BIOCHEMISTRY

Radical chain repair: The hydroalkylation of polysubstituted unactivated alkenes

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The concept of repair is widely used by nature to heal molecules such as proteins, lipids, sugars, and DNA that are damaged by hydrogen atom abstraction resulting from oxidative stress. We show that this strategy, rather undocumented in the field of synthetic organic chemistry, can be used in a radical chain reaction to enable notoriously intractable transformations. By overcoming the radical chain inhibitor properties of substituted alkenes, the radical-mediated hydroalkylation of mono-, di-, tri-, and even tetrasubstituted unactivated olefins could be performed under mild conditions. With a remarkable functional group tolerance, this reaction provides a general coupling method for the derivatization of olefin-containing natural products.

INTRODUCTION

By enabling the buildup of large molecular libraries, the advent of transition metal–catalyzed aryl-aryl, aryl-alkenyl, and aryl-akynyl cross-coupling reactions has been driving a whole segment of bioorganic chemistry toward aromatic frameworks. There is now a considerable effort to develop an equivalent set of Csp^3-Csp^3 cross-coupling methodologies that could sustain wide-ranging derivatization of the pool of nonaromatic natural scaffolds available. Free radicals have emerged as key intermediates in this endeavor as they offer an entry to the use of basic functionalities as coupling partners (*1*), bypassing the sensitive organometallics required in conventional Pd- and Ni-catalyzed approaches (*2*). Similarly, classical nucleophilic addition and substitution reactions remain hampered by strongly basic conditions (enolate chemistry and main-group organometallic species) and/or sensitive reagents (organocopper), making their use on complex systems delicate at best. While photoredox-catalyzed radical formation combined with nickel catalysis has recently flourished as an elegant solution for C–C bond formation from various functional groups, including native carboxylic acids (*3*) and easily oxidized C–H bonds (*4*), the widespread availability of olefinic building blocks and natural products has triggered remarkable advances on radical hydroalkylation reactions. Giese *et al.* (*5*) have pioneered the radical-mediated hydroalkylation of electron-deficient olefins such as acrylates, recently leading to impressive enantioselective versions of this reaction (*6*, *7*). On the other hand, the hydroalkylation of unactivated alkenes remains a highly challenging problem, which can formally be tackled according to two radical-mediated approaches (Scheme 1): (A) The hydrogen atom is added first to the alkene. (B) The carbon residue is added first to the alkene. Following approach A, alkenes have been used as a source of alkyl radicals either via hydroboration with anti-Markovnikov regioselectivity (*8*, *9*) or via a Mn-, Fe-, and Co-catalyzed hydrofunctionalization process, with Markovnikov regioselectivity (*10*). This approach is brilliantly illustrated by the Fe hydride–catalyzed hydroalkylation recently pioneered by Baran and colleagues (*11*, *12*). Approach B, that is, the addition of carbon-centered radicals to nonactivated alkenes, is highly attractive in terms of mildness and functional group tolerance but remains severely limited because the available methods require either two-step procedures (*13*, *14*), a large excess of the alkene (*15*, *16*), or specific enol (*17*) or styrene substrates (*18*). More critically, this approach has remained essentially restricted to terminal olefins due to the poor radical trap properties of nonterminal alkenes resulting from a competition between the slow addition process and undesired side reactions such as hydrogen atom transfers. We report here that the use of 4-*tert*-butylcatechol (TBC) as a source of hydrogen atoms overcomes this issue, providing a simple method for the hydroalkylation of unactivated alkenes, as illustrated with various substrates including terpenes and steroids. The results obtained with tetrasubstituted alkenes suggest that the exceptional efficiency of the process relies on a chain repair mechanism, a concept so far underexploited in organic synthesis.

