Catalytic allylic oxidation of internal alkenes to a multifunctional chiral building block

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The stereoselective oxidation of hydrocarbons is one of the most notable advances in synthetic chemistry over the past fifty years1–3. Inspired by nature, enantioselective dihydroxylations, epoxidations and other oxidations of unsaturated hydrocarbons have been developed. More recently, the catalytic enantioselective allylic carbon–hydrogen oxidation of alkenes has streamlined the production of pharmaceuticals, natural products, fine chemicals and other functional materials4–7. Allylic functionalization provides a direct path to chiral building blocks with a newly formed stereocentre from petrochemical feedstocks while preserving the olefin functionality as a handle for further chemical elaboration. Various metal-based catalysts have been discovered for the enantioselective allylic carbon–hydrogen oxidation of simple alkenes with cyclic or terminal double bonds8–10. However, a general and selective allylic oxidation using the more common internal alkenes remains elusive. Here we report the enantioselective, regioselective and E/Z-selective allylic oxidation of unactivated internal alkenes via a catalytic hetero-ene reaction with a chalcogen-based oxidant. Our method enables non-symmetric internal alkenes to be selectively converted into allylic functionalized products with high stereoselectivity and regioselectivity. Stereoselective transformations of the resulting multifunctional chiral building blocks highlight the potential for rapidly converting internal alkenes into a broad range of enantioenriched structures that can be used in the synthesis of complex target molecules.

Unlike terminal alkenes (1), which contain only a single set of enantiotopic allylic protons that must be differentiated in an enantioselective reaction (Fig. 1a), internal alkenes (2) possess two sets of protons on either side of the olefin moiety, thereby posing the challenge of regioselectivity in addition to stereoselectivity for non-symmetric substrates (Fig. 1b). Furthermore, when the resulting product is an internal alkene, the issue of E/Z selectivity subsists. The inability to control indiscriminate C–H functionalization of electronically and sterically similar allylic protons therefore has the potential to produce a mixture of regio-, diastereo- and enantioisomers that are difficult to separate via preparative methods.

Our goal was to develop a general platform for the construction of chiral olefinic building blocks from inexpensive commodity internal alkenes. To this end, we developed a catalytic enantioselective oxidation that provides access to a multifunctional intermediate capable of stereoselective differentiation towards various products. This strategy allows allylic C–N, C–O, C–S, C–C and C–halogen bonds to be selectively introduced, enabling rapid library synthesis of analogous enantioenriched products (Fig. 1b).

Early reports of racemic allylic oxidation of unfunctionalized alkenes via hetero-ene reactions with chalcogen-based oxidants indicate that this class of enophile might serve as a suitable starting point for the development of a highly selective allylic oxidation of internal alkenes11–15. These reactions proceed through spontaneous thermal hetero-ene reactions that are not enantioselective, but exhibit oxidant-controlled regioselectivity and E/Z selectivity for the allylic oxidation of non-symmetric internal alkenes.

The selection of the electrophilic chalcogen-based oxidant 3d was an essential step in the development of our approach to the stereoselective allylic oxidation of internal alkenes (Extended Data Fig. 1a). We sought to identify a chiral Lewis acid that could catalyse the ene reaction between internal alkenes and oxidant 3d via lowest unoccupied molecular orbital (LUMO)-lowering activation of the electrophilic oxidant. In the absence of a background reaction at –70 °C, a combination of SbCl5 and (R)-BINOL (1,1’-binaphthene-2,2’-diol) was sufficient to catalyse the ene reaction between cis-5-decene 4 and oxidant 3d with regio- and stereochemical control (Extended Data Fig. 1b, entry 10). After an extensive exploration of reaction parameters, SbCl5 and co-catalyst 6 were deemed optimal for the formation of allylic oxidation product 8a in 84% isolated yield and 92.5:7.5 enantiomeric ratio with complete E-olefin selectivity (Fig. 2a). The BINOL-based co-catalysts can be recovered by aqueous workup on completion of the reaction (Supplementary Fig. 5).

To determine an allylic C–H oxidation that can be used successfully in many complex molecular settings, we explored the efficiency of this enantioselective reaction with a diverse range of symmetric internal alkenes. Different acyclic cis-internal alkenes with varying chain length and functionality all afforded the oxidized product with comparably good yield and stereoinduction (8a–8c, Fig. 2a); this result makes our approach the most general strategy for this class of substrate to date. We synthesized chiral enantioenriched allylic sulfinate products with various functional groups, such as aromatic rings (8d), chlorides (8e), bromides (8f), iodides (8g), trifluoromethyl groups (8h),
Figure 2 | Substrate scope of the catalytic enantioselective and regioselective allylic oxidation of internal unactivated alkenes. Reaction conditions: cis-5-decene (1 equiv.), sulfurimide reagent 3d (1.5 equiv.), solvent (0.13 M). Isolated yield (initial diastereometric ratio, d.r. > 20:1). 

a. Enantioselective oxidation of functionalized symmetric internal alkenes. 

