Article

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Molybdenum-Catalyzed Hydroxyl-Directed *anti*-Dihydroxylation of Allylic and Homoallylic Alcohols

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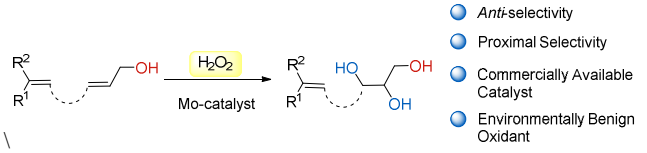
Supporting Information Placeholder

ABSTRACT: A catalytic hydroxyl-directed *anti*-dihydroxylation of allylic and homoallylic alcohols has been developed. This operationally simple method was successfully applied to the direct *anti*-mono-dihydroxylation of allylic alcohols containing at least one distal olefinic unit. Under the catalysis of commercially available $MoO_2(acac)_2$, an array of hydroxylated dienes were successfully converted into various 1,2,3-triols using hydrogen peroxide as an environmentally benign oxidant under aerobic conditions, notably, in complete regioselectivities and in the most cases in diastereospecific pathway.

Key Words: Dihydroxylation • Molybdenum • Regioselective • 1,2,3-Triols • Allylic Alcohols

As a cornerstone reaction in the organic synthesis, dihydroxylation of alkenes provides a simple and direct access to versatile vicinal diols, which are highly useful building blocks for synthesis of naturally occurring products and synthetic biologically active compounds.[1] Therefore, tremendous progress has been achieved in the field of *syn*-dihydroxylation of alkenes based on both transition-metal catalysis and metal-free procedures.[2,3] In contrast, *anti*-dihydroxylation of olefins has received significantly less attention and finds constrained applications in organic synthesis, mainly due to one or more of the following reasons including low step-ecomony, unavailability of the catalysts in the commercial market and the lack of regioselectivity in the case of structurally complex dienes and polyenes as substrates. Generally, *anti*-dihydroxylation can be achieved in indirect or direct pathway.[4,5] In the former case a number of strategies have been developed including hydrolysis of isolated epoxides,[4b-i] saponification of esterified 1,2-diols obtained through the ring-opening of epoxides[4j-m] or dioxonium ion intermediates[4n-p] with carboxylic acids as nucleophiles, as well as the reduction of α-hydroperoxyl hydroxamic acid esters[4q]. However, the low step economy and the use of large excess of corrosive acid or alkali for the hydrolysis or saponification step limit their synthetic applications. Therefore, the development of efficient direct *anti*-dihydroxylation of olefins in one single step avoiding isolation of epoxides and the saponification step is highly desirable and its challenge lies in finding an appropriate catalyst capable of mediating both the epoxidation and the following hydrolysis. It has been reported that sulfonic acids[5a,b], some transition metal oxides[5c-f], iodide[5g] and selenium compounds[5h,i] are able to catalyzed direct *anti*-dihydroxylation of olefins. Furthermore, combination of monooxygenase and epoxide hydrolase as catalysts can also convert various alkenes to vicinal diols without isolation of the oxiranes intermediates.[5j-l] However, all these methods focus on simple olefins containing only one C-C double bond as substrates.

Dihydroxylation of allylic alcohols furnishes 1,2,3-triols as direct products, which are not only key units in natural products but also useful synthetic building blocks.[6] Consequently, our target is development of an operationally simple, catalytic, hydroxyl-directed, proximal selective *anti*-dihydroxylation of allylic alcohols bearing at least one distal olefinic unit to validate its utility in the late stage functionalization of complex molecules (Scheme 1).



Scheme 1. Mo-catalyzed regioselective *anti*-dihydroxylation of allylic alcohols.

