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Conversion of 1-alkenes into 1,4-diols through an auxiliary-mediated formal homoallylic C–H oxidation

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The ubiquitous nature of C–H bonds in organic molecules makes them attractive as a target for rapid complexity generation, but brings with it the problem of achieving selective reactions. In developing new methodologies for C–H functionalization, alkenes are an attractive starting material because of their abundance and low cost. Here we describe the conversion of 1-alkenes into 1,4-diols. The method involves the installation of a new Si,N-type chelating auxiliary group on the alkene followed by iridium-catalysed C–H silylation of an unactivated δ-C(sp^3)–H bond to produce a silolane intermediate. Oxidation of the C–Si bonds affords a 1,4-diol. The method is demonstrated to have broad scope and good functional group compatibility by application to the selective 1,4-oxygenation of several natural products and derivatives.

Transition metal-catalysed C–H activation reactions have emerged as a powerful tool in organic chemistry[1–6]. However, aliphatic C–H bonds, which are ubiquitous in organic molecules, are the most challenging targets for selective functionalization because of the lack of the active frontier orbitals that could interact with a transition-metal centre[7,8]. Among a variety of aliphatic C–H functionalizations[9,10], C–H oxygenation is one of the most attractive transformations because a number of important biochemical processes involve this step[11–13]. Although a number of aliphatic C–H oxygenation reactions catalysed by transition metals are reported, mostly they are limited to functionalization of activated C–H bonds. However, the development of selective oxygenation of an unactivated sp^3 C–H bond is still in its infancy[14–22]. Therefore, the design of new methods that can be applied for the selective oxygenation of unactivated aliphatic C–H bonds is highly warranted.