When BINOL was used instead of co-catalyst 6 in a solvent mixture of CH₂Cl₂:PhMe (1:2), product 8a was formed in 81% yield and with an enantiomeric ratio (e.r.) of 89:11. Yields were determined by ¹H NMR using 1,4-dimethoxybenzene as an internal standard.

| Entry | Internal olefin | Allylic oxidation product | Yield | e.r. |
|-------|----------------|---------------------------|-------|------|
| 1     | CH₂ > CH       | 9a                        | 84%   | >20:1 |
| 2     | CH₂ > CH       | 9b                        | 69%   | >20:1 |
| 3     | CH₂ > CH       | 9c                        | 59%   | >20:1 |
| 4     | CH₂ > CH       | 9d                        | 5%    | >20:1 |
| 5     |                 |                           | 21%   | >20:1 |
| 6     |                 |                           | 62%   | 1:2:1 |
| 7     |                 |                           | 59%   | 1:2:1 |
| 8     |                 |                           | 0%    | 1:2:1 |

b. Regio- and chemoselectivity trends in the enantioselective allylic oxidation of non-symmetric internal alkenes. Blue labels under the reaction arrows in entries 1–5 indicate the inherent regioselectivity of the reaction. EWG, electron-withdrawing group; r.r., regioisomeric ratio; OTFA, trifluoroacetate. BINOL was used instead of co-catalyst 6, in a solvent mixture of CH₂Cl₂:PhMe (1:2). Yields were determined by ¹H NMR using 1,4-dimethoxybenzene as an internal standard. Isolated yield was determined by methylating the allylic oxidation product in the presence of Me₃SO₄ and NEt₃.
trifluoroacetates (8i) and tosylated indoles (8j). In general, the allylic oxidation products were formed in good yields and enantiomeric ratios, with exclusive E-olefin selectivity. X-ray crystallographic analysis of the main diastereomer that formed initially for allylic oxidation product 8e defined the absolute and relative stereochemistry of the ene reaction products. A preliminary functional group robustness screen25 revealed that this reaction is compatible with nitro groups, fluorides, boronic acids, carboxylic acids, alkynes, aldehydes, acetates, cyanides, furans, thiophenes and protected amines (see Supplementary Information). Products from acyclic internal alkenes were generated in greater enantioenrichment than the corresponding products from cyclic alkenes (8k, 8l), presumably owing to unfavourable steric interactions with more rigid cyclic olefins.

Our initial studies identified general trends in regioselectivity for the oxidation of non-symmetric internal alkenes (Fig. 2b). Under optimized reaction conditions, an internal olefin flanked by a methylene and a methine group selectively undergoes enantio- and regioselective ene reactions with the methylene proton (indicated in blue, entry 1). Methylene protons react preferentially to methyl protons (entries 2–4). Competition between methyl and methine protons reveals the more facile reactivity of methyl protons (entry 5), albeit in diminished yield.

We also observed the effect of electronic perturbation on the regioselectivity of the allylic oxidation (Fig. 2b, entries 6–11). An electron-withdrawing group such as a chloride disfavours the enantioselective, regioselective ene reaction of the proximal allylic protons (entries 6 and 7). Instead, the oxidation favours reactivity through the alternative remote allylic protons (indicated in red). The inductive effect of the chloride functionality is modulated by the distance between the electron-withdrawing group and the olefin, which directly affects the regioselectivity of the reaction. If the chloride or other electron-withdrawing group (such as bromide or trifluoroacetate) is positioned too close to the olefin, then it diminishes the π nucleophilicity of the olefin and shuts down the catalytic ene reaction (entry 8). We observed similar outcomes in regioselectivity for other electron-withdrawing groups, including iodide (entry 9), trifluoroacetate (entry 10) and phenyl (entry 11). These results suggest emerging trends that may be exploited in the enantioselective and regioselective allylic oxidation of non-symmetric alkenes in more complex molecular settings. For example, internal competition experiments with certain classes of dienes highlight the chemoselective allylic oxidation of an internal olefin in the presence of a styrene (entry 12) or an allylic halide (entry 13).