RESULTS

Recently, we have shown that catechols can be used to reduce alkyl radicals generated from organoboranes (*19*) and from alkyl iodides (*20*). Trying to expand the scope of this system, we soon realized that simple mixing of methylenecyclohexene, ethyl iodoacetate, TBC, and triethylborane in dichloromethane under nitrogen followed by stirring the reaction mixture in an open-to-air flask cleanly afforded the hydroalkylated product **1**. A rapid optimization showed that good results could be obtained either with a slight excess of the iodide [1.2 equivalents (equiv); method A] or with a twofold excess of the alkene (method B) (Scheme 2). The reaction was first applied to a wide range of di- and monosubstituted terminal alkenes including a styrene derivative using ester-, lactone-, and sulfone-derived radicals. The reaction was further tested with terpenoids such as (+)-longifolene and (−)-limonene leading to **10** (one diastereomer) and **11** (selective monohydroalkylation of the less substituted alkene). The reaction of (−)-carvone with iodomethyl phenyl sulfone afforded exclusively **12** in 64% (A) and 82% (B), leaving the enone moiety untouched. Finally, reactions involving either subsequent cyclobutane ring-opening or ring-closing processes have been performed starting from (−)-β-pinene and (−)-*trans*-caryophyllene, providing the monocyclic ester **13** and the tricyclic ester **14** in good yields.

The hydroalkylation of nonterminal alkenes, known to inhibit radical chain reactions (*21*), was investigated next. On the basis of the reported rated constant (*22*), it was anticipated that this reaction

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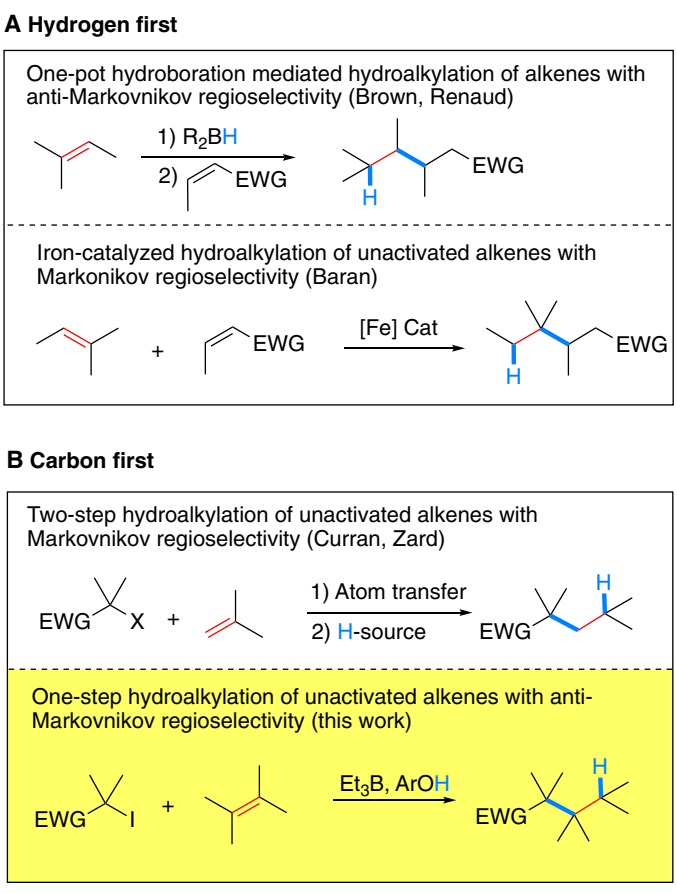


Scheme 1. Strategies for the radical hydroalkylation of unactivated alkenes. EWG, electron-withdrawing group. New bonds are indicated in bold blue.

would be limited to a rather small number of exceptionally reactive nonterminal alkenes such as strained derivatives. This limitation does not apply, and a broad range of cyclic (see products **15** to **20**) and acyclic alkenes (see products **21** to **25**) could be alkylated using either conditions. Several iodides such as iodomethyl phenyl sulfone, mono- and difluoroiodoacetates, and iodoacetonitrile were tested, all affording the corresponding hydroalkylated products **22** to **25** in good to excellent yields. To the best of our knowledge, radical hydroalkylation of tetrasubstituted alkenes has not been reported. Using condition B, good yields for the coupling reaction leading to products **26** to **28** were obtained. The reaction of benzyl iodoacetate with bicyclohexylidene afforded the expected product **29** in 59% yield together with compound **20** (6%), which provides an important hint toward the mechanism of the reaction (see discussion below). The reaction of terpenoid and steroid derivatives including complex frameworks such as cholesteryl benzoate and pregnenolone acetate provides the hydroalkylated products **30** to **32** in 61 to 65% yield. Unprotected aldehydes and ketones are well tolerated as exemplified by the preparation of the formylester **33** in 77% yield from (−)-citronellal and the ketoester **34** in 74% yield.