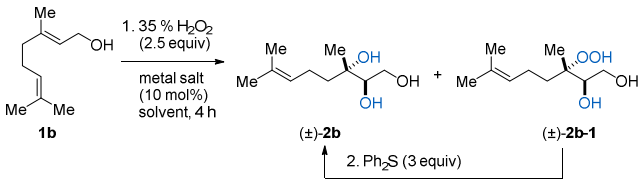
Unlike the well-developed transition metal-catalyzed epoxidation of polyunsaturated allylic alcohols favoring the proximal oxidation,[7] investigations of dihydroxylations of these substrates are scarce. It is known that Os-catalyzed *syn*-dihydroxylation of geraniol and its analogues usually occurs at the electron richer remote olefinic unit, preferentially.[1a,2e] Donohoe et al. reported the only exception that proximal *syn*-dihydroxylation of allylic alcohols could be achieved using stoichiometric OsO_4 with TMEDA as ligand at −78 °C.[2g] However, the level of regiocontrol is significantly dependent on the geometry of the proximal C-C double bond. Furthermore, ruthenium salts tend to promote the oxidative cyclization instead of dihydroxylation in the cases of 1,5- and 1,6-dienes.[8] Therefore, our initial experiments focused on the examination of an assortment of well-established systems with readily available catalysts and oxidants for the dihydroxylation of (2*E*,6*Z*)-nona-2,6-dien-1-ol (**1a**).[9] However, no dihydroxylation system tested was able to deliver the 1,2,3-triol with high regiocontrol. Thus it is necessary to develop a new catalytic system in order to achieve highly proximal-selective dihydroxylation of allylic alcohols.

For optimization of the reaction conditions for the proximal dihydroxylation of allylic alcohols, we used geraniol (**1b**) as standard substrate, since it is commercially available (Table 1). Initially, we screened a series of metal salts as catalysts for this reaction. In the cases of $NbCl_5$ and $TaCl_5$ no reaction occurred (entries 1 and 2), while in the case of $VO(acac)_2$ only the formation of epoxide

was observed (entry 3). When $MoO_2(acac)_2$ and WO_2Cl_2 were utilized as the catalysts, the desired product (±)-**2b** was formed mixed with a certain amount of hydroperoxide (±)-**2b-1**, which could be converted into the triol (±)-**2b** simply through addition of diphenyl sulfide to the reaction mixture. After reduction the product (±)-**2b** was obtained in regio- and diastereomerically pure form, albeit with low yields (entries 4 and 5). Encouraged by these results, several Mo- and W-salts were tested for this reaction. However, no better result could be obtained (entries 6-10). Next, a brief solvent screening was undertaken employing $MoO_2(acac)_2$ as catalyst (entries 11-15) and the best outcome was achieved when the reaction was conducted in MeCN (entry 15).[10] Furthermore, both raising and lowering the reaction temperature resulted in decrease of the reaction efficiency (entries 16 and 17).

After establishing the best reaction conditions we started to evaluate the substrate spectrum of this Mo-catalyzed regioselective dihydroxylation. As demonstrated in Table 2, this method is amendable to various allylic alcohols bearing at least one distal olefinic unit. To our delight, in all cases the regioselectivities were completely proximal independent of the distance between two olefins and their substitution patterns, furnishing the corresponding 1,2,3-triols **2a-q** as the sole regioisomers in moderate to good yields. Remarkably, all the reactions employing achiral dienes **1a-i** and **1l-o** afforded the corresponding products (±)-**2a-i** and (±)-**2l-o** in complete *anti*-selectivities. In the case of D-perillyl alcohol (**1p**) as precursor the product **2p** was also obtained with an excellent level of diastereocontrol. Remarkably, the established method was also applicable to a structurally complex steroid derivative **1q** bearing two olefinic units furnishing the proximally dihydroxylated product **2q** in complete regio- and high diastereoselectivity.

Table 1. Metal salts, solvents and temperature screening for the regioselective *anti*-dihydroxylation of geraniol [a]

