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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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Abstract

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 methodology for C-H functionalization, alkenes are an attractive starting material due to their abundance and low cost. Here we describe the conversion of 1-alkenes into 1,4-diols. The method involves the installation of a Si,N-type chelating auxiliary group on the alkene followed by iridium catalyzed C-H silylation of an unactivated δ-C(sp^3)-H bond to produce an silolane intermediate. Oxidation of the C-Si bonds affords a 1,4-diol. The method is demonstrated to have broad scope and a good functional group compatibility by application to the selective 1,4-oxygenation of several natural products and derivatives.

Transition metal catalyzed 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 due to the lack of the active frontier orbitals, which could interact with a transition metal center. [7,8] Among a variety of aliphatic C–H functionalizations,[9,10] the C–H oxygenation is one of the most attractive transformations, since a number of important biochemical processes involve this step.[11–13] Although, a number of transition metal-catalyzed aliphatic C–H oxygenation reactions have been reported, they are mostly limited to functionalization of activated C–H bonds. On the other hand, the development of selective oxygenation of unactivated sp^3 C–H bond is still in its infancy.[14–22] Therefore, the design of new methods, which can be applied for selective oxygenation of unactivated aliphatic C–H bonds, is highly warranted.

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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 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 are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints.

Competing financial interests

The authors declare no competing financial interests.

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 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-catalyzed method developed by Hartwig for dehydrogehative Si–H/C–H coupling in alkoxysilanes.[23] However, in order for this approach to be synthetically useful for a fully hydrocarbon chain of **2**, a 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 the transition metal-catalyzed Si–H/C–H coupling see references 24, 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. S1).

Next, we proposed that a new Si,N-type chelation-assisted auxiliary could facilitate the dehydrogehative Si–H/C–H coupling reaction. This idea was inspired by Daugulis' N,N-chelation concept, which was proven efficient for a remote Pd-catalyzed aliphatic C–H activation reactions.[28] To this end, we screened a number of potential directing groups and reaction conditions (Supplementary Fig. 1–3, Supplementary Tables 1–5). Gratifyingly, we found that a new Si,N-type chelating group, *tert*-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 analog 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 the six membered chelation stabilized iridacycle **A**, but also, being easily removable from silicon, ensures a successful subsequent oxidation of **3**. The bulky *tert*-butyl substituent at silicon, in turn, proved vital for stability of **2**. Next, we developed an efficient method for installation of TBPicSi directing group onto alkenes **1**. Thus, transition metal-catalyzed hydrosilylation of alkenes with dichlorosilane,[29] followed by a sequential substitution of two chlorine atoms at silicon with *tert*-butyl- and picolyl groups furnished the hydrosilane **2**. Alternatively, synthesis of **2** can be easily achieved via alkylation of ^{t}BuSiHCl$_2$ with organolithium/organomagnesium reagents, routinely available from the corresponding alkyl halides **1′**. Mostly, these 3-step procedures allow to obtain starting hydrosilanes **2** in about 50% overall yields.

Next, the scope of this intramolecular dehydrogenative silylation reaction has been investigated. Thus, unsubstituted *n*-butyl silane **2a** underwent the dehydrogenative Si–C

coupling reaction affording silolane **3a** in high yield (Table 1, Entry 1). The silanes **2b**-**f** bearing α-, β-, and γ-alkyl substituents were efficiently converted into silolanes **3b**-**f** as well (Entries 2–6). Cyclic cyclohexane-containing substrates can also be converted into bicyclic products **3g**, **h** (Entries 7, 8). The substrates containing benzene ring **2i**, as well as protected phenol **2j** and catechol **2k** fragments, were perfectly tolerated. 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**-**p**). Notably, silylation of δ-C–H bond of CH_3 groups in hydrosilanes **2** is highly preferable over 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 (Entry 17).

The obtained silolanes **3** could be efficiently converted into 1,4-diols using Woerpel's oxidation procedure (Fig. 2).[30] For convenience, the diols were isolated as diacetates **4**. We have demonstrated that the oxidation procedure successfully affords aliphatic acyclic or cyclic primary diols (**4c**, **4g**), as well as primary/secondary diol **4h**, in which the alcohol moieties could be routinely differentiated. Bicyclic silolane **3g,** upon 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, since it eliminates prefunctionalization steps.[31] Accordingly, our new method has been tested for modification of natural products and derivatives (Fig. 3). To our delight, camphene, 2-methylenebornane and the derivative of lithocholic acid **1t** were successfully converted into the corresponding 1,4-diols **4r**-**t**. 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.