The utility of the method was further highlighted with the rapid synthesis of the chiral 1,6-heptadiene derivative **35** that was prepared in 55% overall yield via a double hydroalkylation process involving methyl chloroiodoacetate and (−)-β-pinene (Scheme 3). A further demonstration of the potential of the hydroalkylation method is the coupling between chlolesteryl benzoate and the iodoacetylated *N*-Boc-(*S*)-serine methyl ester. The C–C coupling product **36** was obtained in 32% yield, demonstrating the tolerance of the reaction to complex functionalized substrates (Scheme 3).

MECHANISTIC CONSIDERATIONS

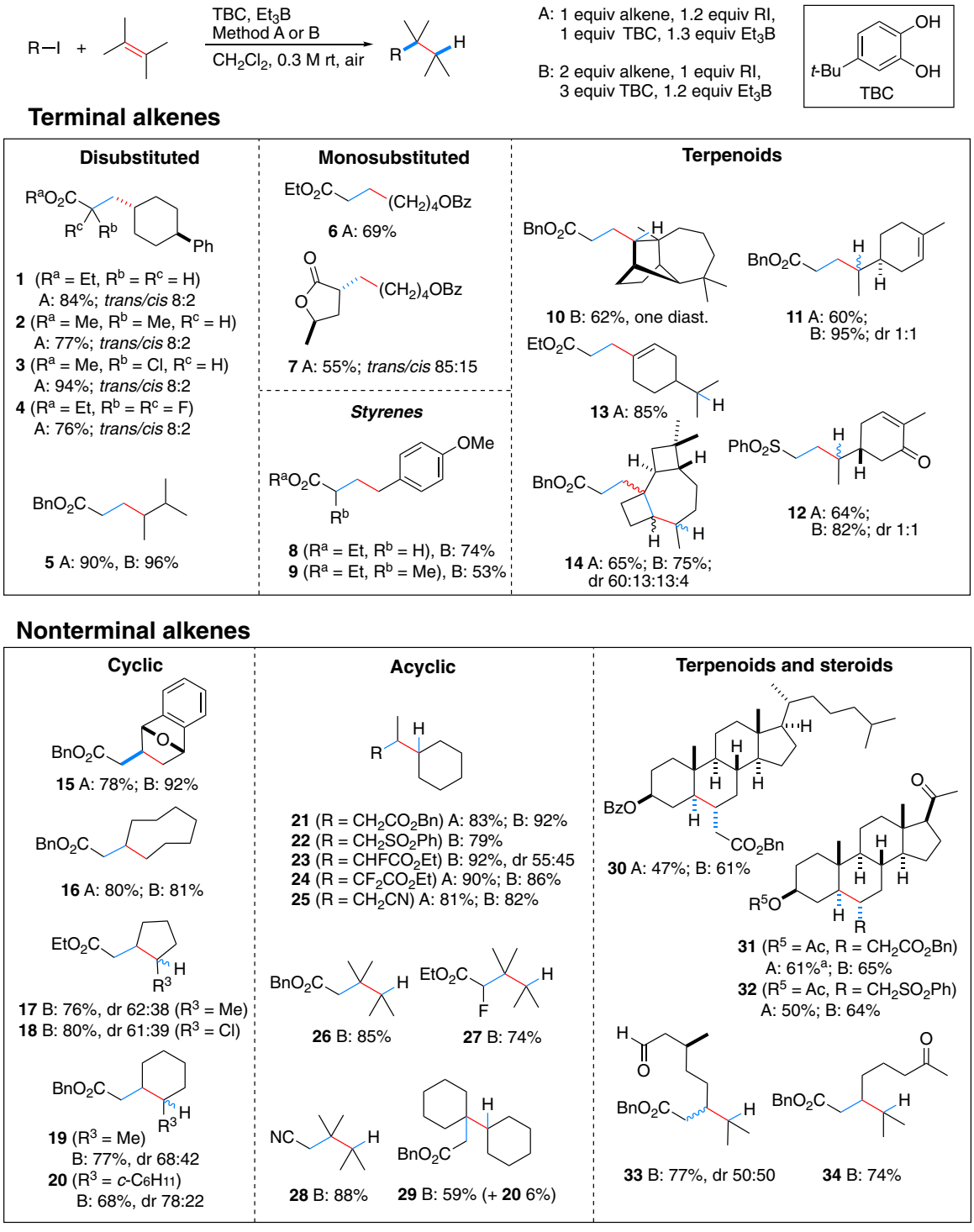
The efficiency of the hydroalkylation of unactivated alkenes reported here exceeds all the initial expectations because all reactions were performed in an all-at-once process at standard concentrations ([TBC] = 0.3 M). The combination of two effects, polar effects and a repair mechanism, may explain this unprecedented efficacy.