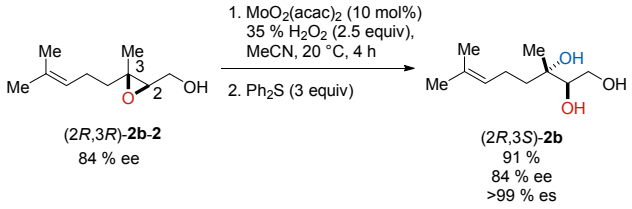


Entry	Metal	Solvent	T (°C)	Yield [%][b]
1	$NbCl_5$	DCM	20	0
2	$TaCl_5$	DCM	20	0
3	$VO(acac)_2$	DCM	20	0
4	WO_2Cl_2	DCM	20	17
5	$MoO_2(acac)_2$	DCM	20	28
6	WO_3	DCM	20	0
7	$W(OEt)_6$	DCM	20	9
8	$MoCl_5$	DCM	20	traces
9	MoO_2Cl_2	DCM	20	traces
10	$Mo_2(OAc)_4$	DCM	20	12
11	$MoO_2(acac)_2$	THF	20	0
12	$MoO_2(acac)_2$	EtOAc	20	15
13	$MoO_2(acac)_2$	NO_2Me	20	8
14	$MoO_2(acac)_2$	H_2O	20	traces
15	$MoO_2(acac)_2$	MeCN	20	83 (78)[c]
16	$MoO_2(acac)_2$	MeCN	30	70
17	$MoO_2(acac)_2$	MeCN	0	traces

[a] Unless otherwise specified, reactions were performed on a 0.5 mmol scale of geraniol (1b) using 2.5 equiv 35 % H_2O_2, and 10 mol% metal salts at 20 °C in 2.0 mL solvent. [b] Yields of (±)-2b based on the ^1H NMR-spectroscopy using mesitylene as internal standard. [c] Yield of the isolated product (±)-2b after flash chromatography.

Furthermore, simple allylic alcohols **1r-dd** were also employed as substrates for this Mo-catalyzed *anti*-dihydroxylation reaction (Table 3). In general, the products **2r-dd** were provided in moderate to excellent yields and complete *anti*-selectivities in most cases. All the reactions using achiral aliphatic allylic alcohols as precursors yielded the products (±)-**2r-t** in complete diastereoselectivities, while a diastereomeric mixture was obtained in the case of cinnamic alcohol **1x** as the starting material. In the cases of secondary allylic alcohols **1y-aa** the level of diastereocontrol depends on the substrate structure. Notably, in the case of enynes **1w** and **1z** as substrates the products were also furnished in moderately good yields indicating that alkyne-moiety is also tolerable under this condition. Moreover, this method is not only limited to allylic alcohols, since homoallylic alcohols **1bb-dd** are also suitable substrates furnishing the products (±)-**2bb-dd** in good to excellent yields.

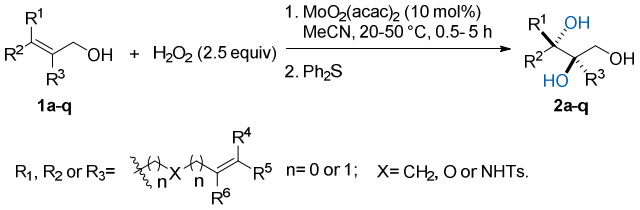
Concerning the reactions mechanism we believe that this Mo-catalyzed *anti*-dihydroxylation reaction contains two stages, which are the initial epoxidation and the followed in situ hydrolysis and perhydrolysis, because formation of a slight amount of epoxides could be observed under the standard conditions and the direct use of epoxy allylic alcohols as substrates under these conditions can also afford the ring-opened products smoothly.[12] Control experiments revealed that both steps are catalyzed by $MoO_2(acac)_2$, since no reactions occurred in the absence of the catalyst. Furthermore, the enantioenriched epoxide (2*R*,3*R*)-**2b-2** prepared from geraniol via Sharpless epoxidation[7a] was subjected to the Mo-catalysis providing the triol (2*R*,3*S*)-**2b** after reduction with the identical enantiomeric excess as its precursor indicating that a C-3 selective stereospecific ring opening of the epoxide intermediate occurs in the second stage of this Mo-catalyzed *anti*-dihydroxylation reaction (Scheme 2).