With a selective allylic oxidation of internal alkenes in hand, we explored the generality of these products as synthetically versatile chiral building blocks for further chemical transformations (Fig. 3). Although the diversification of allylic oxidation products with a broad range of reagents has been reported for terminal alkenes24, this strategy has not yet been demonstrated with internal alkenes. The multiple atoms in the allylic sulfinate provide a unique opportunity to convert the allylic oxidation product to various functional groups. Our approach represents a general platform for formal enantioselective allylic C–X bond formation of internal olefins, in which X can be carbon-, nitrogen-, oxygen-, sulfur- or halogen-based functional groups.

Branched hydrocarbon 10 was generated through an allylic substitution of sulfinate 8a with ethylmagnesium chloride. Although the allylic sulfinate exists as a mixture of diastereomers (because of the configurationally labile sulfur stereocentre), the stereochemistry at the oxidized allylic carbon in the starting material dictates the stereochemistry of product 10, which is formed with complete E-olefin selectivity, high enantioselectivity, and moderate regioselectivity. The regioselective allylic substitution of unbiased internal allylic electrophiles (such as halides, acetates or carbonates) with organometallic reagents remains a challenging synthetic problem25. Therefore, even the moderate regioselectivity of 3:1 (2:3) represents a considerable advance.

Next, we sought to diversify allylic sulfinate 8a to various chiral heteroatom-containing products to enable efficient library synthesis of thiol, alcohol, amine and halogenated building blocks. Enantioenriched allylic thiol 11 was isolated with exclusive E-olefin selectivity after reduction of 8a. Allylic alcohol 12 and allylic amine 13 formed regioselectively with high E-olefin selectivity and enantioselectivity through selective [2,3]-rearrangements via either the oxygen atom or nitrogen atom of allylic sulfinate 8a, respectively. The presence of two diastereomers of allylic sulfinate (epimeric at sulfur) did not affect the stereochemical outcome in the formation of products 12 and 13. Most notably, sulfuryl chloride mediated the formation of allylic chloride 14 in excellent yield, with regioselectivity and stereoselectivity.

Our finding that a catalytic antimony–BINOL system effects remarkably high levels of enantio-, regio-, diastereo- and E-olefin selectivity in the hetero-ene reaction between oxidant 3d and simple internal alkenes prompted us to better understand the mechanism by which this selectivity is derived (Fig. 4). We observed a markedly diminished yield of sulfinate 8a in the absence of BINOL 6 (Fig. 4a), which we attribute to the Lewis-acid-assisted Bronsted acidity (LAB) of BINOL26. This form of activation has been used27 for the development of enantioselective polycyclizations mediated by antimony–BINOL, wherein the acidified proton of BINOL activated an alkene. Our reaction represents a unique application of antimony–BINOL as a catalytic chiral Bronsted acid28–32 for the activation of a heteroatomic electrophile. The lack of product formation in the presence of the sterically hindered Bronsted base 2,6-(t-Bu)$_2$pyridine (which does not exhibit any interaction with SbCl$_5$ in low-temperature $^1$H NMR analysis) is consistent with the proposed LAB mechanism. To examine the structure of the active BINOL–antimony moiety, we conducted a correlation study between the enantiomeric excess of BINOL 6 and the enantiomeric excess of product 8a (Fig. 4b). This experiment revealed a linear relationship, which suggests a 1:1 stoichiometry between the BINOL co-catalyst and the product (Fig. 4b). This experiment revealed a linear relationship, which suggests a 1:1 stoichiometry between the BINOL co-catalyst and the product 14 (entries 10–12).

Figure 3 | Multiple synthetic derivitizations of the synthetically versatile product of the catalytic enantioselective and regioselective allylic oxidation of internal alkenes. Reaction conditions are as follows. To 8a: PhSO$_2$N$_2$=S=O (3d) (1.5 equiv.), SbCl$_5$ (20 mol%), co-catalyst 6 (25 mol%), TFA (0.5 equiv.), CH$_2$Cl$_2$, −70 °C, 16 h. To 10 (C–C bond formation): CuBr$_2$•SMe$_2$ (5 mol%), EtMgCl. DME, −70 °C to 0 °C. To 11 (C–S bond formation): LiAlH$_4$, Et$_2$O, 0 °C to 23 °C; to 12 (C–O bond formation): Me$_2$SO$_4$, Et$_3$N, CH$_2$Cl$_2$, 23 °C; PhMe$_2$Br, THF, 0 °C; (P(OMe)$_3$, MeOH, 23 °C. To 13 (C–N bond formation): TiCl(Oi–Pr)$_3$ (20 mol%), PhMe, 60 °C; P(OMe)$_3$, MeOH, 23 °C. To 14 (C–Cl bond formation): SO$_2$Cl$_2$, Et$_2$O, −70 °C to 0 °C.