Polar effects

The efficiency of the radical addition supposes only negligible reduction of the electron-poor attacking radical by TBC. Using a radical clock experiment, the rate constant k_H for the hydrogen atom transfer from TBC to an ester enolyl radical could be evaluated around 2×10^3 M^{-1} s^{-1} at 80°C (see the Supplementary Materials), that is, about three orders of magnitude slower than to a secondary alkyl radical under similar conditions (*19*). This pronounced polar effect can be understood in terms of the strong polarization of the O–H bond that grants the hydrogen atom a proton character, thus preferentially reacting with electron-rich radicals. This counterintuitive selectivity for the reduction of electron-rich species gives the electron-poor attacking radical sufficient lifetime to undergo even slow addition reactions, while the resulting richer radical adduct is efficiently trapped by TBC. Polar effects are known to be relatively unimportant in reactions involving the weakly polarized Bu_3SnH (*23*, *24*) but have been shown to play an important role in reactions with thiophenol (*25*, *26*).

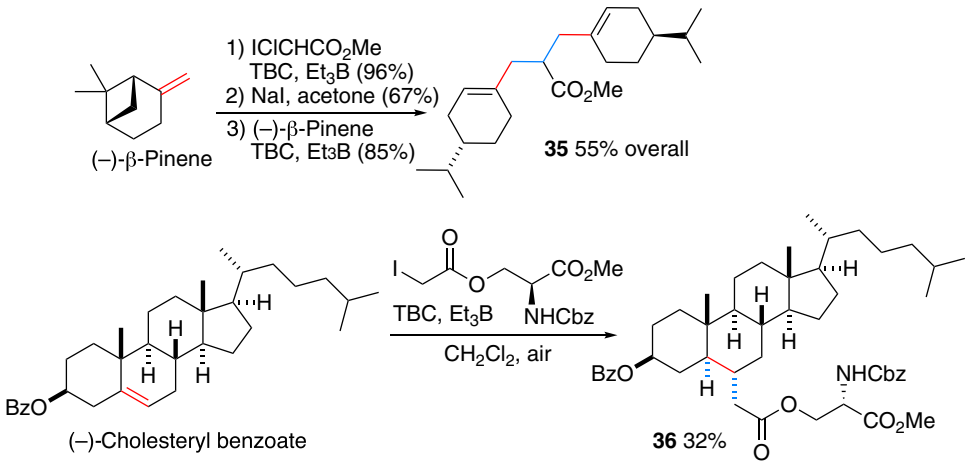
Repair mechanism

The efficacy of the process involving nonterminal alkenes is puzzling, as even trisubstituted alkenes are notoriously reluctant to radical addition (*27*, *28*). Ingold and Bowry (*21*) reported that internal alkenes such as cyclohexene have a strongly retarding effect in radical chain dehalogenation processes involving tin hydride. This effect is due to undesired hydrogen atom transfer from the allylic positions and the formation of delocalized allylic radicals. More than just degrading a fraction of the substrate, these stabilized radicals are inefficiently reduced by tin hydride and mainly contribute to chain disruption processes, thus making the overall reaction unproductive. Hydrogen atom abstraction of an allylic hydrogen atom [bond dissociation enthalpy (BDE) = 86.8 kcal mol^{-1}] (*29*) by an α-ester radical (BDE H–CH_2CO_2Et = 98.4 kcal mol^{-1}) (*30*), an α-cyano radical (BDE H–CH_2CN = 92.4 kcal mol^{-1}) (*29*), or an α-sulfonyl radical (BDE H–CH_2SO_2Ph = 99 kcal mol^{-1}) are all exothermic and are expected to be favored by polar effects (*31*). Recently, we have reported that the system TBC/Et_3B was able to repair the chain reaction of thiol-ene coupling processes involving allyl ethers (*32*). Only such a repair mechanism may explain why the present hydroalkylation process works efficiently despite the inevitable formation of undesired allylic radicals. Because of the chain nature of the process, a damage process leading to chain disruption may strongly diminish the reaction efficiency if it is not repaired. The occurrence of a chain repair process can only be detected when it is imperfect (that is, non-regioselective), as, for instance, during the hydroalkylation of (*E*)-3-hexene that led to the expected product **37** contaminated by a small amount of its isomer **38** (Scheme 4C). A similar observation was made during the hydroalkylation of bicyclohexylidene (Scheme 4D). The crude product of the reaction contains