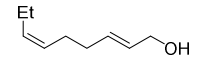
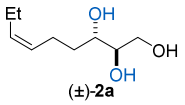
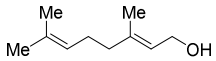
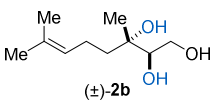
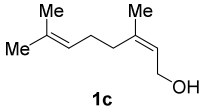
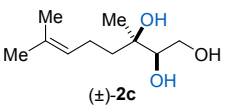
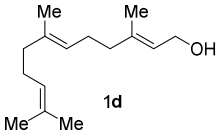
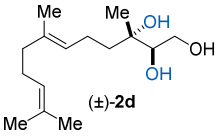
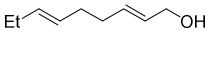
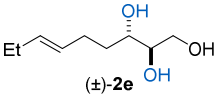
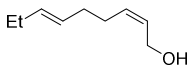
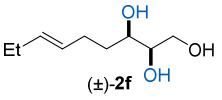
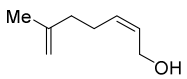
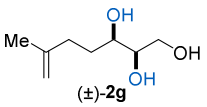
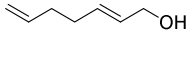
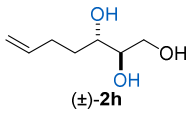
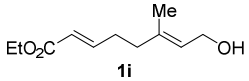
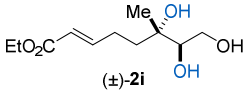


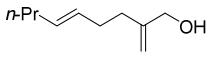
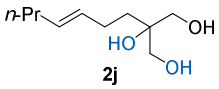
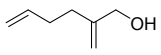
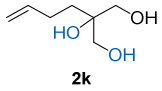
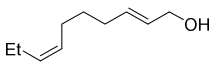
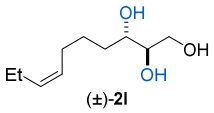
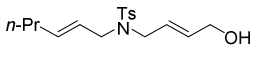
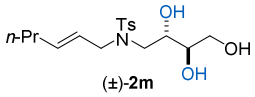
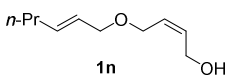
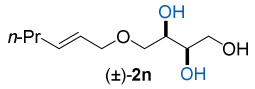
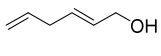
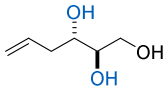
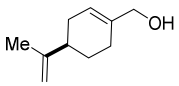
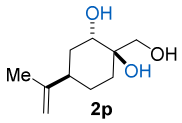
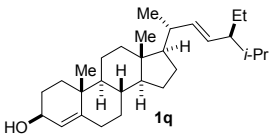
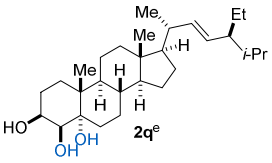
Scheme 2. Mo-catalyzed ring opening of (2*R*,3*R*)-epoxy geraniol

Presumably, the proximal selectivity of this Mo-catalyzed reaction is attributed to the directing effect of the hydroxyl-moiety of the alkene substrates through interaction with the metal center. To confirm it, control experiments employing O-acetylated geraniol, 2-methyl 2-butene and (*E*)-hex-4-en-1-ol were carried out under the same reaction conditions for geraniol (Scheme 3). In all these cases only traces of dihydroxylated products were formed. Furthermore, the relative configurations of the triol **2q**, **2z** and (±)-**2aa** also reveal that the initial epoxidation occurs on the same face of the alkene as the hydroxyl group based on the premise that the following ring opening proceeds on the C-3 position. All the results mentioned above indicate that both the presence of OH moiety as anchoring group and its distance to the olefinic unit are crucial for the efficiency of this Mo-catalyzed *anti*-dihydroxylation reaction.

Table 2. Mo-catalyzed regioselective *anti*-dihydroxylation of allylic alcohols containing at least one distal olefinic unit.[11,a-c]

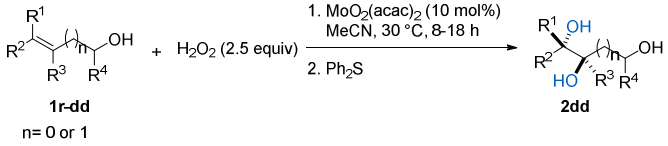


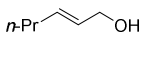
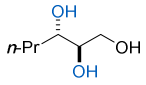
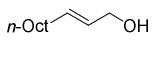
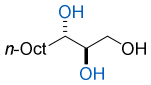
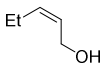
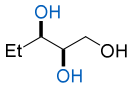
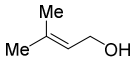
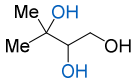
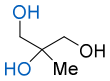
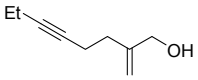
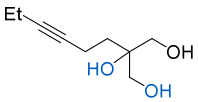
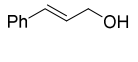
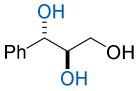
Olefin	Product	Yield (%)
 1a	 (±)-2a	65
 1b	 (±)-2b	78 (74[d])
 1c	 (±)-2c	78
 1d	 (±)-2d	79
 1e	 (±)-2e	75
 1f	 (±)-2f	60
 1g	 (±)-2g	64
 1h	 (±)-2h	78
 1i	 (±)-2i	83