Conclusion

In summary, we developed an unprecedented conversion of 1-alkenes into 1,4-diols. This was accomplished by using a new Si,N-type *tert*-butylpicolylsilicon hydride (TBPicSi) directing group, which can be easily installed onto alkenes. 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 description of experiments as well as analytical data are provided in Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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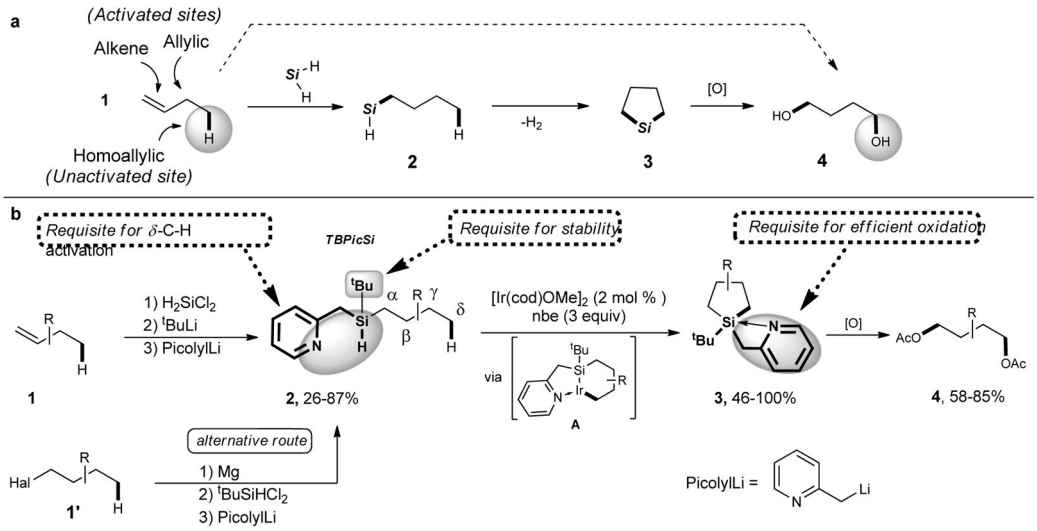


Figure 1. Synthesis of 1,4-diols from 1-alkenes and alkyl halides

a, General concept for formal 1,4-oxygenation of 1-alkenes **1** into 1,4 diols **4** via activation of 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 catalyzed C-H silylation of an unactivated C(sp^3)-H bond (to produce the silolane **3**), and subsequent oxidation. We designed *tert*-butylpicolylsilyl (TBPicSi), a new Si,N-type chelating directing group which can be easily installed on alkenes (and alternatively on alkyl halides). Notably, its picolyl moiety enables an efficient Si–H/C–H activation step (via iridacycle **A**) and, being easily removable from silicon, ensures a successful subsequent oxidation of silolane **3** into the final diol **4**. The bulky *tert*-butyl substituent at silicon is requisite for stability of **2**. cod, cyclooctadiene; nbe, norbornene.

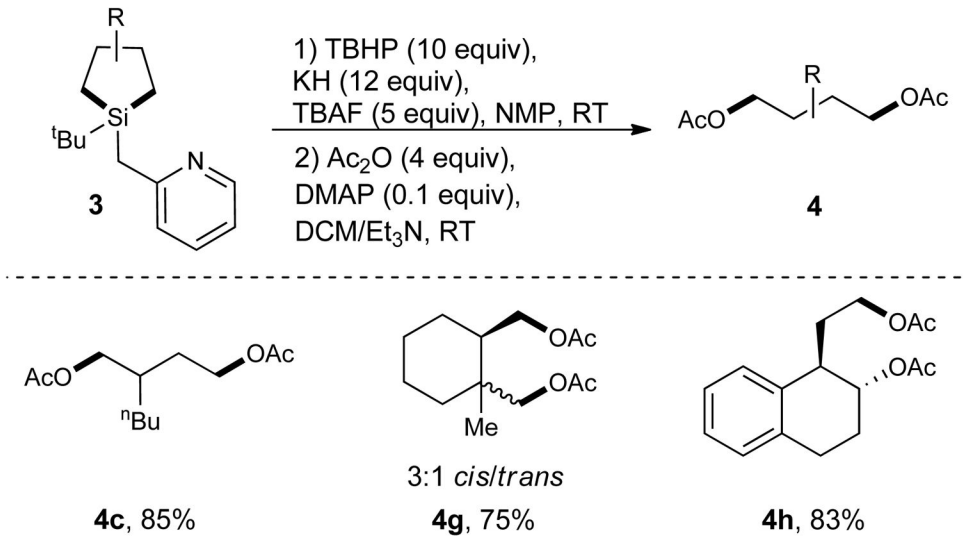


Figure 2. Conversion of silacycle intermediates 3 into 1,4-diol derivatives 4

The reaction was performed under Woerpel's oxidation conditions.[30] TBHP, *tert*-butyl hydroperoxide; TBAF, tetrabutylammonium fluoride; NMP, N-methylpyrrolidone; RT, room temperature; Ac, acetyl; DMAP, 4-dimethylaminopyridine; DCM, dichloromethane.