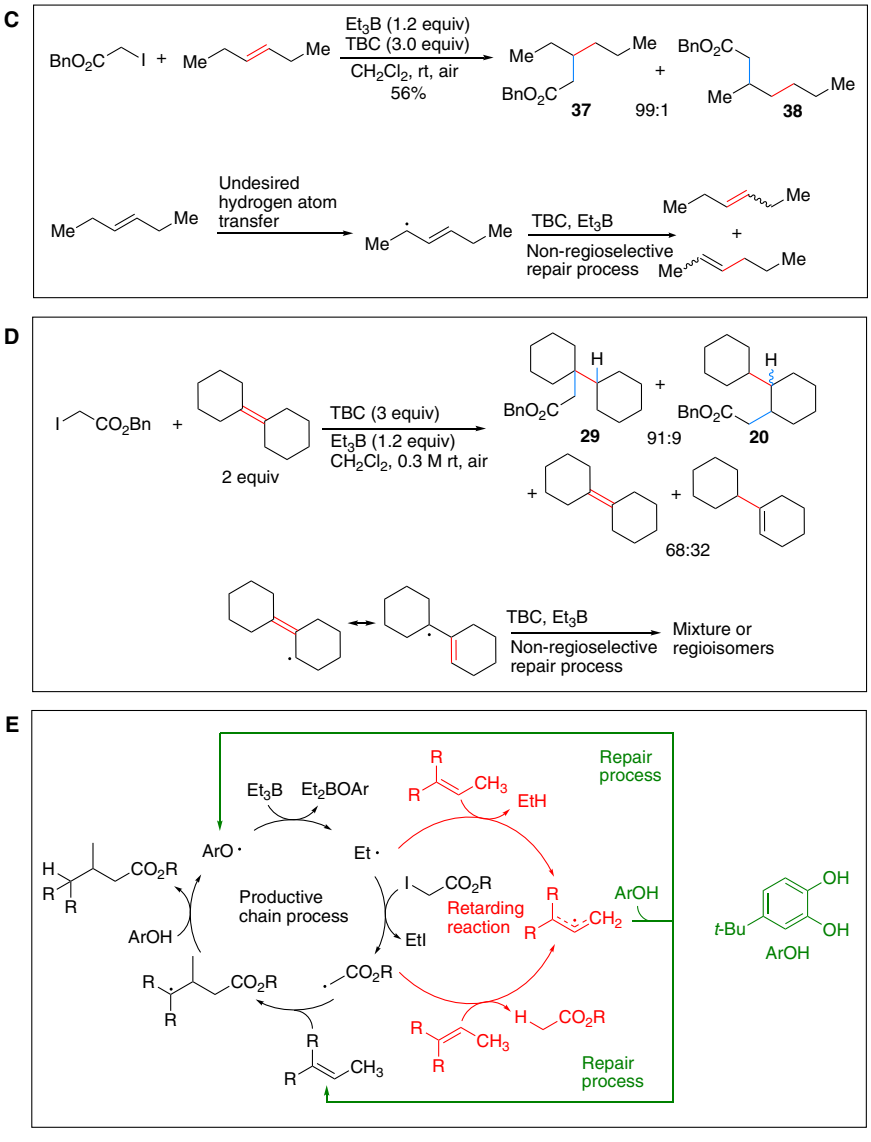


Scheme 2. Radical hydroalkylation of terminal and nonterminal alkenes.