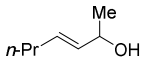
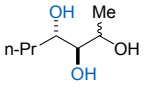
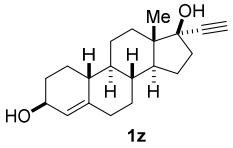
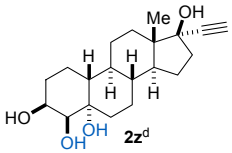
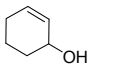
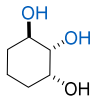
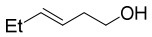
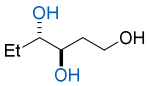
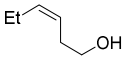
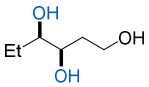
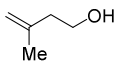
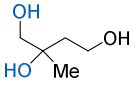
Olefin	Product	Yield (%)
 1j	 2j	62
 1k	 2k	53
 1l	 (±)-2l	75
 1m	 (±)-2m	49
 1n	 (±)-2n	36
 1o	 (±)-2o	54
 2p	 2p	76, dr>99:1
 1q	 2q[e]	62, dr=95:5

[a] Unless otherwise specified, reactions were performed on a 0.5 mmol scale of allylic alcohols 1 using 2.5 equiv 35 % H_2O_2, and 10 mol% $MoO_2(acac)_2$ in MeCN. [b] Unless otherwise specified, the products were obtained with complete regioselectivities and diastereoselectivities, which were determined by ^{1}H-NMR-spectroscopy. [c] Yields of the isolated products after flash chromatography. [d] Reaction performed on a 1 g scale; [e] Reactions performed in 1,4-dioxane using 20 mol% $MoO_2(acac)_2$ and 5 equiv 35 % H_2O_2.

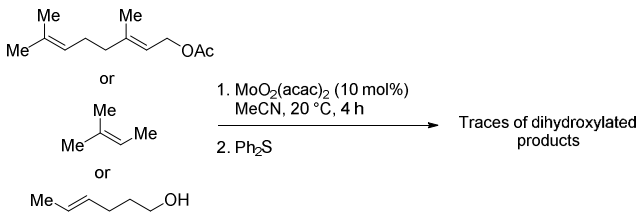
Table 3. Mo-catalyzed *anti*-dihydroxylation of simple allylic and homoallylic alcohols.[11,a-c]



Olefin	Product	Yield (%)
 **1r**	 (±)-**2r**	97
 **1s**	 (±)-**2s**	93
 **1t**	 (±)-**2t**	88
 **1u**	 (±)-**2u**	99
 **1v**	 **2v**	89
 **1w**	 **2w**	51
 **1x**	 (±)-**2x**	94, dr=88:12

Olefin	Product	Yield (%)
 **1y**	 (±)-**2y**	94, dr=67:33
 **1z**	 **2z**[d]	56, dr>99:1
 **1aa**	 (±)-**2aa**	80, dr=94:6
 **1bb**	 (±)-**2bb**	87
 **1cc**	 (±)-**2cc**	88
 **1dd**	 (±)-**2dd**	71