Although the Lewis-acid-annealed catalyst preserves the absolute stereochemistry of the starting material, subsequent synthetic manipulations may affect this stereochemical information. The absolute and relative configurations of products 8a–14 were confirmed by single-crystal X-ray crystallographic analysis.
the chiral-Broénsted-acid-catalysed hetero-ene reaction (Fig. 4c). Under the SbCl₅–BINOL conditions, stereoisomeric alkenes (Z)-4 and (E)-4 yielded different main diastereomeric products, wherein the absolute configurations of the carbon stereocentres were opposite (5a and ent-5b). This observation suggests that olefin configuration dictates π-face selectivity in this transformation. Interestingly, the main diastereomers for products obtained from alkenes (Z)-4 and (E)-4 were opposite to the corresponding products obtained from the thermal ene reactions. In addition, unreacted alkene (Z)-4 did not isomerize at lower conversions under the optimized reaction conditions to the more stable (E)-4 isomer.

On the basis of our mechanistic analysis, we propose that the hetero-ene reaction that occurs between sulfurimide reagent 3d and internal alkenes proceeds through a closed transition state in which the chiral Broénsted acid catalyst is activating the sulfurimide reagent through a LUMO-lowering effect (Fig. 4d). Transition states 15 and 16 benefit from stabilizing π-interactions between the coordinated oxidant 3d and the naphthyl backbone of co-catalyst 6. π-face selectivity may be ascribed to steric shielding by the adjacent naphthyl group. In addition, the switch in diastereoselectivity between the thermal endo-selective hetero-ene reaction and the catalytic reaction suggests that the antimony–BINOL-catalysed transformation proceeds through an exo transition state.

The observed regiopreference in the allylic oxidation of non-symmetric internal alkenes is consistent with the proposed closed transition state (Fig. 4e). The trends in regioselectivity can be rationalized on the basis of steric strain in the developing transition state, in which the lowest-energy chair conformation is consistent with the proposed closed transition state. ‘‡’ denotes a transition state.

**Figure 4** | Mechanistic studies of the catalytic enantioselective allylic oxidation of internal alkenes. a, Lewis-acid-assisted Broénsted acid mode of catalysis. b, Correlation study between the enantiomeric excess (e.e.) of the BINOL co-catalyst 6 and that of product 5. The solid line is a linear fit to the experimental data (diamonds). c, Stereochemical support for a closed transition state. d, Proposed transition state for the catalytic enantioselective allylic oxidation. e, Rationalization of trends in regioselectivity based on the closed transition state. ‘‡’ denotes a transition state.

**Data Availability** The data that support the findings of this study are available within the paper and its Supplementary Information, or are available from the corresponding author upon reasonable request. Crystallographic data are available at the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/; CCDC 1543728).
Online Content Any Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Author Contributions L.B., P.Q.L. and U.K.T. conceived the work and designed the experiments. L.B. and P.Q.L. conducted the experiments. All authors analysed the data and wrote the manuscript.

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Extended Data Figure 1 | Development of an enantioselective and regioselective allylic oxidation of internal unactivated alkenes via an ene reaction. (a) Our approach to generating one allylic oxidation product from unactivated internal alkenes and chalcogen-based oxidants. Sulfurimide reagent 3d was chosen for several reasons. First, compared to diimide oxidants 3b and 3c, sulfurimide 3d is considerably less electrophilic and therefore less reactive in thermal hetero­ene reactions, affording greater opportunity for a catalyst­controlled process. Second, the ene adducts generated between internal olefins and oxidants 3a–3c undergo spontaneous [2,3]­rearrangements, which preclude the ability to diversify the resulting oxidation products. Lastly, the presence of distinct nitrogen and oxygen moieties on the central sulfur atom in the allylic oxidation product provides an opportunity for further chemistry to access synthetically diverse products via C–N and C–O bond formation (see Fig. 1b).

Optimization of the enantioselective allylic oxidation of cis-5-decene. Reaction conditions: cis-5-decene (1 equiv.), sulfurimide reagent 3d (1.5 equiv.), solvent (0.13 M). Yields were determined by 1H NMR using 1,4-dimethoxybenzene as an internal standard. [a] 0.5 equiv trifluoroacetic acid added to reaction. [b] 10 mmol scale. [c] Isolated yield. [d] >20:1 initial d.r. (5a:5b).