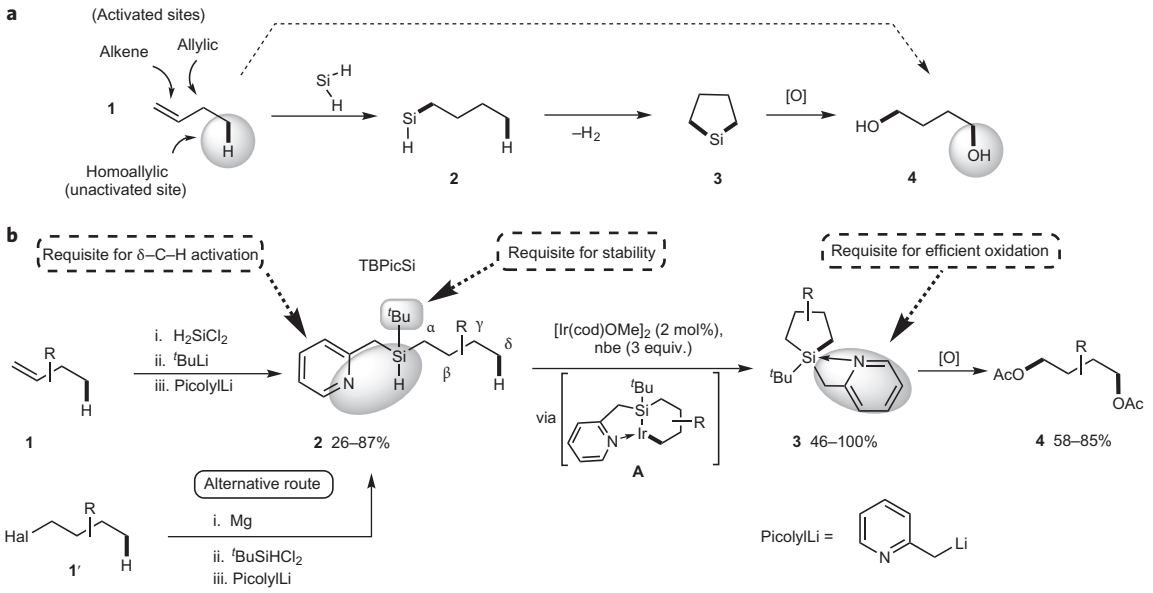

Figure 1 | Synthesis of 1,4-diols from 1-alkenes and alkyl halides. a, General concept for formal 1,4-oxygenation of 1-alkenes **1** into 1,4 diols **4** via activation of a homoallylic C–H bond. **b**, Conversion of 1-alkenes **1** (or 1-haloalkanes **1′**) into 1,4-diols **4** via installation of the TBPicSi to form **2**, followed by its iridium-catalysed C–H silylation of an unactivated C(sp^3)–H bond (to produce the silolane **3**) and subsequent oxidation. We designed TBPicSi, a new Si,N-type chelating directing group that can be installed easily on alkenes (and alternatively on alkyl halides). Its picolyl moiety enables an efficient Si–H/C–H activation step (via iridacycle **A**) and, as it is easily removed from silicon, ensures a successful subsequent oxidation of silolane **3** into the final diol **4**. The bulky *t*-butyl substituent at silicon is requisite for stability of **2**. cod, cyclooctadiene; nbe, norbornene.

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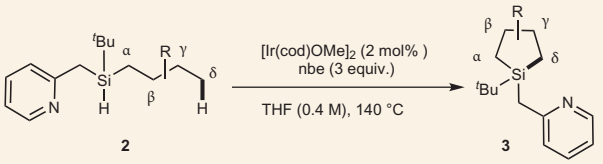
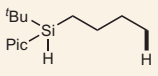
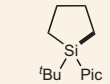
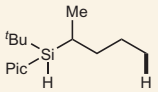
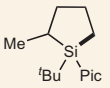
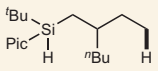
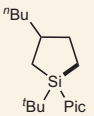
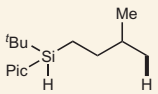
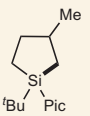
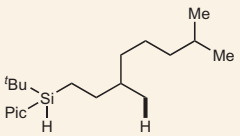
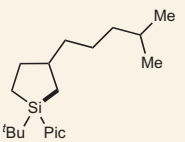
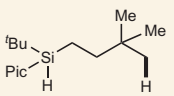
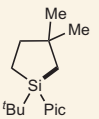
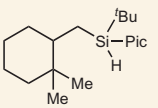
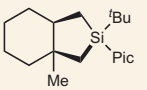
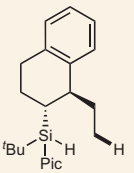
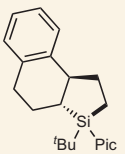
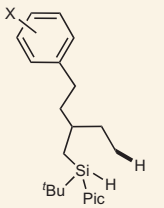
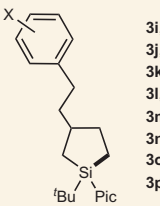
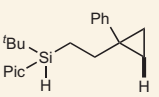
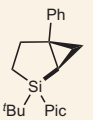
Table 1 | Ir-catalysed δ-C–H dehydrogenative silylation reaction.



2 3

Entry	Substrate		Product	
1		**2a**		**3a**, 84%
2		**2b***		**3b**, 74%*
3		**2c***		**3c**, 100%*
4		**2d**		**3d**, 73%
5		**2e***		**3e**, 46%*
6		**2f**		**3f**, 61%

Entry	Substrate		Product	
7		**2g***		**3g**, 93%†
8		**2h***		**3h**, 77%*
9		**2i***, X = 4-H		**3i**, 64%*
10		**2j***, X = 4-OTBS		**3j**, 67%*
11		**2k***, X = 3,4-OCH_2O-		**3k**, 75%*
12		**2l***, X = 4-F		**3l**, 53%*
13		**2m***, X = 4-Cl		**3m**, 82%*
14		**2n***, X = 4-Br		**3n**, 87%*
15		**2o***, X = 4-CF_3		**3o**, 95%*
16		**2p***, X = 4-$CH_3N^iBu_2$		**3p**, 57%*
17		**2q**		**3q**, 87%

*Mixture of stereoisomers (see Supplementary Information for details). †Major diastereomer is drawn (see Fig. 3 for details). TBS, *t*-butyldimethylsilyl.