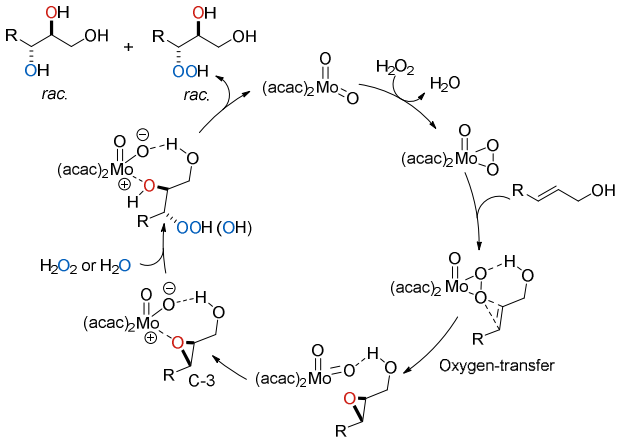
[a] Unless otherwise specified, reactions were performed on a 0.5 mmol scale of allylic alcohols **1** using 2.5 equiv. 35 % H_2O_2, and 10 mol% $MoO_2(acac)_2$ at 30 °C in MeCN. [b] Unless otherwise specified, the products were obtained with complete regioselectivities and diastereoselectivities, which were determined by ^{1}H-NMR-spectroscopy. [c] Yields of the isolated products after flash chromatography; [d] Reactions performed in 1,4-dioxane using 20 mol% $MoO_2(acac)_2$, and 5 equiv H_2O_2.



Scheme 3. Control experiments for the Mo-catalyzed *anti*-dihydroxylation

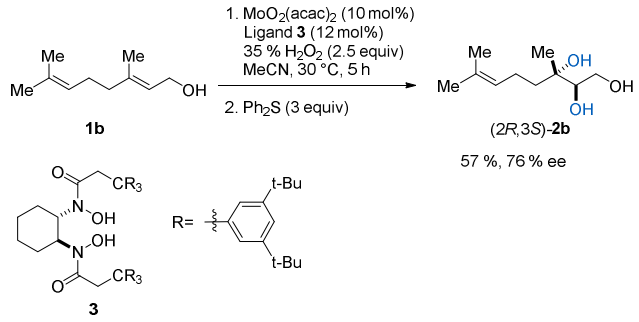
Relying on the experimental results obtained and the known fact that hydroxyl-group favors formation of hydrogen bond instead of coordination with molybdenum (VI) complex in the stoichiometric epoxidation of allylic alcohols[13], we proposed a plausible catalytic cycle for this Mo-catalyzed *anti*-dihydroxylation (Scheme 4). Initially, $MoO_2(acac)_2$ is oxidized by H_2O_2 to an oxoperoxidomolybdenum (VI) complex, the peroxido group of which can form a hydrogen bond with the allylic alcohol, accelerating the oxygen transfer to the proximal C-C double bond. Next, the resulting $MoO_2(acac)_2$ serves as a Lewis acid for activation of the generated epoxy allylic alcohol. Due to the directing effect of the hydroxyl moiety the S_N-2-type nucleophilic ring opening by H_2O_2 or water proceeds on the C-3 position, preferentially.[14]

Finally, the products are released and $MoO_2(acac)_2$ is regenerated for the next catalytic cycle.



Scheme 4. Plausible catalytic cycle of the Mo-catalyzed *anti*-dihydroxylation

We have also studied the asymmetric version of this Mo-catalyzed *anti*-dihydroxylation reaction and a series of privileged chiral ligands were tested for this Mo-catalyzed reaction.[15] The preliminary investigations demonstrate that a good enantiomeric excess could be achieved for the *anti*-dihydroxylation of geraniol by employing an optically pure bishydroxamic acid **3** as chiral ligand (Scheme 5). Further optimizations to improve both the efficiency and the asymmetric induction are ongoing in our laboratory.



Scheme 5. Mo-bishydroxamic acid catalyzed asymmetric direct *anti*-dihydroxylation of geraniol

In summary, we developed a highly *anti*-selective dihydroxylation of allylic and homoallylic alcohols catalyzed by commercially available $MoO_2(acac)_2$ under aerobic reaction conditions using environmentally benign hydrogen peroxide as oxidant. This reported method avoids the isolation of t epoxide intermediates and thus provides a straightforward access to vicinal diols from alkene precursors with *anti*-selectivity, which is complementary to the well-established *syn*-dihydroxylation. Due to the directing effect of the OH-moiety, complete proximal selectivities of this dihydroxylation can be achieved for various allylic alcohols bearing at least one distal olefinic unit. Further investigations into the asymmetric version of this reaction are in progress and will be published in due course.

ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures and necessary characterization data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Graphical Abstract