the two addition products **29** and **20** in a 91:9 ratio. The remaining alkene was partly isomerized and consists of a 68:32 mixture of bicyclohexylidene and 1-cyclohexycyclohexene. The formation of the isomerized alkene and alkylated product **20** is a clear consequence of an imperfect repair process involving the formation of a transient allylic radical. In this reaction, the formation of benzyl acetate (deiodinated product) was observed, demonstrating the involvement of α-ester radicals in the hydrogen atom abstraction process. Ethyl radicals may also be involved in the hydrogen atom abstraction step, as depicted in Scheme 4E. However, this process is probably marginal because the lifetime of ethyl radical under our reaction conditions is much shorter than that of α-ester radicals. This assumption is supported by



Scheme 3. Bis-hydroalkylation of (–)-β-pinene with ethyl chloroiodoacetate and hydroalkylation of cholesteryl benzoate with *N*-Cbz-*O*-iodoacetyl serine.



Scheme 4. Mechanistic studies. (**C** and **D**) Hydroalkylation of *n*-3-hexene and bicyclohexylidene showing a non-regioselective repair process. (**E**) Mechanism of the hydroalkylation process highlighting the productive chain process (in black), the retarding reactions (in red), and the repair process (in green).

the fact that treating bicyclohexylidene with Et_3B, TBC, and air (no α-iodoester) afforded, after a 2-hour reaction time, about 2% of the isomerized 1-phenylcyclohexene (see the Supplementary Materials).

The repair mechanism uses the same reagents (TBC and Et_3B) and produces the same by-product ($ArOBEt_2$) as the hydroalkylation process, making this process particularly smart (it does only require the use of a slight excess of reagents). A complete mechanism for the hydroalkylation process is proposed in Scheme 4E. For clarity, the mechanism depicted here does not take into account a possible iodine atom transfer to the adduct radical that might compete, particularly in case of secondary alkyl radicals, with the reduction by TBC. This process is not a chain-terminating step because it produces α-ester radicals. Moreover, secondary alkyl iodides should reenter the chain process upon reaction with ethyl radicals [see (*20*) for such a deiodination process]. Consequently, this process should not have a negative impact on the yield of the hydroalkylation reaction. The productive chain process is highly favored by polar effects. However, hydrogen atom abstraction from allylic positions produces allylic radicals that are known to strongly retard/inhibit the chain reaction. In the presence of catechol and triethylborane, a repair process takes place, giving back the aryloxyl radical and the alkene, two species involved in the productive chain reaction.

CONCLUSIONS

An efficient radical-mediated hydroalkylation of terminal and nonterminal alkenes has been developed. The reaction is based on the use of weakly toxic reagents such as TBC and triethylborane (after the reaction, the borinates are expected to be easily oxidized to boric acid derivatives). The mildness of this chemistry makes it particularly promising for the direct modification of complex natural products and drug candidates. The results presented here highlight the importance of polar effects in intermolecular reactions. They also demonstrate that alkenes classified as retarding substrates in tin hydride–mediated chemistry (*21*) become suitable for radical-mediated reductive alkylation due to a unique chain repair process. Our results demonstrate that the concept of using a repair mechanism may have a marked influence on the efficacy of a chain process. Nature has been using selective hydrogen atom transfer promoted by antioxidants such as α-tocopherol and glutathione to repair undesired hydrogen atom abstraction processes that lead to biomolecule (proteins, lipids, sugars, and DNA) degradation (*33*–*35*). As shown here, this strategy may be used in synthesis to temper the innate behavior of a reactive species, allowing hitherto unfeasible transformations.

MATERIALS AND METHODS

General information

Unless otherwise stated, all glassware was oven-dried at 160°C or flame-dried under vacuum, assembled hot, and allowed to cool under nitrogen. All reactions were carried out open to air (under a $CaCl_2$ guard tube). Reactions were monitored by thin-layer chromatography (TLC) and carried out on Merck silica gel 60 F_{254} analytical plates. Visualization of TLC plates was performed under ultraviolet (254 nm) or by staining with a solution of $KMnO_4$ (2.5 g), Na_2CO_3 (15 g) in H_2O (250 ml), phosphomolybdic acid (6.25 g), Ce $(SO4)_2.4H_2O$ (2.5 g), and concentrated H_2SO_4 (15 ml) in H_2O (235 ml). Yields refer to chromatographically or spectroscopically pure compounds. Silica gel 60 A (40 to 60 μm) from SDS was used for flash column chromatography (FC).