Results and discussion

The alkene fragment is widely found in feedstock materials, as well as in a variety of organic building blocks and in natural products. Although oxygenations of the double bond and the allylic C–H bonds of alkenes are well developed, the oxygenation of the homoallylic position of 1-alkenes has not been disclosed. Herein we report an unprecedented double 1,4-functionalization of 1-alkenes, which includes a C–H activation of the homoallylic position, as well as a formal anti-Markovnikov hydration of the double bond. Our approach is based on the introduction of hydrosilane functionality, followed by an intramolecular dehydrogenative silylation and a subsequent oxidation step. The overall transformation represents the conversion of abundant 1-alkenes **1** into valuable 1,4-diols **4** (Fig. 1a).

As a key step (**2** → **3**) in the formal homoallylic C–H oxygenation of alkenes, we chose the Ir-catalysed method developed by Hartwig and co-workers for dehydrogenative Si–H/C–H coupling in alkoxysilanes[23]. However, for this approach to be useful synthetically for the fully hydrocarbon chain of **2**, the silicon group should possess at least one non-alkyl substituent (R^1 or $R^2 \neq$ alkyl (for rare examples on synthesis of dialkylsilolanes via Si–H/C–H coupling catalysed by transition metals, see Tsukada and Hartwig[24], and Kuninobu *et al.*[25])), which would ensure a successful subsequent oxidation of Si–C bonds[26,27] of **3** into **4** (Fig. 1b). However, screening a few different removable groups at silicon, including siloxy-, aryl- and benzyl groups, indicated either no reaction (**2** → **3**) or instability of **2** under the reaction conditions (Supplementary Fig. 1).

Next, we proposed that a new Si,N-type chelation-assisted auxiliary could facilitate the dehydrogenative Si–H/C–H coupling reaction. This idea was inspired by the N,N-chelation concept of Daugulis and co-workers, which has proved efficient for remote Pd-catalysed aliphatic C–H activation reactions[28]. To this end, we screened a number of potential directing groups and reaction conditions (Supplementary Figs 1–3 and Supplementary Tables 1–5). Gratifyingly, we found that a new Si,N-type chelating group, *t*-butylpicolylsilicon hydride (TBPicSi), is highly efficient for the dehydrogenative intramolecular silylation of δ-C(sp^3)–H bond (Fig. 1b). A control experiment revealed the importance of the picolyl group, as the benzyl analogue of TBPicSi was not efficient in the C–H activation reaction (see Supplementary Information for details). Moreover, its picolyl moiety has a double duty; it not only enables an efficient Si–H/C–H activation step via iridacycle **A** stabilized by six-membered chelation, but also, being easily removed from silicon, ensures a successful subsequent oxidation of **3**. The bulky *t*-butyl substituent at silicon, in turn, proved vital for the stability of **2**. Next, we developed an efficient method for installation of the TBPicSi directing group onto alkenes **1**. Thus, hydrosilylation

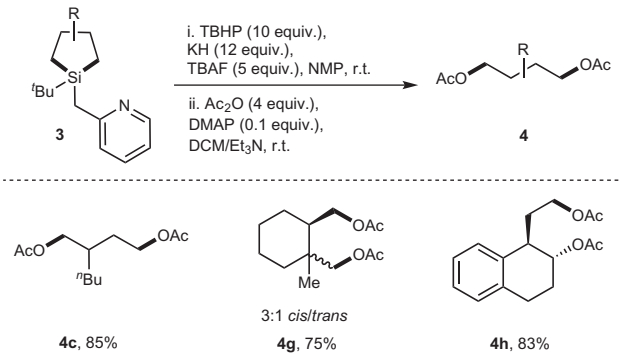


Figure 2 | Conversion of silacycle intermediates 3 into 1,4-diol derivatives 4. The reaction was performed under Woerpel's oxidation conditions[30]. TBHP, *t*-butyl hydroperoxide; TBAF, tetrabutylammonium fluoride; NMP, *N*-methylpyrrolidone; DMAP, 4-dimethylaminopyridine; DCM, dichloromethane; r.t, room temperature.

