18.5 kcal·mol^{-1}, respectively. In contrast to the process with the BF_3 catalyst, the proton migration needs two different steps: first, with an activation barrier of 16.9 kcal·mol^{-1}, the C_{β}-H proton is transferred to the oxygen of the second unity of intermediate II^{b} ($TS_{III\text{-}V}{}^{b}$); then, in a practically barrierless process, involving a relative reorientation of the two subunits, the proton migrates to form the allylic product **4a** (see the Supporting Information). Contrary to what happen for the case of BF_3 catalyzed isomerization, $TS_{III\text{-}V}{}^{b}$ has an energy barrier higher enough with respect the transition state $TS_{II\text{-}IV}{}^{b}$ (4.5 kcal·mol^{-1}) to assure a practically complete (99.5 %) selectivity in favor of the homoallylic alcohol product **3a**, in line with the experimental results. The reasons behind the different performances of the two catalysts can be found on the steric hindrance introduced by the aryl rings of $B(C_6F_5)_3$ that destabilizes the proton migration step by placing the oxygen atom that will accept the proton further away (Figure 3c).

Last, to showcase the applicability of the novel synthetic protocol, we performed the enantioselective hydrogenation of the resulting homoallylic alcohols to give enantioenriched alcohols. Alcohols with an stereogenic center in γ-position constitute an important chemical motif, present in a wide range of natural products, pharmaceuticals, and fine chemicals of perfume industry.[25] Enantioenriched γ-methyl alcohols are also versatile building blocks that are used as synthetic intermediates in the synthesis of complex molecules.[3] For instance, (-)-citronellol is an intermediate for the production of rose oxide.[26]

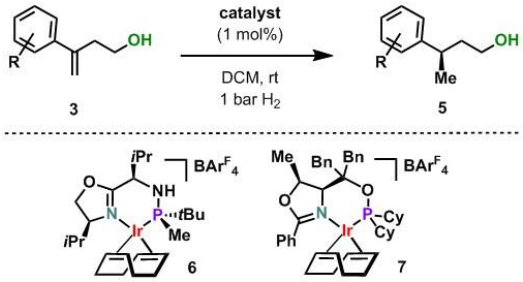
Focusing on catalytic processes, the asymmetric isomerization and/or hydrogenation of primary allylic alcohols have emerged as promising alternatives to synthesize γ-methyl chiral alcohols, where iridium-P,N complexes have come to dominate the field.[25] Despite of this, serious drawbacks remain; the catalytic isomerization[27] of γ-methyl allylic alcohols suffer from very low conversion and moderate enantioselectivities or the asymmetric hydrogenation[28] requires harsh conditions (very high H_2 pressure) to avoid undesired isomerization byproducts. Moreover, the traditional preparation of the starting allylic is highly inefficient. First, their synthesis usually require two steps with poor atom economy: an olefination reaction (Horner–Wadsworth–Emmons -HWE-, or similar), and ester reduction (usually with reactive hydrides). Second, even more important, the usual poor selectivity of the HWE with ketones leads to the formation of mixtures of *E* and *Z* allylic alcohols that require complicated chromatographic separations (Scheme 3). For this reason, we believe that the strategy presented in this work is clearly advantageous to obtain chiral alcohols from cheap and abundant ketones in a greener 3-step synthetic approach. To demonstrate that, we moved to perform the asymmetric hydrogenation of homoallylic alcohols **3**, which can be considered minimally functionalized olefins.[29]



Scheme 3. Comparison of this work with the traditional approach.

During the last decade our group has developed several modular P stereogenic chiral ligands[30] that have proved to be excellent precursors of chiral catalysts. Although our iridium-P,N MaxPHOX[31] family of catalysts (**6**) have been successfully applied to the asymmetric hydrogenation of cyclic enamides,[31a] aryl and alkyl imines[32] and minimally functionalized olefins,[33] including 2-aryl *N*-allyl phthalimides,[34] we found that in this particular case, using **3a** as model substrate, [((4*S*,5*S*)-Cy_2-Ubaphox)Ir(COD)]$BAr^{F}{}_4$ **7**[35] gave the best results.

Table 3. Iridium-catalyzed asymmetric hydrogenations of homoallylic alcohols.



Entry		Catalyst	R	Product	Conv. (%) [a]	ee (%) [b]
1	**3a**	**6**	H	**5a**	>99	71
2	**3a**	**7**	H	**5a**	>99	90
3	**3c**	**7**	*o*-F	**5c**	>99	94
4	**3e**	**7**	*p*-Cl	**5e**	>99	92
5	**3i**	**7**	*p*-Me	**5i**	>99	90
6	**3k**	**7**	*m*-OMe	**5k**	>99	94

The reaction was performed in a pressure reactor using 1 mol% of catalyst **6** and left stirring overnight. [a] Determined by ^{1}H NMR spectroscopy from the crude. [b] Measured by chiral HPLC.

Using 1 mol % of this commercially available catalyst **7** developed by Pfaltz and co-workers in dichloromethane under 1 bar of H_2 pressure, **5a** was obtained in 90% ee (entry 2, Table 3). The scope of this reaction was expanded to other homoallylic alcohols prepared from the corresponding oxetanes **2**. Both electron-withdrawing substituents such as *o*-F, (**3c**, entry 3) and *p*-Cl (**3e**, entry 4) and electron-donating substituents such as *p*-Me (**3i**, entry 5) and *m*-OMe (**3k**, entry 6) gave full conversions and excellent enantioselectivities (up to 94% ee).

Conclusion

In conclusion, we have reported a highly regioselective isomerization of 2,2-disubstituted oxetanes using $B(C_6F_5)_3$ as catalyst, using extremely mild conditions (0.5 mol% of catalyst loading and very short reaction times). DFT calculations shed light on the reaction mechanism and account for the high selectivity toward the homoallylic alcohol product displayed by the $B(C_6F_5)_3$ catalyst. This novel selective isomerization of oxetanes can be used as key step in multiple synthetic organic transformations. As a leading example, we have disclosed a highly efficient 3-step protocol towards the enantioselective synthesis of γ-aryl butanols starting from abundant inexpensive acetophenone derivatives. First, a double Corey-Chaykovksy reaction, which only generates dimethyl sulfoxide as by-product, is carried out. Then, and without further purification, the selective isomerization of the resulting oxetanes takes place followed by iridium-catalyzed asymmetric hydrogenation (Figure 3). These last two steps, which are catalytic, accomplishes a greener, more sustainable and efficient approach to the enantioselective synthesis of valuable alcohols. Moreover, the applicability of the isomerization reaction was further demonstrated by the isomerization of spiranic oxetanes and the preparation of a new estrone-derivative.

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Keywords: catalysis • isomerization • oxetanes • allyl alcohols • asymmetric hydrogenation

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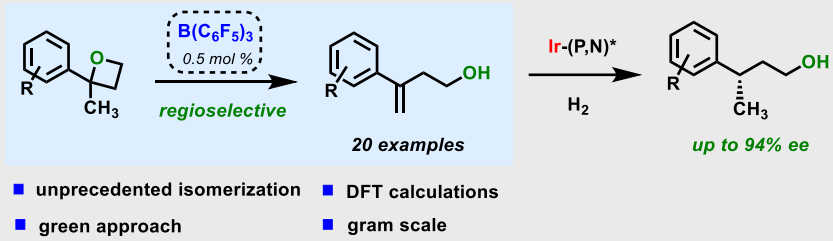

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Catalytic Regioselective Isomerization of 2,2-Disubstituted Oxetanes to Homoallylic Alcohols