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a 300-MHz spectrometer for ^1H and on a 75-MHz spectrometer for ^{13}C at 22°C. Chemical shift data are reported in units of δ (ppm) using the residual $CHCl_3$ as the internal standard (δ = 7.26 for ^1H NMR spectra and δ = 77.0 for ^{13}C NMR spectra). The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintet), sept (septuplet), hept (heptuplet), m (multiplet), and br (broad); the prefix app (apparent) was added when different coupling constants appeared accidentally equal. Coupling constants, *J*, are reported in hertz. Multiplicities were interpreted at the second order following Pople nomenclature when possible. Despite some apparent second-order contributions depending on the processing of the free induction decay (FID; for example, apodization function), some signals were approximated to the first order when the resolution was not sufficient. ^{13}C NMR spectra were run using a proton-decoupled pulse sequence. The number of carbon atoms for each signal is indicated when superior to one. High-resolution mass spectrometry (MS) analyses were recorded on a hybrid quadrupole time-of-flight mass spectrometer using positive electrospray or on a double-focusing magnetic sector mass spectrometer. Infrared (IR) spectra were recorded on a Fourier transform IR spectrometer equipped with a Single Reflection Diamond ATR probe, and the values are reported in wave numbers (in cm^{-1}). Gas chromatography (GC) analyses were performed on a Macherey-Nagel OPTIMA Delta-3 capillary column (20 m, 0.25 mm; carrier gas: He, 1.4 ml/min; injector: 220°C, split mode; flame ionization detector: 280°C, H_2, 35 ml/min; and air, 350 ml/min). GC-MS analyses were carried out on a GC-MS fitted with a quadrupole mass analyzer using an electron impact at 70 eV and equipped with a Macherey-Nagel OPTIMA Delta-3 capillary column (20 m, 0.25 mm; carrier gas: He, 1.4 ml/min; and injector: 220°C split mode).

Unless otherwise stated, all commercial reagents were used as received. Solvents for the reactions (distilled CH_2Cl_2, tetrahydrofuran, and *n*-hexane) were filtered over columns of dried alumina under a positive pressure of argon. Solvents for extractions and FC were of technical grade and were distilled before use. Triethylborane solution (1 M in *n*-hexane) was prepared from pure triethylborane.

General procedures

Method A. Hydroalkylation with a 1.2-fold excess of the iodide

To a solution of α-iodo derivative (1.2 equiv), terminal/nonterminal alkene (1 equiv) in CH_2Cl_2 (10 ml) was added TBC (1 to 2 equiv) followed by Et_3B (1.3 equiv, 1 M solution in *n*-hexane). The resulting solution was stirred at room temperature in the presence of air under a $CaCl_2$ guard tube. Consumption of starting material was monitored by GC or TLC. After 2 hours, the reaction mixture was filtered over a short pad of neutral alumina by using Et_2O as eluent to remove the catechol derivatives and the boron-containing side products. The resulting crude filtrate was concentrated under reduced pressure, and the final purification of the mixture was done by silica gel column chromatography using Et_2O/pentane mixtures.

Method B. Hydroalkylation with a 2- to 2.5-fold excess of the alkene

To a solution of α-iodo derivative (1.0 equiv), terminal/nonterminal alkene (2 to 2.5 equiv) in CH_2Cl_2 (10 ml) was added TBC (3.0 equiv) followed by Et_3B (1.2 equiv, 1 M solution in *n*-hexane). The resulting solution was stirred at room temperature in the presence of air under a $CaCl_2$ guard tube. Consumption of starting material was monitored by GC or TLC. After 2 hours, the reaction mixture was filtered over

a short pad of neutral alumina by using Et_2O as eluent to remove the catechol derivatives and the boron-containing side products. The resulting crude filtrate was concentrated under reduced pressure, and the final purification of the mixture was done by silica gel column chromatography using Et_2O/pentane mixtures.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/4/7/eaat6031/DC1

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