of alkenes with dichlorosilane catalysed by transition metals[29], followed by a sequential substitution of two chlorine atoms at the silicon with *t*-butyl and picolyl groups furnished the hydrosilane **2**. Alternatively, synthesis of **2** can be achieved easily via alkylation of ^{t}BuSiHCl$_2$ with organolithium/organomagnesium reagents, routinely available from the corresponding alkyl halides **1′**. Mostly, these three-step procedures allowed us to obtain starting hydrosilanes **2** in about 50% overall yields.

Next, the scope of this intramolecular dehydrogenative silylation reaction was investigated. Thus, unsubstituted *n*-butyl silane **2a** underwent the dehydrogenative Si–C coupling reaction to afford silolane **3a** in high yield (Table 1, Entry 1). The silanes **2b**–**2f** that bear α-, β- and γ-alkyl substituents were converted efficiently into silolanes **3b**–**3f** as well (Table 1, Entries 2–6). Cyclic cyclohexane-containing substrates can also be converted into bicyclic products **3g** and **3h** (Table 1, Entries 7 and 8). The substrates that contain a benzene ring (**2i**), and those with protected phenol (**2j**) and catechol (**2k**) fragments, were tolerated perfectly. Importantly, C(sp^2)–Hal (Hal = F, Cl, Br) bonds, as well as amine and CF_3 functionalities, remained intact under these reaction conditions (**2l**–**2p**). Silylation of the δ-C–H bond of CH_3 groups in hydrosilanes **2** is highly preferred over that of other competitive CH_2, CH and benzylic CH_2 groups. As an exception, a highly active secondary δ-C(sp^3)–H bond of a cyclopropane ring can also be silylated under these conditions (Table 1, Entry 17).

The obtained silolanes **3** could be converted efficiently into 1,4-diols using Smitrovich and Woerpel's oxidation procedure (Fig. 2)[30]. For convenience, the diols were isolated as diacetates **4**. We demonstrated that the oxidation procedure successfully affords aliphatic acyclic or cyclic primary diols (**4c**, **4g**), as well as the primary/secondary diol **4h**, in which the alcohol moieties can be differentiated routinely. Bicyclic silolane **3g**, on oxidation, yields **4g** as a mixture of *cis*/*trans* isomers in a 3:1 ratio. Obviously, this ratio is a result of activation of both methyl groups in hydrosilane **2g** during the C–H activation step (Table 1, Entry 7).

C–H functionalization is the most promising method for the late-stage modification of natural products and drugs because it eliminates prefunctionalization steps[31]. Accordingly, our new method was tested for the modification of natural products and derivatives (Fig. 3). To our delight, camphene, 2-methylenebornane and the derivative of lithocholic acid **1t** were converted successfully into the corresponding 1,4-diols **4r**–**4t**. In the case of camphene, the method resulted in *endo*-diol **4r**, whereas 2-methylenebornane furnished *exo*-diol **4s**, which can be explained by the preferable hydrosilylation of camphene and 2-methylenebornane from the less sterically hindered face of the double bond.