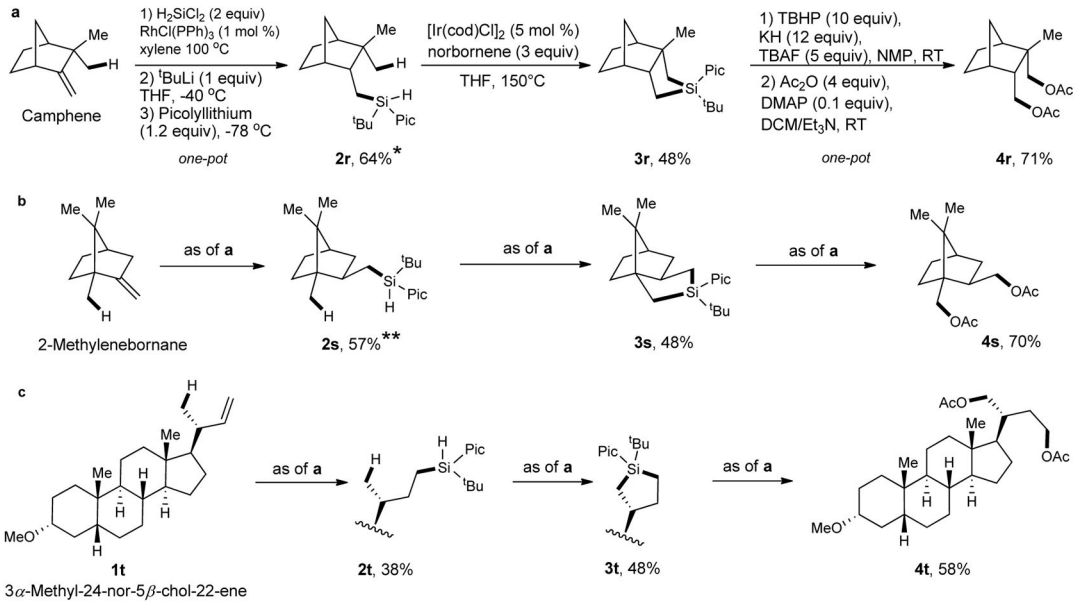
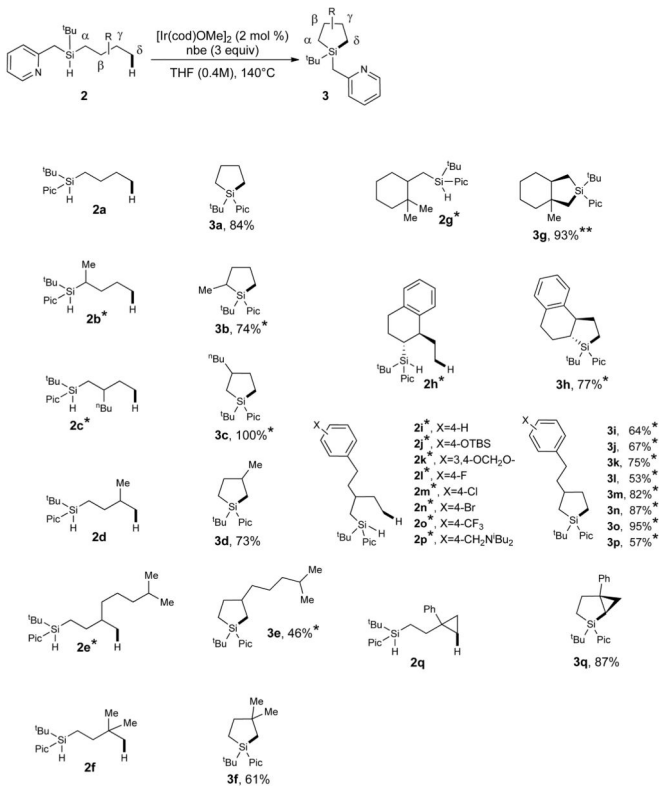


Figure 3. 1,4-Oxygenation of alkene-containing natural products and derivatives

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 Bornane) into 1,4-diol **4s. c**, Conversion of alkene **1t** (derived form Lithoholic acid) into 1,4-diol **4t**. *Mixture of stereoisomers endo/exo 8:1, major isomer is drawn (for details, see Supplementary Fig. S12). **Mixture of stereoisomers endo/exo 1:3, major isomer is drawn (for details, see Supplementary Fig. S13). THF, tetrahydrofuran; Pic, 2-picolyl; cod, cyclooctadiene; nbe, norbornene; TBAF, tetrabutylammonium fluoride; NMP, *N*-methylpyrrolidone; RT, room temperature; Ac, acetyl; DMAP, 4-dimethylaminopyridine; DCM, dichloromethane.

Table 1

Ir-catalyzed δ-C–H dehydrogenative silylation reaction.



*Mixture of stereoisomers (see Supplementary Information for details);

**Major diastereomer is drawn (see Fig. 3 for details); nbe, norbornene; Pic, picolyl; TBS, tert-butyldimethylsilyl.