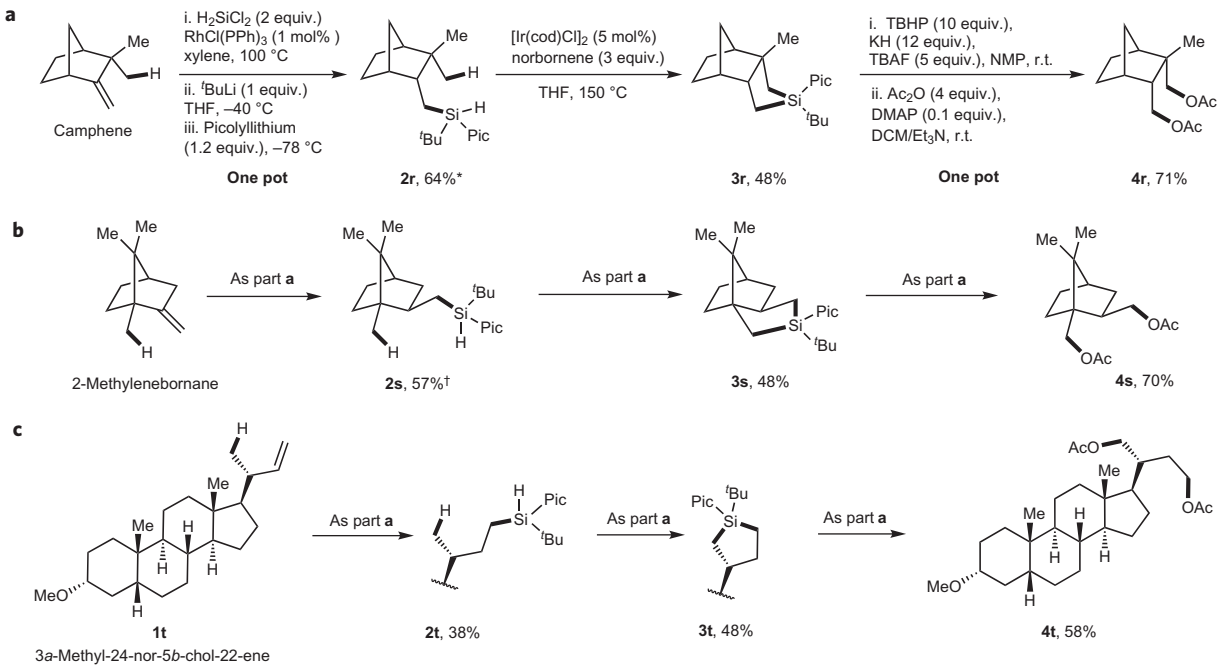


Figure 3 | 1,4-Oxygenation of alkene-containing natural products and derivatives. Application of the developed protocol for conversion of alkene-containing natural products and derivatives into the corresponding 1,4-diols. **a**, Conversion of camphene into 1,4-diol **4r**. **b**, Conversion of 2-methylenebornane (derived from camphor) into 1,4-diol **4s**. **c**, Conversion of alkene **1t** (derived from lithocholic acid) into 1,4-diol **4t**. *Mixture of stereoisomers *endo*/*exo* 8:1, major isomer is drawn (for details, see Supplementary Fig. 12). †Mixture of stereoisomers *endo*/*exo* 1:3, major isomer is drawn (for details, see Supplementary Fig. 13). THF, tetrahydrofuran; Pic, 2-picolyl.

Conclusion

In summary, we have developed an unprecedented conversion of 1-alkenes into 1,4-diols. This was accomplished by using a new Si,N-type TBPicSi directing group that can be installed easily onto alkenes. The TBPicSi group allows for intramolecular dehydrogenative silylation of unactivated δ-C(sp^3)–H bonds, as well as for efficient oxygenation of C–Si bonds. The developed method was successfully applied for the 1,4-dioxygenation of several alkene-containing natural products and derivatives.

Methods

Detailed descriptions of experiments as well as analytical data are provided in the Supplementary Information.

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Author contributions

N.G., F.S.M. and A.V.G. contributed equally to this work. N.G., F.S.M. and A.V.G. designed and performed the experiments and wrote the manuscript. C.H. performed the experiments at an early stage of the project. All authors participated in the discussion of the results. V.G. conceived and guided the research.

Additional information

Supplementary information and chemical compound information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to V.G.

Competing financial interests

The authors declare no competing financial interests.